CASE #01 -- SLIDE #01

**Diagnosis:** Nodular fasciitis

**Case Summary:** 12 year old male with a rapidly growing temple mass. Present for 4 weeks. Nodular fasciitis is a self-limited pseudosarcomatous proliferation that may cause clinical alarm due to its rapid growth. It is most common in young adults but occurs across a wide age range. This lesion is typically 3-5 cm and composed of bland fibroblasts and myofibroblasts without significant cytologic atypia arranged in a loose storiform pattern with areas of extravasated red blood cells. Mitoses may be numerous, but atypical mitotic figures are absent. Nodular fasciitis is a benign process, and recurrence is very rare (1%). Recent work has shown that the MYH9-USP6 gene fusion is present in approximately 90% of cases, and molecular techniques to show USP6 gene rearrangement may be a helpful ancillary tool in difficult cases or on small biopsy samples.


CONTRIBUTED BY KAREN FRITCHIE, MD
Diagnosis: Cellular fibrous histiocytoma

Case Summary: 12 year old female with wrist mass.

Fibrous histiocytoma is a lesion composed of a polymorphous proliferation of foamy histiocytes, multinucleated giants cells (some of which can be Touton giant cells), bland spindle cells and inflammatory cells. One of the most helpful histologic clues to this diagnosis is the prominent collagen trapping at the edge of the lesion. Clinically, fibrous histiocytoma usually presents as a solitary slow-growing nodule in early or middle-adult life. It is most common on the extremities. Many variants of fibrous histiocytoma exist including cellular fibrous histiocytoma, aneurysmal fibrous histiocytoma, epithelioid fibrous histiocytoma and atypical fibrous histiocytoma. Cellular fibrous histiocytoma differs from the conventional form by its monomorphous appearance (typically only bland spindle cells) and lack of secondary elements (giant cells, foamy histiocytes). The characteristic collagen entrapment is still present. Due to the relatively high rate of local recurrence of cellular fibrous histiocytoma (approximately 20%), complete surgical excision is usually recommended.

CONTRIBUTED BY KAREN FRITCHIE, MD
CASE #03 -- SLIDE #03

Diagnosis: Dermatofibrosarcoma protuberans

Case Summary: A 25 year old female with breast mass.

Dermatofibrosarcoma protuberans (DFSP) is a locally aggressive tumor that usually presents during early or middle adulthood. Although there appears to be an increasing number of reports in children, this diagnosis remains relatively rare in the pediatric population. Histologically, DFSP is composed of a diffusely infiltrative proliferation of uniform CD34-positive spindle cells arranged in a storiform architecture. Typically the tumor cells can be seen infiltrating subcutaneous adipose tissue in a ‘honeycomb’ pattern. Areas with myxoid morphology may also be present. This tumor has a high recurrence rate if not completely excised, but the rate of metastatic disease is low. Cytogenetically DFSP is characterized by supernumerary ring chromosomes derived from chromosome 22 or by the presence of the reciprocal translocation t(17;22). At the molecular level, both cytogenetic abnormalities result in the fusion of COL1A1 on chromosome 17q to PDGFB on chromosome 22q. The COL1A1/PDGFB fusion activates the PDGFRB tyrosine kinase signaling pathway, which renders DFSP responsive to tyrosine kinase inhibitors, such as imatinib mesylate.


CONTRIBUTED BY KAREN FRITCHIE, MD
Diagnosis: Giant cell fibroblastoma

Case Summary: 18 year old male with axillary mass.

Although Shmookler and Enzinger who first described giant cell fibroblastoma in 1982 suggested that it was related to dermatofibrosarcoma protuberans (DFSP), it was not until 1996 when this theory was proven by cytogentic studies. Both giant cell fibroblastoma and DFSP are linked by supernumerary ring chromosomes derived from chromosomes 17 and 22. Giant cell fibroblastoma develops as a painless nodule in the dermis or subcutaneous tissue most commonly in infants and children. Sites affected include thigh, inguinal region and chest wall. Histologically these tumors are composed of a loose arrangement of spindle cells with an infiltrative growth pattern. The cellularity of this lesion is quite variable, but a common morphologic feature includes pseudovascular spaces lined by giant cells. These tumors are CD34 positive, like DSFP. Treatment of giant cell fibroblastoma should be wide local excision.


Diagnosis: Hemangioma.

Case Summary: 26 year old female with chest wall mass.

Hemangioma, a benign vascular tumor, is one of the most common soft tissue tumors and usually presents in infancy and childhood. Any site can be affected. There are several morphologic variants including capillary (lobular), cavernous and intramuscular. Most have overlapping histiologies, and it is not uncommon to see both capillary and cavernous features in the same lesion. A helpful histologic clue to the benign nature of hemangioma is its low power architecture: circumscribed and often lobular. This contrasts with angiosarcoma which is typically infiltrative. Additionally, the vascular spaces of hemangioma are lined by bland endothelial cells. The vascular spaces of angiosarcoma are poorly formed, while the endothelial population exhibits hyperchromasia and atypia. By immunohistochemistry, the endothelial cells of hemangioma will be positive for markers such as CD31, CD34, FLI-1 and ERG.
Diagnosis: Angiosarcoma

Case Summary: 57 year old male with supraclavicular mass.

Angiosarcomas are malignant vascular tumors. While angiosarcomas can be broken down into several clinical subgroups (cutaneous angiosarcoma, angiosarcoma associated with lymphedema, radiation-associated angiosarcoma, angiosarcoma of the breast, angiosarcoma of deep soft tissue), all forms are highly aggressive tumors characterized by an infiltrative proliferation of vascular structures lined by atypical endothelial cells. In poorly differentiated angiosarcoma, the endothelial nature may be difficult to recognize. In those cases, immunohistochemistry for CD31, CD34, FLI-1 and ERG may be helpful. It is not uncommon for angiosarcoma to lose reactivity for one or more endothelial markers, so sometimes a panel of immunostains may be necessary. The prognosis for patients with angiosarcoma is poor. Recent work has revealed that post-radiation angiosarcomas are characterized by MYC amplification. Additional studies have shown the either immunohistochemistry for MYC overexpression or FISH for MYC overamplification is a helpful diagnostic tool for differentiating post-radiation angiosarcoma from atypical vascular lesions (AVLs).

CASE #07 -- SLIDE #07

Diagnosis: Epithelioid hemangioma

Case Summary: 11 year old female with postauricular mass.

Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia) is a distinct vascular tumor that usually presents in young or middle-aged adults. The most common site of involvement is the dermis/subcutaneous tissue around the ear. About 50% of patients will describe multiple lesions. Histologically, epithelioid hemangioma is a relatively circumscribed proliferation of small vessels lined by hobnailed (tombstone-like) endothelial cells. Another prominent feature is the inflammatory component which is predominantly eosinophils. There is still debate as to whether this entity is reactive or neoplastic. Some lesions may regress on their own, while others require surgical excision. About 1/3 recur.

CONTRIBUTED BY KAREN FRITCHIE, MD
CASE #08 -- SLIDE #08

**Diagnosis:** Organizing thrombus

**Case Summary:** 74 year old male with cheek mass.

Organizing thrombus/papillary endothelial hyperplasia is an exuberant intravascular proliferation of endothelial cells. This process may occur in pre-existing blood vessels, vascular malformations or vascular neoplasms such as hemangiomas. Histologically, organizing thrombus/papillary endothelial hyperplasia is characterized by small delicate papillae of endothelial cells surrounding a collagenous core. The endothelial cell population is usually only a single cell layer thick and should not show significant atypia or a high mitotic rate, which distinguish this entity from angiosarcoma. Surgical excision is curative, but the therapy should be tailored toward the underlying lesion (ie, hemangioma).
CASE #09 -- SLIDE #09

**Diagnosis:** Spindle cell hemangioma

**Case Summary:** 25 year old with multiple foot masses.

First described by Weiss and Enzinger in 1986, spindle cell hemangioma was initially felt to be a low grade malignancy with metastatic potential. Further study revealed this entity to exhibit benign behavior. Spindle cell hemangioma most commonly affects young adults, and the most frequent site of this lesion is the distal extremity. Histologic review shows a biphasic appearance. Some areas of the lesion are composed of blood-filled cavernous spaces, while other areas are more cellular and resemble Kaposi sarcoma. A characteristic feature is round or epithelioid cells with intracytoplasmic lumens, representing primitive vascular differentiation. Phleboliths are not unusual. Although spindle cell hemangioma may be multi-focal and recur (up to 60%), they do not metastasize. Maffucci syndrome is a rare disorder characterized by multiple enchondromas and spindle cell hemangiomas.


CONTRIBUTED BY KAREN FRITCHIE, MD
CASE #10 -- SLIDE #10

Diagnosis: Myxofibrosarcoma

Case Summary: 74 year old with leg mass.

Myxofibrosarcoma typically presents as a slow growing mass in the extremities of older adults (5th-7th decades). Although they may be found in deep sites (below the fascia), most of these tumors arise in the dermis and subcutaneous tissue. Morphological examination reveals a poorly circumscribed, multinodular, infiltrative proliferation of atypical spindled cells in a variably myxoid stroma. Curvi-linear blood vessels are often prominent, and “pseudo-lipoblasts” may be seen. While the degree of cytologic atypia and amount of myxoid stroma vary, there is some component of each. Clinical behavior seems to be related to several variables including size, percent necrosis and histologic grade. An epithelioid variant of myxofibrosarcoma has been described, and data suggests that it has a more aggressive course. Wide excision may be difficult due to the infiltrative growth pattern but remains the treatment of choice.

CASE #11 -- SLIDE #11

**Diagnosis:** Superficial angiomyxoma

**Case Summary:** 73 year old female with leg mass.

Superficial angiomyxoma (cutaneous myxoma), first described in 1986 by Carney et al., usually occurs in middle-aged adults and may occur at virtually any site. Those lesions arising in the eyelid, nipple and external ear should raise the possibility of Carney complex. Pathologic examination reveals a well circumscribed mass (usually less than 5 cm) with a lobular or multinodular low power appearance. Bland spindled to stellate shaped cells are deposited in a myxoid background admixed with an arborizing vasculature. Other relatively unique features include entrapped epithelial elements and a prominent neutrophilic infiltrate. Cytologic atypia should not be present. Although benign, these lesions have a high propensity to recur if not completely excised.


CASE #12 -- SLIDE #12

Diagnosis: Dermal nerve sheath myxoma.

Case Summary: 57 year old with elbow mass.

Dermal nerve sheath myxoma is a rare benign peripheral nerve sheath tumor that arises in the dermis or subcutis. Although initially referred to as ‘myxoid neurothekeoma,’ this tumor truly exhibits schwannian differentiation, as evidenced by S100 reactivity, which differentiates it from cellular neurothekeoma. Dermal nerve sheath myxoma displays a wide variation in age distribution but typically involve the extremities (finger is the most common site). On histology, dermal nerve sheath myxoma shows a multinodular growth pattern. Each nodule is composed of S100-positive spindled to epithelioid cells in cords or syncytial aggregates within a myxoid background. These tumors are benign but may recur if not completely excised.

CONTRIBUTED BY KAREN FRITCHIE, MD
CASE #13 -- SLIDE #13

**Diagnosis:** Low grade fibromyxoid sarcoma

**Case Summary:** 55 year old female with abdominal wall mass.

Low grade fibromyxoid sarcoma (hyalinizing spindle cell tumor with giant rosettes) most frequently affects young adults and typically arises in the proximal extremities or trunk below the fascia. Rarely, these tumors can occur in a superficial location. On histologic examination, a characteristic features is alternating hyalinized and myxoid zones. The tumor cells are deceptively bland, and the mitotic rate is low. Occasionally, collagen rosettes may be appreciated. MUC4 is positive in the neoplastic population, and the cytogenetic hallmark of low grade fibromyxoid sarcoma is t(7;16)(q33;p11) which fuses FUS and CREB3L2. Less commonly, t(11;16)(p11;p11) resulting in a FUS-CREB3L1 may be seen. Despite relatively bland cytology, these tumors may recur locally and metastasize.


**CONTRIBUTED BY KAREN FRITCHIE, MD**
CASE #14 -- SLIDE #14

**Diagnosis:** Intramuscular myxoma

**Case Summary:** 42 year old female with paraspinal mass.

Intramuscular myomas are benign soft tissue tumors characterized by a hypocellular proliferation of bland spindled to stellate shaped cells in a myxoid stroma. The lesional cells should not show any significant cytologic atypia. The most commonly affected sites are the large muscles of the thigh, shoulder and buttock. These tumors are more frequent in females, and most patients are middle-aged or elderly patients. Mazabraud syndrome is a combination of intramuscular myxomas and fibrous dysplasia. Intramuscular myxomas rarely recur, even if incompletely excised.
Diagnosis: Leiomyosarcoma

Case Summary: 69 year old female with arm mass.

Leiomyosarcomas are malignant tumors of smooth muscle which may occur at numerous sites including skin, deep soft tissue, retroperitoneum and gynecologic organs. On histologic examination, these tumors are characterized by interlacing fascicles of spindled cells with brightly eosinophilic cytoplasm and blunt-ended nuclei. Typically, leiomyosarcoma exhibits some degree of cytologic atypia, although the degree of atypia varies from mild to severe. The mitotic rate also varies, but almost all lesions have at least a few mitoses. The malignant population exhibits reactivity for smooth muscle markers including smooth muscle actin, desmin and h-caldesmon. Occasionally, expression of cytokeratins may be seen. Recent work has suggested that leiomyosarcomas limited to the dermis with no or minimal involvement of the subcutis carry almost no risk of metastasis. However, larger superficial tumors with extension into subcutaneous tissue are capable of local recurrence and metastatic spread.

Diagnosis: Cavernous hemangioma

Case Summary: 48 year old female with temporal mass.

Cavernous hemangioma is a benign tumor of endothelial cells characterized by large dilated vascular spaces. The blood vessels are lined by bland endothelial cells without significant cytological atypia.
Diagnosis: Epithelioid sarcoma

Case Summary: 23 year old male with palm mass.

Epithelioid sarcoma is a malignant mesenchymal tumor of uncertain differentiation. This tumor usually affects young adults in the distal extremity (fingers, hands > feet), and patients present with slow growing painless nodules that may ulcerate. Morphologically, epithelioid sarcoma is composed of a multinodular proliferation of atypical epithelioid cells surrounding areas of geographic necrosis. Areas with spindled morphology may be present, and it is not uncommon to see dystrophic calcification or metaplastic bone formation. Epithelioid sarcoma exhibits reactivity for epithelial markers including low and high molecular weight keratins and EMA. CD34 reactivity is present in over half of cases. However, the most helpful marker to confirm the diagnosis is INI-1 (SMARCB1), which will show loss of nuclear positivity in the malignant population. On cytogenetic analysis, epithelioid sarcoma shows alterations in 22q11-12.

Epithelioid sarcoma is an aggressive neoplasm with high rates of local recurrence and metastasis. Unlike most sarcomas, this tumor has a propensity to metastasize to regional lymph nodes.
Diagnosis: Angiolipoma

Case Summary: 66 year old male with multiple arm masses.

Angiolipoma is a benign lipomatous tumor which classically presents as multiple tender subcutaneous masses on the extremities. On histologic examination, these tumors are characterized by a proliferation of mature adipose tissue with aggregates of small-caliber blood vessels most frequently concentrated at the periphery of the lesion. Fibrin thrombi may be present in the blood vessels.
Diagnosis: Lipoma

Case Summary: 44 year old female with arm mass.

Lipomas are the most common soft tissue tumors. They are benign tumors of mature adipose tissue that typically present as superficial mass in middle aged adults. Grossly, lipomas are usually less than 10 cm and have a homogenous appearance. On morphologic review, lipomas are composed of mature adipose tissue without fibrous septa or atypical hyperchromatic stromal cells. Areas of fat necrosis are commonly identified. These tumors frequently have aberrations of 12q13-15. Lipomas rarely recur; if a lipoma does recur, one should consider the diagnosis of atypical lipomatous tumor which is characterized morphologically by atypical hyperchromatic stromal cells and genetically by amplification of MDM2.

CONTRIBUTED BY KAREN FRITCHIE, MD
Diagnosis: Hibernoma

Case Summary: 39 year old male with arm mass.

Hibernomas are benign lipomatous tumors composed of variable amounts of brown fat. These tumors usually occur in young adults and are most common in the thigh. Other sites of involvement include axillary region, trunk/chest and upper extremity. Hibernomas vary in color on gross examination from yellow to red-brown. The red-brown gross appearance is due to the high vascularity and prominent capillary network. Characteristically these tumors contain polygonal multivacuolated cells with granular cytoplasm (brown fat). Some hibernomas have a significant amount of admixed white fat. Like other fatty tumors, hibernomas have a recurrent cytogenetic finding (aberrations in 11q13). Hibernomas are benign and do not usually recur.

CONTRIBUTED BY KAREN FRITCHIE, MD
CASE #21 -- SLIDE #21

Diagnosis: Fibromatosis.

Case Summary: 19 year old with arm mass.

The fibromatoses can be broken down into two groups based on location: superficial and deep. The superficial fibromatoses include the palmar (Duputryen’s contracture) and plantar (Ledderhose disease) variants, and these lesions typically have relatively indolent behavior. Deep fibromatosis (desmoid-type fibromatosis) may be extra-abdominal, abdominal or intra-abdominal. The extra-abdominal forms can involve virtually any site including chest wall, shoulder and head and neck. Deep fibromatoses are locally aggressive but lack metastatic potential. All forms of fibromatoses are linked by common histology: long sweeping fascicles (spanning a 10x field) of bland spindle cells admixed with thin-walled, sometimes gaping blood vessels. The spindled cells are myofibroblasts and fibroblasts which display an infiltrative growth pattern. Aggregates of lymphocytes are usually noted at the advancing edge of the lesion. No significant cytologic atypia should be seen. While beta-catenin immunohistochemistry has been reported to show nuclear reactivity in most the deep fibromatoses and about 50% of the superficial variants, making this immunostain theoretically helpful in differentiating fibromatosis from other fibroblastic/myofibroblastic proliferations, it is often technically difficult. H&E morphology is diagnostic in most cases.


CONTRIBUTED BY KAREN FRITCHIE, MD
CASE #22 -- SLIDE #22

Diagnosis: Myofibroma.

Case Summary: 28 year old with arm mass.

Myofibroma, along with myopericytoma and glomus tumors, represent a spectrum of tumors of perivascular myoid cells. Myofibroma usually appears during the first two years of life and is more common in males. Common sites of involvement include distal extremities, proximal extremities and head and neck. On morphologic examination, one of the most helpful clues to the diagnosis of myofibroma is the lesion’s biphasic low power appearance. Some areas of the tumor will appear more cellular composed of short spindle cells surrounding hemangiopericytomatosus (branching) blood vessels. These zones alternate with less cellular, frequently hyalinized regions. The prognosis is of these tumors is good.
CASE #23 -- SLIDE #23

Diagnosis: Cellular neurothekeoma.

Case Summary: 50 year old male with arm mass.

Cellular neurothekeoma is a confusing entity that was initially thought to be linked to dermal nerve sheath myxoma. However, due to difference in clinical presentation and immunoprofiles, current thinking is that cellular neurothekeoma is most likely of histiocytic or fibroblastic rather than nerve sheath derivation. These tumors are more frequent in young females and the most common site of involvement is the head and neck region. Histologically, cellular neurothekeomas are composed of nests of epithelioid to slightly spindled cells surrounded by collagen/fibrosis. These tumors may have a lobular or multinodular low power architecture. Some tumors show a great deal of myxoid change. Features such as cytologic atypia and a high mitotic rate do not seem to affect prognosis. The immunoprofile for cellular neurothekeoma is: MiTF positive, NKI/C3 positive, S100 negative.


CONTRIBUTED BY KAREN FRITCHIE, MD
CASE #24 -- SLIDE #24

**Diagnosis:** Desmoplastic fibroblastoma.

**Case Summary:** 58 year old with posterior axillary mass.

Desmoplastic fibroma is a benign mesenchymal tumor that is more common in males and usually presents in the 5th to 7th decades. Commonly affect sites include upper arm, shoulder and back. Histologic examination reveals a hypocellular proliferation of bland spindled to stellate shaped cells in a collagenous or myxocollagenous background. Mitoses are rare.
Diagnosis: Mammary-type myofibroblastoma.

Case Summary: 71 year old with chest wall mass.

Mammary-type myofibroblastoma is a benign tumor likely linked to spindle cell lipoma and cellular angiofibroma by loss of 13q14. Mammary-type myofibroblastoma typically presents in adults but demonstrates a wide age range (35-85 years). Although classically described in the breast of male patients, this entity may be found at a variety of soft tissue sites including the inguinal/groin region, vulvovaginal area, buttock and abdominal wall. Mammary-type myofibroblastoma are generally circumscribed but may reach greater than 10 cm in size. Histologic examination reveals a proliferation of bland spindled cells admixed with thick, ropey collagen and variable amounts of mature adipose tissue. The typical immunophenotype is: CD34 positive and desmin positive. However, the tumors may also exhibit reactivity for smooth muscle actin and estrogen receptor.

CASE #26 -- SLIDE #26

Diagnosis: Chondroid lipoma.

Case Summary: 40 year old male with arm mass.

Chondroid lipoma is distinct but extremely rare lipomatous tumor composed of vacuolated cells admixed with mature fat in a myxochondroid background. While usually deep-seated (intramuscular), chondroid lipomas may also occur in the subcutis. Surgical excision is generally curative.
CASE #27 -- SLIDE #27

This lesion presents as a solitary nodule on the neck. Initial immunohistochemical stains shows the tumor was negative for P63 and CK20 and positive for CK7. Most likely diagnosis is:

A. **Metastatic Papillary Thyroid tumor Correct.** P63 and CK20 should be negative but CK7 positive.
B. Papillary Apocrine Adenoma Incorrect. P63 should be positive.
C. Hyperplastic Apocrine Hidrocystoma Incorrect. P63 should be positive.
D. Metastatic Colon Carcinoma Incorrect. Should be negative for p63 but positive for CK20.
E. Syringocystadenoma Papilliferum Incorrect. P63 should be positive.

Papillary thyroid carcinoma (PTC) is the most common type of thyroid malignant neoplasm (75-80% of thyroid carcinomas). Primary PTC usually presents as painless nodule or mass in neck or cervical node. Cutaneous metastases from thyroid carcinoma are rare. Scalp is the most common site of thyroid carcinoma skin metastases. The metastatic deposits usually present as flesh coloured nodules that are tender, may be itchy, and can ulcerate. Skin metastasis from a thyroid carcinoma is rarely a presenting feature of an underlying malignancy. The prognosis is usually dismal because it usually occurs in the context of disseminated neoplastic disease. Histologically several variants with different histological grading have been described. Basically, the lesion shows complex, branching, randomly oriented papillae with fibrovascular cores associated with follicles with frequent dense fibrosis. The papillae are lined by cuboidal cells; nuclei are overlapping with finely dispersed optically clear chromatin (also called ground-glass, Orphan-Annie nuclei). Micronucleoli, eosinophilic intranuclear inclusions (represent cytoplasmic invaginations) and nuclear longitudinal grooves (represent folding of redundant nuclear membrane are important diagnostic clues.

References:


CONTRIBUTED BY DARIUS MEHREGAN, MD
CASE #28 -- SLIDE #28

A 68-year-old man presents with ulcerated nodular lesions on lower extremities. The immunophenotype seen here is: CD3+, CD20-, CD30+, CD2+, CD4-, CD5-, CD8-, CD56+, and TIA1+. EBV in situ hybridization (EBER) is positive. What is the best diagnosis?

A. Lymphomatoid papulosis (Incorrect. CD30 is an activation marker and is not specific for LyP. The presence of EBV and the lack of a clinical history of self-regressing papules indicate this is not LyP.)
B. Anaplastic large cell lymphoma (Incorrect. CD30 is an activation marker and is not specific for ALCL. Several entities may variably express CD30. The presence of EBV and the full immunophenotype indicate this is not ALCL.)
C. Primary cutaneous diffuse large B-cell lymphoma, leg type (Incorrect. The provided immunophenotype is that of a T-cell process.)
D. Extranodal NK/T-cell lymphoma, nasal type Correct. This angiodestructive lymphoma is characterized by necrosis, cytotoxic phenotype and EBV expression. While CD30 staining may occur and potentially cause diagnostic confusion, CD30 is an activation marker and is not specific for ALCL or LyP.)
E. Subcutaneous panniculitis-like T-cell lymphoma (Incorrect. SPTCL is CD8-positive, EBV-negative and restricted to the panniculus.)

Extranodal NK/T-cell lymphoma, nasal type (ENKL) are aggressive, locally destructive midfacial necrotizing lesions characterized by extranodal involvement, particularly the nasal/paranasal area and represent about 75% of all nasal lymphomas. The lesion typically causes local destruction of cartilage, bone and soft tissues. Lesions may arise de novo at the site or represent a localized progression through stages. ENKL is typically observed in adults but may be seen in children. Studies have shown a male to female ratio of 2:1 to 3:1. Tumors are most common in the nasal cavity but other sites may include the skin, GIT, testis, kidney, upper respiratory tract and rarely the eye/orbit. Cutaneous presentations are usually patches, plaques or nodules with frequent ulceration. The mean survival time for cutaneous ENKL is around 15 months from the diagnosis. Histopathological examination of the lesion exhibits cellular picture, which is pleomorphic with many large or immunoblast-like cells and relatively few small lymphocytes. A striking feature is the angiocentric distribution of the tumor cells and angiodestruction, which sometimes mimics vasculitis. Tumor necrosis is not uncommon. The immunophenotypical and genotypical features are relatively distinctive. Majority of cases are CD3ε+, surface CD3−, CD56+, and positive for cytotoxic molecules, a subset are CD56−, CD3ε+, surface CD3−/+ . All cases are positive for EBV (EBER). T cell receptor gene usually shows germline (non-clonal).

References:

CONTRIBUTED BY ANTONIO SUBTIL, MD, MBA
Diagnosis: Cutaneous involvement with Crohn’s disease

Case Summary:
A 25 year old man presented with erythematous dusky plaques on the buttocks.

Question
The best diagnosis is:
A. Sarcoidosis - Incorrect. Although sarcoidosis is a consideration, the granulomata in sarcoidosis are typically more discrete and the degree of associated non-granulomatous inflammation is relatively low.
B. Mycobacterial infection - Incorrect. While mycobacterial infection is a diagnostic consideration and is important to exclude, the granulomatous inflammation in mycobacterial infection tends to be necrotizing rather than non-necrotizing.
C. Xanthogranuloma - Incorrect. Noncaseating granulomas are not a feature of xanthogranuloma.
D. Cutaneous involvement by Crohn’s disease - Correct. Sections show dense pan-dermal mixed inflammation composed predominantly of lymphocytes, plasma cells, and histiocytes with noncaseating granulomata interspersed throughout the dermis. There is associated dermal fibrosis and granulation tissue, as well as suppurative folliculitis more superficially, with intrafollicular pustule formation. The overlying epidermis demonstrates lichen simplex chronicus. No foreign material is identified with routine or polarizing microscopy and special stains are negative for microorganisms.
E. Hidradenitis suppurativa - Incorrect. Suppurative folliculitis and dermal fibrosis are present, both of which can be seen in hidradenitis suppurative and other acneiform processes; however, the presence of noncaseating granulomas is against this possibility.

Question
Which of the following statements is true regarding this entity:
A. It is part of the follicle occlusion tetrad - Incorrect. This refers to hidradenitis suppurativa, acne conglobata, dissecting cellulitis, and pilonidal sinus.
B. This disease is associated with pyoderma gangrenosum - Correct. In addition to cutaneous involvement by Crohn’s, other cutaneous conditions associated with underlying Crohn’s disease include pyoderma gangrenosum, leukocytoclastic vasculitis, erythema nodosum, polyarteritis nodosa, and oral aphthous ulcers.
C. Hypercalcemia may be present - Incorrect. Hypercalcemia can be seen in a minority of patients with sarcoidosis. It is not a feature of cutaneous Crohn’s disease.
D. Treatment by intralesional steroid injection is contraindicated - Incorrect. In addition to systemic treatment necessitated by the intestinal involvement, cutaneous Crohn’s lesions can be treated with topical or intralesional corticosteroids.
E. Degree of cutaneous involvement correlates with degree of non-cutaneous disease activity - Incorrect. There is no definite correlation between the presence or degree of skin lesions and intestinal Crohn’s disease severity.

Clinical Features
A variety of cutaneous lesions are seen in patients with Crohn’s disease, including erythema nodosum, pyoderma gangrenosum, aphthous ulcers, epidermolysis bullosa acquisita, and vasculitis. ‘Metastatic’ skin lesions are rare, and are defined as cutaneous involvement by noncaseating sterile granulomas that are not contiguous with the gastrointestinal tract. The most
common sites of involvement are the legs, genital and perianal area, perineum, buttocks, and lips. The lesions can be solitary or multiple, and typically present as erythematous dusky plaques, nodules, and/or ulcers. Interestingly, patients with cutaneous Crohn’s disease tend to have large intestine rather than small intestine involvement by Crohn’s. Occasionally, cutaneous lesions can precede the manifestation of intestinal involvement. A definitive diagnosis of cutaneous Crohn’s disease requires clinical confirmation of associated intestinal disease.

**Histopathologic Features**
Microscopically, there is mixed dermal inflammation with interspersed noncaseating granulomas. Collagen necrobiosis can sometimes be seen. Admixed lymphocytes, plasma cells, and eosinophils are usually present. The overlying epidermis can be ulcerated. It is important to exclude an infectious process through the use of microorganism special stains, and culture of tissue should also be considered if clinically appropriate.

**References**
The best diagnosis is?

A. Lupus panniculitis – Incorrect. Lupus panniculitis is a lobular panniculitis with hyaline necrosis but with nodular aggregates of lymphocytes that favor periseptal distribution.

B. Borrelial panniculitis – Incorrect. Panniculitis attributed to Borrelial infection may resemble lymphoid hyperplasia involving subcutaneous fat.

C. Subcutaneous panniculitis-like T-cell lymphoma – Correct. Diffuse lobular infiltration by atypical lymphocytes, with the characteristic (but not specific) feature of adipocyte rimming, is the typical pattern of SPTCL.

D. Erythema nodosum – Incorrect. Chronic erythema nodosum is a mostly granulomatous panniculitis, and acute erythema nodosum is mainly neutrophilic.

E. Localized lipoatrophy – Incorrect. Lipoatrophy may be a clinical presentation of various types of panniculitis including SPTCL, lupus panniculitis, and most commonly trauma- or injection-induced atrophy. Involutional lipoatrophy, with fat lobules composed of small lipocytes and prominent capillaries, is one of the histopathological correlates of idiopathic localized lipoatrophy.

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a lymphoma of mature cytotoxic T cell derivation that involves the subcutaneous fat in a manner reminiscent of panniculitis. Patients present with solitary or multiple nodules or plaques, usually on the lower extremity. The upper extremities and trunk may also be involved. The tumors may be small or measure several centimeters in diameter, but they rarely ulcerate. The indurated appearance may lead to the clinical diagnosis of an abscess, and tumors may undergo incision and drainage without resolution. This tumor may be associated with systemic symptoms, including fever, fatigue, and weight loss. Hemophagocytic syndrome is a rare complication associated with an aggressive clinical course. SPTCL affects men and women, adults and children, with a median age of onset of 35 years. Although there is a slight predominance of tumors in women and the suggestion of an association with lupus erythematosus, the relationship of this tumor to autoimmune disease remains unclear. The 5-year disease-specific survival is estimated at 80%, with dissemination to lymph nodes and other organs a rare event. Local recurrences may occur over a period of several years. Histologically this tumor is characterized by a dense, predominantly subcutaneous infiltrate of small to medium-sized T cells, with occasional large lymphocytes and many histiocytes. The lymphoid atypia is variable from case to case and may be subtle or readily evident. The individual adipocyte spaces show rimming by neoplastic lymphocytes with enlarged nuclei, clumped chromatin, and scant cytoplasm. Macrophages containing cellular debris are characteristically present, with associated fat necrosis and karyorrhexis. In rare cases the histiocytes may aggregate to form granulomas; however, this is not a dominant finding. Vascular invasion is common and may be associated with regions of necrosis. The tumor cells of SPTCL have a mature alpha-beta cytotoxic T-cell phenotype, characteristically CD3+, CD8+, CD4–, and βF1+. The cytotoxic proteins granzyme B, TIA-1, and perforin are usually present. These tumors only rarely express CD56 or CD30. Cases may rarely coexpress CD4 and CD8, but the absence of both CD4 and CD8 suggests a gamma-delta T-cell lymphoma. Clonal rearrangement of TCR genes is detected in most cases. These tumors are negative for EBV. The differential diagnosis of SPTCL includes other forms of lymphoma involving the subcutaneous fat (such as primary cutaneous gamma-delta T-cell
lymphoma), lupus profundus and reactive panniculitis in the setting of a drug reaction or injected antigen.

References:

CASE #31 -- SLIDE #31

A 70-year-old woman hospitalized for a cardiac procedure developed a fever and widespread sterile pinpoint pustular rash. The best diagnosis is:

A. Linear IgA dermatosis secondary to Vancomycin – INCORRECT. Neutrophils collect at the dermal epidermal junction in linear IgA dermatoses, yielding subepidermal rather than subcorneal blisters. Clinically, linear IgA dermatosis typically shows a “string of pearls” appearance rather than pinpoint pustules.

B. Candidiasis - INCORRECT Clinically this would be unusual, and Candida species are usually evident on routine histopathology.

C. Guttate psoriasis – INCORRECT Despite subcorneal pustules as can be seen in psoriasis, the presence of necrotic keratinocytes, eosinophils, and dermal edema with dilated vessels make psoriasis less likely than acute generalized exanthematous pustulosis.

D. Acute generalized exanthematous pustulosis secondary to Diltiazem – CORRECT – The presence of subcorneal pustules associated with necrotic keratinocytes, dermal edema, neutrophils, and dilated vessels stuffed with neutrophils are in keeping with this diagnosis, and the clinical history of recent drug administration helps to increase suspicion of this possibility.

E. Drug rash with eosinophilia and systemic symptoms – INCORRECT This rash typically features a nonspecific dermal infiltrate with lymphocytes and eosinophils, not neutrophils. The clinical presentation usually includes facial edema and other systemic findings, as the name implies.

Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction characterized by the rapid development of nonfollicular, sterile pustules on an erythematous base. It is attributed to drugs in the majority of cases. The pathophysiology of AGEP has been investigated by using patch tests and in vitro tests which have suggested that AGEP is a T cell-mediated disease. After exposure to the causative agent, antigen-presenting cells present the cognate antigen using MHC molecules, causing activation of specific CD4 and CD8 T cells. Once activated, these T cells, referred to as drug-specific T cells, proliferate and then migrate into the dermis and epidermis. The drug-specific CD8 T cells use perforin/granzyme B and Fas ligand mechanisms to induce apoptosis of keratinocytes within the epidermis, leading to tissue destruction and epidermal vesicle formation. Antibiotics are the most common cause of acute generalized exanthematous pustulosis; however, a wide variety of drugs has been associated with this condition. Typically, within 48 hours of ingesting the causative medication, there is acute onset of fever and pustulosis with leukocytosis. In severe cases there can be mucous membrane and systemic organ involvement. Histologic findings include intracorneal, subcorneal, and/or intraepidermal pustules with papillary dermal edema containing neutrophils and eosinophils. Treatment focuses on removal of the causative drug, supportive care, infection prevention, and the often beneficial use of a potent topical steroid.

CONTRIBUTED BY JENNIFER MCNIFF, MD
CASE #32 -- SLIDE #32

Diagnosis: Dermatophytosis

Case Summary: Compact orthokeratosis, the presence of neutrophils within the stratum corneum, and the “sandwich sign” (hyphae located between a superficial layer of orthokeratosis and a deeper layer of either ortho- or parakeratosis) are clues to the diagnosis. Occasional subcorneal or intraepidermal pustules may be present. In Majocchi granuloma, hyphal elements and arthroconidia may be seen in follicles along with adjacent granulomatous inflammation.


CONTRIBUTED BY CLAY COCKERELL, MD
Diagnosis: Coccidiomycosis

Case Summary: Coccidiomycosis is caused by infection with Coccidioides immitis or Coccidioides posadasii. Inhalation of spores leads to respiratory infection that can disseminate. Coccidiomycosis can be asymptomatic or cause a self limited pulmonary infection ("Valley Fever"). Infection is most common in the Southwestern United States. Dry conditions allow arthroconidia to develop that can remain suspended in the air. Serological testing is helpful for diagnosis and for monitoring therapy. Culture may take days or even weeks, and poses a risk to laboratory personnel. PCR testing is very sensitive and specific.

- Biopsy may reveal spherules in tissue associated with abscess and granulomatous inflammation.
- A methenamine silver stain highlights the organism and is considered more sensitive than a PAS stain which can also be used to highlight organisms.

Treatment
Not all infections require treatment. When treatment is initiated, ketoconazole, fluconazole, and itraconazole are all effective although oral ketoconazole is the only FDA approved treatment. Treatment is usually given for 3-6 months. Amphotericin B therapy is reserved for complicated or particularly severe cases. In the setting of HIV-1, treatment is recommended for all patients with a CD4 count < 250/ul with clinically active disease

References:
CASE #34 -- SLIDE #34

1. A 33 y.o. male presented with a single 1.0 cm erythematous polypoid lesion on the scalp, which had been present for several months, and was slowly growing. The clinical differential diagnosis was “skin tag versus other.” What is the best diagnosis for this tumor?

A. Rippled pattern sebaceoma - Correct: The tumor is composed of nodules of basaloid to focally clear cells in a distinctive cord-like or palisaded pattern, consistent with a rippled pattern sebaceoma.

B. Sebaceous carcinoma - Incorrect: While there is nuclear hyperchromasia and crowding, there is no significant atypia, increased mitotic activity, or infiltrative features to suggest a sebaceous carcinoma.

C. Rippled pattern trichoblastoma - Incorrect: while trichoblastoma can also show cords of basaloid cells in a rippled pattern, it lacks the clear sebaceous differentiation of sebaceoma.

D. Basal cell carcinoma with sebaceous differentiation - Incorrect: although the differential with BCC with sebaceous differentiation can be difficult, BCC typically shows areas of peripheral palisading, mucinous stroma, and tumor-stromal retraction artifact.

E. Sebaceous trichofolliculoma - Incorrect: trichofolliculoma can show sebaceous features, but is characterized by a central folliculocystic structure surrounded by small, primitive radiating follicles.

Sebaceomas can show a cribriform or reticular pattern as in trichoblastoma/trichoepithelioma, and mimic cylindroma/spiradenoma on low magnification. Some sebaceomas contain only scattered sebaceous cells, and trichoblastoma can present areas of sebaceous differentiation and only scant fibrotic stroma without prominent follicular differentiation. Furthermore, a close relationship between sebaceoma and trichoblastoma has been suggested. Accordingly, distinguishing sebaceoma and trichoblastoma is sometimes extremely difficult.

A rippled pattern in epithelial neoplasm was originally reported in trichomatricoma (trichoblastoma), and some cases of rippled-pattern trichoblastoma have been described. On the other hand, RPS was first reported by Misago and Narisawa. Clinical differentiation between trichoblastoma and sebaceoma is sometimes difficult when the neoplastic cells with sebaceous differentiation contained in the lesion are very small in number because these 2 tumors consist of similar basaloid germinative cells. However, trichoblastoma is a benign neoplasm differentiating toward follicular germinative cells; therefore, it consists of dermal aggregations of basaloid cells with palisading of nuclei in the periphery of tumor cell nests and features differentiation toward the lower part of hair follicles such as the dermal bulb or papilla. On the other hand, sebaceoma contains not only germinative cells with small, monomorphous, basaloid features but also mature sebocytes with vacuolated cytoplasms and tiny duct-like spaces. In sebaceoma, the numbers of mature sebocytes in tumors vary from case to case. Therefore, we believe that such differentiation can be made from the findings of these 2 neoplasms as mentioned above. Ohata and Ackerman 5 reported that most cases described as rippled-pattern trichoblastoma are RPS.

Reference:


CONTRIBUTED BY DAVID CASSARINO, MD, PhD
Diagnosis: Pyoderma gangrenosum
Case summary: 49 year old woman with erosive inflammatory arthritis and acne presented with ulcerative papules and pustules on her extremities. An early lesion without ulceration is biopsied.

Question
The best diagnosis is:
A. Pyoderma gangrenosum – Correct. A nodular and interstitial neutrophilic infiltrate with limited leukocytoclasis is present. Culture was performed to exclude infection.
B. Neutrophilic urticaria – Incorrect. The suppurative inflammation in neutrophilic urticaria is typically sparse and perivascular. Ulceration is not seen in this condition.
C. Wells syndrome – Incorrect. Wells syndrome demonstrates a diffuse interstitial eosinophilic infiltrate with flame figures.
D. Neutrophilic eccrine hidradeninitis – Incorrect. This condition presents with a peri-eccrine neutrophilic infiltrate with eccrine gland degeneration.
E. Ecthyma gangrenosum – Incorrect. While this condition typically demonstrates a dense neutrophilic infiltrate, there are typically signs of infarction with necrosis of the epidermis and upper dermis. Vascular thrombosis is typically present and bacteria (Gram-negative) are often seen within the dermis.

Question
The patient’s presentation is suggestive of a mutation in which gene?
A. NOD2 - Incorrect. The NOD2 gene product acts as an intracellular receptor for bacterial products and leads to NFkB activation in immune cells. Mutations in NOD2 are associated with Crohn disease and Blau syndrome.
B. FLG – Incorrect. This gene codes for filaggrin, also known as filament-aggregating protein, expressed in the stratum corneum. Mutations in FLG cause ichthyosis vulgaris and predispose to atopic disease.
C. PTEN – Incorrect. PTEN encodes a phosphatase that antagonizes the PI3K signaling pathway. Germline mutations result in the PTEN hamartoma tumor syndrome. Somatic mutations are found in melanoma.
D. RECQL2 – Incorrect. Mutations in RECQL2, a DNA helicase, cause Werner syndrome. Patients present with scleroderma-like skin changes, premature arteriosclerosis, and aged facies.
E. PSTPIP2 – Correct. Missense mutations in this gene cause PAPA (pyogenic arthritis, pyoderma gangrenosum, acne) syndrome, inherited in autosomal dominant fashion.

Clinical Features
PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne, OMIM #604416) is an autosomal dominant disorder due to missense mutations in the PSTPIP1 gene. The protein product of PSTPIP1 is proline-serine/threonine phosphatase-interacting protein 1 that is involved in the regulation of ABL. Mutant PSTPIP1 appears to increase levels of PSTPIP1-pyrin binding. Sequestration of pyrin may interfere with the normal immunoregulatory functions of pyrin, resulting in increased IL1-beta. Treatment with anakinra (an IL-1 receptor antagonist) can be effective.

Histopathologic Features
The histopathologic features of pyoderma gangrenosum are quite variable. Early lesions show follicular and perifollicular neutrophilic abscesses. Later lesions demonstrate necrosis of the epidermis and superficial dermis that leads to ulceration. In active ulcers, undermining inflammation at the edge of the ulcer is characteristic. A leukocytoclastic vasculitis is sometimes present. Culture is performed to exclude infectious processes.

References
CASE #36 -- SLIDE #36

**Diagnosis:** Vasculitis. Livedoid vasculopathy

**Case Summary:** Biopsy taken from the dorsal foot of a 48 y/o man with ulceration in the setting of a Livedoid vascular pattern.

**Clinical Features**
The major finding is that of a persistent Livedoid pattern which generally becomes more prominent over time. Eventually ulcers may form which typically are very small and somewhat linear or “chevron-shaped” in the beginning before expanding. Pain is typical and may appear out of proportion to clinical findings. Nodules or nodose lesions should be absent in the areas of ulceration which can be episodic or seasonal (Winter ulcerations/Summer ulcerations) and not necessarily seen more often in cooler weather. Sensations of burning or stinging of skin are often reported with onset of ulceration. Thorough evaluation for underlying cause will reveal some disorder of coagulation/fibrinolysis in about half of patients. Secondary infection can complicate course and create confusion with other ulcerating skin disorders, especially pyoderma gangrenosum.

**Histopathologic Features**
Once ulceration develops granulation response is invariably present, particularly in the superficial dermis
Look for hyalinized blood vessels deep and somewhat away from the overlying ulceration if possible
Leukocytoclasis should be minimal
Thrombi may be observed in some vessels
Clinical correlation is important

**References**
Callen JP. Livedoid vasculopathy: what it is and how the patient should be evaluated and treated. Arch Dermatol. 2006;142(11):1481-1482.
**CASE #37 -- SLIDE #37**

**Diagnosis:** Hypocomplementemic Urticarial Vasculitis (HUV)

**Case Summary:** Biopsy taken from the thigh of a 49 y/o man with a several month history of “hive-like” lesions that develop on the extremities and buttock and resolve over a period of a few days.

**Clinical Features**
There are basically two major types of urticarial vasculitis that require some degree of clinical correlation to differentiate with confidence. The more common variant is associated with other disorders that cause severe urticarial eruptions (drug, infection, etc.) and is most often not confused for a connective tissue disease such as lupus erythematosus. Eosinophils likely play a role both in the clinical lesions as well as the pathologic changes. Complement levels are normal. A smaller percentage of cases develop urticarial-like skin lesions, which can be seen in association with other signs and symptoms such as joint pain and abdominal pain. Elevated eosinophils may or may not be seen in the peripheral blood or on biopsy of the skin. Skin lesions resolve with or without treatment in 24 to 72 hours and often leave a small purpuric area in the involved skin. Serum complement is most often reduced (HUV).

**Histopathologic Features**
The major pathologic changes combine those of an urticarial tissue reaction (dermal edema/dilated lymphatics) with mild Leukocytoclastic vasculitis (LCV). Neutrophils most often dominate the inflammatory cellular component
Nuclear dust should be seen but may be subtle
Neutrophils may be seen in the interstitial areas of the collagen and may create some confusion with other neutrophilic disorders including Sweet syndrome, Snitzler’s syndrome and lupus erythematosus.

**References**

**CONTRIBUTED BY LAWRENCE GIBSON, MD**
Diagnosis: Cutaneous Polyarteritis nodosum (CPAN)

Case Summary
73 year-old male with a two month history of painful nodule on all four extremities. Biopsy taken from a nodule on the forearm. Systemic evaluation reveals no evidence of disease outside of the skin.

Question
The best diagnosis is:

A. Erythema induratum – Incorrect. In addition to vasculitis, this condition is characterized by a lobular panniculitis with a mixed infiltrate that usually includes neutrophils, which is not present in this case.
B. Small vessel leukocytoclastic vasculitis – Incorrect. This condition affects capillaries, small arterioles and venules, not medium-sized arterioles, which is the size of the vessel affected in this case.
C. Polyarteritis nodosa – Correct. This biopsy shows typical findings, including an infiltrate composed of neutrophils, eosinophils and lymphocytes in the wall of a muscular arteriole present within the subcutaneous tissue. An adjacent subcutaneous inflammatory reaction is present which is located in close proximity to the affected vessel.
D. Erythema nodosum – Incorrect. This is not typically associated with vasculitis and shows inflammation through the subcutaneous septae rather than just in a perivascular configuration, as is present in this specimen.
E. Erythema elevatum diutinum – Incorrect. This condition displays small vessel vasculitis in concert with extensive dermal fibrosis, neither of which are present herein.

Question
The most likely associated finding is:

A. Infection with Mycobacterium tuberculosis – Incorrect. This is associated with erythema induratum.
B. Pain, fever, malaise, arthralgias – Correct. Polyarteritis nodosa is frequently associated with these symptoms.
C. Pulmonary sarcoidosis – Incorrect. This is an association sometimes seen with erythema nodosum.
D. IgA antineutrophil cytoplasmic antibodies (ANCAs) in the serum – Incorrect. This has been reported in some patients with erythema elevatum diutinum.
E. Antibodies to p-ANCA in the serum – Incorrect. This is often seen in patients with Churg-Strauss syndrome.

Clinical Features
Polyarteritis nodosa (PAN) can present either systemically or locally (cutaneous only). In this case, the clinical history indicated that the patient did not have evidence of systemic disease, and thus this case would constitute cutaneous PAN. Clinically, PAN
is characterized by painful subcutaneous nodules in combination with livedo reticularis. Ulceration can be present as well. The nodules are typically between 0.5 – 2 cm in diameter and last from a few days to up to a few months. The lower legs are almost invariable involved. Other body sites can be affected as well, including the arms (as in the case), trunk, head, neck and buttocks. Patients with PAN usually exhibit a prolonged although benign course with episodes of active disease followed by quiescent periods. Neither a gender nor an age predilection has been reported. Although elevated serum levels of pANCA are associated with a minority of systemic PAN, they have not been reported in cutaneous PAN. All patients diagnosed with PAN by a skin biopsy should undergo a systemic evaluation to exclude systemic PAN. Patients diagnosed with cutaneous PAN who are not found to have systemic PAN at the time of diagnosis generally do not develop systemic PAN.

**Histopathologic Features**

- Infiltrate of neutrophils, eosinophils, lymphocytes around muscular arteries in the deep dermis and/or subcutaneous tissue associated with necrosis.
- Older lesions contain more lymphocytes and less neutrophils and eosinophils.
- Thrombi sometimes present.
- Early, there is often only segmental vessel wall involvement, although circumferential involvement often develops over time.
- If multiple vessels are captured in a biopsy, lesions at varying stages of development are often present.

**References**

CASE #39 -- SLIDE #39

**Diagnosis:** Churg-Strauss Granuloma (CSG) [Extravascular granuloma, Winkelmann granuloma]

**Case Summary:** Biopsy taken from the left elbow of a 16 y/o boy hospitalized for hemoptysis

**Clinical Features**
These lesions most often develop on the extensor acral areas such as the fingers and elbows. Most often they first erupt as papules which may be multiple and may eventually ulcerate. Purpuric change may be clinically evident but is not essential. Considerable confusion surrounds this entity as it was first noted in patients with the systemic vasculitic process of Churg-Strauss Granulomatosis (since renamed Eosinophilic granulomatosis with polyangiitis; EGPA) but in reports to follow these same changes have been reported in other antineutrophil cytoplasmic antibody associated (ANCA-associated) illnesses such as granulomatosis with polyangiitis (GPA: formerly referred to as Wegener’s granulomatosis). Several other clinical associations are possible including connective tissue diseases and possibly reactions to anti-tumor necrosis factor medications. This pattern is not specific and clinical correlation is required. Another more general term which encompasses this entity but may also include other more palisaded neutrophilic dermatoses has been used (PNGD: Palisaded Neutrophilic Granulomatous Dermatitis) but the slide on display would best fit with the more classic description of the Churg-Strauss granuloma.

**Histopathologic Features**
The histopathologic features are fairly distinctive when fully developed.
Foci of sharply defined basophilic damage to the collagen in several areas is observed
Surrounding these areas of basophilic change are variable numbers of histiocytes which may form giant cells
Eosinophils may or may not be obvious in the surrounding tissue

**References**
Finan MC, Winkelmann RK. The cutaneous extravascular necrotizing granuloma (Churg-Strauss granuloma) and systemic disease: a review of 27 cases. Medicine (Baltimore) 1983; 62: 142-158
CASE #40 -- SLIDE #40

Diagnosis: Granulomatous vasculitis (GV)

Case Summary
A 69-year-old woman with a history of smoldering chronic lymphocytic leukemia and a recent blistering eruption at the left posterior shoulder presents with painful, purple, barely palpable 3-to 4-mm papules at the left arm and palm of 3 days’ duration.

Question
The best diagnosis is:
A. Cutaneous polyarteritis nodosa (PAN) (Incorrect) In early lesions of cutaneous PAN, the perivascular infiltrate is composed of neutrophils, with some eosinophils and lymphocytes, rather than a histiocytic infiltrate. The clinical presentation of cutaneous PAN is that of nodules, often painful, livedo reticularis or ulceration involving the legs rather than small papules on the arm.
B. Granulomatosis with polyangiitis (Incorrect) The full picture of a necrotizing vasculitis with granulomatosis is seen in the skin in 20% or less of cases of granulomatosis with polyangiitis, or Wegener's granulomatosis. The preceding blistering eruption in this patient would not be consistent with a diagnosis of granulomatosis with polyangiitis.
C. Leukemia cutis (Incorrect) The cellular infiltrate in chronic lymphocytic leukemia cutis consists of a monomorphous population of small lymphocytes and does not cause vessel destruction. The infiltrate in this specimen is primarily histiocytic.
D. Lymphomatoid granulomatosis (Incorrect) Although the histopathology of lymphomatoid granulomatosis is often angiocentric and angioinvasive, the clinical presentation consists of violaceous nodules and plaques that may ulcerate.
E. Post-zoster granulomatous vasculitis (Correct) The presence of an inflamed medium-sized vessel in the deep dermis with surrounding granulomatous inflammation in a patient with a preceding localized blistering eruption supports this diagnosis.

Question
Which of the following would most likely have prevented the painful papules on this woman’s arm?
A. Aggressive treatment of her chronic lymphocytic leukemia (Incorrect) Although some reports of post-zoster granulomatous vasculitis have been in patients with leukemia/lymphoma, cases have occurred outside of this setting as well.
B. High-dose acyclovir (Incorrect) Antiviral treatment of the acute zoster infection has not been shown to prevent this reaction.
C. Prednisone taper (Incorrect) Steroid therapy has not been shown to prevent this reaction.
D. Shingles vaccine (Correct) Post-zoster granulomatous vasculitis occurs in patients after an acute outbreak of herpes zoster virus (shingles) and so preventing the acute outbreak will also prevent the post-zoster reactions. The zoster vaccine decreases the incidence of shingles by approximately 50% and is believed to act by boosting varicella zoster virus-specific cell mediated immunity.
E. Combination therapy with prednisone and acyclovir (Incorrect) Although sometimes used in clinical practice for the treatment of recent onset (<72 hours) herpes zoster in an otherwise immune-competent patient, there is no evidence to suggest it would prevent this complication.
Clinical Features
- Granulomatous vasculitis presents as persistent and often painful papules or nodules at the site of previous herpes simplex or herpes zoster virus infection.
- The lesions can develop either immediately after the acute vesicular eruption or anywhere from two weeks to four years after the viral infection.

Histopathologic Features
- A myriad of post-zoster granulomatous reactions have been described.
- These reactions can mimic granuloma annulare, sarcoidosis, granulomatous vasculitis and lymphoma histologically.
- Since the reaction can be delayed, a good clinical history is important to make the appropriate diagnosis.
- Some, but not all, lesions have had positive polymerase chain reaction (PCR) for herpes virus.

References
CASE #41 -- SLIDE #41

**Diagnosis:** Monoclonal cryoglobulin vasculopathy

**Case Summary:** Cryoglobulins can be divided into 3 groups, Type I, consisting of monoclonal proteins, Type II, consisting of IgG and monoclonal IgM, and Type III, mixed, consisting of polyclonal IgG and IgM. Type I is seen in patients with lymphoma or monoclonal protein disease including monoclonal gammopathy of undetermined significance (MGUS). Type II is also seen most often in patients with autoimmune or inflammatory diseases. Type III is seen most often in patients with chronic Hepatitis C infection but may be of unknown origin, referred to as “essential”. Typically there is a long period of time between initial infection and manifestation of the disease as purpura. The clinical manifestations of disease can be very similar, and most often include distal or acral purpura. However, patients with Type I disease more often have more severe skin lesions which can include livedo, necrosis and ulcerations. Biopsy of skin lesions is very helpful as the monoclonal types of cryoglobulinemia tend to have vascular occlusion, particularly of the small capillaries of the papillary dermis and demonstrate secondary inflammatory changes. Type III consists of immune complexes of IgG and IgM and as such yields a Leukocytoclastic vasculitic pattern. The IgM component can also be readily seen by immunofluorescence technique.

**Reference**
CASE #42 -- SLIDE #42

Diagnosis: North American Blastomycosis

Case Summary: Blastomycosis is a dimorphic fungus endemic to the Ohio and Mississippi river valleys of North America. Skin findings are common in blastomycosis and typically present as warty lesions with irregular borders that may mimic squamous cell carcinoma. Microabscesses are encountered. Skin lesions usually result from dissemination of pulmonary infection, so there is usually an absence of accompanying lymphadenopathy.

Histology:
- Granulomatous inflammation and microabscesses
- Broad based budding yeast with double contoured walls
- Pseudoepitheliomatous hyperplasia
- Staining of organisms with PAS and GMS

Budding yeast can also be identified on KOH prep or with calcofluor. Culture as well as PCR testing can aid in diagnosis.

Treatment
Mild to moderate cases of blastomycosis that are devoid of CNS involvement can be treated with oral itraconazole, ketoconazole, or fluconazole. Sever or progressive disease is treated with intravenous Amphotericin B.

References:
Diagnosis: Trichotillomania

Case Summary: Trichotillomania is a form of mechanical alopecia caused by forcefully plucking or twisting the hair. Patients will often deny plucking hair. A history suggestive of emotional stress can often be obtained, especially in adolescents. A minority of patients have severe psychiatric disturbances.

On examination, there are markedly thinned, but not denuded, irregularly shaped patches of alopecia, often with a bizarre distribution atypical for other forms of alopecia. Short hairs of various lengths are found within thinned area.

The act of plucking results in several histologic changes that are highly suggestive or diagnostic of trichotillomania. The appearance of a given follicle will depend on: 1) the amount of damage done to the follicle during plucking, and 2) the amount of time elapsed between the act of plucking and the biopsy. **The presence of incomplete and distorted anatomy without inflammation is convincing evidence of follicular injury and the most distinctive histologic feature of trichotillomania.**

Follicles respond to the trauma of plucking by entering the catagen and subsequently telogen phases. This is true even for hairs that are badly distorted during plucking. Therefore, a marked increase in catagen and telogen hairs is common in trichotillomania. As mentioned earlier, an increased number of catagen and telogen hairs can also be found in alopecia areata (although inflammation is often present).

Pigment casts, clumps of pigmented hair matrix cells that become "stranded" in the upper follicle as they are torn out, are commonly found in trichotillomania. With time, the casts become compact, black, acellular structures within the interior of a shaftless follicle. Trichomalacia is also a common finding in trichotillomania. Shafts demonstrating trichomalacia are abnormally small, distorted or bizarre in shape, incompletely keratinized, and show irregular pigmentation. Occasionally trichomalacia is also found in alopecia areata, so this finding is not diagnostic for traumatic alopecia.

The frequency with which the histologic findings of trichotillomania are found will depend on whether biopsy specimens are examined by transverse or vertical sectioning. The changes seen with vertical sections have been extensively reviewed. The AFIP experience has been that when transverse sections are performed, incomplete or distorted follicular anatomy can be found in over 50% of cases. This diagnostic finding is present in less than a quarter of specimens sectioned vertically, even when 20 or more sections are obtained. Typically, multiple findings are present when two or three levels of transversely sectioned specimens are studied.
References:
Diagnosis: Traction alopecia ("late" disease)

Case Summary: Excessive tension on the hair from tight braiding or other styling techniques causes temporary thinning early in the course of the disease. Regrowth is expected if gently styling is instituted. However, with excessive traction over a period of many years, and the passage of time, the hair loss becomes permanent. In black females with such "late" or end-stage disease, there is usually a history of tight braiding during childhood. Careful history of hair styling techniques may reveal a mechanism for excessive traction.

On examination, most hair loss is at the periphery of scalp, especially temporal, frontal and periauricular regions. Fine vellus hairs may be present, but scarring and inflammation are absent. Histologic counterparts to "early" and "late" clinical disease can be identified. Histologically, early traction alopecia is very similar to trichotillomania, except that the findings are more subtle and affect fewer follicles. There may be a mild reduction in the total number of hairs, and the number of terminal catagen and telogen hairs is increased. Occasionally a biopsy specimen will contain a follicle showing clear-cut anatomical disruption. Pigment casts and trichomalacia may be found, but less commonly than in trichotillomania. The number of vellus hairs is normal.

"Late" disease shows a marked decrease in the number of terminal hairs. The few terminal hairs present may be outnumbered by vellus hairs, which are found in normal numbers. Some terminal follicles are replaced by columns of fibrous tissue, thus resembling a "burnt out" scarring alopecia. However, sebaceous glands persist. There is no significant inflammation.

References:
CASE #45 -- SLIDE #45

**Diagnosis:** Telogen effluvium

**Case Summary:** Telogen effluvium is a common form of non-inflammatory, non-scarring alopecia. Typically, a precipitating event can be identified, occurring about 3 months before the onset of hair loss. Examples of precipitating events are labor and delivery of a baby (postpartum telogen effluvium), major surgery, severe illness, starvation, and other major physiologic stresses. Chronic forms of telogen effluvium do occur (e.g. drug-induced, hypothyroidism).

On examination, the scalp surface is normal and diffuse hair thinning affects all portions of the scalp. Increased numbers of normal telogen hairs can be extracted from the scalp with gentle pulling.

The following histologic features are characteristic of telogen effluvium: a normal total number of follicles; a reduced number of terminal anagen hairs found at the level of the fat and deep dermis; an increased number of terminal telogen hairs; a normal number of vellus hairs; and a total absence of peribulbar inflammation. To calculate the telogen count from a biopsy specimen, the number of terminal telogen follicles is divided by the total number of terminal follicles. Vellus follicles are not counted.

**References:**

CONTRIBUTED BY LEONARD SPERLING, MD
CASE #46 -- SLIDE #46

Diagnosis: Normal scalp biopsy (African-American)

Case Summary: Recognition of what is normal is essential for making a confident diagnosis. Most often, the normal-appearing specimen has been submitted to provide a normal control for comparison with the “involved” area of hair loss. However, sometimes the biopsy is supposedly from the actual area of alopecia. The diagnosis of “normal scalp” in the clinical setting of apparent alopecia can be seen in several situations. First, the problem may be a hair shaft disorder, with external hair breakage. The area that was sampled may be in the recovery phase of a preexisting form of alopecia, such as a telogen effluvium or a patch of alopecia areata that has gone into remission. Also, the patient’s concern about hair loss may be more perceived than real. The findings may be so subtle as to be at or just below a diagnostic threshold, as might be found in very early androgenetic alopecia.

The slide presented for your review is actually an "average" specimen for a normal African-American scalp. The shape of the hair shafts and their eccentricity within the follicle help to identify the race of the patient. Hair density in African-Americans and Asians is significantly lower than in Caucasians. This must be taken into consideration when evaluating a biopsy specimen from an African-American patient. Data from Caucasian patients may not provide adequate guidance when evaluating scalp biopsy specimens from African-Americans, and could lead to incorrect diagnosis. The data presented in reference #1 below shows that the average total follicles (4mm punch biopsy specimen) in Caucasians is 36, but only 22 in African-Americans. The figures for terminal anagen hairs are 30 in Caucasians, but only 17 in African-Americans.

References:

CONTRIBUTED BY LEONARD SPERLING, MD
Diagnosis: Chronic Cutaneous Lupus Erythematosus

Case Summary: Although the slide presented here is sectioned at only one level, the features present are sufficient for a confident diagnosis. Note the vacuolar interface alteration and the prominent peri-eccrine and peri-arrector pili inflammation. This condition is typically found in adult women and usually is not associated with systemic disease. 50% of patients with disease isolated to skin have alopecia, and some patients have scalp lesions only. Establishing the diagnosis is more difficult when lesions are confined to the scalp, and certainly non-scalp lesions are supportive of the diagnosis. Itching or tenderness may be present. Typical lesions of DLE (erythema, scaling, "follicular plugging") may be present in the scalp, but clinically "non-inflammatory" disease resembling alopecia areata may also be present.

Vacuolar interface alteration of the epidermis and follicular epithelium is typical, although the epidermis may be spared in lesions of CCLE involving the scalp. The interface change is usually vacuolar rather than lichenoid. In other words, lymphocytic inflammation at the DE junction is less prominent. Dyskeratosis and colloid (Civatte) bodies are occasionally seen, but less commonly than in LPP. Moderate to dense chronic inflammation, often including plasma cells, is seen in both perivascular and periadnexal locations. When perifollicular inflammation is noted, it usually is most severe at the level of the infundibulum, and inflammatory cells may invade the follicular epithelium. Similar inflammation may be found in and around the follicular tracts that lie below telogen follicles or have been destroyed. Increased dermal mucin is often present and is helpful in differentiating CCLE from LPP. Granular deposits of IgG and C3 (rarely IgM or IgA) at the dermoepidermal junction and/or the junction of the follicular epithelium and dermis are typical of CCLE. Globular deposits of IgM representing colloid bodies may be present, but not as commonly as in LPP.

References:


CONTRIBUTED BY LEONARD SPERLING, MD
CASE #48 -- SLIDE #48

**Diagnosis:** Alopecia Areata

**Case Summary:** Alopecia areata has a spectrum of severity ranging from a small, solitary patch of hair loss to disease affecting every hair on the body. The clinical spectrum of disease severity is matched by a histologic spectrum of abnormalities. Rapidly progressive hair loss may appear very different histologically than stable, longstanding disease. The example presented here is “subacute” disease, and a few terminal (large) hairs and peribulbar inflammation are evident. In early (acute) disease, the following features are commonly seen: normal total number of hairs; increased number of catagen and telogen follicles; mononuclear cell infiltrate around the bulbs of some terminal anagen and catagen hairs; hair matrix changes such as intercellular edema, exocytosis of inflammatory cells, nuclear pyknosis, cellular necrosis and vacuole formation; trichomalacia and marked narrowing of hair shafts. Longstanding (chronic) disease may differ in the following ways: there are normal or nearly normal numbers of follicles, but almost all are miniaturized; majority of hairs are in catagen or telogen phases (may approach 100%); the peribulbar infiltrate may be scanty or absent, and is usually associated with anagen hairs. A few eosinophils may be present in the infiltrate, but plasma cells are not seen. The hair matrix may appear normal, but often it is infiltrated by a few inflammatory cells, and may appear "blurry" because of intercellular and intracellular edema. Necrotic keratinocytes and vacuole formation may be found in the portion of the matrix just above the dermal papilla (the portion responsible for hair shaft formation). Minute, cystic spaces filled with necrotic, acantholytic cell are occasionally seen, a finding which, if present, is highly characteristic of alopecia areata. Associated with hair matrix changes is pigment incontinence found in the hair papilla. In acute disease, the majority of affected hairs are still terminal (large) hairs. Many of these follicles will have a peribulbar, mononuclear cell infiltrate that can be remarkably scanty, even in severe disease. In almost all cases there is an increase in the number of catagen and telogen hairs. Peribulbar inflammation tends to subside as affected follicles enter the telogen phase, but occasionally a few inflammatory cells can still be found around telogen hairs. Some affected anagen hairs do persist, but produce a shaft that is smaller than normal, incompletely keratinized and distorted in shape, an appearance termed trichomalacia. Other follicles produce shafts that are progressively thinner, so that they taper down to a point. The attenuated shaft is extremely fragile and will separate from the follicle with the most trivial force, such as combing, shampooing or the gentle pull test. These are the "pencil-point hairs" that are so typical of an anagen effluvium. Tapered constrictions of anagen hairs are evidence of active disease, and affected follicles will prematurely exit the anagen phase and become catagen and telogen hairs.

Below each catagen/telogen follicle is a collapsed fibrous root sheath (stela). Inflammatory cells and clumps of melanin may be found in and around some, but not all, of the stelae. Non-inflamed stelae are morphologically identical to the "fibrous streamers" described in androgenetic alopecia.

**References:**

CONTRIBUTED BY LEONARD SPERLING, MD
Diagnosis: Inflammatory, non-scarring alopecia in SLE

Case Summary: The clinical and histological features of non-scarring forms of hair loss in systemic lupus erythematosus have been largely ignored in the medical literature. Diffuse hair loss may be noted several months after a severe flare of SLE (telogen effluvium pattern), or may occur as patchy or diffuse hair loss a few weeks after a disease flare has begun (anagen arrest pattern). In either case, the diagnosis of SLE is usually obvious from numerous other signs and symptoms.

One histological pattern that has been well described in patients with patches of partial or total alopecia closely resembles alopecia areata, both clinically and histologically. A peribulbar, mononuclear cell infiltrate is found around anagen bulbs, many of which are miniaturized. The percentage of catagen and telogen hairs is markedly increased and can be as high as 80-100%. Melanin pigment and some inflammation can often be found in the collapsed fibrous root sheath below telogen hairs. One minor difference from alopecia areata is that the infiltrate in SLE tends to be more pronounced. Another difference is that deep mucin is often seen in SLE specimens. When vacuolar interface alteration is also present, the diagnosis of SLE (versus alopecia areata) becomes more obvious.

References:
CASE #50 -- SLIDE #50

Diagnosis: Frontal Fibrosing Alopecia (FFA)

Case Summary: Clinical correlation: Most often a postmenopausal woman with pruritus and progressive hair loss along the anterior hairline, temples, and eyebrows.

Histologic findings:
- Lichenoid interface dermatitis affecting the infundibulum and isthmus
- Apoptotic keratinocytes scattered throughout the affected (infundibular and isthmic) follicular epithelium
- Blurring of the epithelial-stromal junction
- Squamatization of the outer root sheath
- Concentric, lamellar perifollicular fibroplasia with artifactual clefting between the follicular epithelium and the stroma
- Clinical correlation is required to suggest a diagnosis of FFA vs. LPP, as the histological findings of both entities are too similar to be reliably separated. Unless actively inflamed areas are sampled, histological changes may only show an end-stage, cicatricial alopecia.

Histologic differential diagnosis:
- Lichen planopilaris: inflammation often more dense and apoptotic cells less numerous than in FAA. Interfollicular epidermal changes (occasionally seen in LPP) are absent in FFA, and vellus hairs are less likely to be affected in LPP.
- Fibrosing alopecia in a pattern distribution: shows increased vellus:terminal hair ratio, a feature not typical of the involved areas of FFA.
- Discoid lupus erythematosus: differentiating features include deep perivascular/periadnexal inflammation, mucin deposition, and interfollicular epidermal changes including follicular plugging and vacuolar alteration with epidermal atrophy, none of which are seen in FAA.

References:
CASE #51 -- SLIDE #51

**Diagnosis:** Leukocytoclastic vasculitis

**Case Summary:** This biopsy was taken from the upper arm of a 43-year-old woman with a several week history of raised somewhat painful urticarial-like lesions.

**Question**
The best diagnosis for this case is:
A. **Urticaria (Incorrect).** There are urticarial changes seen in this biopsy including perivascular mixed inflammation with eosinophils and lymphatic dilation but there are also several foci of actual subtle vascular wall damage surrounded by nuclear dust
B. **Sweet syndrome (Incorrect).** There is insufficient dermal interstitial neutrophilia to make a diagnosis of a neutrophilic dermatosis
C. **Urticarial vasculitis (Correct).** Changes of acute urticaria are seen together with subtle vessel wall damage with surrounding nuclear dust
D. **Angiolymphoid hyperplasia with eosinophils (Incorrect).** There are insufficient changes in the blood vessels and insufficient numbers of eosinophils to make this diagnosis
E. **Urticarial phase of lupus erythematosus (Incorrect).** Although these changes could be seen in patients with lupus erythematosus but there are insufficient inflammatory changes at the basement membrane zone or around appendages to make this diagnosis.

**Question**
Based on the combination of clinical information and histopathology, this patient should initially be evaluated for:
A. **Biopsy for direct immunofluorescence and serologic tests including complement and ANA (Correct).** Given the combination of clinical information and the histopathology, this is the best answer as this patient may be hypocomplementemic or may have other signs and symptoms to suggest a connective tissue disease or lupus erythematosus.
B. **Inhalent sensitivity (Incorrect).** The clinical description of the lesions is not typical for ordinary “hives” or urticaria and this clinical information combined with the pathology would not suggest a usual cause of urticaria in this patient.
C. **Malignancy (Incorrect).** Malignancy has been reported in patients with cutaneous vasculitis but given the clinical information and the histopathology, this diagnosis would not be highly likely and would not be the focus of the initial workup for this case.
D. **Contact sensitivity (Incorrect).** The clinical description of the skin lesions combined with the histopathology do not suggest a contact sensitivity where one would expect to see spongiosis or eosinophilic spongiosis in addition to the dermal edema and mixed perivascular inflammation.
E. **Food sensitivity (Incorrect).** While a specific food sensitivity could uncommonly create these changes, the combination of clinical information and histopathology does not suggest this more ordinary cause of urticarial tissue reaction.

**Discussion**
Urticarial vasculitis (UV) can be a challenging diagnosis at times. Microscopic features combine those of urticarial tissue reactions with those of subtle leukocytoclastic vasculitis. Dilated superficial dermal lymphatics are typical and the infiltrate is most often predominantly composed of neutrophils admixed with eosinophils. Blood vessel wall damage can be very subtle at times but most often the inflammatory cells can be seen traversing the wall of several vessels and the vessel
walls can be thickened or hyalinized slightly. Interstitial dermal neutrophilia can be seen and at times can be so prominent as to suggest a neutrophilic dermatosis, especially Sweet syndrome. In addition, a predominantly neutrophilic infiltrate suggests the hypocomplementememic variant of UV. Approximately 15% of patients with UV will have depressed total complement or C4. These patients in addition to having dermal neutrophilia may also have neutrophils coalesced near the interface of the epidermis and dermis, closely mimicking an autoimmune blistering disease or bullous lupus erythematosus. Biopsy for direct immunofluorescence may show granular basement membrane zone fluorescence in addition to vascular fluorescence with several conjugates including IgM and C3. Skin lesions are urticarial-like but have some pain associated with them instead of just itch and most often persist for over 24 hours before resolving, leaving a bruised area at times. The skin lesions can be located in any area and are not necessarily photo-distributed. Triggering factors may be difficult to elicit. Patients with hypocomplementemia typically also have some degree of joint pain as well as potentially abdominal pain and chest pain. These same patients may have several criteria for lupus erythematosus but most often do not fulfill sufficient criteria for diagnosis of systemic lupus erythematosus. Long term complications can include emphysema. Those patients with normal complement should be evaluated in an identical fashion as those above but in addition depending on age, gender and other detailed clinical information may need a systemic workup to eliminate a systemic cause which can range from drug sensitivity to malignancy. UV can be notoriously difficult to treat in those patients where no underlying cause is identified. The histopathologic changes may be understated in terms of the degree of difficulty this disease can pose to patients and careful clinical correlation is always needed.

References

CONTRIBUTED BY LAWRENCE GIBSON, MD
CASE #52 -- SLIDE #52

1. A 4mm punch biopsy specimen was taken from crown of the scalp of a 45 year old African-American woman. The most appropriate diagnosis is:

   a. end-stage traction alopecia -- is incorrect because sebaceous glands remain intact in this disorder, and significant perifollicular inflammation would not be expected
   b. central, centrifugal scarring alopecia (CCCA) -- is correct because of the premature desquamation of the inner root sheath, concentric lamellar fibroplasia, perifollicular inflammation, and loss of some sebaceous glands
   c. folliculitis decalvans -- is incorrect because dense, superficial acute and chronic inflammation with polytrichia would be expected in this condition
   d. lichen planopilaris -- is incorrect because clear-cut vacuolar interface alteration would be expected in this condition
   e. chronic, cutaneous lupus erythematosus (discoid LE) -- is incorrect because deep inflammation and vacuolar interface alteration would be expected

Central centrifugal cicatricial alopecia (CCCA) occurs primarily in African–American women and is the most common cause of permanent hair loss in this group. Prevalence increases with age as women are most commonly affected in the late second or third decade of life, and many do not seek treatment until the hair loss is extensive and/or permanent. In cicatricial alopecias, the hair follicle is destroyed and replaced by fibrous tissue. In CCCA, hair loss begins at the vertex or mid scalp and slowly progresses centrifugally. Histopathologically, the predominate inflammatory cellular infiltrate of CCCA is lymphocytic.

Two 4-mm punch biopsies of an active edge should be obtained to confirm diagnosis; one for horizontal and the other for vertical viewing histopathologically. In CCCA, a reduction in terminal hair follicles, increased and widened fibrous tracts, and perifollicular infundibular lymphocytic infiltrate would be present. In late stages, there is loss of sebaceous glands and hair follicles with prominent hyalinization or fibrosis of the dermis.

References:


CONTRIBUTED BY LEONARD C. SPERLING, MD
**CASE #53 -- SLIDE #53**

**Diagnosis:** Granuloma annulare-like tattoo reaction

**Case Summary:** A 67 year-old woman presented with a 6-month history a rash on her left medial ankle at the site of a tattoo that was placed 7-years prior. She also more recently noted similar bumps in tattoos on her forearms that were placed 8-years prior (see biopsy).

**Question**
The pigmented material seen in the biopsy is most likely:
A. Cadmium sulfide – **Incorrect.** Cadmium sulfide is found in yellow tattoo pigment, which rarely has associated allergic reactions.
B. Chromic oxide – **Incorrect.** Chromium is found in green tattoo pigment, and has been associated with localized eczematous reactions.
C. Mercuric sulfide – **Correct.** Tattoo reactions, including granulomatous reactions, most commonly occur to red pigments, particularly mercuric sulfide (cinnabar). Mercury in red pigment also causes most lichenoid tattoo reactions. In 1976, the FDA limited mercury in tattoo dyes to 3 ppm, but despite this, inflammatory reactions still occur even to mercury-free red pigments.
D. Paraphenylene-diamine (PPD) – **Incorrect.** PPD, a textile dye, is often contained in temporary henna tattoos and can cause a contact dermatitis.
E. Titanium oxide – **Incorrect.** Titanium oxides are one of the least reactive white pigments with no described allergic reactions.

**Question**
The most appropriate next step in evaluation and/or management:
A. Chest x-ray – **Incorrect.** This would be appropriate if concerned about sarcoidosis, which can involve the skin within tattoos, but this biopsy demonstrates a palisading necrobiotic granuloma, not a sarcoideal granuloma.
B. Intralcsionai corticosteroids – **Correct.** Conservative management for tattoo reactions includes topical or intralcsionai corticosteroids. Destructive methods are another option, including excision or ablation.
C. Patch testing – **Incorrect.** Unlike eczematous tattoo reactions which may have positive patch test results, granulomatous reactions are more commonly associated with negative patch test results.
D. Q-switched laser treatment – **Incorrect.** Q-switched laser is contraindicated for tattoos demonstrating signs of an allergic reaction, since rapid thermal expansion fragments the pigment containing cells causing the pigment to become extracellular. This extracellular ink may then be released into the circulation, resulting in a hypersensitivity response.
E. Tissue culture – **Incorrect.** Infection is always a consideration when cutaneous lesions develop within a tattoo. Various bacterial and mycobacterial infections have been reported to occur within tattoos, but this generally manifests shortly after the tattoo procedure, not years later.
**Clinical Features**

Most hypersensitivity reactions to tattoo pigment can be classified as lichenoid or granulomatous. Lichenoid reactions are most common. Additionally, pseudo-lymphoma and pseudoepitheliomatous hyperplasia have been infrequently reported. Hypersensitivity reactions to tattoo pigment are thought to occur due to a T-cell mediated, delayed hypersensitivity response.

Granulomatous tattoo reactions most often present as an indurated papule, plaque, or nodule within a specific color of the tattoo. Granulomatous reactions are most commonly associated with mercury in red pigment (cinnabar), but may occur in association with other pigments. The lesions may be pruritic and inflamed. Various granulomatous reaction patterns have been reported within tattoos; the majority being sarcoideal granulomas. A number of cases have been reported where sarcoideal granulomas within a tattoo indicated underlying pulmonary sarcoidosis. Other granulomatous tattoo reactions include a hypersensitivity pattern with few giant cells and foreign body granulomas with numerous pigment-containing giant cells. Only a few previous cases of palisaded granulomatous inflammation resembling granuloma annulare have been reported.

**Histopathologic Features**

- Palisading necrobiotic granuloma, with collections of epithelioid histiocytes and perivascular lymphocytic inflammation.
- Tattoo pigment deposits, both intra- and extra-cellular.
- Focal mucin deposition.

**References**


CONTRIBUTED BY MARK A. CAPPEL, MD
Diagnosis: Adenomyoepithelioma

Case Summary: A 77 year-old man presented with a 6-year history of slowly growing mass on the left elbow.

Question
The best diagnosis is:
A. Adenomyoepithelioma – Correct. Sections show a well circumscribed dermal nodule composed of an epithelial component forming ductal and glandular structures and a spindled myoepithelial cell component.
B. Chondroid syringoma – Incorrect. This neoplasm is characterized by a prominent chondromyxoid stroma in addition to glandular structures lined by epithelial and myoepithelial cells.
C. Metastatic adenocarcinoma – Incorrect. The neoplastic glands of adenocarcinoma are lined by atypical epithelial cells with frequent mitoses and necrosis may be seen. A component of myoepithelial cells is not typical.
D. Microcystic adnexal carcinoma – Incorrect. This is a poorly circumscribed deeply infiltrative neoplasm composed of keratin filled cysts and duct-like structures embedded in a desmoplastic stroma. Perineural invasion may be seen.
E. Papillary eccrine adenoma – Incorrect. This is a well-circumscribed dermal neoplasm composed solely of dilated tubular structures lined by two layers of epithelial cells and embedded in a fibrotic stroma. A prominent myoepithelial cell component is not seen.

Question
Which of the following immunohistochemical stains are typically positive in this neoplasm?
A. Cytokeratin and Melan-A – Incorrect. Cytokeratin highlights the epithelial component but the spindled cells in this lesion do not show melanocytic differentiation.
B. Cytokeratin and desmin – Incorrect. Cytokeratin highlights the epithelial component but the myoepithelial cells are typically negative for desmin.
C. Cytokeratin and smooth muscle actin – Correct. Cytokeratin highlights the epithelial component while smooth muscle actin is positive in the myoepithelial component.
D. Estrogen receptor and HER2 – Incorrect. These markers can be positive in a metastatic adenocarcinoma of breast origin but are shown to be negative in the index case.
E. S-100 protein and HMB-45 – Incorrect. S-100 protein may be positive in the myoepithelial cells; however these cells are negative for HMB-45.

Discussion
Adenomyoepithelioma is a rare but microscopically distinctive cutaneous sweat gland tumor analogous to adenomyoepithelioma of the breast. It presents as a slow growing nodule in adult patients and ranges in size from 1.5 cm to 3 cm. Sites of involvement include trunk and extremities.
Histopathologically, adenomyoepithelioma is a biphasic neoplasm composed of duct/gland
forming epithelial cells and myoepithelial cells. Cytologic atypia and mitotic figures are not
prominent. By immunohistochemistry, the epithelial cells express cytokeratins, CEA and
EMA while the myoepithelial cells variably express vimentin, smooth muscle actin and S-
100 protein.

The growth pattern and the bland morphologic features favor a benign neoplasm but complete
excision is the recommended therapeutic option.

References
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tumor? Dermatol Pract Conc. 201

CONTRIBUTED BY VIJAYA B. REDDY, MD, MBA
CASE #55 -- SLIDE #55

Diagnosis: Porocarcinoma

Case Summary: An 88 year-old woman presented with a 3 cm ulcerated nodule on the right calf.

Question
The best diagnosis is:

A. Merkel cell (neuroendocrine) carcinoma – Incorrect. The neoplastic cells are often arranged in a trabecular pattern and contain scant cytoplasm, round and vesicular nuclei with a finely granular cytoplasm and inconspicuous nucleoli characteristic of neuroendocrine differentiation.
B. Metastatic poorly differentiated adenocarcinoma – Incorrect. Metastatic carcinoma should be considered in the differential diagnosis of high grade carcinoma of the skin. However, the intraepidermal growth pattern seen in this case is not typical of a metastasis.
C. Nodular basal cell carcinoma – Incorrect. Basal cell carcinoma is characterized by basaloïd cell aggregates with peripheral palisading and stromal retraction artifact. Epidermal expansion by tumor cells is not typical.
D. Poorly differentiated squamous cell carcinoma – Incorrect. This can be a challenging differential diagnosis. Discrete aggregates of intraepidermal cells centered on acrosyringeal openings are not typically seen in squamous cell carcinoma.
E. Porocarcinoma (malignant eccrine poroma) – Correct. The epidermis is markedly expanded by intraepidermal proliferation of neoplastic cells. Discrete aggregates of similar cells are present around the openings of the acrosyringia. Lobules of highly atypical epithelial cells with significant cytologic/nuclear atypia, frequent mitotic figures and central necrosis infiltrate the dermis.

Question
Which of the following is characteristic of this neoplasm?

A. Indolent course with local excision – Incorrect. These tumors have an aggressive biologic course.
B. Propensity for cutaneous and distant metastasis – Correct. These tumors have a propensity for local and distant metastasis and poor outcome.
C. Perineural invasion – Incorrect. Perineural invasion is not commonly seen.
D. Typically occurs de-novo – Incorrect. Usually develops within a long-standing poroma.
E. Scalp is the most frequently involved site – Incorrect. Extremities, particularly the lower legs and the feet are the favored sites of involvement.

Discussion
Eccrine porocarcinoma is a relatively uncommon malignant neoplasm that presents as an ulcerated nodule or a warty plaque most commonly on the lower legs or feet and occasionally the trunk and scalp. It may arise as a de novo neoplasm but more often occurs in association with a long standing poroma.
Histopathologically, there is marked expansion of the epidermis by the neoplastic cells with a preserved basal cell layer reminiscent of Bowen’s disease. Cords and lobules of atypical cells with marked nuclear atypia, mitotic figures and comedo-type necrosis infiltrate into the dermis. Ductal lumina when present and highlighted with a PAS stain or CEA stain are helpful clues to sweat gland differentiation. Areas of eccrine poroma may be recognized in some cases.

Porocarcinoma is a highly malignant neoplasm with propensity for cutaneous, lymph node and visceral metastasis.

References
CASE #56 -- SLIDE #56

1. A clinical feature common to the disorder represented on the slide is:

a. Longitudinal erythronychia incorrect. Nail psoriasis does not commonly present clinically with longitudinal erythronychia.

b. Pterygium incorrect. Dorsal pterygium can be seen with lichen planus. A ventral pterygium, otherwise known as pterygium inversum unguis, can be associated with a number of causes, but is well known to be associated with systemic connective tissue diseases.

c. Longitudinal melanonychia incorrect. Nail psoriasis does not commonly present clinically with longitudinal melanonychia.

d. Nail malalignment incorrect. Nail malalignment can present post-surgically after a lateral longitudinal excision, or in young children, most often on the great toenails. It is not seen commonly in nail unit psoriasis.

e. Pitting Correct. Pitting, along with subungual hyperkeratosis, oil spots, nail crumbling, and onycholysis, are common clinical presentations of nail unit psoriasis.

Nail disease is seen in 40-45% of patients with skin psoriasis. Conversely, up to 5% of patients have isolated nail psoriasis without skin manifestations. The prevalence of nail involvement increases to 87% in patients with psoriatic arthritis, and nail disease is significantly associated with distal interphalangeal (DIP) joint involvement, a sign of more severe arthritis. The lifetime incidence of nail psoriasis among patients with psoriatic arthritis has been estimated to be between 80% and 90%.

Pits represent superficial punctate depressions in the nail plate. Since pitting involves the dorsal layer of the nail plate, which originates from the proximal nail matrix, the main pathology lies in the proximal nail matrix. Within psoriatic lesions in the nail matrix, columns of parakeratotic cells in the stratum corneum interfere with normal keratinization. As the nail plate grows out dorsally, these cells are shed off to leave pits in the nail plate. Nail pitting may also be seen in other dermatoses such as atopic eczema, lichen planus, and alopecia areata. Deeper pits are usually seen in nail psoriasis, which signifies additional involvement of the intermediate and ventral nail matrix.

Reference:

CASE #57 -- SLIDE #57

**Diagnosis:** The H syndrome

**Case Summary:** A 9 year-old boy with sensorineural hearing loss was seen with hyperpigmented and indurated plaques involving the lower abdomen, scrotum, thighs and lower legs. He also had alopecia totalis, short stature, hepatosplenomegaly, hypogonadism and hyperglycemia.

**Question**
The best diagnosis is:

A. Deep morphea – **Incorrect.** The biopsy in deep morphea would show sclerosis of the connective tissue septa of the subcutaneous tissue, with no involvement of the fat lobule.

B. Nephrogenic systemic fibrosis – **Incorrect.** Induration of the extremities would be a more typical clinical presentation, and the histopathologic findings would include deep dermal and subcutaneous fibrosis with interstitial mucin deposits.

C. H syndrome – **Correct.** The dermatologic findings (hyperpigmented, hypertrichotic and hard plaques on the thighs and lower legs), the systemic manifestations (sensorineural hearing loss, low height, heart anomalies, hepatosplenomegaly, scrotal masses, hypogonadism and hyperglycemia) and the histopathologic findings (dermal and mostly septal subcutaneous infiltrates of plasma cells and histiocytes with large pale cytoplasm expressing CD68 and S-100 protein) are characteristic of this syndrome.

D. Scleromyxedema – **Incorrect.** Scleromyxedema would show waxy papular lesions of the face, around the neck and on the dorsum of the hands. The histopathology would show a dermal fibroblastic proliferation and interstitial mucin deposits.

E. Eosinophilic fasciitis – **Incorrect.** The histopathology would show sclerosis of the connective tissue septa of the subcutaneous fat and underlying fascia and infiltrate with abundant number of eosinophils.

**Question**
The cause of this process is:

A. Mutations in nucleoside transporter in hENT3 – **Correct.** The H syndrome is a genodermatosis with autosomal recessive inheritance due to mutations in the *SLC29A3* gene on chromosome 10q21.3-q22, which encodes the human equilibrative nucleoside transporter 3 (hENT3).

B. Gadolinium-based contrast agents used in magnetic resonance imaging – **Incorrect.** This is the etiologic factor of nephrogenic systemic fibrosis.

C. *Borrelia burgdorferi* infection – **Incorrect.** This is the microorganism causing erythema chronica migrans and acrodermatitis chronica atrophicans.

D. Congenital immunodeficiency – **Incorrect.** No immunoglobulin anomalies have been described in H syndrome.

E. IgG lambda monoclonal gammopathy – **Incorrect.** Paraproteinemia is seen in over 80% of patients with scleromyxedema, but not in patients with H syndrome.
Clinical Features

- Genodermatosis with autosomal recessive inheritance. Mutations in the SLC29A3 gene on chromosome 10q21.3-q22, which encodes the human equilibrative nucleoside transporter 3 (hENT3).
- Dermatologic findings: Hyperpigmented, hypertrichotic and hard plaques on the thighs and lower legs.
- Systemic manifestations: Sensorineural hearing loss, low height, heart anomalies, hepatosplenomegaly, scrotal masses, hypogonadism and hyperglycemia.

Histopathologic Features

- Hyperpigmentation of the basal layer of the epidermis.
- Dermal and mostly septal subcutaneous infiltrates of histiocytes, mast cells and plasma cells.
- Large pale histiocytes express CD68 and S-100 protein.
- Lymphoid aggregates express B-cell markers (CD20 and CD79a).

References


CONTRIBUTED BY LUIS REQUENA, MD
CASE #58 -- SLIDE #58

**Diagnosis:** Folliculocystic and collagenous hamartoma of tuberous sclerosis complex

**Case Summary:** A 7 year-old boy was seen with indurated subcutaneous masses on the right side of the abdominal wall. The lesions were present at birth. He had also multiple angiomatous papules involving the cheeks.

**Question #25**
The best diagnosis is:

A. Collagenoma – **Incorrect.** Collagenoma is a connective tissue nevus composed of thick collagen bundles irregularly arranged in the dermis, but without infundibular associated anomalies.

B. Multiple infundibular cysts grouped in plaque – **Incorrect.** Infundibular cysts arranged in plaque do no show the thick collagen bundles deposition seen in this lesion.

C. Folliculocystic and collagenous hamartoma of tuberous sclerosis complex – **Correct.** This is a recently described hamartoma characteristic of patients with tuberous sclerosis.

D. Nevus lipomatosus cutaneous superficialis - **Incorrect.** Nevus lipomatosus cutaneous superficialis is a connective tissue nevus mostly composed of clusters of mature adipocytes which appear abnormally located in the superficial dermis. The collagen and the cutaneous adnexa do no show anomalies.

E. Steatocystoma multiplex – **Incorrect.** Steatocystoma is cystic sebaceous hamartoma, characterized by cystic structures lined by epithelium showing sebaceous ductal differentiation (crenulated eosinophilic cuticle) and lobules of mature sebocytes within the cyst wall.

**Question #26**
The characteristic histopathologic features of this disorder are:

A. Infundibular cyst surrounded by scar tissue – **Incorrect.** Infundibular cysts grouped in plaque do no show collagen deposition and the periadnexal concentric fibrosis.

B. Thick collagen bundles in deep dermis and the connective tissue septa of the subcutaneous tissue – **Incorrect.** The infundibular cysts and the perifollicular fibrosis are characteristic findings of this lesion.

C. Sclerosis of the collagen bundles of deep reticular dermis – **Incorrect.** These are the findings or morphea or scleroderma, but the hamartoma presented in this case has infundibular cysts as one of the components of the lesion.

D. Thick collagen, concentric perifollicular fibrosis and large keratin-containing cysts lined by infundibular epithelium – **Correct.** These are the characteristic histopathologic features seen in folliculocystic and collagenous hamartoma of tuberous sclerosis complex.

E. Hamartomatous arrangement of collagen and elastic tissue of the dermis – **Incorrect.** These are the histopathologic features of some connective tissue nevi, but folliculocystic and collagenous hamartoma of tuberous sclerosis complex has infundibular cysts as one of its components.
Clinical Features

- The skin lesions consist of large plaques first noticed at birth or during early infancy, present on the abdomen, thigh, back, or scalp.
- In time, the plaques become studded with numerous follicular comedo-like openings, which progress to form small infundibular cysts and then to form a big mass of cysts containing and draining a keratinous and purulent material.
- This hamartoma seems to be characteristic of patients with tuberous sclerosis.

Histopathologic Features

- Abundant collagen deposition in the form of thick, hyalinized, eosinophilic collagen bundles occupying the whole width of the dermis and extending into subcutaneous tissue.
- Concentrical perifollicular fibrosis surrounding the hair follicles, eccrine coils and blood vessels of the dermis.
- Comedo and large keratin-containing cysts lined by infundibular epithelium. Some of them may be ruptured with foreign body granuloma formation.

References

CASE #59 -- SLIDE #59

1. A 71 year old female presents with a tender foot mass. What is the correct diagnosis?

a. Angiosarcoma Incorrect. Angiosarcoma exhibits an infiltrative growth pattern and shows cytologic atypia.

b. Nodular fasciitis Incorrect. Nodular fasciitis is a tumor of fibroblasts and myofibroblasts in a loose storiform growth pattern.

c. Angiolipoma. Incorrect. Angiolipomas are benign lipomatous tumors with a vascular component.

d. **Papillary endothelial hyperplasia. Correct.** Histologic examination of papillary endothelial hyperplasia shows a circumscribed lesion with pseudocapsule containing papillary structures lined by a single layer of endothelial cells without significant atypia.

e. Epithelioid hemangioendothelioma. Incorrect. EHEs are malignant vascular tumors composed of cords and chains of epithelioid cells in a myxochondroid stroma.

Intravascular papillary endothelial hyperplasia is now generally regarded as an unusual pattern of organization of a thrombus within a vein or within one or more of the component vessels of various vascular abnormalities. These include cavernous hemangiomas, pyogenic granulomas, and lymphangiomas. Organizing hematomas of soft tissues may also show this pattern. In most cases, there is a single lesion, but multiple lesions have also been described. They usually present clinically as firm, sometimes painful nodules that appear blue or purple through the overlying skin.

The proliferation is limited to the lumen of an identifiable vein or vessel in a vascular abnormality. Occasionally, there is only a fibrous capsule lacking definite features of a vessel wall. Rarely, the proliferation extends outside the lumen, possibly due to rupture of the wall of the vessel. Masses of papillary processes are present within the lumen, and they are almost always associated with some thrombus. Each papillary frond is covered by a single layer of plump endothelial cells. Mitotic figures may be present, but they are never frequent. There is no multilayering of the cells, and solid cellular areas, cellular tufts, atypia, and necrosis are not usually evident; however, Renshaw and Rosai described severe cytological atypia in lesions from the lip. The core of the papillae consists of fibrin or collagenous connective tissue, depending on the stage of organization.

Reference:

CASE #60 -- SLIDE #60

**Diagnosis:** Omphalomesenteric duct cyst

**Case Summary:** A 16-month old female with no prior medical or surgical history presented with a 1 cm friable papule on the umbilicus.

**Question**
The best diagnosis is:
A. Metastatic adenocarcinoma (Sister Mary Joseph nodule) – **Incorrect.** The epithelial cells are usually very atypical and crowded, and numerous mitotic figures are evident among them.
B. Ostomy site – **Incorrect.** The clinical presentation does not fit with this. C. Omphalomesenteric duct cyst – **Correct.** This biopsy shows the typical histopathologic findings in this entity, including gastrointestinal mucosa adjoining stratified squamous epithelium.
D. Syringoma with clear cell change – **Incorrect.** The entity is characterized by solid and ductal structures composed of cuboidal epithelium enmeshed within sclerotic stroma. The ducts do not connect with the overlying surface epithelium, as they do in this case. In addition, the epithelium does not contain goblet cells or Paneth cells, which are also seen in this case.
E. Syringocystadenoma papilliferum – **Incorrect.** Although this is composed of glandular epithelium that can connect with the overlying epithelium, as in this case, the glandular epithelium in this entity does not contain goblet cells or Paneth cells. Also, well developed lesions display a papillary architecture.

**Question**
The most likely associated finding is:
A. Meckel’s diverticulum – **Correct.** Patients with omphalomesenteric duct cysts are also at risk for having Meckel’s diverticulum.
B. Trisomy 21 – **Incorrect.** Patients with Down syndrome (characterized by Trisomy 21) can exhibit multiple syringomas.
C. Nevus sebaceous – **Incorrect.** Syringocystadenoma papilliferum is often associated with nevus sebaceous.
D. Inflammatory bowel disease – **Incorrect.** Patients with inflammatory bowel disease sometimes require resections which are repaired with ostomies.
E. Brooke-Spiegler syndrome – **Incorrect.** This syndrome is associated with numerous trichoepitheliomas, spiradenomas and cylindromas.

**Clinical Features**
The omphalomesenteric (vitelline) duct is a tubular structure which links the mid-gut to the yolk sac during embryogenesis. By around 6 weeks of age, the omphalomesenteric duct is normally incorporated into the umbilical cord and loses its attachment to the mid-gut. However, if either of these processes are incomplete, a range of anomalies can form anywhere along the normal course of the duct from gastrointestinal tract (GI) to the skin at the umbilicus. The spectrum of abnormalities includes Meckel’s diverticulum, umbilical-enteric fistulae, umbilical sinuses, and cysts. These anomalies may or may not have attachments to the GI tract.
The clinical presentation of an omphalomesenteric duct cyst is often that of an umbilical polyp. The clinical differential diagnosis includes an umbilical granuloma and an urachal remnant. Radiologic studies should be considered to exclude communication to the GI tract.

**Histopathologic Features**
- Ectopic gastrointestinal epithelium is seen lining a sinus, cyst, or duct.
- The ectopic epithelium can resemble any aspect of the GI mucosa including colonic tissue with goblet cells and regularly spaced glandular crypts; intestinal tissue with goblet cells, Paneth cells, and lymphoid follicles in the submucosa; or gastric tissue with columnar epithelium, chief cells in tubular glands, mucous neck cells, and parietal cells.

**References**
CASE #61 -- SLIDE #61

**Diagnosis:** Galli-Galli disease

**Case Summary:** A 39 year-old female with a 10-year history of reticulate hyperpigmentation and erythematous hyperkeratotic papules involving the groin, axilla, abdomen, and legs.

**Question**
The best diagnosis is:

A. Multiple seborrheic keratoses – **Incorrect.** Acantholysis is not a feature typically seen in seborrheic keratoses and the clinical presentation does not fit well.

B. Acantholytic acanthoma – **Incorrect.** This typically refers to a solitary lesion, and this patient has multiple lesions. In addition, the epidermis does not display elongate and club-shaped hyperpigmented rete ridges as it does in this case.

C. Darier’s disease – **Incorrect.** Histopathologically, the epidermis does not display elongate and club-shaped hyperpigmented rete ridges as it does in this case.

D. Galli-Galli disease – **Correct.** Both the clinical presentation and the histopathology, which shows elongate and club-shaped hyperpigmented rete ridges along with acantholysis, are classic for this condition.

E. Grover’s disease – **Incorrect.** Clinically, this condition is usually confined to the trunk and, although erythematous papules are a feature, it does not also include reticulate hyperpigmentation. In addition, the epidermis usually does not display well-developed elongate and club-shaped hyperpigmented rete ridges.

**Question**
The most likely associated finding is:

A. *Keratin 5* mutation – **Correct.** Studies have demonstrated that most patients with Galli-Galli disease have mutations in keratin 5.

B. *ATP2A2* mutation – **Incorrect.** This is associated with Darier’s disease.

C. *ATP2C1* mutation – **Incorrect.** This is associated with Hailey-Hailey disease.

D. *Keratin 10* mutation – **Incorrect.** Mutations in this gene are associated with bullous ichthyosis in which the histopathology shows epidermolytic hyperkeratosis.

E. *Keratin 17* mutation – **Incorrect.** Mutations in this gene are associated with Pachyonychia congenita.

**Clinical Features**

Galli-Galli disease is characterized by reticular pigmented macules, most notably in the flexure areas, along with erythematous to hyperpigmented hyperkeratotic papules. Some reports have documented patients with this condition in which the clinical lesions are located on the trunk and lower extremities rather than flexure regions. The age of presentation of reported cases has varied from 15-56 years of age. Although initially described as a unique disease, most authorities now consider Galli-Galli disease to be a variant of Dowling-Degos disease, due to the overlap in clinical presentation and since mutations in keratin 5 have been detected in both conditions.
**Histopathologic Features**
- Elongate and club-shaped hyperpigmented rete ridges.
- Basilar hyperpigmentation.
- Acantholysis within the epidermis, typically suprabasilar, but the split can occur within the upper layers of the epidermis as well.
- Variable underlying infiltrate that typically includes lymphocytes, histiocytes and sometimes eosinophils.

**References**
Diagnosis: Trichodysplasia spinulosa
Case Summary: A 68 year-old woman with a history of follicular lymphoma presented with a 4-6 week history of numerous asymptomatic nasal papules that had progressively increased in size and number.

Question
The best diagnosis is:

A. Phrynoderma – Incorrect. Phrynoderma typically does not affect the face unless it is very advanced. Histopathologically it is associated with hyperkeratosis and keratotic follicular plugging.
B. Follicular spicules associated with multiple myeloma – Incorrect. The patient does not have a known history of multiple myeloma. The histopathology of the spicule would reveal compact, eosinphilic material.
C. Trichodysplasia spinulosa – Correct. The histopathology reveals dilated hair follicles with compact hyperkeratotic and parakeratotic debris with expanded inner root sheath cells and prominent trichohyaline granules.
D. Multiple minute digitate hyperkeratosis – Incorrect. The histopathology reveals a column of hyperkeratosis. This new category of diagnoses incorporates the old terminology for diseases including music box spicules, spiny keratoderma, arsenical keratoses, etc.
E. Keratosis pilaris – Incorrect. The histopathology would reveal a keratin plug in the follicular infundibulum.

Question
This condition is caused by which of the following:

A. Polyomavirus – Correct. Trichodysplasia spinulosa is caused by a polyomavirus infection of an immunocompromised host.
B. Vitamin A deficiency – Incorrect. This finding is associated with phrynoderma. C. Multiple myeloma – Incorrect. This malignancy is associated with follicular spicules.
D. Genetic predisposition – Incorrect. This condition is not known to have a genetic association.
E. Idiopathic – Incorrect. The cause of this condition is well-known; therefore, it is not idiopathic.

Clinical Features
Trichodysplasia spinulosa is a rare eruption of follicular spiny papules that occurs on the central face of immunosuppressed patients. It is caused by infection with a polyomavirus. It is usually asymptomatic and progressive with gradual development of alopecia. Improvement has been reported in patients treated with both systemic and topical antiviral therapy.
**Histopathologic Features**

- Dilated hair follicles without hair shafts.
- Compact keratotic and parakeratotic debris filling the hair follicle.
- Hair follicles with expanded dystrophic inner root sheath cells with very prominent trichohyaline granules.

**References**


Case Summary
A 57 year-old male female presented with a slow growing skin-colored nodule on the left elbow.

Question 1
The best diagnosis is:
A. Dermatofibroma – Incorrect. The lesion is biphasic with areas of increased cellularity and has a wedge-shaped configuration. Dermatofibroma is typically a mid dermal lesion.
B. Desmoplastic melanoma – Incorrect. There is no atypical junctional melanocytic proliferation. There is no patchy inflammatory infiltrate at the periphery. There is minimal cytological atypia in the spindle cell component. Desmoplastic melanoma would not be expected to show biphasic architecture with hypercellular nodules extending into deep reticular dermis.
C. Cellular blue nevus – Correct. The diagnosis is best established by observing wedge-shaped architecture, biphasic cellularity with blue-nevus like spindle cell component in the superficial and mid dermis and cellular nodules in the deep reticular dermis. The cellular nodules show mild cytological pleomorphism and are composed of oval to spindled cells with clear cytoplasm and oval to spindle nuclei with one or two nucleoli and minimal chromatin granularity. Occasional multinucleated wreath-like cells are present. Melanin pigmentation is rather sparse but can be observed at higher magnification.
D. Neurofibroma – Incorrect. Biphasic architecture would be very unusual for neurofibroma. The cells are spindled and slender rather than angulated as would be expected in neurofibroma. Neurofibroma typically involves periadnexal adventitia, whereas this lesion spares it.
E. Leiomyoma – Incorrect. The cytology of the spindle cell proliferation is wrong. The cytoplasm is not pink and the nuclei are not cigar-shaped.

Question 2
Which of immunohistochemical stains results are expected in this lesion?
A. Positive: S100. Negative: Mart1, Hmb45 – Incorrect. Cellular blue nevi are typically positive for all melanocytic markers including Mart1 and Hmb45.
B. Positive: S100, Mart1, Hmb45 – Correct. Cellular blue nevi are typically positive for all melanocytic markers including Mart1 and Hmb45.
C. Positive: desmin. Negative S100, Mart1, Hmb45 – Incorrect. Cellular blue nevi are typically positive for all melanocytic markers including Mart1 and Hmb45.
D. Negative: S100, Mart1, Hmb45 - Variable staining with smooth muscle actin, Factor 13A and CD68 - Incorrect. Cellular blue nevi are typically positive for all melanocytic markers including Mart1 and Hmb45 and are negative for smooth muscle actin, Factor 13A and CD68.
E. Positive: S100, Mart1. Negative: Hmb45 – Incorrect. Cellular blue nevi are typically positive for all melanocytic markers including Mart1 and Hmb45.

Clinical Features
Most cellular blue nevi occur on the scalp and hands and feet. They present as a pigmented nodule. However, hypomelanotic and amelanotic cellular blue nevi can present as skin-colored nodules and a melanocytic lesion may not be suspected clinically.

Histopathologic Features
The sections show a wedge-shaped dermal spindle cell proliferation extending into deep reticular dermis and subcutaneous tissue. The lesion is composed of 2 cell populations embedded in desmoplastic stroma. The superficial portion of the lesion is composed of slender spindle cells
with hyperchromatic nuclei. The second deep dermal and subcutaneous component is composed of nested proliferation of more plump oval to spindled cells with clear cytoplasm and oval to spindle nuclei with one or two nucleoli and minimal chromatin granularity. There is only mild cytological pleomorphism. Mitotic activity is rare but can be usually identified in cellular areas. Cellular blue nevi vary in degree of pigmentation. Some cases can be hypomelanotic or melanin can be entirely absent.

References
4. Weedon D. Skin pathology. 2002; Churchill Livingstone.

CONTRIBUTED BY ARTUR ZEMBOWICZ, MD, PhD
CASE #64 -- SLIDE #64

**Diagnosis:** Nasal glioma (glial heterotopia)

**Case Summary:** A 2 month-old boy presented with a mass on the nasal dorsum.

**Question**
The best diagnosis is:
A. Cutaneous meningioma – **Incorrect.** The biopsy does not show islands and cords of meningothelial cells with associated collagen bundles and psammoma bodies.
B. Cellular neurothekeoma – **Incorrect.** This biopsy lacks cellular fascicles of epithelioid and spindled cells associated with a fibrotic stroma.
C. Nasal glioma (glial heterotopia) – **Correct.** This biopsy shows characteristic features including numerous prominent astrocytes embedded in a neurofibrillary stroma with delicate blood vessels and calcification.
D. Dermoid cyst – **Incorrect.** This biopsy lacks a cyst wall that contains follicles and sebaceous lobules.
E. Nodular amyloidosis – **Incorrect.** This biopsy does not show nodular collection of amorphous waxy material with associated plasma cells.

**Question**
Which of the following stains would help confirm the diagnosis:
A. EMA – **Incorrect.** EMA staining highlights meningothelial cells but not astrocytes. B. GFAP – **Correct.** GFAP staining highlights the ectopic astrocytes that are a diagnostic feature of the nasal glioma.
C. NKI-C3 – **Incorrect.** NKI-C3 staining highlights the constituent cells of the cellular neurothekeoma.
D. Congo Red – **Incorrect.** Congo red staining highlights amyloid deposits which are not present in a nasal glioma.
E. Neurofilament – **Incorrect.** Neurofilament stains highlight nerve fibers. While nerve fibers may sometimes be seen in nasal gliomas they are a minor component.

**Clinical Features**
Nasal gliomas (also known as “nasal glial heterotopias”) typically present in the perinatal period as a mass on the nasal bridge or as a mass in the nasal cavity. Clinically they may cause nasal obstruction. With modern prenatal imaging they can be detected in utero. Imaging studies are necessary in the work up of these lesions to identify any connection to the central nervous system (which is uncommon). Surgical excision is curative.

**Histopathologic Features**
Nasal gliomas show astrocytes embedded in a neurofibrillary stroma. GFAP immunostains may help to identify this astrocytic component. Other features include delicate vasculature, variable inflammatory infiltrates, and calcifications.

**References**
2. Fitzpatrick E, Miller RH. Congenital midline nasal masses: dermoids, gliomas, and

CONTRIBUTED BY THADDEUS W. MULLY, MD
CASE #65 -- SLIDE #65

**Diagnosis:** Tufted angioma

**Case Summary:** The patient is a three year old boy with a lesion on the hand.

**Question**
The best diagnosis is:

A. Pyogenic granuloma – **Incorrect.** This biopsy shows a large subcutaneous vascular proliferation with well formed vascular lobules and fibrous septae. Pyogenic granulomas also have a lobular architecture but are typically smaller, more superficial, and also show a mixed inflammatory infiltrate.

B. Tufted angioma – **Correct.** This biopsy shows a large subcutaneous vascular proliferation with well formed vascular lobules divided by fibrous septae. The lobules are comprised of cellular aggregates of small endothelial cells that form slit like vascular lumina.

C. Kaposi’s sarcoma – **Incorrect.** This biopsy lacks cellular clusters of spindled cells, slit like lumina, eosinophilic globules, and a lymphoplasmacytic infiltrate.

D. Glomeruloid hemangioma – **Incorrect.** This biopsy lacks ectatic vascular spaces that contain aggregates of capillaries that resemble renal glomeruli. There is also no evidence of deposition of proteinaceous hylanine material in the vessels.

E. Hobnail hemangioma – **Incorrect.** This biopsy lacks the biphasic appearance of the hobnail hemangioma which shows dilated vessels centrally lined by plump “hobnail” endothelia. At the periphery of the lesion delicate thin walled vessels are interspersed between collagen bundles. Siderophages are also present.

**Question**
Associated findings might include:

A. Kasabach-Merritt syndrome – **Correct.** Similar to the Kaposiform Hemangioendothelioma, the tufted angioma has been associated with the Kasabach-Merritt syndrome (platelet trapping by the lesion, consumptive coagulopathy, disseminated intravascular coagulation). Some consider these two entities to represent ends of a spectrum.

B. Monoclonal gammopathy – **Incorrect.** Monoclonal gammopathies are a component of the POEMS syndrome (Polyneuropathy, Organomegaly, endrocrinopathy,monoclonal gammopathy, and skin lesions). The glomeruloid hemangioma is found in association with this syndrome.

C. Positivity for Human Herpes virus VIII – **Incorrect.** Positivity for HHV-8 is typical of Kaposi’s sarcoma (as well as Castleman’s disease and primary effusion lymphoma).

D. Numerous siderophages – **Incorrect.** Numerous siderophages may be seen in the hobnail hemangioma (aka Targetoid hemosiderotic hemangioma) and in Kaposi’s sarcoma.

E. A history of prior trauma – **Incorrect.** A history of prior trauma is sometimes elicited in patients with pyogenic granulomas. It is not typically noted in tufted angiomas.
**Clinical Features**
Tufted angiomas typically affect children and young adults. They may involve the trunk, neck, and less commonly the extremities. They are slowly growing and may regress spontaneously. They have been associated with the Kasabach-Merritt syndrome, which is caused by platelet trapping in the lesion, thrombocytopenia, consumption of clotting factors, and sometimes a hemolytic anemia. This process may be fatal.

**Histopathologic Features**
Tufted angiomas are characterized by vascular lobules in the dermis and subcutaneous tissue. These lobules are divided by connective tissue and are comprised of bland endothelial cells and small capillaries. Some of the constituent vessels at the periphery of the cellular lobules may show a “semilunar” appearance.

**References**
CASE #66 -- SLIDE #66

Diagnosis: Botryomycosis

Case Summary: The patient is a 40 year-old man with purpuric patches and ulcerated lesions on the bilateral legs.

Question
The best diagnosis is:

A. Botryomycosis – Correct. This biopsy shows “grape” like clusters of apparent cocci surrounded by a thin rim of eosinophilic material associated with dense neutrophil rich infiltrates.
B. Leishmaniasis – Incorrect. Leishmaniasis shows dense and diffuse infiltrates of parasitized histiocytes associated with mixed inflammatory infiltrate including plasma cells.
C. Histoplasmosis – Incorrect. Histoplasmosis can be confused with Leishmaniasis in that both show dense infiltrates of parasitized histiocytes and mixed inflammatory infiltrates. Neither histoplasmosis nor Leishmaniasis shows histopathologic similarity to botryomycosis.
D. Majocchi’s granuloma – Incorrect. Majocchi’s granuloma shows fungal hyphae within degenerated hair shafts. There is a surrounding dense suppurative and granulomatous infiltrate. Fungal hyphae may also be seen in the overlying cornified layer.
E. Chromomycosis – Incorrect. Chromomycosis is characterized by pigmented fungal forms with an associated suppurative and granulomatous infiltrate.

Question
Which of the following statements about the above condition is true:

A. PAS positivity is common – Incorrect. The layer of eosinophilic material surrounding the clusters of bacteria maybe pas positive (Splendore-Hoeppli effect) but the organisms are not.
B. The condition is mostly seen in otherwise healthy adults – Incorrect. Botryomycosis is more common in individuals with chronic diseases such as diabetes, cystic fibrosis, and HIV disease.
C. The infectious organisms are scant – Incorrect. The disease is characterized by clusters of tightly packed bacterial forms.
D. Trans-epidermal elimination is rare – Incorrect. The clusters of bacteria are often preset within draining sinuses.
E. Appropriate culture study may be necessary for treatment – Correct. The most common bacteria implicated is Staphylococcus aureus, but other bacteria including Gram negative organisms such as Pseudomonas may also cause this condition. Antibiotic treatment necessitates bacterial culture and sensitivity studies.

Clinical Features
Botryomycosis is a chronic bacterial infection, usually of the skin, but sometimes other organ systems such as the lung, liver, kidney, and brain. A history of antecedent trauma is sometimes present in cutaneous lesions and draining sinuses may be seen. Patients usually have impaired immunity secondary to HIV disease, diabetes, or other chronic conditions. The most common
etiological agent is *Staphylococcus aureus*, although other types of bacteria may be identified.

**Histopathologic Features**
Clusters of granular appearing bacteria are seen in the dermis. They have a basophilic appearance and can be surrounded by a thin rim of eosinophilic material, the so-called “Splendore-Hoeppli” effect. This protein rich material is a combination of host antibodies and pathogen antigens. It is PAS positive. It may also be seen in association with fungal and parasitic infections.

**References**
CASE #67 -- SLIDE #67

**Diagnosis:** Bacillary angiomatosis

**Case Summary:** The patient is a 52 year-old renal transplant patient. She was bitten by a kitten. She presents with a 1.5 cm hemorrhagic nodule.

**Question**
The best diagnosis is:

A. Pyogenic granuloma – **Incorrect.** This lesion has some similarities to a pyogenic granuloma which is its most likely stimulant. In this case one notes numerous blood vessels, a dense neutrophilic infiltrate, and clusters of vaguely granular appearing basophilic material which corresponds to colonies of the etiologic bacteria *Bartonella henselae.* Pyogenic granulomas typically do not show a neutrophilic infiltrate which is one clue.

B. Cryptococcosis – **Incorrect.** Cryptococcal infections can show variable histologic features but usually one identifies a suppurative and granulomatous inflammatory infiltrate that contains scattered yeast forms. In the “gelatinous variant” innumerable forms are noted with minimal inflammation. The fungal forms as PAS positive.

C. Bacillary angiomatosis – **Correct.** One notes an ulcerated proliferation of delicate vessels, a neutrophil rich infiltrate, and clusters of granular appearing bacterial colonies.

D. Kaposi’s sarcoma – **Incorrect.** Kaposi’s sarcoma typically shows nodules of spindled cells, slit like vascular spaces, eosinophilic globules, and a lymphoplasmacytic infiltrate.

E. Angiolymphoid hyperplasia with eosinophilia – **Incorrect.** In this condition one notes a proliferation of blood vessels with plump endothelia with an associated infiltrate of lymphocytes and eosinophils.

**Question**
Additional testing that may be helpful to establish the diagnosis:

A. Brown-Brenn stain – **Incorrect.** The causative agent is demonstrable with a Warthin- Starry or Grocott methenamine silver stain.

B. PAS-D stain – **Incorrect.** See above.

C. HHV-8 stain – **Incorrect.** See above. D.

Warthin-Starry stain – **Correct.**

E. Fite stain – **Incorrect.** See above.

**Clinical Features**
Bacillary angiomatosis is caused by the bacteria *Bartonella henselae.* It is typically acquired through a cat scratch or bite. The cat acquires the bacterial infection from fleas and therefore flea control is important in prevention. Patients are immunosuppressed most commonly from HIV infection, but other immunosuppressed patients such as organ transplant recipients may be affected. The disease can be systemic and involve the bones, lymph nodes, brain, liver, and spleen. It can be fatal if untreated.
**Histopathologic Features**

One sees lobular masses of delicate blood vessels in and edematous stroma. Superficial lesions may have a polypoid architecture reminiscent of a pyogenic granuloma. There is an inflammatory infiltrate that contains some neutrophils. Lightly basophilic granular material is scattered throughout and it is this material that represents the bacterial colonies.

**References**


**CONTRIBUTED BY THADDEUS W. MULLY, MD**
CASE #68 -- SLIDE #68

Case Summary
A 72 year-old Caucasian woman with 3 year history of 1 cm slowly enlarging swelling on the left lower eyelid

Question 3
The best diagnosis is:

A. Sebaceous carcinoma – **Incorrect.** There are no sebaceous cells. The lesion does not show bubbly cytoplasm, high-grade atypa, comedo or single cell necrosis which are all typical for ocular sebaceous carcinoma.
B. Endocrine mucin-producing sweat gland carcinoma - **Correct.** This is a cystic, solid and papillary adnexal neoplasm composed of moderately atypical epithelioid cells with bland oval nuclei, abundant bluish cytoplasm showing intra and extraepithelial mucin.
C. Nodular hidradenoma – **Incorrect.** Endocrine mucin producing sweat gland carcinoma is often misdiagnosed as nodular hidradenoma. However, nodular hidradenoma typically shows focal ductal differentiation and its cells are more squamoid and, importantly, lack intracellular and extracellular mucin.
D. Apocrine adenoma – **Incorrect.** There is no apocrine differentiation in this lesion.
E. Papillary eccrine adenoma/adenocarcinoma – **Incorrect.** The site of origin is incorrect since this neoplasm typically affects acral sites and papillary architecture is only focal. Papillary eccrine adenoma/adenocarcinoma does not produce mucin.

Question 4
This tumor is positive for which immunohistochemical stain?

A. Androgen receptor – **Incorrect.** Endocrine mucin-producing sweat gland carcinoma is negative for this marker.
B. CK20 – **Incorrect.** Endocrine mucin-producing sweat gland carcinoma is negative for this marker.
C. Desmin – **Incorrect.** Endocrine mucin-producing sweat gland carcinoma is negative for this marker.
D. Neuroendocrine markers - **Correct.** Endocrine mucin producing sweat gland carcinomas always express at least one neuroendocrine marker such as synaptophysin or chromogranin.
E. TTF-1 – **Incorrect.** Endocrine mucin-producing sweat gland carcinoma is negative for this marker.

Clinical Features
Endocrine mucin-producing sweat gland carcinoma typically presents as a slow growing swelling on the lower or the upper eyelid. Multiple lesions can occur. There appears to be slight female predilection. It is a tumor of older individuals with peak of occurrence in 7-8\textsuperscript{th} decade.

Histopathologic Features
Endocrine mucin-producing sweat gland carcinoma presents as a dermal nodule with solid, cystic, papillary and sometimes clinging architecture. The lesion is composed of moderately atypical epithelioid cells (1.5x size of ductal cells of eccrine ducts). Sometimes, the tumor appears to arise in association with hidrocystoma. The cells have round to oval finely granular nuclei with inconspicuous nucleoli. The cytoplasm is abundant and contains intracytoplasmic mucin.
Extracellular mucin is present. Mucin can be highlighted by mucicarmine stain. Immunohistochemical stains show expression of estrogen and progesterone receptors, membranous expression of EMA (most prominent in luminal cells) and cytokeratin 7. The expression of neuroendocrine markers such as synaptophysin or chromogranin is usually observed but can be focal or absent, especially on a small biopsy. Therefore, the “(neuro)endocrine” in this tumor’s name is a misnomer.

References


CONTRIBUTED BY ARTUR ZEMBOWICZ, MD, PhD
Diagnosis: Coma-type blister

Case Summary: A 70-year-old immunosuppressed woman is 5-years status post renal transplantation and has warfarin-treated atrial fibrillation. She is hospitalized because of symptomatic profound bradycardia, and Dermatology is consulted to evaluate lesions on the chest that were noted the day after placement of a transcutaneous pacer.

Question
The best diagnosis is:
A. Necrotizing vasculitis – Incorrect. This biopsy shows perieccrine and interstitial rather vascular neutrophilic inflammation, and basophilic rather than fibrinoid necrosis of small vessels. In addition, when eccrine structures appear abnormal in biopsies of vasculitis, mainly the ducts are affected, while there is prominent necrosis of eccrine glands in a coma-type blister (CB).
B. Coma-type blister – Correct. The pronounced basophilic necrosis of eccrine glands, plus small vessel necrosis, sloughed epidermis, and mild neutrophilic inflammation are characteristic of CB.
C. Neutrophilic eccrine hidradenitis – Incorrect. Neutrophilic eccrine hidradenitis may exhibit focal sweat gland necrosis, but the dominant feature is brisk neutrophilic inflammation of eccrine glands.
D. Electrical burn – Incorrect. Unless so severe as to produce ulceration, the abnormalities caused by electrical injury usually are confined to epidermis (necrosis with polarization of epidermal nuclei) and superficial dermis.
E. Ecthyma gangrenosum – Incorrect. Often containing organisms visible on H&E- stained sections, echthyma gangrenosum is characterized by ulceration with overlying inflamed crust.

Question
Which of the following histopathologic features is most helpful in diagnosis?
A. Necrosis of vessels – Incorrect. Necrosis of vessels is a minor feature of CB. B. Necrosis of epidermis – Incorrect. Epidermal necrosis is inconstant in CB.
C. Necrosis of eccrine glands – Correct. Basophilic eccrine gland necrosis is the diagnostic feature of CB.
D. Neutrophils – Incorrect. Neutrophilic inflammation alone does not distinguish CB from other disorders in the differential diagnosis.
E. Leukocytoclasia – Incorrect. This is a nonspecific and minor feature.

Clinical Features
Coma-type blister (CB) classically occurs in adult patients with loss of consciousness related to barbiturate overdose or carbon monoxide poisoning but also has been observed in the setting of coma due to other agents, such as opiates and benzodiazepines, or diseases, particularly neurological disorders, and in non-comatose adult or pediatric patients. Initial erythema is soon followed by development of tense blisters, then erosions. Single or multiple lesions usually occur at sites of pressure, within 24-72 hours of drug overdose or other associated factor, and are self-limited.
Histopathologic Features

- Basophilic eccrine gland necrosis.
- Scattered neutrophils.
- Epidermal necrosis.
  - Subepidermal blister or absent epidermis due to sloughing.
  - Extent of epidermal necrosis does not correlate with extent of sweat gland necrosis.
- Necrosis of small vessels.
  - Hemorrhage, thrombosis.

References

Diagnosis: Reactive eccrine syringofibroadenomatosis

Case Summary: An 87 year-old woman with an 8-year history of venous insufficiency and stasis dermatitis presented with a 5-year history of violaceous papules and plaques of the feet and legs.

Question
The best diagnosis is:
A. Fibroepithelioma of Pinkus – Incorrect. At low-magnification, the architecture of eccrine syringofibroadenosis or syringofibroadenomatosis (ESFA) resembles fibroepithelioma of Pinkus (FEP), but the latter has anastomosing cords of basal cell carcinoma, rather than ductal structures, and is embedded on edematous rather than fibrous stroma. In addition, FEP usually is solitary rather than multiple and located on the trunk rather than the distal extremities.
B. Stasis dermatitis – Incorrect. Epidermal hyperplasia and dermal fibrosis may be features of stasis dermatitis but not proliferation of ductal structures.
C. Microcystic adnexal carcinoma (MAC) – Incorrect. MAC is embedded on a sclerotic stroma and may exhibit ductal differentiation, but the neoplasm consists of multiple isolated, rather than anastomosing, nests or strands of squamoid or basloid cells with keratin cysts.
D. Reactive eccrine syringofibroadenomatosis – Correct. The pattern of curled cords or anastomosing thin ductal structures, with connection to hyperplastic epidermis, embedded in a fibrovascular stroma in context with the clinical history of chronic venous insufficiency is characteristic of reactive ESFA.
E. Eccrine carcinoma – Incorrect. Eccrine carcinoma exhibits a deeply infiltrative pattern and atypia of the epithelial cells that line its ductal structures.

Question
These lesions have been associated with:
A. Birt–Hogg–Dubé syndrome (B-H-D) – Incorrect. B-H-D is associated with fibrofolliculomas, not ESFA.
B. Hidrotic ectodermal dysplasia – Correct.
C. Kaposi’s sarcoma – Incorrect. The clinical presentation with violaceous papules of the distal lower extremities may be reminiscent of Kaposi’s sarcoma, but there is no association between the two disorders.
D. Pemphigus vulgaris – Incorrect. ESFA has been reported in association with bullous pemphigoid, not pemphigus.
E. Squamous cell carcinoma (SCC) of lung – Incorrect. ESFA has been reported in association with cutaneous, not pulmonary, SCC.
Clinical Features
Described by Mascaro in 1963 as a neoplasm, ESFA is a rare and distinctive type of fibroepithelial proliferation with eccrine ductal differentiation that may represent a neoplasm, hamartoma, or reactive phenomenon, depending on the setting. Variants of ESFA include: 1) solitary; 2) multiple linear, zosteriform, or diffuse; 3) multiple, in association with hidrotic ectodermal dysplasia (Clouston or Schöpf syndrome); 4) diffuse plantar hyperkeratosis; 5) reactive ESFA in association with non-neoplastic disorders such as pemphigoid, erosive lichen planus, ulcers or venous insufficiency; and 6) reactive ESFA in association with cutaneous melanocytic or nonmelanocytic neoplasms. Patients present with single or multiple often keratotic papules, nodules or plaques, usually involving lower extremities. Except in patients with ectodermal dysplasia, onset of ESFA typically occurs in late adult life.

Histopathologic Features
• Dermal involvement with individual curls or cords of thin anastomosing ductal structures with eccrine differentiation, with connection to overlying epidermis.
• Epithelial lining composed of 1-2 layers of small basophilic cuboidal cells.
• Ductal structures are embedded in a fibrovascular stroma.
• Hyperplastic epidermis.

References

CONTRIBUTED BY MARGOT S. PETERS, MD
CASE #71 -- SLIDE #71

Diagnosis: Poxvirus infection

Case Summary: A 17 year-old female heart transplant recipient presented with several itchy papules on forehead. Has contact with animals, including horses.

Question
Pending additional studies, the most likely diagnosis is:
A. Human papillomavirus infection – Incorrect. The cytoplasmic changes in HPV infection are more basophilic and represent altered keratohyalin granules.
B. Poxvirus infection – Correct. The biopsy shows distinctive cytoplasmic inclusion, but additional diagnostic studies remain necessary for confirmation. C.
Allergic contact dermatitis – Incorrect.
D. Molluscum contagiosum – Incorrect. Characteristic Henderson-Patterson bodies displacing nuclei to one side are not present.
E. Parvovirus B19 infection – Incorrect. In the skin, parvovirus B19 is associated with Fifth disease/ exanthema infectiosum/ slapped cheek syndrome in children.

Question
Electron microscopy will likely demonstrate which one of the following:
A. Well preserved morphology, even out of paraffin embedded (FFPE) tissue – Incorrect. Taking ultrathin electron microscopy sections out of formalin fixed paraffin embedded (FFPE) tissue typically reveals poorly preserved ultrastructure. Primary fixation in gluteraldehyde gives optimal fixation and ultrastructural morphology. There is, however, often sufficient preservation to identify specific features such as viral inclusions in FFPE tissue.
B. Cowdry A intranuclear rhomboidal inclusions – Incorrect. Poxvirus inclusions are cytoplasmic. Cowdry A bodies are seen in Herpesvirus infection.
C. Brick or oval shaped cytoplasmic inclusions – Correct. Poxvirus inclusions are typically this shape ultrastructurally.
D. Tennis racket shaped intracytoplasmic inclusions – Incorrect. Such inclusions are seen in Langerhans cell histiocytosis / histiocytosis X.
E. Intracytoplasmic dense core granules and aggregates of intermediate filaments – Incorrect. These inclusions are seen in neuroendocrine tumors such as Merkel cell carcinoma.

Clinical Features
A range of infectious agents may cause skin lesions in patients receiving immunosuppression for heart transplants. About ten percent of clinically significant infections affect the skin, including by Staphylococcus, Aspergillus and Candida. Among viral diseases, Herpesvirus stomatitis, shingles and cytomegalovirus predominate.

This patient’s lesions show inclusions that most closely resemble those seen in Milker’s nodule or orf. The causative organisms for these conditions are Parapoxviruses. Humans may be infected from sheep or goats (orf) or cows (milker’s nodule). These diseases may be acquired from live infected animals, dead animals, or from contaminated inanimate objects where the virus persists despite heat, cold or desiccation.

Ancillary studies that may be used include electron microscopy examination,
immunohistochemistry and virologic culture. The Center for Disease Control in Atlanta GA is available to assist diagnosing individual clinical lesions. They accept formalin fixed paraffin embedded tissue.

**Histopathologic Features**
- Verrucous hyperplasia.
- Eosinophilic / amphophilic, spinous layer cytoplasmic inclusions.
- Varying degrees of lymphocytic inflammation, including with CD30 positive cells.

**References**
CASE #72 -- SLIDE #72

Diagnosis: Perniosis

Case Summary: A 44 year-old man presented in January with painful itchy papules on the fingers, unresponsive to topical steroids. The patient is a cyclist. Blood workup was negative, including antinuclear antibodies.

Question
The best diagnosis is:

A. Erythema ab igne – Incorrect. This is a reaction to cold, not heat.
B. Discoid lesion of chronic cutaneous lupus erythematosus – Incorrect. Perniosis may be associated with systemic lupus erythematosus or antiphospholipid antibodies. C. Polymorphous light eruption – Incorrect. The histology resembles PMLE, but the clinical is not consistent.
D. Arthropod bite reaction – Incorrect. The clinical history is typical for perniosis and eosinophils are not prominent.
E. Perniosis – Correct. The clinical features and histology are characteristic.

Question
Which of the following is true?

A. Viral etiology is recognized in most patients – Incorrect. HIV and viral hepatitis associations are infrequent.
B. The lesions are never associated with systemic disease – Incorrect. Association with systemic lupus erythematosus is well recognized.
C. Clinical presentation may follow horse riding or other activities where there is cold exposure – Correct.
D. Immunohistochemistry is required for diagnosis – Incorrect. Research studies have demonstrated majority CD3 T-lymphocyte composition of the infiltrate, but this is not indicated for routine diagnosis.
E. The majority of cases have a single genetic abnormality, accompanying the unique clinical appearances – Incorrect. Perniosis may be more common among first degree relatives. There are only rare recognized genetic forms of chilblain associated with lupus erythematosus.

Clinical Features
This is a reaction to cold, and is seen in outdoor activities such as horse riding and other outdoor winter pursuits. Chilblains occur after exposure to air temperatures of 32°F to 60°F for one to five hours. Other cold related injuries include trench foot, frostbite and hypothermia.

Histopathologic Features
- Superficial and deep perivascular lymphocytic infiltrate.
- Subepidermal edema.
- Focal necrotic keratinocytes / interface vacuolar changes.
- Perieccrine distribution of lymphocytes suggested for non-systemic associated cases.
- No increased dermal mucin (versus lupus.)
References

CONTRIBUTED BY MICHAEL G. HITCHOCK, MBChB
CASE #73 -- SLIDE #73

Case summary
A 55 year-old female presented with a 2.5 mm pink-brown papule on her left shoulder. Her history was notable for a prior procedure in the area. The provided clinical differential diagnosis on the pathology requisition sheet was nevus versus pigmented basal cell carcinoma versus melanoma.

Question 9
What is the best diagnosis?

A. Combined melanocytic nevus (banal and blue) – Incorrect. Histologically combined melanocytic nevi show oval and dendritic shaped melanocytes and melanophages admixed with nests of round and oval melanocytes.

B. Desmoplastic melanocytic nevus – Incorrect. Also known as a sclerosing melanocytic nevus, these lesions show dermal sclerosis in the deeper aspect of the nevus.

C. Malignant melanoma with focal spindle cell component – Incorrect. Nuclear atypia of the dermal spindled cells, features that can be seen in desmoplastic and spindle cell melanoma, are not evident.

D. Melanocytic nevus with nerve sheath differentiation – Correct. The slide shows a conventional melanocytic nevus in the superficial dermis. There is focal dermal fibrosis seen consistent with the history of a prior procedure. More strikingly, there is a well circumscribed, but unencapsulated nodule of bland spindled cells in a delicate collagenous background – a finding consistent with nerve sheath differentiation.

E. Persistent / recurrent melanocytic nevus – Incorrect. Although this lesion has focal features of a persistent or recurrent melanocytic nevus consistent with the provided clinical history, the spindled cell proliferation consistent with a perineurioma component is incompatible with a routine recurrent nevus.

Question 10
Which is the combination of immunohistochemical markers that will highlight the spindled cells and be most helpful in confirming the diagnosis?

A. EMA and CD34 expression – Correct. The spindled cells situated more deeply in the dermis generally lack expression of melanocytic markers and express EMA and CD34, the latter in a “fingerprint” pattern.

B. HMB-45 and S-100 – Incorrect. Although the spindled cells in the dermis can express S-100, S-100 is also a marker of melanocytes and thus does not help in confirming the nerve sheath component of this lesion.

C. MART-1/Melan A and HMB-45 – Incorrect. Both MART-1/Melan A and HMB-45 are melanocytic markers and do not stain the nerve sheath component of this lesion.

D. MART-1/Melan A and S-100 – Incorrect. Although the spindled cells in the dermis can express S-100, S-100 is also a marker of melanocytes and thus does not help in confirming the nerve sheath component of this lesion.

E. S-100 and Sox-10 expression – Incorrect. S-100 and Sox-10 are expressed by both melanocytic and neural tumors and would thus not help in the differentiation.

Clinical Features
Melanocytic nevi with nerve sheath differentiation are a unique subset of tumors that display both conventional melanocytic nevus morphology and a distinct spindled cell population enmeshed in a delicate collagenous or myxoid stroma akin to benign nerve sheath tumors.¹² The benign nerve sheath tumors include schwannoma, neurofibroma and perineurioma with hybrid tumors showing overlapping features of each tumor reported in the literature.³ Melanocytic nevi with nerve sheath differentiation are clinically indistinguishable from common melanocytic nevi; the distinction is based on histologic features.

**Histologic features**
Microscopically, melanocytic nevi with nerve sheath differentiation have been divided into three groups: 1. neurotized melanocytic nevi, which are the most common, and argued by some not to truly fit into this category 2. nevi with nerve fascicle-like structures, and 3. melanocytic nevi with palisaded arrangement of melanocytes resembling Verocay bodies.²

The lesion presented falls into the second category where structures closely resembling peripheral nerve fascicles, such as Schwann cells and endoneurial fibrillary collagen, and perineurium-like sheaths, are present in the middle to deep part of the dermis.

**References**
Diagnosis: Relapsing polychondritis

Case Summary: A 46 year-old woman attended a dermatologist with a 6-day history of bilateral, red, swollen ears. She had recently dyed her hair.

Question
The best diagnosis is:
A. Allergic contact dermatitis – Incorrect. The history of a recent hair dye raised the possibility of allergic contact dermatitis but the histopathological correlate of this would be a spongiotic dermatitis which is not present in this case.
B. Cellulitis – Incorrect. Clinically the bilaterality of the condition is against this diagnosis as is the distinct perichondrial distribution of the neutrophilic inflammatory infiltrate.
C. Relapsing polychondritis – Correct. The clinical presentation and the alignment of the neutrophilic inflammatory infiltrate along the perichondrium are characteristic of this condition.
D. Discoid lupus erythematosus – Incorrect. The superficial and deep perivascular and periadnexal lymphocytic infiltrate and associated vacuolar interface dermatitis which characterize discoid lupus erythematosus microscopically are not evident in this case.
E. Acne rosacea – Incorrect. The folliculocentric granulomatous inflammation seen microscopically in acne rosacea is absent in this case.

Question
Which of the following statements is true:
A. The condition is a manifestation of a systemic autoimmune disease – Correct. An autoimmune reaction to cartilage (at various sites) is thought to be responsible for this condition.
B. It is responsive to antibiotics – Incorrect. As is the case for other autoimmune diseases relapsing polychondritis does not respond to antibiotic therapy.
C. It has no serious implications for the patient – Incorrect. Involvement of the trachea and bronchi by this condition is associated with a poor prognosis
D. It is a common condition – Incorrect. This is a rare condition with an estimated annual incidence of 3.5 cases per million in western countries.
E. There is a specific serological marker of this disease – Incorrect. The diagnosis of relapsing polychondritis is made on clinico-pathologic grounds. There is no specific serological marker of the condition.

Clinical History
Relapsing polychondritis, initially reported as “polychondropathia” in 1923, is a rare autoimmune disorder which primarily targets cartilage. The average age of onset is 47 years and there is a slight predilection for females. The most common initial clinical manifestation is erythema, swelling and tenderness of one or both ears due to
involvement of aural cartilage. Fever, arthritis, ocular inflammation, nasal and tracheopulmonary manifestations, cardiac problems and vasculitis also occur. Specific diagnostic criteria for this condition were established by Damiani in 1979. In accordance with its name, repeated relapses occur and the ultimate outcome is variable. Corticosteroids have been shown to reduce the frequency and severity of the relapses but in refractory cases more potent immunosuppressive agents are required. Pulmonary involvement with respiratory compromise calls for stenting of the airways, among other measures, and is associated with a poor prognosis.

**Histopathologic Features**
Early microscopic changes include decreased basophilia of involved cartilage, degeneration of marginal chondrocytes (cytoplasmic vacuolization and nuclear pyknosis) and perichondrial inflammation. The latter is characterized by a neutrophilic infiltrate in the acute stage and lymphohistiocytic inflammation later. In the course of time the cartilaginous matrix is altered and ultimately replaced by fibrous tissue with or without calcification and/or metaplastic bone formation.

**References**

 CONTRIBUTED BY NOREEN M.G. WALSH, MD, FRCP(c), FRCPath
**CASE #75 -- SLIDE #75**

**Diagnosis:** Perifollicular fibroma in Birt-Hogg-Dube Syndrome

**Case Summary:** A 57 year-old woman who has had a 25-year history of skin lesions increasing in number on the face, neck, upper chest, lower back and abdomen. She mentions multiple paternal family members have similar skin lesions, but reports no personal or family history of cancer.

**Question**
The mutated gene is:
A. CYLD – **Incorrect.** Brooke-Spiegler syndrome (multiple familial trichoepithelioma) is an autosomal dominant defect in CYLD.
B. FLCN – **Correct.** Birt-Hogg-Dube syndrome is characterized by multiple fibrofolliculomas/trichodiscomas, and is an autosomal dominant defect in FLCN. This patient had a genetically confirmed defect in the folliculin gene.
C. MSH2 – **Incorrect.** Muir-Torre syndrome is characterized by multiple sebaceous neoplasms and hereditary non-polyposis colorectal cancer, and is an autosomal dominant defect in MSH2, MSH6, PMS2, or MLH1.
D. PTEN – **Incorrect.** Cowden syndrome (multiple hamartoma syndrome) is an autosomal dominant defect in PTEN, and carries an increased risk of neoplasia.
E. TSC – **Incorrect.** Tuberous sclerosis complex is an autosomal dominant multisystem disorder characterized by hamartomas in multiple organ systems, including the brain, skin (angiofibromas), heart, kidneys, and lung. The mutated genes include TSC1 or TSC2.

**Question**
Screening CT scan will most likely demonstrate findings consistent with:
A. Renal angiomyolipoma – **Incorrect.** Renal angiomyolipomas and pulmonary lymphangioleiomyomatosis are characteristic of tuberous sclerosis.
B. Colonic polyposis – **Incorrect.** Cowden syndrome is classified as a hamartomatous polyposis syndrome, however a wide variety of other polyp histologic findings have been described.
C. Lung cysts – **Correct.** Birt-Hogg-Dube syndrome is characterized by a risk for developing spontaneous pneumothorax and renal cell carcinoma. When BHD patients undergo CT scans to screen for pulmonary abnormalities, lung cysts are identified in approximately 89% of patients. Pneumothorax occurs in about 25% of BHD patients, and renal cancer occurs in about 15% of BHD patients. This patient had several scattered pulmonary cysts noted on CT scan.
D. No abnormalities – **Incorrect.** There are no associated internal diseases with Brooke-Spiegler syndrome.
E. Transitional cell carcinoma – **Incorrect.** There is an increased risk of transitional cell carcinoma of the ureter and renal pelvis in Muir-Torre syndrome.

**Clinical Features**
Birt-Hogg-Dube syndrome (BHD) is an autosomal dominant condition that presents with multiple characteristic skin lesions (perifollicular fibromas, fibrofolliculomas, and/or trichodiscomas) and an increased risk for spontaneous pneumothorax and renal tumors. Multiple firm papules begin developing after age 25 years, and are typically distributed on the
face, neck, and trunk. Some lesions may resemble acrochordons. Patients also develop multiple lung cysts, which results in the increased risk for spontaneous pneumothorax throughout adulthood. Early onset, bilateral and multifocal renal tumors with a mixed chromophobe and oncocytic histologic pattern are characteristic of BHD-associated renal cell carcinoma.

**Histopathologic Features**

- Perifollicular fibroma is characterized by a concentric ‘onion skin’ proliferation of fibrous tissue surrounding an otherwise normal hair follicle. The fibrous lesion is accentuated by clefting from the adjacent connective tissue.
- Fibrofolliculomas are characterized by an oval proliferation of spindled cells within a fibromyxoid stroma surrounding a hair follicle, which forms elongated retiform epithelial strands within the dermis.
- Trichodiscomas are elliptical parafollicular lesions with the hair follicle at the periphery of an adjacent dermal fibromyxoid nodular proliferation with admixed thin-walled vessels.
- Both fibrofolliculomas and trichodiscomas are CD34+, supporting that these lesions both develop from the hair follicle mantle, and many now use the combined term fibrofolliculoma / trichodiscoma.
- There is considerable overlap between perifollicular fibroma, fibrofolliculoma, and trichodiscoma; as clinically they are indistinguishable and histopathologic features of each can be seen in the same biopsy specimen or in a different biopsy specimen from the same patient. This patient had 3 biopsies with variable features: one consistent with perifollicular fibroma, one consistent with fibrofolliculoma, and one consistent with trichodiscoma.
- The epithelial strands / mantle diagnostic of fibrofolliculoma may not be seen on initial sections, and step sectioning may reveal this component. Some now consider perifollicular fibroma on the spectrum of fibrofolliculoma / trichodiscoma, as all are hamartomas composed of perifollicular connective tissue and a hair follicular epithelial component. BHD should be considered in patients with multiple lesions demonstrating any of these features.

**References**


**CONTRIBUTED BY MARK A. CAPPEL, MD**
CASE #76 -- SLIDE #76

**Diagnosis:** Sclerotic Fibroma / Storiform Collagenoma (with multinucleate cells) in Cowden syndrome

**Case Summary:** A 60 year-old woman with a chronic history of palmoplantar punctate keratoses presents with a white papule on the upper cutaneous lip, a hyperkeratotic papule on the finger, and a smooth skin-colored dome-shaped papule on the left thigh (see biopsy).

**Question**
Additional pathognomonic criteria to confirm the patient’s diagnosis include:
A. 1 facial trichilemmoma – **Incorrect.** 6 or more facial papules, and 3 or more must be trichilemmomas, is pathognomonic of Cowden syndrome.
B. 6 lipomas – **Incorrect.** Lipomas are one minor criterion; 4 minor criteria are needed for a diagnosis of Cowden syndrome.
C. Acrokeratosis verruciformis – **Incorrect.** This is the acral lesion which occurs in Darier’s disease.
D. Giant cells within this lesion – **Incorrect.** Fibromas with giant cells (so-called Cowden’s fibroma) may be suggestive of Cowden syndrome, but fibromas are only one minor criterion in making the diagnosis.
E. Oral mucosal papillomatosis – **Correct.** Oral mucosal papillomatosis + acral keratoses and/or facial papules is pathognomonic of Cowden syndrome.

**Question**
The most likely associated neoplasm:
A. Breast cancer – **Correct.** In Cowden syndrome, the cumulative lifetime risk for breast cancer is 81% for women.
B. Colorectal cancer – **Incorrect.** In Cowden syndrome, the cumulative lifetime risk for colorectal cancer is 16%.
C. Dysplastic cerebellar gangliocytoma – **Incorrect.** Lhermitte-Duclos disease is pathognomonic of Cowden syndrome, with a cumulative lifetime risk of 32%.
D. Endometrial cancer – **Incorrect.** In Cowden syndrome, the cumulative lifetime risk for endometrial cancer is 19% for women.
E. Thyroid cancer – **Incorrect.** In Cowden syndrome, the cumulative lifetime risk for thyroid cancer is 21%.

**Clinical Features**
Cowden syndrome (CS) is an autosomal dominant disorder characterized by benign hamartomas and in increased risk of breast, thyroid, and other cancers. CS is one of several syndromes associated with mutations in the PTEN gene.
Diagnostic criteria for Cowden syndrome include:
Pathognomonic:
- Lhermitte-Duclos disease (dysplastic cerebellar gangliocytoma.)
- Mucocutaneous features:
  - 6 or more facial papules, 3 or more must be trichilemmomas.
  - Oral mucosal papillomatosis + facial papules and/or acral keratosis.
  - 6 or more palmoplantar keratosis.
Major criteria:
• Breast cancer.
• Thyroid cancer.
• Endometrial cancer.
• Macrocephaly.

Minor criteria:
• Structural thyroid lesions.
• Mental retardation.
• Gastrointestinal hamartomas.
• Fibrocystic breast disease.
• Lipomas.
• Fibromas.
• Genitourinary tumors.
• Genitourinary malformations.

Histopathologic Features
• Well-circumscribed polypoid dermal fibrous proliferation with epidermal collarette.
• Collagen bundles distinctly interweaving in a storiform pattern.
• Numerous small dilated blood vessels within the background of the collagenous stroma.
• Cellular proliferation of stellate fibroblasts and frequent multinucleate cells are noted (which are unique features in this case.)

References

CONTRIBUTED BY MARK A. CAPPEL, MD and LAWRENCE GIBSON, MD
Diagnosis: Lymphogranuloma venereum

Case Summary: A 51 year-old male, HIV+, consulted by swelling of the glans penis and difficulty for retraction of foreskin. He had also lymphadenopathy in both inguinal chains.

Question
The best diagnosis is:
A. Primary syphilis – Incorrect. Primary syphilis usually shows a painless erosion or ulcer on the glans penis and unilateral inguinal lymphadenopathy.
B. Lymphogranuloma venereum – Correct. These are the typical clinical features of lymphogranuloma venereum.
C. Candidiasis balanitis – Incorrect. Candidiasis balanitis shows diffuse erythema of the mucosa of glans penis, sometimes with some scattered pustule. Usually, no inguinal lymphadenopathy is present.
D. Genital herpes simplex – Incorrect. Genital herpes simplex shows grouped vesicles that rapidly erode resulting in painful erosions.
E. Fix drug erythema – Incorrect. Fix drug erythema usually shows a well demarcated area of violaceous erythema, which may evolve to bullous or eroded lesions, but no lymphadenopathy is present.

Question
The characteristic histopathologic features of this disorder are:
A. Superficial perivascular infiltrates of lymphocytes and plasma cells and swelling of endothelial cells – Incorrect. These are the histopathologic features of primary syphilis.
B. Superficial perivascular infiltrates of lymphocytes and plasma cells and more granulomatous infiltrate, composed of epithelioid histiocytes, in deep dermis – Correct. These are the histopathologic features usually seen in early lesions of lymphogranuloma venereum.
C. Neutrophilic spongiosis of the epithelium and mild perivascular superficial lymphocytic infiltrate – Incorrect. These are the histopathologic features of candidiasis involving genital mucosa.
D. Keratinocytes with peripheral clumping of chromatin and homogeneous ground-glass appearance and ballooning of the nucleus – Incorrect. These are the histopathologic features of genital herpes simplex.
E. Vacuolar degeneration of the basal layer with scattered necrotic keratinocytes and sparse lymphocytes intermingled with melanophages in superficial dermis – Incorrect. These are the histopathologic features of fix drug erythema.
Clinical Features

• Etiology: *Chlamydia trachomatis* L1, L2 and L3.
• The only disease by Chlamydias that may have systemic complications:
  o Fever, arthralgia, malaise.
  o Hepatitis/perihepatitis.
  o Meningitis/meningoencephalitis.
  o Arthritis.
• Involvement of the lymph nodes.
• 3 stages:
  o 1º: Painless papule or painless vesicle. More uncommon: slightly painful ulcer or nonspecific urethritis.
  o 2º: Inguinal, rectal or pelvic syndrome.
  o 3º: Elephantiasis, chronic ulcers, fistulae and rectal/urethral/vaginal stenosis.

Histopathologic Features

• Dense infiltrates of lymphocytes and plasma cells involving the full thickness of the dermis.
• Discrete swelling of endothelial cells.
• Aggregations of epithelioid histiocytes.
• By direct immunofluorescence or by immunohistochemistry is possible demonstrate the presence of *Chlamydia trachomatis* within the cytoplasm of the histiocytes.

References


CONTRIBUTED BY LUIS REQUENA, MD
CASE #78 -- SLIDE #78

Diagnosis: Scleredema

Case Summary: A 39 year-old male with a 2-year history of marked skin thickening of the posterior neck.

Question
The best diagnosis is:

A. Follicular mucinosis – Incorrect. In this condition, mucin is present within follicular epithelium and not within the deep dermis, as it is in this case.
B. Focal mucinosis – Incorrect. This condition is characterized by a discrete zone of the superficial dermis containing abundant mucin material rather than an interstitial array of mucin, as is present in this case.
C. Scleromyxedema – Incorrect. This condition is characterized by both an increase in interstitial dermal mucin AND an increase in fibroblasts. There is no increase in fibroblasts in scleredema.
D. Tumid lupus erythematosus – Incorrect. This condition is characterized by a perivascular and periadnexal lymphocytic infiltrate along with an increase in interstitial mucin. Scleredema lacks a concomitant lymphocytic infiltrate.
E. Scleredema – Correct. This biopsy shows the typical histopathology of this entity, including increase in dermal mucin, thickening of the dermis, and no significant increase in dermal cellularity.

Question
The most likely associated finding is:

A. Detection of IgG lambda monoclonal gammopathy in almost all cases – Incorrect. This is associated with scleromyxedema. Scleredema is only rarely associated with an IgG paraproteinemina.
B. Elevated fasting glucose – Correct. Some patients with scleredema have diabetes mellitus.
C. Cutaneous T-cell lymphoma in some cases – Incorrect. This is associated with follicular mucinosis.
D. Graves’ disease – Incorrect. This is associated with pretibial myxedema.
E. HIV disease – Incorrect. This is associated with a localized form of lichen myxedematosus.

Clinical Features
Scleredema typically causes non-pitting induration and hardening of the skin with sites of predilection including the upper trunk (particularly the neck) and the face. Occasionally, the condition can be widespread. Approximately half of the reported cases have occurred in children, although it can present at any age. It can present abruptly often following an infectious process with resolution after the infection (which is typical of the pediatric presentation) or more slowly with a prolonged course. It can also be seen in patients with diabetes mellitus (which is more typical of the adult presentation). There are reports of a few cases that were associated with an IgG paraproteinemia. Rarely, it can be systemic, manifesting as serosal effusions and parotid gland
involvement, among other systems involved.

**Histopathologic Features**
- Thickening of the reticular dermis by swollen collagen fibers.
- Collagen fibers are separated by interstitial mucopolysaccharide.
- Sometimes, the mucopolysaccharide can be difficult to appreciate (special stains can help bring it out), while, in other cases, it can be quite conspicuous (as in this case.)
- Paucicellular.

**References**
CASE #79 -- SLIDE #79

Case Summary
A 9 year old girl presents with a solitary, 2 cm round area of thickened, rough, slightly pink skin of the glabella (duration ~ 2 months).

Question 19
Based on the clinical and histologic features, the most likely diagnosis is:

A. Eosinophilic folliculitis – Incorrect. Eosinophilic folliculitis is characterized by a dense infiltrate of eosinophils involving follicles.
B. Demodex folliculitis – Incorrect. This degree of mucin accumulation is not typical of Demodex folliculitis, and no Demodex were detected in the sections examined.
C. Follicular mucinosis – Correct. In a child with a solitary lesion of the head and neck region, the features in this slide are best interpreted as representing follicular mucinosis.
D. Tick bite – Incorrect. Tick bites have been described inducing a follicular mucinosis-like reaction pattern, however in that instance we would expect to see also see a perivascular nodular infiltrate of lymphocytes, histiocytes, plasma cells, eosinophils, and occasionally giant cells or even germinal centers.
E. Discoid lupus erythematosus – Incorrect. This biopsy shows a lymphocytic infiltrate involving the follicular epithelium, but there is no evidence of epidermal involvement / interface change. In addition, mucin would not be expected in the follicles in lupus.

Question 20
The most likely immunophenotype is:

A. CD2+, CD3+, CD4+, CD5+, CD7+, CD8+ Correct. Normal immunophenotype; most children with follicular mucinosis do NOT have an associated T-cell lymphoproliferative disorder.
B. CD2+, CD3+, CD4+, CD5+, CD7- CD8- Incorrect. This immunophenotype would be expected in mycosis fungoides.
C. CD2+, CD3+, CD4-, CD5+, CD7- CD8- Incorrect. This immunophenotype would also be compatible with a subset of mycosis fungoides.
D. CD2+, CD3-, CD4+, CD5+, CD7- CD8- Incorrect. This immunophenotype would also be compatible with a subset of mycosis fungoides.
E. CD2+, CD3+, CD4-, CD5-, CD7- CD8+ Incorrect. This immunophenotype would be compatible with primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma.

Clinical Features
Alopecia mucinosa (AM) and follicular mucinosis (FM) refer to the same entity: the former describes the clinical manifestation and the latter denotes the classic histopathologic feature. First reported by Pinkus in 1957, it presents most commonly as a focal erythematous, infiltrated scaling plaque on the head and neck, sometimes with follicular prominence. After observing the concomitant development of alopecia mucinosa and mycosis fungoides (MF) in select patients, Braun-Falco classified alopecia mucinosa into two types: a primary or idiopathic type unrelated to...
lymphoma and a secondary type seen in the setting of lymphoma. Primary follicular mucinosis generally occurs in young adults without concomitant cutaneous or extracutaneous disease and often resolves spontaneously within a few years. Non-scarring alopecia is prominent when terminal hair-bearing areas are affected. Less often, in adults, FM persists as a chronic and relapsing disease. The bulk of the literature examining secondary (lymphoma-associated) follicular mucinosis is derived from studies in adults; only a small number of studies have examined the clinical features, histologic features, and outcomes in the pediatric population. Those studies suggest that the majority of children presenting with follicular mucinosis (especially as solitary lesions of the head / neck) do not have concurrent mycosis fungoides nor do they go on to develop lymphoma. Thus the limited data seems to suggest that follicular mucinosis should NOT be regarded unequivocally as early follicular mycosis fungoides in this age group. That being said, published authorities seem to agree that a diagnosis of follicular mucinosis in a child warrants long-term follow-up.

Histologic Features
The histologic picture is characterized by mucin accumulation within the follicular epithelium and sebaceous glands (leading to their distortion and expansion), along with an infiltrate of lymphocytes and eosinophils. In this case the lymphocytes are small and without any appreciable cytologic atypia or nuclear halos. There is considerable infiltration of the follicular epithelium by the inflammatory infiltrate. Not surprisingly, immunohistochemical stains for CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30 showed a mixed inflammatory infiltrate composed of a small number of B-cells but mostly T-cells (without any evidence of an aberrant immunophenotype).

References
CASE #80 -- SLIDE #80

Diagnosis: Sclerosing sweat duct carcinoma

Case Summary: A 22 year-old man presented with a firm lesion of the left cheek.

Question
The best diagnosis is:

A. Desmoplastic trichoepithelioma – Incorrect. This lesion lacks deep infiltration, perineural invasion and ductal differentiation.
B. Morpheaform basal cell carcinoma – Incorrect. Ductal differentiation is uncommon. C. Sclerosing sweat duct carcinoma – Correct. There is a deeply infiltrative and neurotropic tumor composed of small aggregates of epithelial cells demonstrating ductal structures. The tumor cells are surrounded by dense fibrous stroma.
D. Syringoma – Incorrect. There is some histologic overlap but this lesion typically presents as multiple small papules of the face and does not display deep infiltration or perineural invasion.
E. Poorly differentiated squamous cell carcinoma – Incorrect. Ductal differentiation is not observed.

Question
All of the following statements are CORRECT EXCEPT:

A. This tumor is frequently misdiagnosed on initial biopsy – Correct. Common misdiagnoses include basal cell carcinoma, syringoma, squamous cell carcinoma and desmoplastic trichoepithelioma.
B. An association with prior radiation therapy has been described – Correct.
C. Tumor recurrence is common – Correct. Reported rates range from 15-50% of cases.
D. This tumor is locally aggressive but systemic spread is unusual – Correct.
   According to SEER data, recorded metastatic disease and lymph node involvement are rare occurrences (≤1%).
E. This tumor is locally aggressive and systemic spread is common – Incorrect.
   Although locally aggressive, systemic spread of disease is rare.

Clinical Features
Sclerosing sweat duct carcinoma (microcystic adnexal carcinoma) is a rare and locally aggressive adnexal carcinoma that occurs primarily on the head of older adults. However, the age range affected is wide and includes young adults. The tumor typically presents as a slow-growing, firm plaque or nodule on the face measuring up to 2.0 cm. Most patients are asymptomatic but some may experience pain, burning or parathesia due to perineural invasion. Tumor recurrence is common with inadequate excision but systemic spread and tumor-associated mortality are unusual. There are reports of lower recurrence rates following Mohs’ micrographic surgery.
Histopathologic Features

- Poorly circumscribed and deeply infiltrative tumor composed of small-medium sized keratinous cysts, solid nests and strands of epithelial cells (some tadpole-like) displaying ductal differentiation.
- Cytologic atypia and mitoses not prominent.
- Dense fibrous stroma surrounding infiltrative epithelial nests.
- Perineural invasion is common.
- CK positive, EMA positive; EMA and CEA highlight ductal differentiation.

References
CASE #81 -- SLIDE #81

Diagnosis: Benign mixed tumor of the skin

Case Summary: A 41 year-old female presented with a 3 cm lobulated mass in the scalp.

Question
The best diagnosis is:
A. Soft tissue chondroma – Incorrect. Soft tissue chondroma is an intradermal and subcutaneous mass composed of mature hyaline cartilage that lacks evidence of epithelial differentiation.
B. Benign mixed tumor of the skin – Correct. This case is an example of benign mixed tumor of the skin (chondroid syringoma) with extensive cartilaginous metaplasia. At the center and towards the periphery of the lesion, there is evidence of epithelial differentiation with the formation of variably sized nests and glandular formations within myxoid stroma. At the superficial aspect of the lesion there is ossification.
C. Malignant mixed tumor – Incorrect. Malignant mixed tumor (malignant chondroid syringoma) has a predilection for distal extremities (foot > hand) and female patients (2:1). The cytology can be deceptively bland, but the lesion will exhibit infiltrative growth, mitotic activity, poorly formed matrix, and tumor necrosis.
D. Mesenchymal chondrosarcoma – Incorrect. Mesenchymal chondrosarcoma is characterized by sheets of primitive blue cells with islands of mature cartilage.
E. Well differentiated soft tissue chondrosarcoma – Incorrect. At present, there are no reported cases of a well differentiated form of soft tissue chondrosarcoma. Extraskeletal myxoid chondrosarcoma lacks true hyaline cartilage and is actually a tumor of uncertain origin rather than a true “chondrosarcoma”. It is composed of eosinophilic cells arranged in cords and strands within abundant myxoid stroma. It may resemble malignant mixed tumor, but differs in that it lacks epithelial differentiation.

Question
The correct diagnosis can be associated with:
A. Predilection for hands and feet – Incorrect. Soft tissue chondroma and malignant mixed tumor both have a predilection for the hands and feet, while benign mixed tumor of the skin has a predilection for the head and neck region.
B. EWSR1 gene rearrangement – Incorrect. EWSR1 gene rearrangements have been reported in angiomatoid fibrous histiocytoma, extraskeletal myxoid chondrosarcoma, Ewing sarcoma, myxoid liposarcoma, desmoplastic small round cell tumor, myoepithelial tumor of soft tissue, and clear cell sarcoma.
C. Presence of hyaline cells – Correct. Hyaline cells are plasmacytoid appearing cells with abundant ground glass eosinophilic cytoplasm, eccentrically placed nuclei, and a myoepithelial cell immunophenotype. These cells represent one of the three stromal cell types that have been described in benign mixed tumor of the skin (hyaline cells, polyhedral cells, spindle cells).
D. Loss of nuclear INI-1 expression – Incorrect. INI-1 gene inactivation with loss of nuclear INI-1 expression by immunohistochemistry has been reported with epithelioid sarcoma, extrarenal rhabdoid tumor, atypical teratoid tumor, extraskeletal myxoid chondrosarcoma, and epithelioid malignant peripheral nerve sheath tumor.
E. Nuclear expression of SOX-9 – Incorrect. Mesenchymal chondrosarcoma can be
associated with nuclear expression of SOX-9.

**Clinical Features**
Benign mixed tumor of the skin (chondroid syringoma) is an uncommon adnexal neoplasm that commonly arises in the skin of the head and neck region with a reported predilection for middle aged to elderly males. The lesion tends to be slow-growing and asymptomatic. Benign mixed tumor of the skin with extensive chondroid metaplasia has been reported as a 3.1 cm scalp mass in a 29 year old male.

**Histopathologic Features**
- Lobulated non-encapsulated mass involving the dermis and subcutis.
- Epithelial component with tubules and ducts lined by a two cell layer and exhibiting eccrine or apocrine differentiation.
- Stromal cells may be hyaline cells, polyhedral cells, or spindle cells.
- The stroma is variably myxoid or chondroid, and there may be areas of ossification.
- Tumors with extensive hyaline cartilaginous metaplasia can mimic soft tissue chondroma.

**References**

CONTRIBUTED BY KELLY DAKIN HACHÉ, MD, PHD, FRCP(C)
CASE #82 -- SLIDE #82

Diagnosis: Desmoplastic granular cell tumor

Case Summary: The patient is a 55 year-old woman with a “cyst” on the chest.

Question
The best diagnosis is

A. Scar with sarcoidosis – Incorrect. Sarcoidosis typically presents as nodular infiltrates of mono and multinucleated histiocytes. In the setting of scar or trauma these cells may localize around portions of foreign material. They lack granular cytoplasm.

B. Metastatic breast carcinoma – Incorrect. Cutaneous metastasis of breast carcinoma usually manifests itself as thin cords and tubules of malignant cells interspersed between collagen bundles. Sometimes aggregates of tumor cells are noted within dilated lymphatics. The cells lack a granular morphology.

C. Lepromatous leprosy – Incorrect. Lepromatous leprosy shows large aggregates of foamy appearing histiocytes and a few lymphocytes. Large masses of mycobacteria are present within the histiocytes (globi).

D. Leiomyoma – Incorrect. Leiomyomas are comprised of fascicles of bland smooth muscle cells with eosinophilic cytoplasm arranged in a trabecular fashion in the dermis. Rare leiomyomas have a granular cell morphology. Their immunophenotype indicates smooth muscle origin.

E. Desmoplastic granular cell tumor – Correct. In foci this lesion has features of a typical granular cell tumor namely nodular collections of medium sized cells with ample eosinophilic cytoplasm in which numerous fine granules are present. In other areas the tumor infiltrates as small aggregates through a fibrotic stroma.

Question
Useful diagnostic information might include:

A. Positivity for low molecular weight keratin – Incorrect. Granular cell tumors are of neural origin (most likely a Schwann cell precursor) and do not express keratins.

B. S100 protein positivity – Correct. S100 positivity is characteristic. The granules in the lesional cells may also express NK1-C3 and are PAS positive.

C. Elevated ACE levels – Incorrect. This finding is typically seen in active sarcoidosis.

D. Fumarate hydratase mutation – Incorrect. Mutations in fumarate hydratase are seen in patients with a syndrome of multiple cutaneous piloleiomyomas and uterine leiomyomas.

E. A history of trauma – Incorrect. No history of trauma is usually elicited. Traumatic implantation of foreign material including tattoo pigment may elicit sarcoidal reactions.

Clinical Features
Granular cell tumors arise in a wide variety of sites including the skin, oral cavity and visceral organs. They are usually less than 2.0 cm in greatest dimension.
**Histopathologic Features**
Granular cell tumors are comprised of nodules of medium sized cells with rounded nuclei, small nucleoli and ample cytoplasm that contains fine granules. They often have ill defined somewhat infiltrative borders and tumor aggregates can be seen between collagen bundles. Overlying pseudoepitheliomatous hyperplasia may be seen in superficially located lesion. The so-called “desmoplastic” variant has a more infiltrative pattern than usual and is associated with dermal fibrosis.

**References**
CASE #83 -- SLIDE #83

**Diagnosis:** Erythema nodosum

**Case Summary:** A 41 year-old man presented with history of recurrent tender nodules of the anterior legs that resolve without sequelae.

**Question**
The best diagnosis is:

A. Sarcoidosis – **Incorrect**. Subcutaneous lesions of sarcoidosis exhibit predominantly lobular rather than septal involvement with sarcoidal granulomas.

B. Lipodermatosclerosis – **Incorrect**. Lipodermatosclerosis is characterized by lobular fat necrosis with lipomembranous microcysts, fibrosis, and stasis changes in overlying dermis.

C. Erythema nodosum – **Correct**. This mainly septal panniculitis with granulomatous inflammation and widening of fat septae, in context with the clinical history, is typical for erythema nodosum.

D. Pancreatic panniculitis – **Incorrect**. Pancreatic panniculitis is lobular, with necrosis and saponification of lipocytes.

E. Erythema induratum – **Incorrect**. Erythema induratum is a mainly lobular panniculitis with vasculitis, with predilection for the calves rather than anterior legs.

**Question**
The most common site of this disorder is the:

A. Anterior legs – **Correct**. Erythema nodosum most commonly involves the anterior legs.

B. Posterior legs – **Incorrect**. Erythema induratum has predilection for the posterior legs.

C. Upper arms – **Incorrect**. Lupus panniculitis favors the upper arms, as well as thighs and buttocks.

D. Thighs – **Incorrect**. Erythema nodosum uncommonly involves the thighs.

E. Buttocks – **Incorrect**. Lupus panniculitis, alpha-1-antitrypsin panniculitis, traumatic panniculitis, and localized lipoatrophy often involve the buttocks.

**Clinical Features**
The most common type of predominantly septal panniculitis, erythema nodosum (EN) typically presents as tender erythematous nodules or plaques with bilateral involvement of anterior lower legs, usually in young adult women. In contrast with other panniculitides of the lower extremities such as erythema induration, pancreatic panniculitis, and gouty panniculitis, EN does not ulcerate and lesions heal without scarring. Clinical variants include erythema nodosum migrans, subacute nodular migratory panniculitis, and chronic erythema nodosum. EN appears to be a reactive phenomenon attributed to factors that include infections, drugs, and systemic inflammatory disorders. Streptococcal infection is the most common association with EN in children. In adults, EN most often is related to drugs, sarcoidosis, or inflammatory bowel disease.
**Histopathologic Features**

- Mainly septal panniculitis, with inflammation that extends to periseptal fat lobules.
- Early lesions show mainly neutrophils and hemorrhage.
- Mature lesions exhibit predominantly granulomatous inflammation.
  - Miescher’s radial granulomas.
- Widening of septae.
- Limited inflammatory infiltrate in old lesions.

**References**

CASE #84 -- SLIDE #84

Case Summary:
A 78-year-old male presents with 2 weeks of progressive dysphagia as well as oral mucosal ulcers and cutaneous lesions.

Question 23
The best diagnosis is:

A. Pemphigus vulgaris – Incorrect. Necrotic keratinocytes with interface inflammation are not seen in pemphigus vulgaris.
B. Paraneoplastic pemphigus – Correct. The combination of suprabasal acantholysis, necrotic keratinocytes, and interface changes are characteristic of paraneoplastic pemphigus.
C. Toxic epidermal necrolysis – Incorrect. Acantholysis is not observed in biopsies of patients with SJS. Blistering is secondary to full thickness epidermal necrosis causing the epidermis to separate from the underlying dermis. Less inflammation is observed.
D. Erythema multiforme – Incorrect. Acantholysis is not observed in biopsies of patients with EM. Interface vacuolar changes are present.
E. Graft versus host disease – Incorrect. Acantholysis is not observed in biopsies of patients with GVHD. Interface vacuolar changes are present.

Question 24
Which of the following is the most probable association with this patient’s disease?

A. A recent Herpes virus flare – Incorrect. This is an association of erythema multiforme.
B. A medication – Incorrect. Medications may be the inciting event for toxic epidermal necrolysis.
C. Recent bone marrow transplant – Incorrect. This history would be pertinent in graft versus host disease.
D. Non-Hodgkins Lymphoma – Correct. This is the most common category of neoplasia associated with paraneoplastic pemphigus.
E. Breast cancer – Incorrect. Breast cancer is not typically associated with paraneoplastic pemphigus.

Clinical Features
• Pemphigus variant associated with variety of tumors; non-Hodgkin’s lymphoma most frequently associated
  • Other hematopoietic malignancies, Castleman’s disease, Waldenstrom’s macroglobulinemia, thymoma, Hodgkin’s lymphoma, carcinomas, sarcomas
• Previously defined by Sapadin and Anhalt:
  • Painful mucosal erosions and skin eruption
  • Confirmed or occult neoplasm
  • Biopsy demonstrates acantholysis and interface changes
  • Intracellular IgG and complement + linear or granular complement at the DE junction on direct immunofluorescence
  • Circulating antibodies specific for stratified squamous or transitional epithelia on indirect immunofluorescence
• Circulating autoantibodies that immunoprecipitate a complex of proteins with typical molecular weights (250, 230, 210, 190, 170 KD)
• Since modified to include: painful progressive stomatitis, histopathologic changes or acantholysis or interface dermatitis, demonstration of antiplakin antibodies, and demonstration of an underlying lymphoproliferative neoplasm (important to note association with other tumors)
• Any age can be affected but most common in 5th – 8th decades; Male predominance
• Painful, persistent, progressive erosions of the oral mucosa and vermilion border of the lips. Tongue, gingival tissues, floor of mouth, palate, oropharynx, and nasopharynx can all be affected.
  • Patients may also have esophageal, tracheal, and bronchial involvement
  • Latter is a cause of mortality
  • Ocular and genital disease rarely present
• Cutaneous lesions polymorphic:  diffuse erythema, vesiculobullous lesions, papules, scaly plaques, erosions, ulcerations.
  • Erythematous lesions may be macular, urticarial, targetoid, or some combination thereof.
• Poor prognosis with high mortality rate of up to 90%

**Histopathologic Features**

• Admixture of acantholysis (typically suprabasal) and interface change with necrotic keratinocytes (present at all levels of the epidermis)
• Lymphocytic inflammation can be minimal or marked, but some level of inflammation is typically present, even in early lesions.
• Oral mucosa typically demonstrates the most acantholysis but challenging to get an intact or non-ulcerated biopsy.
• Cutaneous lesions may sometimes lack acantholysis demonstrating only interface changes.
• DIF: Uninvolved perilesional skin demonstrates IgG and usually complement in an epidermal intercellular pattern + granular or linear deposition of complement (and sometimes IgG, IgM) at the dermoepidermal junction.
• IDIF: Good screening test using patient’s sera where circulating antibodies bind to cell surface of stratified squamous epithelia. Binding to transitional epithelium (rat bladder) is specific to paraneoplastic pemphigus.
• Antibodies to envoplakin and periplakin are sensitive and specific for paraneoplastic pemphigus.

**References**


CONTRIBUTED BY SOON BAHRAMI, MD
CASE #85 -- SLIDE #85

Diagnosis: Acute Leishmaniasis

Case Summary: A 53-year-old immigrant from Yemen presents with an eroded lesion on the nose. The patient is otherwise healthy. A deep shave biopsy is performed.

Microscopic Features:
- Mixed inflammatory infiltrate in the superficial and deep dermis
- Neutrophils, lymphocytes, histiocytes and plasma cells present
- Epidermis is acanthotic
- Leishmania amastigotes visible within histiocytes
- Leishmania amastigotes highlight with Giemsa stain
- Later lesions show epithelioid cell granulomas with multinucleated giant cells
- Organisms rare in late lesions

Discussion:
Cutaneous leishmaniasis may be classified by organism into “Old World” and “New World” cutaneous leishmaniasis. The cause of “Old World” leishmaniasis includes leishmania major in Central and West Asia and Africa, leishmania tropica in East Africa and the Western Mediterranean and leishmania aethiopica in East Africa. “New World” leishmaniasis may be caused by leishmania Mexicana in Central America and leishmania Braziliensis in South America. Leishmaniasis is a zoonotic disease transmitted to humans from wild and domesticated animals primarily via the Phlebotomus (Sandfly) in “Old World” leishmaniasis and Lutzomyia and Psychodopygus in “New World” leishmaniasis. The clinical spectrum may include localized cutaneous disease as well as disseminated infection. Localized cutaneous disease represents the majority of cases of leishmaniasis. Most cases will heal spontaneously within a year. Disease lasting greater than one year is termed chronic leishmaniasis.

In acute leishmaniasis, the primary inflammatory lesion shows a mixed granulomatous process including histiocytes, lymphocytes, and plasma cells with an acanthotic epidermis. Organisms are usually demonstrable on H&E but may be highlighted with a Giemsa stain. With a chronic progressive course, the infiltrate forms epithelioid granulomas, resembling lupus vulgaris. In these cases, organisms are more rare.

The diagnosis of cutaneous leishmaniasis may be made relatively easily in acute cases and with more difficulty in chronic cases. Direct smear or fine needle aspirates stained with Giemsa stain may be sufficient for diagnosis of acute lesions. For indeterminate cases, culture may be performed on NNN (Novy-Macneal-Nicole) medium. Use of polymerase chain reaction also has been described as highly specific and sensitive for both acute and chronic lesions of cutaneous leishmaniasis.

The differential diagnosis includes tuberculoid leprosy and cutaneous tuberculosis. In both cases, staining with acid fast for identification of mycobacteria would be useful. Rhinoscleroma may show similar mixed granulomas with numerous plasma cells. However, in these cases, large histiocytes (Mikulicz cells) containing large numbers of bacilli may be seen. Both cutaneous leishmaniasis and rhinoscleroma may show plasma cells containing Russell bodies. Deep fungal infections including histoplasmosis, atypical mycobacteria, and tertiary syphilis also may be in the differential diagnosis. These should be differentiated by special stains and/or culture results.
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CONTRIBUTED BY DARIUS MEHREGAN, MD
CASE #86 -- SLIDE #86

Diagnosis: Benign Cephalic Histiocytosis

Case Summary: A 6-month-old girl presented with a single ulcerated nodule on the scalp growing for several months. The child was otherwise healthy and reached normal milestones. There was no evidence of mucosal involvement.

Microscopic Features:
- Superficial and deep infiltrate of histiocytes filling the dermis.
- Thinned epidermis with focal erosion and involvement of the epidermis by histiocytic cells.
- Mixture of histiocytic cells with abundant eosinophilic cytoplasm.
- There are scattered lymphocytes and rare eosinophils.
- Staining for S-100 protein and CD1a were negative.
- The histiocytes stained uniformly positive for CD68.
- Electron microscopy shows comma-shaped intracytoplasmic bodies and absence of Birbeck granules.

Discussion:
Benign cephalic histiocytosis was described in 1971 by Gianotti. Cases of benign cephalic histiocytosis show some overlapping histologic and clinical features with other non-X histiocytoses, including generalized eruptive histiocytosis and juvenile xanthogranuloma. Several authors have noted that these may represent various stages of the same process. Benign cephalic histiocytosis represents a non-Langerhans cell histiocytosis. These cells fail to react with S-100 or Langerhans cell marker CD1a. Cells do express a variety of macrophage markers, including CD68. Electron microscopy confirms the non-Langerhans cell nature of the cells by the absence of Birbeck granules and the presence of comma-like bodies.

Histologic features show a nodular infiltrate filling the upper to upper and lower dermis. The infiltrate often involves the lower portions of the epidermis, which may show atrophy. The infiltrate is composed of histiocytes with foamy to glassy cytoplasm. Touton giant cells are rare. The histologic features overlap with those of generalized eruptive histiocytosis.

Cases of benign cephalic histiocytosis typically are marked by one or few asymptomatic, slightly raised, yellow to reddish-brown lesions located primarily on the face, head, and neck. Lesions also may be seen on the shoulders and arms. In cases of generalized eruptive histiocytosis, larger numbers of lesions are seen in a more generalized distribution. In general, the patients are asymptomatic. There typically is no association with internal organ involvement. Lesions may evolve over years and spontaneously regress.

The differential diagnosis of benign cephalic histiocytosis includes juvenile xanthogranuloma. In early juvenile xanthogranuloma, Touton-type giant cells may be rare. Hashimoto-Pritzker disease (congenital self-healing reticulohistiocytosis) may show clinically similar lesions on newborn to infants. However, these lesions stain with antibodies to S-100. Other cases of Langerhans cell granulomas (Histiocytosis X) also may be differentiated histologically by the presence of staining for S-100 and CD1a.
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30.

CONTRIBUTED BY DARIUS MEHREGAN, MD
**CASE #87 -- SLIDE #87**

**Diagnosis:** Pleomorphic Hyalinizing Angiectatic Tumor

**Case Summary:** A 60-year-old woman presents with a nodule on the top of the right foot. The lesion has been slowly growing for several years. The patient presents to her podiatrist because of increasing pain in the lesion. Upon excision, the lesion appears to “shell out”.

**Microscopic Features:**
- Proliferation of blood vessels and spindle cells.
- The blood vessels are surrounded by eosinophilic hyalinized collagen.
- There is extensive hemorrhage and hemosiderin deposition.
- Between the hyalinized vessels is a proliferation of spindle cells with rare mitotic figures.
- The spindle cells form intersecting bundles.
- There is a sparse inflammatory cell infiltrate within the stroma.
- The spindle cells show some evidence of nuclear pleomorphism.
- Intranuclear cytoplasmic inclusions may be seen.
- Immunohistochemistry shows the spindle cells to express vimentin and CD34.
- The spindle cells fail to stain with antibodies to S-100 protein, desmin, cytokeratin, Factor VIII or CD31.

**Discussion:**
The pleomorphic hyalinizing angiectatic tumors are relatively rare neoplasms originally described by Smith, et al. The lesion typically arises in adults as a slow growing subcutaneous mass. Because of the hemorrhage within the lesion, the PHAT may be mistaken for a vascular tumor. Lesions may range in size from 2cm to 8cm. Grossly, the lesions may be lobulated or somewhat circumscribed but not encapsulated.

Microscopically, the lesions are marked by their presence of ectatic blood vessels ranging in size and surrounded by a thick rim of hyalinized eosinophilic material and laminated collagen. Between the blood vessels is a proliferation of spindle cells in short fascicles. The spindle cells show some evidence of nuclear pleomorphism and may show intranuclear inclusions; however, mitotic figures are rare. The surrounding stroma contains a variably inflammatory infiltrate including lymphocytes, plasma cells, and numerous hemosiderophages.

The PHAT is believed to be benign. Metastases have not been documented; however, local recurrence is not unusual. Wide local excision is recommended whenever possible.

The differential diagnosis includes vascular neoplasms, such as Kaposi’s sarcoma or spindle cell neoplasms such as Schwannoma and malignant fibrous histiocytoma. Immunohistochemical staining helps with the differential diagnosis. The lack of staining for Human Herpes Virus 8 rules out the possibility of Kaposi’s sarcoma. The Schwannoma may be ruled out by the lack of staining for S-100 protein. The presence of extensive hyalinization along with the relative lack of mitotic activity helps to rule out the possibility of a malignancy fibrous histiocytoma.
References:

**CONTRIBUTED BY DARIUS MEHREGAN, MD**
Diagnosis: Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma

Case Summary
A 66-year-old woman presented with a 4-week history of multiple ulcerative lesions involving trunk, proximal extremities, face and vulva.

Question
The best diagnosis is:
A. Lymphomatoid papulosis (LYP) – Incorrect. The clinical presentation of multiple necrotic lesions and atypical lymphoid infiltrate may suggest LYP, but the nonremitting course, and diffuse epidermal infiltration of atypical lymphocytes rule out LYP.
B. Mycosis fungoides (MF) – Incorrect. The histopathological features could be compatible with MF, but the rapid onset of multiple ulcerative lesions is atypical.
C. Pagetoid reticulosis – Incorrect. Although prominent epidermotropism is a characteristic feature of pagetoid reticulosis, this entity is defined as a solitary clinical lesion.
D. Pityriasis lichenoides et varioliformis acuta (PLEVA) – Incorrect. The acute onset and interface lymphoid infiltrate bring PLEVA into the differential diagnosis, but the extent of disease and epidermotropism of atypical lymphocytes are incompatible with this diagnosis.
E. Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (AECTCL) – Correct. The rapid onset of multiple ulcerative lesions and histopathology of a prominently epidermotropic atypical lymphoid infiltrate favors this diagnosis, even without knowledge of the immunophenotype.

Question
This characteristic immunophenotype is:
A. CD3+ CD4+ CD8- CD30- - Incorrect. This profile favors mycosis fungoides.
B. CD3+ CD4- CD8+ CD30- - Correct. This pattern is typical of AECTCL.
C. CD3+ CD4- CD8- CD30- - Incorrect. Dual loss of CD4 and CD8 expression is observed in a subset of mycosis fungoides.
D. CD3- CD4+ CD8+ CD30+ - Incorrect. Loss of CD3 with expression CD4 and CD30 are not features of AECTCL.
E. CD3- CD4- CD8+ CD30+ - Incorrect. AECTCL typically is CD3+ and CD30-.

Clinical Features
- Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (Berti lymphoma) is a rare neoplasm in the category of peripheral T-cell lymphomas
- Rapid wide-spread development of multiple ulcerative or erosive plaques and nodules
  - Mucosal and internal organ involvement
- 5th – 7th decade of life, more common in men
- “Aggressive” reflects the fulminant onset and poor prognosis
  - Median survival < 3 years, 5-year survival < 20%
Histopathological Features

- Lymphocytic infiltrate
  - Small-medium/medium-large pleomorphic T-lymphocytes
  - Prominent epidermotropism of single and clustered lymphocytes or diffuse involvement of epidermis
  - Superficial band-like infiltrate (pattern of interface dermatitis) associated with deep dermal and sometimes subcutaneous lymphocytic infiltration, with occasional angiocentricity
- Necrotic keratinocytes
- Epidermal necrosis, erosion or ulceration, hemorrhage
- Cytotoxic T-cell immunophenotype
  - CD3+ CD45RA+ CD8+ TIA-1+ beta F1+
  - CD2- CD5- CD45RO- CD4- CD30-

References

Diagnosis: Aggressive Digital Papillary Adenocarcinoma

Case Summary: A 44 year old man attended a physician because of a nodule on his right thumb. The clinical suspicion was of an abscess. In the course of surgical intervention the lesion seemed solid and a biopsy was obtained.

Histopathology:
- glandular tumour with solid and cystic components in variable proportions.
- solid areas characterized by closely aggregated tubular structures, lined by cuboidal or columnar epithelium, often containing eosinophilic luminal secretions
- cystic components usually exhibit papillations, lined by apocrine-type epithelium
- cytology can be bland (‘low grade’) or markedly atypical (‘high grade’)
- necrosis en masse sometimes evident.

Discussion:
The entity known as aggressive digital papillary adenocarcinoma (ADPA) was first described by Helwig in 1979. Almost a decade later, investigators at the AFIP, having studied a series of such lesions, concluded that they fell into two groups, a ‘low grade’ variant thought to represent adenomas and a ‘high grade’ variant regarded as adenocarcinomas. Over time, it became clear that, irrespective of the histopathological grade, the tumours proved capable of metastasis and now they are all deemed to be adenocarcinomas. The lesions occur almost invariably on the volar surfaces of the digits, mainly in males in the 6th decade. Local recurrence and metastases (nodal and systemic) can occur and death has ensued in a minority of patients. An aggressive surgical approach to treatment is warranted and sentinel lymph node (SLN) excision is sometimes used in search of regional metastases. While the ‘high grade’ variant of the tumour can simulate other adnexal carcinomas or even a metastatic papillary carcinoma, the most treacherous diagnostic pitfall lies in mistaking the ‘low grade’ variant for an adenoma. The tumour in our patient was completely excised and the SLN was benign. Regardless, he developed bilateral pulmonary metastases 4 years after his initial presentation.

References:


CONTRIBUTED BY NOREEN M.G. WALSH, MD, FRCP(c), FRCPath
CASE #90 -- SLIDE #90

Diagnosis: PUSTULAR MYCOSIS FUNGOIDES

Case Summary: A 72 year old man with known prostate cancer and aortic valve disease was seen by a dermatologist because of an acute, generalized, pustular, cutaneous eruption. The clinical differential diagnosis included pustular psoriasis, a pustular drug eruption and a paraneoplastic phenomenon. Successive skin biopsies were obtained.

Histopathology:

Early
- subcorneal pustules
- superficial perivascular lymphocytic infiltrate

Late
- subcorneal pustules
- lichenoid lymphocytic infiltrate with atypical lymphocytes
- epidermotropism

Discussion:
The pustular variant of mycosis fungoides (MF) is a rare manifestation of the disease. It can be palmoplantar or generalized in distribution. Not uncommonly, the pustular morphology, clinically and microscopically, masks the underlying lymphoma. Information in the literature about this variant of MF is limited. Of interest, the course of the case presented here parallels that of the patient described by Ackerman AB et al in 1966. In both instances the disease was pustular from the outset and resistant to different modalities of therapy. The diagnosis could not be established clinically or histopathologically in its early stage but it declared itself unequivocally after 2 to 3 years. In the case described by Ackerman a remission was achieved following electron beam therapy. Our patient died. The exact histogenesis of pustular MF is not known but there is evidence in the literature that the neoplastic T-cells can secrete IL-17 and may participate in the recruitment of neutrophils to the site by a paracrine mechanism involving keratinocyte release of IL-8. While pustules may occur in cases of follicular MF due to a secondary acneiform process this should be distinguished from the true pustular variant of the disease.

References:

CONTRIBUTED BY NOREEN M.G. WALSH, MD, FRCP(c), FRCPath
In this patient, who is +45 days following allogeneic stem cell transplantation for acute myeloid leukemia, the most likely diagnosis is:

A. Dermatomyositis  
B. Acute graft-versus-host disease  
C. Erythema multiforme  
D. Leukemia cutis  
E. Lupus erythematosus

Answer: Acute graft-versus-host disease.

Acute graft-versus-host disease (GVHD), a common complication of stem cell transplantation, most often affects the skin, liver, and gastrointestinal system. Patients may develop a morbilliform eruption that can affect the acral surfaces. In severe cases, extensive mucocutaneous desquamation may occur and may be associated with increased mortality.

Accurate diagnosis of cGVHD has major implications for patient care, since treatment of clinically significant disease generally requires escalation of immunosuppressive therapies. It can be difficult to diagnose acute GVHD on the basis of histopathologic features alone, since the changes may be non-specific. Microscopic features favoring aGVHD include vacuolar interface inflammation (including around the hair follicles), scattered dyskeratotic keratinocytes, satellite cell necrosis, lack of spongiosis, and lack of eosinophils.

Treatment is optional in mild cases. In symptomatic cases, topical corticosteroids or phototherapy may suffice. Escalation of systemic immunosuppression may be required in severe cases.

References:

CONTRIBUTED BY ROGER WEENIG, MD AND JULIA LEHMAN, MD
CASE #92 -- SLIDE #92

Diagnosis: Ebv-Related Hydroa Vacciniforme-Like Lymphoproliferative Disorder

Case Summary: A 27 year-old man was seen for extensive ulcerative lesions of the face and sun-exposed areas

Histopathology:
- Marked epidermal spongiosis
- Follicular infundibular spongiotic change
- Papillary dermal edema
- Perivascular and periappendageal lymphocytic inflammation

Discussion:
This patient has skin lesions that at least to initial evaluation appeared to be related to sun exposed skin or were found to be more concentrated in these areas. Various clinical disorders were considered including photosensitive eruptions, lymphomatoid papulosis or pityriasis lichenoides and hydroa vacciniforme. His first lesion was actually thought to have arisen from an area of a mosquito bite, raising the question of exaggerated insect bite reaction or infection. His past history is important in that he was documented to have mononucleosis about 6 years prior to the skin eruption and afterwards had lingering abnormalities of liver function and white blood cell count suppression. Episodic pancytopenia has been documented in the years since. From 2006, onward, he has had intermittent bouts of significant skin lesions with ulceration, fever, malaise and lymphadenopathy.

The key to the diagnosis is clinical correlation with the microscopic findings. Although the patient has lesions in sun exposed areas, it does not appear sun exposure is necessarily the stimulus for new lesion eruption and lesions actually develop in other areas of the skin not exposed to the sun. Hypersensitivity to mosquito bites (HMB) may have been operative in this case. Failure to clear the EBV infection prompted additional serum and tissue studies which confirm the ongoing presence of EBV and likely explain the ulcerative nature of the skin lesions. Given all the facts in this case, Hydroa vacciniforme would be extremely uncommon in this patient and so the best diagnosis is EBV-related lymphoproliferative disorder. Although sensitivity to UV light may be seen, this group of “EBV-related skin lesion” patients also often has systemic symptoms and experience fever, lymphadenopathy, splenomegaly and weight loss. HMB may also be part of the clinical picture. EBV can often be detected in the actual skin lesions. The clinical course in these patients varies from one of improvement to more commonly continued recurrences and at times progression to overt lymphoma. It has been suggested that the prognosis may be related in a quantitative way to the percentage of EBV-infected lymphocytes seen in the skin biopsies.

References:

CONTRIBUTED BY LAWRENCE E. GIBSON, MD
CASE #93 -- SLIDE #93

Diagnosis: Necrobiotic Xanthogranuloma

Case Summary: A 58 year-old woman with a 2 year history of indurated, xanthomatous lesions on the legs and thighs

Histopathology:
- Dense and diffuse granulomatous infiltrate
- Layers of necrosis
- Lymphocytic and plasmacytic inflammation
- Multiple giant cells, many with “polarized” appearance
- Cholesterol clefts

Discussion:
This patient presented with cutaneous findings first on the legs and then thighs. She had a history of gestational diabetes with her only pregnancy. Given the gender and age, necrobiotic lipoidica (NL) was a reasonable initial clinical and pathologic correlation. Periocular lesions developed later in the course of her disease, making the clinical/pathologic correlation more likely to represent necrobiotic xanthogranuloma (NXG).

NXG was first considered a rare variant of NL associated with paraproteinemia but later after the collection of several cases, NXG was coined to encompass a special clinical picture of xanthomatous yet destructive skin lesions together with the special variation in the NL-like pathology demonstrated in this case. NXG commonly involves the face or orbital area and can lead to significant ocular morbidity or even blindness in severe cases.

Paraproteinemia is most often present but not often evolving to myeloma. Internal organs can also be affected by this process.

The presence of lymphocytes and plasma cells together with paraproteinemia raised the possibility that this disease is actually a manifestation of a monoclonal B-cell process in the skin. Recent studies have been unable to confirm this theory. Currently, this process is considered a reactive one with close ties to lymphocytic and plasmacytic inflammation. Microscopically, the extensive necrosis combined with the unusual giant cells and plasmacytic inflammation separates this entity from NL or other palisaded granulomatous disorders. Cholesterol clefts are also more commonly seen in NXG than NL but are not entirely specific.

References:

CONTRIBUTED BY LAWRENCE E. GIBSON, MD
Diagnosis: Subcutaneous panniculitis like T cell lymphoma

First described in 2005, subcutaneous panniculitis-like T cell lymphoma (SPTCL) is a rare lymphoma, representing < 1% of primary cutaneous lymphomas (Huppman, Deonizio). The median age at onset is 36 years, and children represent approximately 20% of cases (Willemze, Deonizio). Clinically, patients exhibit multiple, indurated asymptomatic nodules and plaques (Willemze), mainly involving the lower extremities (Willemze). Half of patients report constitutional symptoms or laboratory abnormalities such as cytopenias or elevated liver function tests (Deonizio). Systemic involvement is rare (Deonizio). An association of SPTCL with autoimmune diseases such as lupus erythematosus, rheumatoid arthritis and Sjögren syndrome, in up to 20% of patients, further complicates differential diagnosis with lupus panniculitis (Deonizio, Willemze).

SPTCL is considered in the differential diagnosis of lobular lymphocytic panniculitis. However, as in the present case, the lymphocytes exhibit nuclear pleomorphism. Lymphocyte rimming of adipocytes is characteristic of but not specific for SPTCL. Variable fat necrosis and karyorrhexis are additional features (Willemze). The CD4-/CD8+/CD56-/alpha-beta phenotype and above histopathologic features define the WHO-classified entity SPTCL, which is associated with a favorable prognosis. In contrast, subcutaneous gamma/delta T-cell lymphoma, provisionally classified as a rare type of peripheral T-cell lymphoma, exhibits dermal (and sometimes epidermal) involvement, CD4-/CD8-/CD56+ phenotype, and a poor prognosis.

Lupus panniculitis is the entity most often cited in differential diagnosis with SPTCL. Helpful distinguishing features of lupus panniculitis include lymphoid nodules with reactive germinal centers, clusters of B-cells, a mixed infiltrate including plasma cells, as well as epidermal-dermal interface features of lupus erythematosus in some cases.

Standard treatment of SPTCL currently consists of doxorubicin-based multi-agent chemotherapy, typically CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) (Willemze). Sometimes alemtuzumab is added to this regimen (Willemze). F-18 FDG PET/CT is recommended to assess disease activity and response to treatment in SPTCL.

References
CASE #95 -- SLIDE #95

Diagnosis: Lymphomatoid papulosis

Lymphomatoid papulosis is a CD30-positive T-cell lymphoproliferative disorder of the skin (WHO-EORTC classification) with generally relapsing but self-remitting course.

Clinical features:
- Presents most often in the middle aged, although young adults and children may be affected
- Male predilection
- Recurrent crops of erythematous to violet-colored, small (2 to 3 mm to up to 2 to 3 cm) papulonodules
- Individual lesions are self-limiting and often heal with scarring
- Ulceration not uncommon
- Trunk and extremities are typically affected

Prognosis and treatment:
- Generally remitting and relapsing course involving only skin and often lasting many years
- May be treated with topical corticosteroids, tetracycline, methotrexate, photochemotherapy (PUVA)
- Small risk of developing anaplastic large cell lymphoma in lesions that become large, persistent
- Small association with mycosis fungoides and Hodgkin’s lymphoma

Pathology:
- Three histological patterns recognized:
  - Type A (most common): wedge-shaped mixed infiltrate containing large anaplastic CD30-positive lymphoid cells with irregular vesicular nuclei containing prominent eosinophilic nucleoli set amidst smaller lymphocytes, histiocytes, neutrophils, and scattered eosinophils. Mitoses are often conspicuous and may be abnormal. Epidermal necrosis and ulceration are commonly present. Necrotizing vasculitis is very rare.
  - Type B: pleomorphic lymphocytes with cerebriform nuclei and resembling atypical lymphocytes of mycosis fungoides in a band-like pattern. Epidermotropism is variably present. Pautrier’s microabscesses, perinuclear halos, basal layer alignment of lymphocytes not a feature.
  - Type C: resembles anaplastic large cell lymphoma, lacks mixed infiltrate of type A, dermal epicenter. Overlapping patterns in same specimen or same patient in up to 10% of cases.

Immunopathology/special stains:
- CD30-positive atypical lymphoid cells are hallmark; however, number of CD30-positive cells in type B may be small
- CD15-negative
- Involved lymphoid population typically CD3-positive, CD4-positive T cells
- ALK-1 negative
- Rare CD4-negative/CD8-positive and CD4/CD8- negative variants
- Monoclonal TCR gene rearrangement in up to 2/3 of cases.

CONTRIBUTED BY ANTONIO SUBTIL, MD, MBA
CASE #96 -- SLIDE #96

Case Summary:
A 14-year-old female presents with a hemorrhagic papule that has been present for one month on the left thigh. The lesion has been traumatized during shaving.

Question 27
The best diagnosis is:

A. Spitz nevus – Incorrect. The lesion is large, not well circumscribed, lacks Kamino bodies, lacks maturation, and demonstrates deep mitoses, which are features of malignancy.

B. Spitz nevus with atypia secondary to irritation/trauma – Incorrect. Though trauma can impart atypia in melanocytic lesions but is characteristically seen in the superficial portions of the lesion, there still should be evidence of maturation and deep mitoses should not be present.

C. Desmoplastic Spitz nevus – Incorrect. Desmoplastic Spitz nevus rarely has a junctional component or when present it is minimal. Almost entirely dermal tumor composed of single epithelioid, spindle, or round melanocytes that mature with depth. Mitoses are absent. Extremely dense stroma that often isolates individual nevus cells.

D. Spitzoid melanoma – Correct. The combination of nuclear pleomorphism, lack of maturation with descent, and deep mitotic figures are consistent with Spitzoid melanoma.

E. Nevus associated with BAP-1 loss – Incorrect. While these nevi can demonstrate epithelioid cytomorphology, they are typically mostly dermal and mitotic figures are inconspicuous. May demonstrate a “halo” type reaction with lymphocytes. Sometimes combined type with an adjacent benign nevic component. Sporadic solitary lesions are felt to have benign behavior. Individuals with multiple lesions may harbor a germline mutation that predisposes to uveal and cutaneous melanoma as well as visceral tumors (mesothelioma, clear cell renal carcinoma). Immunohistochemistry evaluating for BAP-1 loss is useful and the majority of lesions also harbor a BRAF mutation.

Question 28
Which immunophenotypical feature or genetic alteration is expected in this lesion?

A. BAP-1 loss – Incorrect. Loss of BAP-1 expression is characteristic of nevus associated with BAP-1 loss.

B. HRAS mutation – Incorrect. A subset of desmoplastic Spitz nevi have been shown to harbor an HRAS mutation.

C. Decreased nuclear immunoreactivity for p16 – Correct. Spitz nevi typically retain p16 expression throughout the entire lesion whereas spitzoid melanomas demonstrate decreased reactivity, especially in the deeper portions of the lesion.

D. MIB-1 expression < 5 percent – Incorrect. MIB-1 is a proliferation marker and a low rate is more indicative of benignity.

E. Diminution of Cyclin D1 expression with depth of lesion – Incorrect. This feature is expected with Spitz nevi, whereas spitzoid melanomas demonstrate overexpression throughout the tumor.

Clinical Features
- May occur in children but more common in adults. Be cautious in the diagnosis of conventional Spitz nevus in individuals greater than 40 years of age.
• In pediatric populations, spitzoid melanoma most commonly presents on the extremities, followed by the trunk. Seen equally in male and female patients in the pediatric population. More common in females in the adult population.

• Nodules that are often 1 cm or more. May arise with rapid evolution or exhibit change in shape, size, and color. May be amelanotic. Patients often report tenderness or frank pain.

• Clinically may be mistaken for a vascular lesion (hemangioma, pyogenic granuloma).

Histopathologic Features
• Epidermis may be uneven or demonstrate regions of atrophy (as opposed to Spitz nevi which may have epitheliomatous hyperplasia.

• Poor circumscription in junctional component; irregular shaped and unevenly distributed nests, single melanocytes at periphery.

• Pagetoid spread lateral to the central portion of the lesion; lack of cohesion and sometimes consumption of the epidermis.

• Invasive component with incomplete or absent maturation.

• Mitotic figures, especially in the deep aspects of the tumor and/or demonstrating atypical forms.

• Comparative genomic hybridization may be useful in especially difficult cases or those classified as “atypical Spitz tumor”. Spitz nevi rarely show abnormalities, though rare gains in 11p have been found in some cases. Melanoma often demonstrates multiple aberrations, both gains and losses.

Histopathological differences between Spitz nevus and spitzoid melanoma (ref 1)

<table>
<thead>
<tr>
<th></th>
<th>SPITZ NEVUS</th>
<th>SPITZOID MELANOMA</th>
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<tbody>
<tr>
<td>Size</td>
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</tr>
<tr>
<td>Ulceration</td>
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<td>Yes</td>
</tr>
<tr>
<td>Symmetry</td>
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<td>No</td>
</tr>
<tr>
<td>Depth of infiltration</td>
<td>Superficial dermis</td>
<td>Deep dermis</td>
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<tr>
<td>Cell density</td>
<td>Low</td>
<td>High</td>
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<td>Mild</td>
<td>Marked</td>
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<tr>
<td>Mitoses</td>
<td>Absent or few</td>
<td>Superficial</td>
</tr>
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<td></td>
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<td>Maturation</td>
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<td>No</td>
</tr>
<tr>
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<td>Junctional nests- epidermis</td>
<td>Subepidermal</td>
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<td>Pushing</td>
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<td>Pagetoid spread</td>
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<td>Nuclear:cytoplasmic ratio</td>
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<tr>
<td>Eosinophilic nucleoli</td>
<td>Scant, superficial</td>
<td>Many, deep</td>
</tr>
</tbody>
</table>
Cytoplasm | Eosinophilic, homogenous | Vacuolated, irregular

References

CONTRIBUTED BY SOON BAHRAMI, MD
CASE #97—SLIDE #97

**Diagnosis:** Silicone granuloma

Granulomatous inflammation directed to exogenous (foreign) material or endogenous material normally not present free in the dermis.

**Clinical features:**
- Any age, race, and gender may be affected
- Causative material includes:
  - Endogenous: Hair shaft, Oxalate crystals, Keratin, Calcium Cyst contents
  - Exogenous: Wood, Zirconium, Starch, Beryllium, Silica, Aluminum, Talc, Arthropod parts, Suture, Silicone, Hyaluronic acid, Bovine collagen, etc.
    - Beryllium was associated with fluorescent light manufacturing
    - Zirconium was present in antiperspirants
    - Silica exposure from sand, soil, glass, rocks.

**Presentation:**
- Variable clinical features: erythematous to violaceous papules or plaques, may ulcerate, variable scale
- Direct inoculation of beryllium into skin results in cutaneous disease
- Inhalation of beryllium results in pulmonary disease

**Pathology:**
- Intradermal foreign-body giant cell reaction
- Giant cells may include foreign-body, Langhans’, and touton types
- Sarcoidal granulomata: silica, zirconium, beryllium
- Esthetic microimplants:
  - Hyaluronic acid (e.g., Restylane): pools of basophilic mucin surrounded by giant cells and eosinophils
  - Collagen (e.g., Artecoll): granulomatous infiltrate surrounding cystic spaces containing translucent foreign bodies
- Polarizability:
  - Birefringent: Wood, Starch, Silica, Talc, Suture, Sea urchin spine
  - Nonbirefringent: Zirconium, Beryllium, Hair shaft, Keratin, Tattoo pigment (including dental amalgam, carbon)

CONTRIBUTED BY LAWRENCE GIBSON, MD
Case Summary
A 38 year old man presented with numerous papules on the dorsal hands. He has a history of marked photosensitivity (since childhood) and gallstones.

Question # 41
The most likely diagnosis is:
A. Lipoid proteinosis Incorrect. Lipoid proteinosis has similar eosinophilic material but there is additional involvement of eccrine glands. Lipoid proteinosis can usually be excluded on clinical grounds in this age group.
B. Colloid milium Incorrect. Colloid milia characteristically shows a fissured appearance
C. Erythropoetic protoporphyria Correct.
D. Porphyria cutanea tarda Incorrect. PCT shows thickening of capillaries but the extensive eosinophilic material is not seen.
E. Amyloidosis (nodular) Incorrect. This can be morphologically similar but the history of photosensitivity is not consistent with amyloidosis. Congo red or thioflavin T are negative in EPP

Question # 42
This disorder is associated with:
A. Mutations in the gene encoding extracellular matrix protein 1 (ECM1). Incorrect. This is the expected abnormality in lipoid proteinosis
B. An inherited mutation impairing activity of ferrochelatase Correct.
C. No other medical problems Incorrect. EPP patients often have hepatobiliary problems (gallstones are common)
D. An inherited or acquired disorder impairing activity of the uroporphyrinogen decarboxylase Incorrect. This is the disorder seen in PCT
E. Localized accumulation of immunoglobulin light chains Incorrect. This causes amyloid deposition

Clinical features:
In EPP, severe sun sensitivity is typically noted which may lead to blistering, erosions and persistent erythema. The diagnosis of EPP can be confirmed with an increased serum erythrocyte-free protoporphyrin concentration. Gallstones are common (typically presenting at a young age) and hepatotoxicity may occur. When extensive hyaline deposition is present (as seen in this case) there is progressive disfiguring, furrowing and thickening of the skin. Papules may form, usually on the hands and face.

Lipoid proteinosis can have similar histopathologic features but clinically this would be unlikely if the disfigurement is found solely on photoexposed skin. In addition, lipoid proteinosis should show other features such as a hoarse voice, hair loss or neuropsychiatric symptoms.

Histopathologic features:
Histology reveals deposits of amorphous eosinophilic material throughout the papillary and mid-dermis, centred around and compressing dermal capillaries. This pattern of hyaline deposition is not seen in lipoid proteinosis, in which there is additional involvement of eccrine glands.

Periodic acid–Schiff (PAS) staining of this hyaline material is positive, but amyloid stains (Congo red and thioflavin T) are negative.

References:

CASE #99—SLIDE #99

**Diagnosis:** Protothecosis

**Case Summary:** A 68-year-old male presented with a fluctuant lower leg mass that began 6 months ago. The patient was chopping firewood and accidentally pierced his lower leg with a piece of wood prior to the onset of the mass. He recently completed chemotherapy for B-cell lymphoma.

**Question #1**
The best diagnosis is:
A. Necrotic lymphoma cells – **Incorrect.** Although at low power this seems reasonable, higher power displays sheets of thick walled organisms.
B. Coccidioidomycosis – **Incorrect.** Although the spores of Coccidioides are aggregated within cysts bearing a vague resemblance to Prototheca, they are much larger than Prototheca.
C. Entamoebiasis – **Incorrect.** It has abundant cytoplasm and a central nucleus, features lacking in this case.
D. Blastomycosis – **Incorrect.** It is composed of spherical budding yeast forms of roughly regular size and lacks the daisy-like sporangia.
E. Protothecosis – **Correct.** Prototheca wickerhamii is characterized by sporangia surrounded by small endospores arranged in a pattern resembling a morula, daisy, floret, or soccer ball depending on your visual preference. Larger empty spherical cysts are also seen.

**Question #2**
The causative organism is currently classified as:
A. Fungal yeast – **Incorrect.** While the organisms may resemble yeast, Prototheca is not fungal.
B. Dimorphic fungus – **Incorrect.** While the organisms may resemble yeast, Prototheca is not fungal.
C. Algae – **Correct.** Although there has been some debate over this for decades, Prototheca is currently thought to represent an achlorophyllous (colorless) algae rather than a fungus.
D. Amoeba – **Incorrect.** Amoeba are a type of single celled protozoa.
E. Protozoan – **Incorrect.** Protozoa are single-celled eukaryotes (organisms whose cells have nuclei) that commonly are motile.

**Question #3**
This infection is usually contracted via:
A. Fecal-oral route – **Incorrect.** Infection is not related to ingestion.
B. Direct contact – **Incorrect.** Contact alone is not sufficient. Inoculation or wound contamination is required.
C. Sexual activity – **Incorrect.** Protothecosis is not a sexually transmitted disease.
D. Traumatic inoculation – **Correct.** Most cases occur after skin trauma, often with subsequent contamination by soil or contaminated water.
E. Soil inhalation – **Incorrect.** Prototheca is not a respiratory infection.
**Question #4**

Of the following, the most common presentation in immunocompetent patients is:

A. Olecranon bursitis – **Correct.** This unique presentation is often seen in cases of protothecosis in immunocompetent patients.

B. Disseminated skin lesions – **Incorrect.** This pattern may rarely be seen in immunocompromised patients with protothecosis, but not usually in immunocompetent patients.

C. Sepsis – **Incorrect.** This is not a typical presentation of protothecosis.

D. Brain abscess – **Incorrect.** This is not a typical presentation of protothecosis.

E. Pulmonary granulomas – **Incorrect.** This is not a typical presentation of protothecosis.

**Clinical Features**

Protothecosis is an algal skin infection that usually occurs on an extremity secondary to traumatic inoculation. It may present as a solitary skin lesion or may be disseminated. It is typically associated with immunosuppression, but may also occur in immunocompetent hosts where it may present as olecranon bursitis.

Various therapeutic approaches have been reported including surgical debridement, pharmaceutical therapy with antifungals such as amphotericin or -conazoles, and, interestingly, local thermal therapy (since the algae are intolerant of heat). Treatment failure is not uncommon, but fatality from disease is quite unusual (estimated at less than 3% from literature review).

The patient in this case decided to return to a smaller outside hospital for surgical treatment; he died in the hospital several months after presentation, several days before receiving planned surgical debridement. It is difficult to be sure of the cause of death, since no autopsy was performed and he had other co-morbidities.

**Histologic Features**

- Often necrotizing granulomatous infiltrate with giant cells.
- Sporangia surrounded by small endospores arranged in a pattern resembling a morula, daisy, floret, or soccer ball. Larger empty spherical cysts are also seen.
- Organisms are PAS+ and GMS+.
- This case had so many organisms that there were only sheets of organism with little background tissue or inflammation.

**References**


**CONTRIBUTED BY JERAD M. GARDNER, MD**
CASE #100 — SLIDE #100

Diagnosis: Lobomycosis

Case Summary: A 50 year-old man from Surinam, South America, presented with keloid-like nodule on the lower extremity.

Question
What is the infectious agent?
A. Cryptococcus neoformans – Incorrect. Cryptococcus is a 5-15µm yeast in tissue sections with a refractile wall and surrounding clear space representing the capsule.
B. Histoplasma capsulatum – Incorrect. Histoplasma organisms are small, 3-5µm, predominantly intracellular organisms within histiocytes, with a surrounding “pseudocapsule” representing retraction artifact.
C. Lacazia loboi – Correct. Lobomycosis is characterized by a histologic pattern of uniform sized, 6-12µm, thick-walled, yeast-like organisms connected by tubular projections resembling “pop beads.”
D. Blastomyces dermatitidis – Incorrect. Blastomyces is a 7-15µm, thick walled yeast, difficult to see on H&E stained sections, that shows “broad based budding.”
E. Paracoccidioides brasiliensis – Incorrect. These thick walled organisms are characterized by small and large budding yeast arranged in a pattern resembling a “mariner’s wheel.”

Question
Chromoblastomycosis (chromomycosis) can be distinguished from lobomycosis by:
A. Pigmented cell wall – Correct. Chromoblastomycosis is a dematiaceous (pigmented) fungal organism. Lobomycosis does not contain visible pigment in the cell wall, though it has been shown to stain with Fontana Masson. Lobomycosis may have sparse melanin not visible with H&E.
B. Broad based budding – Incorrect. Chromomycosis replicates by internal septation whereas blastomycosis is characterized by broad based budding.
C. “Mariner’s wheel” appearance of budding yeast – Incorrect. Paracoccidioidomycosis is characterized by the “mariner’s wheel” of budding yeast.
D. Hyphal growth in tissue – Incorrect. Neither organism shows hyphal growth in tissue sections.
E. Angioinvasive growth pattern – Incorrect. Neither organism shows angioinvasive growth in tissue sections.

Question
Which of the following organisms must be cultured in a living host?
A. Cryptococcus neoformans – Incorrect. Organism can be cultured in the laboratory.
B. Histoplasma capsulatum – Incorrect. Organism can be cultured in the laboratory.
C. Blastomyces dermatitidis – Incorrect. Organism can be cultured in the laboratory.
D. Lacazia loboi – Correct. This is the only organism of those that were listed that cannot be cultured in the laboratory using routine methods. However, it can be cultured in living hosts such as the armadillo.
E. Paracoccidioides brasiliensis – Incorrect. Organism can be cultured in the laboratory.
Clinical Features
Lobomycosis classically presents as “keloidal” cutaneous lesions on exposed areas of the extremities and ears and was once referred to as “keloidal blastomycosis”. Lesions present as papules, nodules or plaques of various sizes and may be isolated or aggregated, solitary or multiple. They start with a smooth, shiny surface and are mobile and firm, but they can also be verrucous or ulcerated. The lesions are usually painless.

Lobomycosis is caused by the dimorphic fungi Lacazia loboi. It remains a poorly understood organism due to its inability to be cultured as well as its unresponsiveness to antifungal treatments. It was first described by Brazilian dermatologist Jorge Lobo in the 1930s. It is known to cause infections in both humans and dolphins. Soil and vegetation were thought to be the source of infection, but increasing reports in marine mammals has implicated the aquatic environment. Infection in humans has also been associated with proximity to water, suggesting that L. loboi may be a hydrophilic microorganism that infects the skin through areas of trauma while in an aquatic environment. Though once thought to be restricted to New World tropical countries, its recent description in African patients and patients from other continents argues against this. Systemic antifungals used in the treatment of other deep or disseminated fungal infections have proven disappointing, and no satisfactory therapeutic approach for this cutaneous infection currently exists.

Histopathologic Features
- Granulomatous dermatitis with histiocytes and giant cells containing numerous organisms.
- Fibrosis of the surrounding dermis with acanthosis and hyperkeratosis of the epidermis.
- Characteristic oval-to-round-shaped cells with connecting tubular projections resembling “pop beads.”

References
Case Summary
A 46 year old woman presented with a solitary, slow growing isolated verrucous tumour between the toes. She is on no medications.

Question # 43
The best diagnosis is:
A. CD4 positive small-medium pleomorphic T-cell lymphoma Incorrect. This may be difficult to exclude without immunohistochemical studies. Typically this entity is more polymorphous, with a mixture of other inflammatory cells and lymphocytes which range from small and bland to some lymphocytes which are highly atypical.
B. Mycosis fungoides, tumor stage Incorrect. The described clinical history of an isolated lesion should suggest this is much less likely.
C. Indolent CD8-positive lymphoid proliferation of acral sites Correct. Immunohistochemical studies, gene rearrangement studies and clinical correlation (possibly including staging) would be helpful to confirm the diagnosis.
D. T-cell pseudolymphoma Incorrect. The nuclear atypia and monomorphous infiltrate would be highly unusual for a pseudolymphoma.
E. Aggressive cutaneous CD8-positive lymphoma Incorrect. The described clinical history of an isolated lesion should suggest this is much less likely.

Question # 44
Which following statement is associated with the diagnosis:
A. Positive for CD8 Correct. This entity is consistently positive for CD8.
B. Positive for CD4 Incorrect. This entity is consistently positive for CD8.
C. Positive for CD1a Incorrect. CD1a is negative in this entity.
D. Ki-67 proliferative index should be very high Incorrect. The atypical cells typically show a very low Ki-67 index.
E. Positive for CD20 Incorrect. This is a T-cell disorder not a B-cell disorder.

Clinical findings:
This entity presents as a slow growing discrete cutaneous papule and nodule. The lesion is usually solitary but occasionally there are multiple lesions. Cases reported to date have not shown progression to systemic disease. To date, lesions have been managed with radiotherapy, surgery or observation following biopsy. Local recurrence is rare.

Histopathology findings:
There is a dense monotonous dermal proliferation of medium-sized lymphocytes, with folded nuclei and small nucleoli. A Grenz zone is often present. There is no epidermotropism, angiocentricity or necrosis. An accompanying population of small bland lymphocytes is often present.

Immunohistochemical studies reveal the atypical cells are CD8+, CD4− T-cells. These have a low proliferative index with Ki-67. A clonal rearrangement of the T-cell receptor gamma gene is typically found. CD68 is often positive – this is a newly proposed discriminative marker which is reported to be helpful to distinguish indolent CD8+ lymphoid proliferations from other CD8+ cutaneous lymphomas.
References:

CONTRIBUTED BY PATRICK EMANUEL, MB, CHB
CASE #102 — SLIDE #102

Diagnosis: Eosinophilic fasciitis

Case Summary
A 50-year-old man presents with history of sudden onset of tightening and induration of the forearms.

The best diagnosis is:
A. Eosinophilic fasciitis — correct
B. Morphea profunda
C. Nephrogenic systemic fibrosis
D. Pseudosclerodermatous post-irradiation panniculitis
E. Radiation fibrosis

Which of the following clinical or microscopic features is most helpful in diagnosis?
A. History of bone marrow transplant
B. History of gadolinium exposure
C. History of sudden onset — correct
D. Tissue eosinophils
E. Lobular panniculitis

Eosinophilic fasciitis (EF)
Patients with EF usually present with sudden onset of woody induration, sometimes with peau d’orange morphology and restricted range of motion of the extremities bilaterally. A “groove” that results from retraction of the subcutaneous tissues along the tract of superficial veins may be seen when an involved extremity is elevated. As in deep morphea, and in contrast with systemic sclerosus, there is sparing of the digits. EF has been reported as a manifestation of chronic graft-versus-host disease. Peripheral blood eosinophilia and hypergammaglobulinemia are common in patients with EF. The histopathologic features of morphea profunda and EF may be identical and include sclerosis and thickening/widening of fat septa and fascia, with lymphoplasmacytic inflammation. Tissue eosinophils are a variable component of the inflammatory infiltrate and are not necessary for diagnosis. Clinicopathological correlation is important for distinction among the sclerosing diseases.

References

CONTRIBUTED BY MARGOT S. PETERS, MD
CASE #103—SLIDE #103

Diagnosis: Post-radiation morphea

Case Summary
A 65-year-old woman presented with an approximately 4-cm plaque involving right breast skin, which developed 7 years after wide local excision and radiation therapy for ductal carcinoma in situ of the right breast.

The best diagnosis is:
A. Lupus erythematosus
B. Lichen sclerosus
C. Radiation dermatitis
D. Morphea- correct
E. Drug reaction

This disorder may be associated with:
A. Radiation therapy- correct
B. Paclitaxel
C. Aromatase inhibitors
D. Inflammatory carcinoma
E. Peripheral blood eosinophilia

Post-radiation morphea
Morphea that develops in patients who have had radiation therapy, most often for breast cancer, usually involves the irradiated field. Patients present months to years after completion of radiotherapy, with indurated, thickened skin often with ‘peau d’orange’ features, white shiny plaques, and/or erythema. The characteristic histopathological pattern includes dermal sclerosis, mild lymphoplasmacytic inflammation, and decrease in periadnexal fat, sometimes with loss of adnexal structures. Some patients also show features if lichen sclerosus, and a mainly septal panniculitis with lymphoplasmacytic inflammation of fat and sclerosis of subcutaneous septa.

References

BRAF-associated panniculitis
Painful subcutaneous nodules with overlying erythema, in combination with arthralgias, have been reported to occur in patients undergoing therapy of metastatic melanoma with the BRAF-inhibitors, particularly vemurafenib. Lesions typically affect upper and lower extremities. Other cutaneous abnormalities associated with BRAF-inhibitors include photosensitivity, pruritus, generalized erythematous eruptions, palmar-plantar erythrodysesthesia, androgenic-like alopecia, subungual hemorrhage, facial erythema, verrucal keratoses, keratosis pilaris-like lesions, plantar hyperkeratosis, Grover’s disease, and squamous cell carcinoma. Drug-induced neutrophilic panniculitis has been reported rarely, in association with other agents such as imatinib mesylate, dasatinib, and granulocyte colony-stimulating factor therapy.
Histopathologic features include a mainly lobular and predominantly neutrophilic panniculitis, with focal granulomas and occasionally vasculitis with fibrinoid necrosis of small subcutaneous vessels.

References
CASE #104 — SLIDE #104

Diagnosis: BRAF associated panniculitis

Case Summary
A 62-year-old woman undergoing treatment for metastatic melanoma presents with sudden onset of multiple subcutaneous nodules of the lower extremities.

The best diagnosis is:
A. Alpha-1-antitrypsin panniculitis
B. Pancreatic panniculitis
C. Infectious panniculitis
D. Panniculitis associated with BRAF-inhibitor treatment – correct
E. Subcutaneous Sweet’s syndrome

BRAF-associated panniculitis
Painful subcutaneous nodules with overlying erythema, in combination with arthralgias, have been reported to occur in patients undergoing therapy of metastatic melanoma with the BRAF-inhibitors, particularly vemurafenib. Lesions typically affect upper and lower extremities. Other cutaneous abnormalities associated with BRAF-inhibitors include photosensitivity, pruritus, generalized erythematosus eruptions, palmar-plantar erythrodysesthesias, androgenic-like alopecia, subungual hemorrhage, facial erythema, verrucal keratoses, keratosis pilaris-like lesions, plantar hyperkeratosis, Grover’s disease, and squamous cell carcinoma. Drug-induced neutrophilic panniculitis has been reported rarely, in association with other agents such as imatinib mesylate, dasatinib, and granulocyte colony-stimulating factor therapy. Histopathologic features include a mainly lobular and predominantly neutrophilic panniculitis, with focal granulomas and occasionally vasculitis with fibrinoid necrosis of small subcutaneous vessels.

References

CONTRIBUTED BY MARGOT S. PETERS, MD
CASE #105 — SLIDE #105

**Diagnosis:** Liposclerotic panniculitis

**Case Summary**
This 60 year old woman is admitted from the EDU for a presumptive diagnosis of cellulitis of the lower extremity. A dermatology consult is arranged after she fails to respond to 24 hours of IV antibiotics. An excisional biopsy is done and shows the following:

- Inflammation in the panniculus and nonspecific inflammation in the dermis
- Hyalinized and sclerotic changes in several septae of the fat
- Areas of “pseudocyst” formation in the panniculus

The changes above are characteristic for liposclerotic panniculitis and would fit the clinical picture. Most often seen involving the lower extremity in persons with a history of venous insufficiency and often obesity, this condition can be easily mistaken for cellulitis and is sometimes referred to as “pseudocellulitis”. The changes microscopically are not entirely specific but the changes seen in this slide are quite characteristic for this disorder. At times there can also be accumulation of PAS+ material in the interior of the pseudocysts which has been likened to a “frost-like” pattern or “arabesque” pattern. Clinical correlation is required as this pattern can also be seen in morphea profunda or connective tissue diseases as well.

**CONTRIBUTED BY LAWRENCE GIBSON, MD**
Case Summary
A 21 year-old man presents with a penile mass.

Question 47
The most likely diagnosis is:
A. Chancroid - Incorrect. Histology typically shows 3 zones of inflammation: necrotic tissue, fibrin, neutrophils on the surface, granulation tissue in the middle, lymphocytes and plasma cells deep
B. Primary Syphilis - Correct. Typical histologic features include epidermal thinning or ulceration centrally, spongiosis and lichenoid interface dermatitis with exocytosis of lymphocytes, plasma cells and neutrophils.
C. Lymphogranuloma Venereum - Incorrect. Typically presents with unimpressive 2-3mm papules on genitalia which are usually not biopsied; severe inguinal lymphadenopathy. Histology shows normal or ulcerated epidermis with diffuse dermal mixed infiltrate composed of lymphocytes, histiocytes, and plasma cells and non-specific granulation tissue.
D. Plasma Cell Balanitis - Incorrect. Clinically tends to have a moist, erythematous appearance and is not indurated. Thin epidermis with flattened keratinocytes. Lichenoid infiltrate composed mostly of plasma cells
E. Granuloma Inguinale - Incorrect. Ulcer with dense dermal infiltrate of histiocytes and plasma cells; as well as small neutrophil microabscesses. Parasitized macrophages may be large and have a typical vacuolated appearance (Donovan bodies).

Question 48
Which of the following stains will most likely confirm the above diagnosis?
A. CD138 - Incorrect. CD138 will mark plasma cells but will not confirm a diagnosis of primary syphilis.
B. Giemsa stain - Incorrect. Giemsa stain can be used to detect *haemophilus ducreyi* (chancroid) or *calymmatobacterium granulomatis* (granuloma inguinale) from a tissue smear, but not treponema pallidum.
C. IgG spirochete antibody immunohistochemistry - Correct. In primary syphilis, organisms can successfully be detected in tissue sections from the chancre with IgG spirochete antibody immunohistochemistry.
D. Fite stain - Incorrect. Fite stain is used to detect *mycobacteria leprae* (leprosy) but not spirochetes in syphilitic chancres.
E. Organisms can be recognized on H&E sections - Incorrect. *Calymmatobacterium granulomatis* (granuloma inguinale) can be recognized, though often with some difficulty, on H&E sections, but spirochetes are not typically visualized on H&E sections.

Clinical Features
Syphilis is a sexually transmitted disease caused by the spirochete, *Treponema pallidum*. The primary stage of syphilis is marked by the appearance of a syphilitic chancre, which typically presents as a firm, round, painless papule, nodule, or plaque on the genitalia that progresses to a punched out ulceration. Lesions occasionally can be multiple, especially in the setting of HIV infection, and at least 5% of syphilitic chancres occur in extragenital locations.
Syphilis is spread by direct contact with a syphilitic chancre. The time period between infection and onset of a chancre is approximately 3 weeks, but can range from 10 to 90 days. Once it appears, a chancre lasts approximately 3-6 weeks and heals regardless of whether a person is treated or not. With a tissue biopsy of a chancre, syphilis can be diagnosed with an immunohistochemical stain for *treponema*, which confirms their presence in the tissue. Treatment of primary syphilis with a single intramuscular injection of long acting Benzathine penicillin G (2.4 million units administered intramuscularly) will cure a person who has primary, secondary or early latent syphilis.

**Histopathologic Features**
- Epidermal acanthosis peripherally with epidermal thinning or ulceration centrally
- Spongiosis and exocytosis of lymphocytes, plasma cells and neutrophils
- Lichenoid interface dermatitis occasionally
- Papillary dermal edema and a dense perivascular and interstitial lymphohistiocytic and plasma-cellular infiltrate with endothelial cell swelling
- Immunohistochemical staining shows abundant spirochetes

**References**
**CASE #107 — SLIDE #107**

**Diagnosis:** Intravascular fungus
Alternaria intravascular infection

This specimen from a 7 year old male who underwent stem cell transplantation shows numerous hyphae in extra- and intra vascular spaces. The specimen was obtained from a painful 1cm shin red macule that arose 1 month after attempted transplantation. This infection proved fatal. Tissue cultures were essential to isolate *Alternaria* spp. Sections of these organisms show narrow septate hyphae with acute angle branching, indistinguishable from *Aspergillus* spp. *Fusarium* spp., *Scedosporium* spp. *Cladophialophora* spp. and other hyalohyphomycoses. The fungi that reside in the soil and grow on degraded plant material are referred to as the dematiaceous fungi. The non-pigmented hyalohyphomycoses and pigmented phaeohyphomycoses can be distinguished on H&E stained sections.

*Alternaria* spp., *Phialophora* spp. and *Bipolaris* spp. are among the more common causes of dematiaceous fungal subcutaneous nodules. Disseminated dematiaceous fungal infection is rare, however most all reported cases occur in immunocompromised hosts. In one study, the most common isolate was *Scedosporium prolificans*, accounting for over a third of cases. *S. prolificans* is generally resistant to all available antifungal agents. Other fungi commonly observed include *Bipolaris* spp., *Curvularia* spp. and *Exophiala* spp.

The differential diagnosis of intravascular or vasculotropic fungi includes the Zygomycetes which are not self-pigmented. Culture of these (Mucor spp., Rhizopus spp, Mucorhizo spp. etc.) is challenging due to the fragility of the hyphae. Therefore if zygomycetous infection is suspected alert the microbiology laboratory and request specific minced tissue processing which shows improved recovery and culture identification (Walsh 2012).


**CONTRIBUTED BY LAWRENCE GIBSON, MD and DANIEL COHEN, MD, PHD**
CASE #108 — SLIDE #108

Diagnosis: Pemphigus vegetans

Question:
The best diagnosis is:
A. Papular acantholytic dyskeratosis of the vulva – Incorrect. This entity can present in the anogenital area, but the histopathologic findings consist of epidermal acantholysis without a significant inflammatory component.
B. Pemphigus vegetans – Correct. Pemphigus vegetans presents with vegetative plaques involving the flexural areas and oral cavity. Histopathologically there is suprabasilar acantholysis (often subtle), extensive epidermal hyperplasia and intraepidermal microabscesses with numerous eosinophils.
C. Pemphigoid gestationis – Incorrect. The features in pemphigoid gestationis are similar to bullous pemphigoid, including a subepidermal blister with numerous eosinophils and eosinophilic spongiosis.
D. Paraneoplastic pemphigus – Incorrect. There may be overlapping features such as suprabasilar acantholysis; however, in paraneoplastic pemphigus, eosinophils are rare and there are often interface changes.
E. Contact dermatitis with superimposed herpes simplex infection – Incorrect. Contact dermatitis will also have eosinophilic spongiosis, but not extensive epidermal hyperplasia with intraepidermal microabscesses. Viral cytopathic changes are not present.

Clinical Features
Pemphigus vegetans is a rare variant of pemphigus that presents with vegetative plaques involving the flexural areas and oral cavity. Two clinical subtypes are described: the Neumann variant (more extensive erosive lesions) and the Hallopeau variant (pustular lesions that evolve into vegetative plaques and may result in spontaneous remission).

Histopathologic Features
• Suprabasilar acantholysis (often subtle.)
• Extensive epidermal hyperplasia and papillomatosis.
• Intraepidermal microabscesses with numerous eosinophils.
• Eosinophilic spongiosis.

Immunopathologic Features
• Similar to pemphigus vulgaris.
• DIF – Epithelial cell surface staining with IgG and C3.
• ELISA testing positive for desmogleins (Dsg3>Dsg1).

References

CONTRIBUTED BY CARILYN WIELAND, MD
Diagnosis: Cutaneous Sarcoidosis

The pathogenesis of sarcoidosis is poorly understood. The demonstration of familial clustering suggests hereditary susceptibility to sarcoidosis in at least a subset of patients.

Despite intensive studies, the etiology and pathogenesis of sarcoidosis remains elusive. It is likely, however, that sarcoidosis represents a reaction pattern that may develop in a predisposed patient on exposure to one or more infective agents or other antigens.

Histologically, sarcoidosis is characterized by a dense, noncaseating granulomatous infiltrate in the dermis, which sometimes extends into the subcutaneous fat. The granulomata are discrete and strikingly uniform in size and shape. They are composed of epithelioid histiocytes with abundant eosinophilic cytoplasm and oval or twisted vesicular nuclei often containing a small central nucleolus. Variable numbers of Langhans giant cells are present and sometimes a scattering of lymphocytes is seen at the peripheral margin of the granuloma. Discrete small central foci of fibrinoid necrosis are sometimes present but caseation necrosis is rare.

Transepidermal elimination is sometimes seen. The epidermis is usually normal although occasional cases display acanthosis and sometimes the granulomata are focally lichenoid. A predominantly lichenoid pattern may exceptionally be seen. Exceptional cases of sarcoidosis may display histologic findings that focally overlap with granuloma annulare, palisading neutrophilic and granulomatous dermatitis, and interstitial granulomatous dermatitis. Further histologic findings described include elastophagocytosis, perineural granulomas resembling leprosy, mucin deposition, and an infiltrate rich in plasma cells.

CONTRIBUTED BY LAWRENCE GIBSON, MD
Diagnosis: Intravascular histiocytosis

This proliferation is commonly seen in the setting of:
A. Celiac disease – Incorrect. Intravascular histiocytosis has not been reported in association with Celiac disease.
B. Hepatitis C – Incorrect. Intravascular histiocytosis has not been reported in association with Hepatitis C.
C. Renal cell carcinoma – Incorrect. Intravascular histiocytosis has not been reported in association with renal cell carcinoma.
D. Renal transplantation – Incorrect. Intravascular histiocytosis has not been reported in association with renal transplantation.
E. Rheumatoid arthritis – Correct. Fewer than 40 cases have been reported, but the majority of cases have occurred in association with rheumatoid arthritis. Other associations include diabetes mellitus, lupus anticoagulant, anticardiolipin antibodies, tonsillitis, Merkel cell carcinoma, and breast cancer. There have also been reports of intravascular histiocytosis in association with metal implants.

Massi and LeBoit. Histologic Diagnosis of Nevi and Melanoma. 2014.

Clinical Features
Intravascular histiocytosis (IH; also known as intravascular lymphangitis) is a rare condition first reported in 1994 by O’Grady et al. This indolent lesion has a predilection for the lower extremity overlying or near a joint and often presents as ill-defined, livedoid patches with mild erythema or hyperpigmentation. Fewer than 40 cases have been reported, but the majority of cases have occurred in association with rheumatoid arthritis, hence the term “RA-associated intravascular histiocytopathy.” Other associations include diabetes mellitus, lupus anticoagulant, anticardiolipin antibodies, tonsillitis, Merkel cell carcinoma, and breast cancer. There have also been reports of IH in association with metal implants. This process is thought to be reactive. Histologic similarities to reactive angioendotheliomatosis (RAE), a reactive proliferation of intravascular endothelial cells, have also motivated theories that IH represents an early stage of RAE; however, RAE is a proliferation of endothelial cells rather than histiocytes.

Histopathologic Features
• Intraluminal proliferation of mononuclear cells that stain for histiocytic markers within dilated reticular dermal vascular structures.
• Histiocytes are normal-appearing, epithelioid and without atypia.
• Immunohistochemistry:
  o Endothelial cells: CD31+, CD34+, D2-40+, Lyve-1+, Prox-1+
  o Intravascular histiocytes: CD68+

References

CONTRIBUTED BY VALENCIA D. THOMAS, MD
CASE #111—SLIDE #111

**Diagnosis:** Desmoplastic melanoma

**DESMOPLASTIC MALIGNANT MELANOMA**

Desmoplastic malignant melanoma is a subtype of melanoma that most commonly occurs on sun-damaged skin in patients greater than 60 years of age. It can also occur in young patients. The head and neck are most common, but it can arise anywhere including sun-protected skin. Histologically, many desmoplastic melanomas are amelanotic and are characterized by non-pigmented spindle cells in the dermis. There may be an intraepidermal “melanoma in situ” component that is often of the lentigo maligna type. The dermal spindle cells can show very bland cytology or marked pleomorphism. Characteristically, there are lymphoid aggregates at the periphery of the spindle cell proliferation. Immunohistochemistry may be necessary to confirm the diagnosis. The vast majority of desmoplastic melanomas are positive with S100, but rare cases are negative. Other melanocytic markers such as MART-1/Melan-A, MITF, and HMB45 are usually negative in the spindle cell component. Other markers that may be positive include: SOX10, P75NGFR, smooth muscle actin, and epithelial membrane antigen.

The differential diagnosis includes other spindle cell neoplasms as well as some inflammatory processes, and therefore, it is always important to keep the possibility of desmoplastic melanoma in the back of your mind. In differentiating desmoplastic melanoma from scar tissue, both may have S100 positive cells, although they are usually more numerous and closely associated with one another in melanomas than scar tissue. Several studies have shown that SOX10 is diffusely positive in melanomas, but not scar tissue.

Regarding prognosis, patients with desmoplastic melanoma may have a longer survival compared to those with conventional melanoma of similar thickness, and they may also have a lower incidence of positive sentinel lymph node biopsy than conventional melanomas of similar thickness. Several studies have separated desmoplastic melanoma into “pure” (90% of the tumor shows stromal desmoplasia) versus “mixed” (at least 10% of the tumor lacks fibrosis). Pure desmoplasia has been associated with longer disease free survival and lower incidence of dissemination to regional lymph nodes.

**References**


**CONTRIBUTED BY ROSALIE ELENITSAS, MD**
Case Summary
A 58 year-old man with a history of bone marrow transplantation for peripheral T-cell lymphoma presents with exfoliative erythroderma.

Question 53
The most likely diagnosis is:
A. Eczematous drug reaction – Incorrect. Histology typically shows spongiotic dermatitis with an inflammatory infiltrate typically extending to the mid-dermis. Dyskeratosis may be present, but usually only in the basal layer and not to degree seen in GVHD.
B. Psoriasis- Incorrect. Psoriasis would be expected to have neutrophils in the stratum corneum and suprapapillary plate thinning. Although erythrodermic psoriasis can show less specific histology, there should minimal dyskeratosis.
C. Sezary syndrome- Incorrect. Histology would be expected to show epidermotropism, atypical lymphocytes, and occasionally Pautrier microabscesses. Prominent dyskeratosis is not expected.
D. Eczematous GVHD- Correct. Typical histologic features include parakeratosis and spongiosis with numerous apoptotic keratinocytes and satellite cell necrosis.
E. Seborrheic Dermatitis - Incorrect. Histology shows a spongiotic dermatitis, typically admixed with psoriasiform features. Dyskeratosis is minimal-to-absent.

Question 54
Which of the following is a useful clue to the above diagnosis?
A. Shoulder parakeratosis- Incorrect. Shoulder parakeratosis can be a histologic clue to seborrheic dermatitis, but not GVHD.
B. Presence of tissue eosinophils- Incorrect. Several of the above entities, including GVHD, eczematous drug reactions, and sezary syndrome can display presence of tissue eosinophils.
C. Intracorneal neutrophil microabscesses- Incorrect. Intracorneal neutrophil microabscesses (Munro microabscesses)can be a useful clue to the diagnosis of psoriasis, but not eczematous GVHD.
D. Dyskeratosis and satellite cell necrosis- Correct. Both dyskeratosis and satellite cell necrosis are typically seen in eczematous GVHD. Although no study has shown a single histologic feature that can reproducibly help distinguish between GVHD and drug reactions, several studies have concluded the best way to distinguish between these is to correlate histologic findings with clinical findings.
E. Clinical presence of pruritus- Incorrect. Any of the above entities can be clinically associated with pruritus.

Clinical Features
Eczematous GVHD is a recently described chronic GVHD subtype that mostly has arisen in patients who have undergone allogeneic stem cell transplantation for hematologic malignancies. Clinically, patients tend to present with diffuse erythema and scaling suggestive of eczema that rapidly progresses to exfoliative erythroderma. Secondary impetiginization, palmoplantar hyperkeratosis and weeping in inflamed areas is common. Pruritus tends to be severe and patients suffer from thermoregulatory dysfunction and dependent edema because of erythrodermic involvement.
The course is prolonged and chronic. Most patients develop extracutaneous chronic GVHD, which may involve the liver, lungs, or GI tract. The prognosis is poor, with 6/10 patients in one case series dying. The most common cause of death was infection. Initial treatment consists of topical corticosteroids, antihistamines, and oral antibiotics when impetiginization is present. However, most patients require systemic treatment with a variety of steroid-sparing immunosuppressive agents or PUVA. PUVA has been reported to be particularly useful, having resulted in complete cutaneous clearance in 4/6 patients receiving it in one study.

**Histopathologic Features**

- Parakeratosis, spongiosis, and lymphocyte exocytosis consistent with eczematous dermatitis
- Keratinocyte apoptosis and satellite cell necrosis compatible with GVHD
- Usually a sparse-to-mild superficial perivascular inflammatory infiltrate +/- eosinophils

**References**


**CONTRIBUTED BY ANTHONY FERNANDEZ, MD, PhD**
CASE #113 – SLIDE #113

Diagnosis: Pigmented epithelioid melanocytoma

PIGMENTED EPITHELIOID MELANOCYTOMA

Pigmented epithelioid melanocytoma (PEM) is a term developed to describe lesions that histologically show features of epithelioid blue nevi (which are seen in patients with Carney complex) and so-called “animal type melanoma”. Since biopsies from these two entities are indistinguishable histologically, the term pigmented epithelioid melanocytoma was developed. Most PEM lose expression of protein kinase A regulatory subunit 1 alpha, a protein that is mutated in 44% of Carney complex patients.

Histologically, there is a symmetrical predominantly dermal melanocytic proliferation with marked melanization. There may be overlying epidermal hyperplasia which may contain heavily pigmented dendritic melanocytes. The dermal lesion is densely cellular in the center with infiltrative cells at the periphery. These cells are large and epithelioid or dendritic, or they may have a polygonal shape. The cells have an abundance of pigmentation and many associated melanophages. Given the difficulty of this diagnosis, many authorities recommended that these lesions be completely excised.

References

Case Summary
A 21-year-old woman complains of recent growth in a flesh-colored nodule on her posterior scalp which has been present since birth.

Question 57
The best diagnosis is:
A. Cellular neurothekeoma — Incorrect. Meningothelial whorls and psammomatous calcification would not be expected in neurothekeoma.
B. Cutaneous meningioma — Correct. The whorling growth of ovoid cells, psammoma bodies, and fibrotic/hyalinized stroma are consistent with meningioma.
C. Cellular fibrous histiocytoma — Incorrect. Whorls, psammoma bodies, and packeted growth would not be expected in cellular fibrous histiocytoma.
D. Plexiform fibrohistiocytic tumor — Incorrect. Plexiform fibrohistiocytic tumors are deeply infiltrating biphasic tumors, with nodules of histiocytic cells and fascicles of fibroblastic cells. These features are not observed in the current case.
E. Syncytial myoepithelioma — Incorrect. These tumors display sheetlike growth, and lack calcifications.

Question 58
Likely immunohistochemical staining results would include:
A. EMA (positive), cytokeratin (negative) — Correct. This is the classic immunohistochemical staining pattern of meningioma.
B. EMA (positive), cytokeratin (positive) — Incorrect.
C. p63 (negative), S100 (positive), cytokeratin (positive) — Incorrect. Cutaneous meningiomas may express p63, and are expected to be cytokeratin negative. S100 is negative in reports of cutaneous meningiomas.
D. Smooth muscle actin (positive), CD34 (negative) — Incorrect. Both would be negative in meningioma.
E. MiTF (positive), PGP9.5 (positive) — Incorrect. Melanocytic markers are negative in cutaneous meningioma. PGP9.5 has not been explored in this context.

Clinical Features
Cutaneous meningiomas are generally divided into 3 categories: type I (congenital), type II (acquired), and type III (spread from intracranial meningioma). Some have proposed that type I and II tumors represent heterotopias or hamartomas rather than true neoplasms. Type I lesions classically present as a scalp nodule or plaque, whereas type II lesions may present on the head and neck around sensory organs or cranial nerves. Type I and II lesions follow a benign course, although compression of adjacent structures may be a concern. Radiologic evaluation is advisable to exclude the possibility of intracranial meningioma.

Histopathologic Features
Cutaneous meningiomas are often located in the deep dermis or subcutis. Type I lesions may show cystic or pseudovascular architecture. Constituent meningothelial cells may be small round cells, or larger ovoid/spindled cells more reminiscent of intracranial meningioma (especially in type III lesions). Cells are arranged in nests or lobules. Meningothelial whorls
and psammoma bodies may be present. Tumor cells show characteristic collagen entrapment. Mitoses are not typically seen. By immunohistochemistry, tumor cells are EMA positive and cytokeratin negative. Expression of p63 may be present. S100 expression has been reported in some intracranial meningiomas, but has not been shown in cutaneous meningiomas.

References
CASE #115 — SLIDE #115

**Diagnosis:** Benign Migratory Glossitis (Geographic tongue)

The best diagnosis for this biopsy from the oral cavity is?

A. **Benign migratory glossitis – correct**
B. Lichen planus
C. Candidiasis
D. Oral hairy leukoplakia
E. Black hairy tongue

This condition is most commonly associated with?

A. Immunosuppressed status
B. HIV/AIDS
C. Poor oral hygiene
D. **Normal health status – correct**
E. Progression to oral squamous cell carcinoma

Benign migratory glossitis (geographic stomatitis, stomatitis/erythema areata migrans, geographic tongue, annulus migrans, and erythema circinata) occurs in 1–2% of the population (usually adults) although this figure may be low because of the evanescent nature of the condition. Lesions are recurrent, erythematous, and atrophic areas with a serpiginous white, slightly raised border that may appear annular or scalloped. These ‘map-like’ areas migrate and change in shape over the tongue dorsum as the condition resolves at one edge and involves another. Some lesions, however, are stationary. Pain, in the form of a burning or sensitivity, may or may not be present. Twenty to 60% of patients have concurrent fissured tongue.

The tongue dorsum exhibits loss of the filiform papillae. There are superficial spongiotic pustules and microabscesses (often involving up to one-third of the thickness of the epithelium) in the absence of Candida infection. The adjacent epithelium shows variable spongiosis and leukocyte exocytosis. Additional features commonly present are psoriasiform epithelial hyperplasia with broad rete ridges sometimes becoming confluent at their bases, edema of the lamina propria, and a variable lymphocytic infiltrate with conspicuous capillary dilatation.

**CONTRIBUTED BY CLAY COCKERELL, MD**
CASE #116—SLIDE #116

**Diagnosis:** Pustular psoriasis

What is the best diagnosis for this generalized eruption in a 55-year-old male?

A. Acute generalized exanthematous pustulosis  
**B. Pustular psoriasis**  
C. Subcorneal pustular dermatosis  
D. Dermatophyte infection  
E. Reiter’s syndrome

The most likely abnormal finding in this patient is?

A. Hypocalcemia  
B. Abnormal DIF finding  
C. Chlamydia infection  
D. Leukopenia  
E. Peripheral eosinophilia

Pustular psoriasis (von Zumbusch) is an acute variant, characterized by fever of several days' duration, together with the sudden appearance of sterile pustules, 2–3 mm across, over the trunk and extremities. The surrounding skin is erythematous and confluence may result in a generalized erythroderma. Usually, recurrent episodes of fever occur, followed by fresh outbreaks of pustules. Systemic signs include weight loss, weakness, and hypocalcemia, with a raised white cell count and high erythrocyte sedimentation rate (ESR). Although the precipitating factor is often unknown, pustular psoriasis may follow a streptococcal or viral infection. Withdrawal of systemic steroid therapy is also a known predisposing cause. Treatment with systemic steroids or intensive topical regimens has also been incriminated. Other risk factors for developing a pustular episode include drugs, pregnancy, and hypocalcemia. In generalized pustular psoriasis and its three variants the histological picture is slightly different in that the spongiform pustule occurs as a macropustule and is the characteristic lesion. As the spongiform pustule increases in size, the epidermal cells die, with resulting central cavitation. At the edges, a shell of thinned epidermal cells remains. Eventually there is migration of neutrophils into the horny layer and the picture resembles that of a large Munro abscess. Although the epidermal and dermal features may be similar to those of psoriasis vulgaris, particularly if the pustule has developed against a background of plaque-type disease, more often the features are much less well developed. Frequently, therefore, there is no or only minimal epidermal hyperplasia although tortuous and dilated capillaries accompanied by a lymphocytic or mixed lymphocytic and neutrophil infiltrate are usually seen.

**CONTRIBUTED BY CLAY COCKERELL, MD**
CASE #117—SLIDE #117

Case Summary
A 6 year-old febrile and intubated girl was transferred to an academic medical center with skin peeling over 30% of her body surface area (sparring mucosal surfaces). Her mother stated that the girl had recently experienced swollen tonsils. Before her transfer and preceding the clinical desquamation, the previous hospital had administered antibiotics.

Question 65
The best diagnosis is:
A. Linear IgA bullous dermatitis – Incorrect. Linear IgA disease is characterized by a subepidermal blister with neutrophils typically predominating over other inflammatory cells. A subset of cases are vancomycin-induced.
B. Staphylococcal scalded skin syndrome – Correct. There is a split within the granular cell layer with accompanying acantholysis. There is no epidermal necrosis or spongiosis and only a sparse mixed cell inflammatory infiltrate is seen in the superficial dermis and stratum corneum (inflammation is often absent altogether).
C. Toxic epidermal necrolysis – Incorrect. Toxic epidermal necrolysis exhibits nearly confluent necrosis of the epidermis with overlying orthokeratosis, often with an associated subepidermal split. A sparse lymphocytic infiltrate is present, and lymphocytes may be seen causing satellite cell necrosis of individual keratinocytes at all levels of the epidermis.
D. Bullous impetigo – Incorrect. Bullous impetigo is also characterized by a subcorneal split, occasionally with acantholytic keratinocytes. Gram-positive cocci are usually visualized within the stratus corneum or blister, as are neutrophils. The dermis also shows a more significant inflammatory infiltrate than is seen in this specimen. Also, a disseminated clinical process argues against impetigo.
E. Pemphigus vulgaris – Incorrect. Pemphigus vulgaris (PV) also shows intraepidermal acantholysis, but it is typically seen in a suprabasal location, not within the granular cell layer. PV commonly presents with mucosal involvement.

Question 66
Which of the following additional testing methods would typically yield a positive result, supporting the diagnosis?
A. Tissue gram stain on the current specimen – Incorrect. Cutaneous bacteria are expected to be absent at the sites of skin disease.
B. Direct immunofluorescence on a biopsy from lesional skin – Incorrect. This would be positive in a histologic mimic, but not in this entity.
C. A bacterial culture of a swab of lesional skin – Incorrect. Bacterial cultures from skin swabs are almost always negative since the involved skin is not infected.
D. A bacterial culture from the nasopharynx or conjunctivae – Correct. Staphylococcal scalded skin syndrome usually has a proceeding upper respiratory tract infection and cultures from the nasopharynx and/or conjunctivae are likely to be positive for Staphylococcus aureus.
E. A GMS/PAS stain on the current specimen – Incorrect. This process is not mediated by fungi.

Clinical Features
Staphylococcal scalded skin syndrome (SSSS) most commonly affects infants and young children and is characterized by an abrupt onset of flaccid bullae and desquamation. This desquamation typically follows an upper respiratory tract infection or conjunctivitis. The trunk, face, and neck are the most common sites; mucosal surfaces are not involved. No bacteria are present in the desquamated skin since the cutaneous effects are mediated by an exfoliative toxin released by *Staph. aureus* at a distant site. The toxin targets desmoglien 1, hence the clinical and histopathologic similarities to pemphigus foliaceus. The toxin is cleared by the kidney, and patients that have diminished kidney function have a significantly increased mortality rate; similarly NSAIDs are contraindicated for treatment for pain in these patients since they decrease renal clearance of the toxin.

**Histopathologic Features**
SSSS shows a split that may appear to be subcorneal, but is best categorized as intraepidermal within the granular cell layer, in a pattern identical to pemphigus foliaceus. There is often accompanying acantholysis, but there should be no epidermal necrosis or spongiosis and any inflammatory infiltrate should be sparse. As a rule, bacteria should not be visualized. Direct immunofluorescence is also negative.

**References**


CASE #118—SLIDE #118

Diagnosis: Primary cutaneous follicle center cell lymphoma

A 67-year-old man presents with grouped lesions on the scalp. The immunophenotype of the atypical lymphocytes is: CD3-, CD20+, CD79a+, CD5-, CD10-, CD43-, BCL2-, BCL6+, MUM1-, and Cyclin D1-.

What is the best diagnosis?

A. Primary cutaneous marginal zone B-cell lymphoma
B. Primary cutaneous follicle center lymphoma
C. Primary cutaneous diffuse large B-cell lymphoma, leg type
D. Small lymphocytic lymphoma/chronic lymphocytic leukemia
E. Mantle cell lymphoma

Primary cutaneous follicle center cell lymphoma the most common type of primary cutaneous B-cell lymphoma.

Clinical features:
- Older persons
- Male predilection

Pathology:
- Diffuse or nodular lymphoid infiltrate filling the dermis with variably defined neoplastic follicle formation
- Follicular, follicular to diffuse, and diffuse patterns recognized.
- Most cases are diffuse.
- Grenz zone typically present
- Perivascular, periadnexal accentuation
- Scattered centroblasts (larger cells with noncleaved, vesicular nuclei containing 1 to 3 nucleoli rim of cytoplasm) amidst a majority of centrocytes (cells with cleaved nuclei, inconspicuous nucleoli, scant cytoplasm)
- Follicles ill defined, no tingible-body macrophages, absent to poorly developed mantle zone
- Tumors graded according to the number of centroblasts

Immunopathology/special stains:
- Neoplastic lymphocytes positive for CD20, CD79a, bcl-6. Negative for CD5, CD43.
- CD10 variable expression: positive in cases with follicular pattern
- CD3 positive in reactive T cells
- Bcl-2 usually negative in primary cutaneous disease.
- Recent studies demonstrate bcl-2 expression in small subset of PCFCL. Further studies necessary to determine significance.
- Bcl-2 positive in systemic disease secondarily involving skin
- MUM-1 negative
• Pax-5 positive (helpful if lesions have been treated with rituximab) CD21-positive follicular dendritic cells outline follicular architecture
• Monotypic light-chain expression
• t(14;18) usually characteristic of nodal follicular lymphoma

CONTRIBUTED BY ANTONIO SUBTIL, MD, MBA
CASE #119 – SLIDE #119

Diagnosis: Primary cutaneous diffuse large B cell lymphoma, leg type

A 90-year-old woman presents with two violaceous nodules on the right forearm. The immunophenotype seen here is: CD3-, CD20+, CD79a+, CD5-, CD10-, BCL2+, BCL6+, MUM1+, and Cyclin D1-.

What is the best diagnosis?

A. Large cell transformation of granulomatous mycosis fungoides
B. Primary cutaneous follicle center lymphoma
C. **Primary cutaneous diffuse large B-cell lymphoma, leg type**
D. Burkitt lymphoma
E. Mantle cell lymphoma

Primary cutaneous counterpart to nodal, diffuse, large B-cell lymphoma; may develop in other preexistent cutaneous B-cell lymphomas. WHO-EORTC recognizes entities of “cutaneous, diffuse, large B-cell lymphoma, leg-type” and “cutaneous, diffuse, large B-cell lymphoma, other.”

Clinical features:
- Primary cutaneous disease shows a wide age distribution but generally presents in the elderly
- Lesions on the legs show a marked female predilection

Presentation:
- Erythematous to violaceous, plum-colored, plaques, nodules, tumors, measuring up to several centimeters
- Smooth-surfaced, sometimes ulcerated
- Often solitary or clustered, multiple scattered lesions can also be seen
- May be distributed on head, neck, and trunk, but lower extremities more often affected
- Lesions on legs classified separately due to prognostic differences

Pathology:
- Diffuse infiltrate of large atypical lymphoid cells often extending into the subcutaneous fat
- Medium- to large-sized lymphoid cells resembling immunoblasts and centroblasts
- Mitotic figures generally numerous
- T-cell–rich B-cell lymphoma variant demonstrates preponderance of small T cells in sheets, with occasional scattered, large, atypical neoplastic B cells
- Anaplastic variant may mimic Hodgkin’s lymphoma, undifferentiated carcinoma, or amelanotic melanoma
Immunopathology:
- CD20 positive (in patients treated with -rituximab, CD20 may be negative; in this setting, Pax-5 immunopositivity is useful)
- Pax-5 positive
- CD5 negative
- CD10 negative
- Bcl-2 strongly positive
- Bcl-6 variable
- MUM-1 positive
- t(14;18) absent
- Surface/cytoplasmic immunoglobulin restriction
- Anaplastic variant is CD30 positive
Diagnosis: Trichoepithelioma

A 39 year old male presented with a single, slowly growing papular lesion on the nose. The clinical diagnosis was: “BCC vs other”.

What is the most likely diagnosis for this tumor?

A. Trichoepithelioma  
B. Trichoblastoma  
C. Microcystic adnexal carcinoma  
D. Basal cell carcinoma arising in a trichoepithelioma  
E. Trichadenoma

If the patient had a history of multiple similar-appearing tumors and skeletal and neurologic abnormalitis, what syndrome could this be associated with?

A. Cowden syndrome  
B. Brooke-Spiegler syndrome  
C. Gardner (FAP) syndrome  
D. Multiple familial trichoepitheliomas  
E. Gorlin (nevoid basal cell carcinoma) syndrome

Clinical features:
- Adults usually affected, although inherited form may manifest in children
- Most commonly occurs in whites; blacks also affected
- Solitary variant
- Familial disseminated form inherited in autosomal dominant fashion
- Brooke-Spiegler syndrome: inherited multiple trichoepitheliomas plus cylindromas and spiradenomas (linked to mutation in CYLD gene)

Presentation:
- Skin-colored, often dome-shaped, firm, smooth, 2- to 3-mm papule; may resemble basal cell carcinoma
- Distributed over face, particularly nasolabial folds, nose, upper cutaneous lip, scalp
- Trunk and extremities less commonly affected • Multiple lesions seen in familial forms
- Giant solitary trichoepithelioma located in perianal area (now classified as trichoblastoma)

Pathology:
- Follicular epithelial tumor within the dermis arranged in small basaloid cords and nests with peripheral palisading
- Variable continuity with epidermis
• Rare mitoses • Keratinous cysts common but may be absent
• Rudimentary hair follicular papillae seen with papillary mesenchymal bodies
• Tumor set within fibrotic stroma
• Artifactual retraction and mucinous stroma absent
• Foreign-body reaction to keratin and calcification may be prominent.

**Immunopathology/special stains:**
• Trichoepitheliomas positive for CK20 and CD34 (stroma) and negative for androgen receptor
• Bcl-2 stains periphery of trichoepithelioma, diffuse in basal cell carcinoma

**CONTRIBUTED BY DAVID CASSARINO, MD, PHD**
CASE #121 – SLIDE #121

Case Summary

A 61-year-old man presented with multiple enlarging red brown nodules on both legs and left arm. Extensive lymphadenopathy and pleural effusion were present.

Question 69
The best diagnosis is:
A. Melanoma – Incorrect – The cells lack a nested pattern and a junctional component
B. Anaplastic large cell lymphoma – Correct – cells are discohesive suggesting hematological origin. The marked atypia is in keeping with an anplastic large cell lymphoma.
C. Leukemia cutis – Incorrect – The marked pleomorphism and lymphadenopathy would be atypical for leukemia cutis
D. Metastatic gastric carcinoma – Incorrect – The dyshesive growth pattern argues against a metastatic carcinoma.
E. Metastatic colorectal carcinoma – Incorrect – The dyshesive growth pattern argues against a metastatic carcinoma.

Question 70
The most useful immunostain to support the diagnosis is:
A. CD3 – Incorrect – Although positive in anaplastic large cell lymphoma, it is not specific.
B. CD30 – Correct – Anaplastic large cell lymphoma is positive for this marker and this marker is critical in establishing the diagnosis.
C. Cytokeratin – Incorrect – Anaplastic large cell lymphoma is negative for cytokeratin
D. Myeloperoxidase – Incorrect – Anaplastic large cell lymphoma is negative for myeloperoxidase
E. SOX10 – Incorrect - Anaplastic large cell lymphoma is negative for SOX10

Clinical Features:
Anaplastic large cell lymphoma is defined as a CD30 positive large T-cell lymphoma. It may be a primary cutaneous neoplasm or represent skin involvement by a nodal anaplastic large cell lymphoma. There are important differences in biologic behavior and prognosis between primary cutaneous and nodal anaplastic large cell lymphoma. The WHO Classification list them as separate entities. Although ALK -1 positivity is absent in most primary cutaneous cases, absence of ALK-1 expression cannot be interpreted as synonymous of primary cutaneous diasese and systemic investigations are mandatory. Clinically, patients present with solitary or clustered, often ulcerated, reddish-brown tumors

Histopathologic Features:
Nodular or diffuse infiltrate composed of sheets of large CD30 positive atypical cells. Rarely signet-ring morphology can be observed.

References:


CONTRIBUTED BY SYLVIA PASTERNAK, MD
CASE #122 — SLIDE #122

**Diagnosis:** Phototoxic drug eruption

There are two types of photosensitive drug reactions: phototoxic and photoallergic. Phototoxic reactions are more common; however, they are not necessarily mutually exclusive and are not always clinically distinguishable. The clinical appearances of acute phototoxic reactions mimic severe sunburn and include erythema, edema, and blistering with subsequent desquamation and postinflammatory hyperpigmentation. Typically, only exposed skin is affected and it occurs minutes to hours after sun exposure. Phototoxicity has also been associated with onycholysis.

The histological appearances of acute phototoxic reactions include conspicuous apoptotic keratinocytes (sunburn cells) which in severe cases may affect the entire epidermis, with variable neutrophil exocytosis, dermal edema, and a perivascular lymphohistiocytic infiltrate with small numbers of neutrophils and eosinophils.
CASE #123 — SLIDE #123

Diagnosis: Clear cell sarcoma

A 14 year-old female presents with a 4 cm foot mass. FISH assay was positive for EWSR1 translocation. The best diagnosis is:

A. Synovial sarcoma  
B. Spindle cell melanoma  
C. Pecoma  
D. **Clear cell sarcoma**  
E. Dermatofibrosarcoma protruberans

Clear cell sarcoma is a malignant mesenchymal tumor that usually occurs in deep soft tissue and has a tendency to affect young adults. Most cases involve the extremity, and the foot/ankle region is the most common site. These tumors are usually slow growing, but lymph node involvement is frequent. Histologic examination reveals a nested architecture, and the tumor cells are predominantly epithelioid or slightly spindled. Multinucleated cells may be present. The immunoprofile of clear cell sarcoma is similar to malignant melanoma with tumor cells showing expression of S100, HMB45 and other melanocytic markers. Most clear cell sarcomas show a t(12;22)(q13;12) translocation which fuses EWSR1 to ATF1. Occasionally tumors harbor EWSR-CREB1. Clear cell sarcoma is associated with poor outcome with 20 year survival of only 10%.


**CONTRIBUTED BY RAJIV PATEL MD**
**Case Summary**
A 38-year-old woman presented with a 2-3 month history of a purpuric eruption involving the trunk. Few nodules have developed over the last month.

**Question 71**
The best diagnosis is:
A. Metastatic carcinoma – **Incorrect**. This malignant neoplasm shows a diffuse infiltrate of neoplastic cells with blastic morphology. The cells are discohesive and show no morphologic evidence of epithelial differentiation.
B. Melanoma – **Incorrect**. The clinical presentation would be rather unusual for a melanoma. In addition, the morphology does not suggest melanocytic differentiation.
C. Burkitt lymphoma – **Incorrect**. Burkitt lymphoma is a highly aggressive hematological malignancy with high proliferation rates. The typical “starry sky” morphology is not present here. In addition, cutaneous involvement by Burkitt lymphoma is extremely rare.
D. Blastic plasmacytoid dendritic cell neoplasm – **Correct**. This case shows the classic morphological features of this neoplasm. Diffuse, monomorphic infiltrate of medium sized cells with a blastic morphology.
E. Follicular center lymphoma – **Incorrect**. Follicular lymphoma is a low grade B-cell lymphoma. The lymphocytes are usually small and with a low proliferation rate.

**Question 72**
The following, if positive, will confirm your morphologic impression:
A. Monokeratin, EMA and p63 – **Incorrect**. This profile would suggest a carcinoma.
B. S-100 protein, HMB-45 and Melan-A – **Incorrect**. This profile would suggest a melanoma.
C. CD20, CD10, EBER-1 and cMYC – **Incorrect**. This is the profile is of a Burkitt Lymphoma
D. CD4, CD56, CD123 and TCL-1 – **Correct**. This is the immunohistochemistry profile of a Blastic plasmacytoid dendritic cell neoplasm
E. CD20, CD79a, BCL-6 – **Incorrect**. This profile would suggest a follicular lymphoma

**Clinical Features:**
Patients are mostly adults and elderly presenting with solitary, localized or generalized plaques and tumors. A characteristic “bruise-like” violaceous aspect due to intratumoral hemorrhage is commonly observed. Cutaneous lesions are the first manifestation of the disease in over 90% of the patients. Leukemic spread after a variable but usually short period is the rule.

**Histopathologic Features:**
Blastic plasmacytoid dendritic cell neoplasm is characterized by a diffuse, monomorphic infiltrate of medium-sized neoplastic cells with a blastoid morphology. Intratumoral hemorrhage is common and prominent in cases characterized by a bruise-like presentation clinically. Neoplastic cells express CD4, CD56 and CD123, TCL-1 and CD303.

**References:**


CONTRIBUTED BY SYLVIA PASTERNAK, MD
CASE #125—SLIDE #125

**Diagnosis:** Poorly differentiated synovial sarcoma

A 27 year-old male presented with a penile mass. Past medical history was significant for an inguinal sarcoma resected 5 years earlier. The tumor demonstrated nuclear positivity for TLE-1.

The best diagnosis is:

A. Malignant peripheral nerve sheath tumor  
B. Malignant solitary fibrous tumor  
C. Poorly differentiated synovial sarcoma  
D. Sarcomatoid melanoma  
E. Sarcomatoid squamous cell carcinoma

Synovial sarcoma is a malignant soft tissue tumor which, despite its name, does not arise from synovium. The origin of the neoplastic cells remains unknown. This tumor typically affects young adults and tends to arise in deep soft tissue sites near joints. Calcification may be identified on radiologic studies providing a clue to the diagnosis. The gross appearance of the tumor depends on the rate of growth. Slowly growing tumors tend to be circumscribed than rapidly growing lesions. Cyst formation, hemorrhage, necrosis and calcification may present. Synovial sarcoma may be a monophasic or biphasic neoplasm. Biphasic tumors are composed of epithelial and spindle cell components while monophasic cases typically consist of only the spindle cell population. The epithelial cells are characterized by cuboidal to columnar cells organized in cords, nests or glands. The spindle cells have plump, hyperchromatic nuclei, scant cytoplasm and are arranged in a fascicular (herringbone) growth pattern. Mast cells, calcification and branching blood vessels may be noted. Some tumors are poorly differentiated and exhibit round cell morphology with prominent nucleoli. These tumors typically stain for cytokeratins focally and are negative for CD34. Cytogenetic and molecular studies can be helpful in poorly differentiated cases as synovial sarcomas consistently have a balanced reciprocal translocation between the SYT gene on chromosome 18 and either the SSX1 or SSX2 gene on the X chromosome.


**CONTRIBUTED BY RAJIV PATEL, MD**
Diagnosis: Cutaneous myopericytoma

A 30 year-old female presented with a right forearm “cyst”. The lesion is smooth muscle actin positive and desmin negative. The best diagnosis is:

A. Glomus tumor
B. Myopericytoma
C. Myofibroma
D. Pyogenic granuloma
E. Leiomyoma

Myopericytoma is a tumor of perivascular myopericytes.

Clinical features:
- Middle-aged adults

Presentation:
- Extremities, especially lower
- Mostly solitary, but may be multiple
- Typically less than 2 cm

Pathology:
- Circumscribed
- Solid spindled cell “nodules” and dilated vessels
- Perivascular orientation giving an onion-skin appearance
- Minimal atypia
- Mitoses extremely rare
- Myxoid change sometimes present
- Pseudovascular invasion
- Sometimes tumor cells have a glomoid appearance (glomerangiopericytoma)
- Angioleiomyoma-like appearance also sometimes seen
- Myofibroma-like appearance occasionally evident

Immunopathology/special stains
- Smooth muscle actin positive

CONTRIBUTED BY RAJIV PATEL, MD
CASE #127 – SLIDE #127

Case Summary
A 69-year-old female presented with progressive infiltrative erythematous plaques on the chest and breast. Lymphadenopathy was evident. A punch biopsy revealed a superficial and deep perivascular infiltrate.

Question 75
The best diagnosis is:
A. Mycosis fungoides – Incorrect. There is a superficial and deep perivascular infiltrate and MF could be considered. However, there is no involvement of the epidermis and abundant plasma cells are noted.
B. Skin involvement by angioimmunoblastic T-cell lymphoma – Correct. A superficial and deep perivascular infiltrate of small lymphocytes associated with plasma cell and eosinophils is compatible with cutaneous involvement in angioimmunoblastic T-cell lymphoma. A proliferation of B-lymphocytes is commonly present and occasionally a monoclonal rearrangement of immunoglobulin genes is present.
C. Skin involvement by anaplastic large cell lymphoma – Incorrect. The infiltrate consists mainly of small lymphocytes, plasma cells and eosinophils.
D. Skin involvement by myelogenous leukemia – Incorrect. The cells in the infiltrate appear to represent small lymphocytes and not myeloid precursors.
E. Cutaneous plasmacytoma – Incorrect. The infiltrate contains some mature plasma cells but also lymphocytes and eosinophils. The infiltrate of a plasmacytoma would consist of almost all plasma cells.

Question 76
The best approach to establish a definitive diagnosis is to obtain:
A. Immunohistochemical stains – Incorrect. This may help but definitive diagnosis will require systemic investigation.
B. Biopsy of an involved lymph node – Correct. The clinical lymphadenopathy is suggestive of cutaneous involvement by a systemic lymphoma. A lymph node biopsy is essential to arrive at the correct diagnosis
C. Clinical history – Incorrect. It may help but will not provide definitive diagnosis
D. Imaging studies – Incorrect. It may help but will not provide definitive diagnosis
E. Molecular studies – Incorrect. It may help but will not provide definitive diagnosis

Clinical Features:
Patients are elderly adults and skin lesions may be the first manifestation of the disease. Papules, plaques and tumors are not distinctive and resemble other cutaneous lymphomas

Histopathologic Features:
Nodular infiltrates of small, medium or large pleomorphic lymphocytes intermingled with reactive cells (plasma cells, eosinophils, histiocytes) are seen. The number of neoplastic lymphocytes is often a minority. Venules with prominent endothelial lining are typically found (“high endothelial venules”)
References:


CONTRIBUTED BY SYLVIA PASTERNAK, MD
CASE #128 — SLIDE #128

Diagnosis: Nodular fasciitis

A 15 year old male presented with this rapidly growing mass on his forearm. What is the correct diagnosis:

A. Nodular fasciitis  
B. Dermatofibrosarcoma protuberans  
C. Synovial sarcoma  
D. Fibromatosis  
E. Rhabdomyosarcoma

Nodular fasciitis is a rapidly growing myofibroblastic reactive lesion of unknown cause

Clinical features:
- Younger individuals, including children
- Not specific to either sex

Presentation:
- Typically exhibits rapid growth
- Tenderness
- Predilection for the upper extremity, especially the forearm; can also occur in the trunk
- Usually several centimeters
- Although generally arises in the subcutaneous fat, occasionally may be restricted to the dermis (dermal fasciitis)
- Cranial fasciitis: a variant in infants involving scalp with occasional extension into bone
- Proliferative fasciitis: a related condition affecting the fascia and characterized by the presence of ganglionlike giant cells

Pathology:
- Circumscribed or infiltrative border
- Variably cellular areas of spindled, myofibroblastic cells
- Myxoid areas, resulting in “feathery” appearance
- Microcystic foci
- Extravasated red blood cells and lymphocytic infiltrate
- Prominent blood vessels
- Normal mitoses often conspicuous

Immunopathology/special stains:
- Smooth muscle actin and calponin positive
- Desmin and S100 protein negative

CONTRIBUTED BY KAREN FRITCHIE, MD
CASE #129 — SLIDE #129

Diagnosis: Dermatofibrosarcoma protuberans

A 35 year old female undergoes scalp biopsy. What is the correct diagnosis?
  A. Benign fibrous histiocytoma
  B. Nodular fasciitis
  C. Cellular neurothekeoma
  D. Dermatofibrosarcoma protuberans
  E. Spindle cell carcinoma

DFSP is a low-grade malignant fibroblastic tumor of young adults characterized by a monotonous storiform growth pattern

Clinical features:
  • Predilection for young adults

Presentation:
  • Slow-growing plaque that evolves into multiple nodules or protuberances (hence the name)
  • Trunk and lower extremities most often affected

Pathology:
  • Grenz zone often present
  • Monotonous storiform growth pattern
  • Tumor composed of spindled cells that are, in general, more uniform and less pleomorphic than may be seen in a dermatofibroma
  • Mitoses are usually inconspicuous
  • The classic picture is one of a lace-like pattern with trapped lobules of fat between spindled cells (so-called honeycomb)
  • In some tumors, less classic appearances predominate: hypocellular, myxoid, and giant cell fibroblastoma–like
  • Bednar tumor refers to those lesions containing pigmented dendritic cells (pigment is melanin)
  • Fibrosarcomatous transformation is characterized by a typical herringbone morphology of more-closely packed spindled cells with increased mitoses
  • Evaluating adequacy of excisions is problematic, because the peripheral portions may appear quite bland
  • Especially in the setting of recurrences, it may be difficult to distinguish scar from hypocellular DFSP (even more problematic on frozen sections).

Immunopathology/special stains:
  • The majority are CD34 positive
  • CD99 positivity has also been described
  • Cytogenetics: a translocation, t(17;22)(q21;q13), is seen in many cases Pigmented cells in Bednar tumor are S100 positive

CONTRIBUTED BY KAREN FRITCHIE, MD
**Diagnosis:** Angiomatoid Fibrous Histiocytoma

A 20 year old male presents with this subcutaneous mass. What is the correct diagnosis?

- A. Benign fibrous histiocytoma
- B. Undifferentiated sarcoma
- C. Metastatic melanoma
- D. Epithelioid sarcoma
- E. **Angiomatoid fibrous histiocytoma**

Angiomatoid fibrous histiocytoma (AFH) is a distinct entity that usually involves children and young adults and presents as a slow growing multinodular or cystic mass. The most common site of involvement is the extremity. Some patients may present with systemic symptoms such as anemia, pyrexia or weight loss. Histologically, angiomatoid fibrous histiocytoma is characterized by a solid proliferation of histiocyte-like cells with cystic areas of hemorrhage surrounded by a fibrous pseudocapsule and a lymphoid cuff. Occasionally, these tumors are mistaken for lymph nodes with a metastatic process. About 50% of cases stain for the triad of: desmin, EMA and CD68. Most AFH harbor the fusion gene EWSR1/CREB1 due to the chromosomal t(2;22)(q33;q12). However, other fusion genes have been described, including EWSR1/ATF1 and FUS/ATF1. FISH studies showing these fusions/translocations may be helpful in diagnostically challenging cases. AFH has a local recurrence rate of approximately 10% with less than 1% of cases metastasizing.

CASE #131 – SLIDE #131

Diagnosis: Androgenetic alopecia

A 4mm punch biopsy specimen was taken from the scalp of a 45 year old woman who was complaining of progressive thinning of the hair. The best diagnosis is:

A. normal scalp  
B. telogen effluvium  
C. androgenetic alopecia  
D. alopecia areata  
E. traction alopecia

Androgenetic alopecia is a nonscarring form of hair loss mediated by androgens; also known as common or pattern baldness.

Clinical features:
- Most common type of hair loss affecting both women and men
- May begin in early adulthood, affects 50% of men by the fifth decade
- Family history of baldness is common

Pathology:
- Normal total number of follicles
- Increased number of miniaturized vellus follicles
- Increased numbers of telogen follicles
- Increased fibrous streamers (stellae)

CONTRIBUTED BY LEONARD SPERLING, MD
Diagnosis: Leprosy

The best diagnosis is:

A. Erythema annulare centrifugum
B. **Hansen disease (leprosy)**
C. Foreign body granuloma
D. Granuloma annulare
E. Localized chronic fibrosing vasculitis

*M. leprae* is an intracellular organism most commonly transmitted from human to human. The course and presentation of an individual infected with *M. leprae* depends on the host response to the bacillus. The incubation period of leprosy is variable, on average 5 years. The organism is of low infectivity and transmission requires prolonged or close contact. The portals of entries are thought to be skin and upper respiratory tract, particularly the nasal mucosa. The spectrum of clinical presentation and histopathologic findings of leprosy are currently classified according to the Ridley-Jopling classification. At one end of the spectrum is tuberculoid leprosy, which is a paucibacillary form with few lesions. On the other end is lepromatous leprosy, in which there are numerous lesions with myriad bacilli. In between are the clinical forms classified as borderline-tuberculoid, borderline, and borderline-lepromatous leprosy. This clinical-histologic classification has been shown to correlate closely with the level of cell-mediated immunity to the pathogen.

Indeterminate leprosy is a form better recognized in the endemic regions, seen before the appearance of well-developed lesions of leprosy. It usually manifests as single or multiple ill-defined hypopigmented or slightly erythematous macules, usually on the limbs. Slight impairment of sensation may be present. Most indeterminate leprosy lesions heal spontaneously, but approximately 25% of cases progress.

Tuberculoid leprosy is a relatively stable form seen in patients with strong immunologic host resistance and a markedly positive lepromin test result. Very well-demarcated annular patches or plaques with raised erythematous borders and central clearing are distributed asymmetrically on the trunk or extremities. Sensory impairment is an essential feature, and enlarging regional nerves often lead to palsy. The lesion is characteristically anesthetic and anhidrotic.

Borderline-tuberculoid leprosy is usually associated with more numerous, smaller lesions than classic tuberculoid leprosy. Hair impairment and hypoesthesia are more prevalent. Borderline leprosy represents the middle of the spectrum, but it is unstable, with patients quickly upgrading or downgrading to a more stable stage. Cutaneous lesions are larger, usually ill-defined, erythematous or copper-colored, annular patches or plaques. Borderline-lepromatous leprosy has more numerous and poorly defined lesions than borderline-tuberculoid leprosy. These lesions are shinier and less anesthetic than the tuberculoid type. Nodular lesions may be present.

Lepromatous leprosy occurs in patients with minimal or absent host response. The cutaneous lesions are usually symmetric, poorly demarcated, erythematous and hypopigmented macules, patches, and nodules, frequently involving the earlobes and nasal mucosa. Multiple facial
nodules, which spare the eyebrows, give a classical leonine appearance. When local nerves are involved, lepromatous leprosy causes hypoesthesia of the affected areas. Multiple autoantibodies are frequently detected in lepromatous leprosy, and there is an increased incidence of vitiligo.

Histoid leprosy—a rare, nodular variant of lepromatous leprosy—usually develops in longstanding cases, possibly associated with drug resistance. It is characterized by cutaneous or subcutaneous nodules and plaques.

Erythema nodosum leprosum is an immune complex–mediated reaction associated with multidrug therapy. It occurs in 25% to 70% of lepromatous leprosy cases and occasionally in borderline-lepromatous cases during therapy. The clinical features include widespread eruptions of painful, erythematous, and violaceous nodules, often involving the extremities, and associated with systemic symptoms. Individual lesions last for 1 to 3 weeks. Lucio’s phenomenon, a diffuse non-nodular form of lepromatous leprosy, is primarily observed in Mexican patients and is associated with irregularly shaped, jagged purpuric lesions and hemorrhagic ulcers as a result of the underlying vasculitic changes.

Indeterminate leprosy is characterized by a superficial and deep perivascular and periannexal lymphohistiocytic infiltrate, which involves less than 5% of the dermis. A mild proliferation of Schwann cells may be observed, but marked neural thickening is usually absent. Bacilli are only occasionally seen with Fite stain. Skin biopsies of tuberculoid leprosy resemble those of cutaneous tuberculosis, especially lupus vulgaris. Well-formed granulomas without caseation can be seen throughout the dermis without a Grenz zone; they are composed of epithelioid cells, giant cells, and lymphocytes and they frequently surround neurovascular bundles and erector pili muscle and may destroy the eccrine glands. They can erode the overlying epidermis or extend into peripheral nerves or pilar muscles. AFB is rarely identified with the Fite stain.

In borderline-tuberculoid leprosy, the noncaseating granulomas are less evident, and nerve destruction is less prominent. The lymphocytic mantles about tubercles may be incomplete or poorly developed. A subepidermal grenz zone may or may not be present. AFB are often absent. Borderline leprosy shows collections of epithelioid histiocytes with no giant cells and very few lymphocytes. AFB are easy to find in this condition. Borderline-lepromatous granulomas consist of aggregates of lymphocytes and macrophages containing abundant granular to foamy cytoplasm.

Numerous AFB are seen with Fite stain. Lymphocytes and histiocytes infiltrate the nerve, producing laminated perineurium. Sheets of macrophages with a granular to foamy cytoplasm arranged in a perineural, perivascular, and periappendiceal fashion characterize lepromatous leprosy. The foamy histiocytes of leprosy resemble those seen in xanthoma; they are called lepra or Virchow cells. AFB load the cytoplasm of macrophages, endothelial cells, sweat glands, nerves, and Schwann cells. Effacement of the epidermal rete ridges with a distinct Grenz zone is often present along with scattered lymphocytes and plasma cells. The histology of histoid leprosy is characterized by relatively circumscribednodules that are composed of predominantly spindle cells intermixed with small collections of foamy macrophages and arranged in a storiform pattern. Because the spindle-shaped cells are of dermal
dendritic origin (expressing factor XIIIa), the histologic findings may closely resemble a fibrous histiocytoma. Both spindle-shaped cells and foamy macrophages are heavily infected with AFB.

At the sites of preexisting lepromatous leprosy, erythema nodosum leprosum shows a mixed dermal infiltrate of lymphocytes and a variable number of neutrophils. The cytoplasm of dermal macrophages contains fragmented AFB. Leukocytoclastic vasculitis or panniculitis may also be present.

In Lucio’s phenomenon, necrotizing vasculitis of the small dermal vessels is found, often associated with epidermal infarction. Less commonly, vascular occlusion occurs when the superficial vessels thrombose or endothelial cells swell.
CASE #133—SLIDE #133

**Diagnosis:** Tinea Nigra

A 44 year old man has noted a new pigmented lesion on the foot. The best diagnosis is:

A. Solar lentigo  
B. Acral lentiginous melanoma  
C. **Tinea nigra**  
D. Acral nevus  
E. Ochronosis

Tinea nigra is caused by Phaeoannellomyces werneckii, and the lesions consist of brown-black macules, usually located on the palms, that enlarge slowly and can be confused clinically with a melanocytic proliferation. Tinea nigra is characterized by black-brown, septate hyphae present in a compact stratum corneum.
CASE #134 — SLIDE #134

Diagnosis: Cryptococcosis

Case Summary:
A 62 year old man with a history of renal transplantation develops umbilicated papules on the face. The best diagnosis is:

A. Cryptococcosis  
B. Blastomycosis  
C. Leishmaniasis  
D. Paracoccidiomycosis  
E. Lacaziosis

Clinical features:
- Caused by Cryptococcus neoformans
- The organism is found in bird droppings (pigeons)
- Occurs worldwide
- Occurs in immunocompromised patients, including those with HIV/AIDS

Presentation:
- Skin is secondarily involved (very uncommonly) after primary infection in the lung
- Mostly on the head and neck
- Widespread papules, pustules, nodules, and ulcers
- Meningitis and meningoencephalitis are common features of this infection
- Primary inoculation of the skin is exceedingly rare

Pathology:
- Granulomatous (high host immune response), gelatinous (low host immune response), and suppurative
- The organism is a 3- to 6-μm yeast surrounded by a conspicuous mucoid capsule
- Narrow-based budding is characteristic
- Few organisms in granulomatous form
- Numerous organisms in gelatinous form; larger organisms may be seen, giving rise to a pseudoclear cell appearance; this form does not exhibit much inflammation.

Immunopathology/special stains:
The organisms are positive with silver and PAS stains. The capsule stains with mucicarmine and alcian blue.

CONTRIBUTED BY THOMAS HELM, MD
CASE #135 — SLIDE #135

**Diagnosis:** Mycobacterium Marinum

A 47 year old man has tender nodules on the forearm. The best diagnosis is:

A. Leishmaniasis  
B. Chromomycosis  
C. Foreign body reaction  
D. Ruptured cyst  
E. **Mycobacterium marinum infection**

Important questions to ask include:

A. How many miles does he jog each day  
B. **Does he have a fish tank**  
C. Does he eat raw oysters  
D. Is he in the military  
E. Has he lost weight

Nontuberculous ("atypical") mycobacterial infections are caused by a heterogeneous group that excludes M. tuberculosis. They are AFB that are present in many different environments worldwide. There has been an increase in the incidence of infections caused by these organisms over the past decades. Although they often lead to systemic disease in immunocompromised patients, they may affect the skin in many ways. The microorganisms are often introduced at a site of trauma.

*Mycobacterium marinum* is found worldwide in salt or fresh water. Lesions are usually limited to the skin because the organisms require a temperature of 30° to 32° C for optimal growth. Systemic dissemination is rare except for immunocompromised hosts. Cutaneous infections are often referred to as swimming pool granuloma or fish tank granuloma.

The histologic findings in *M. marinum* infection vary. They range from suppurative dermatitis with ulceration and necrosis in early lesions to tuberculoid granulomas at the late stage. The epidermis often shows hyperkeratosis and papillomatosis and is occasionally ulcerated. The early lesions may have AFB evident with Fite stain.

CONTRIBUTED BY THOMAS HELM, MD
CASE #136 — SLIDE #136

**Diagnosis:** Pyoderma Gangrenosum -like changes in granulomatosis with polyangiitis

Case summary: A 17 year-old boy was seen for progressive ulceration of his ear for the past several months

The presence of ulceration with mixed granulomatous inflammation with epitheliomatous hyperplasia is most consistent with:

A. Atypical Mycobacterial Infection
B. Pyoderma gangrenosum
C. Granulomatosis with polyangiitis (Wegener’s granulomatosis) – Correct
D. Deep fungal infection
E. All of the above are valid considerations

GPA can involve the skin during the course of illness and may create specific skin lesions in approximately one third of patients. Most often skin lesions develop in the midst of other systemic symptoms and signs of active disease although rarely the skin may be the first sign of disease. The most common skin lesion seen in GPA is palpable purpura which correlates with Leukocytoclastic vasculitis but other patterns are possible including ulceration of the skin which can closely resemble pyoderma gangrenosum. The pathologic correlate to these ulcerations can include granulomatous vasculitis but more often the changes are inflammatory, with a mixture of acute and granulomatous inflammation without obvious vasculitis. In this situation, clinical input is essential as this microscopic pattern is not diagnostic in a specific way but requires correlation with the clinical findings as well as serologic testing. Most of these patients with PG-like lesions will be ANCA positive. Stains for micro-organisms should be done as there is the possibility of secondary infection.

Reference:
CASE #137 — SLIDE #137

**Case Summary**
A 42 year old man presented to the Emergency Department with recent onset of fevers, sore throat, and a vesicular rash. Multiple small, targetoid vesicles were seen on the palms, dorsal hands, and feet (with no extension beyond the ankles). Mucosal lesions were not appreciated, but a few papules were seen around the mouth.

**Question 79**
What is the most likely diagnosis?
A) Herpetic dermatitis- **Incorrect.** Herpes virus infection may cause an intraepidermal blister due to ballooning degeneration, but classically demonstrates viral cytopathic effect within keratinocytes (multinucleation, margination of chromatin, and nuclear molding).
B) Erythema multiforme- **Incorrect.** Erythema multiforme classically shows interface dermatitis with scattered apoptotic keratinocytes at all levels of the epidermis. Sometimes the intensity of interface alteration results in subepidermal vesiculation.
C) Orf – **Incorrect.** In orf, there is marked suprapidermal edema and vacuolization of superficial keratinocytes with eosinophilic cytoplasmic inclusions. A history of contact with goats or sheep can often be elicited from patients, and involvement of the feet would be unusual.
D) Hand-Foot-Mouth disease – **Correct.** The biopsy shows a predominantly intraepidermal blister with reticular degeneration of keratinocytes and necrosis of the blister roof, features described in hand-foot-mouth disease.
E) Erythema infectiosum- **Incorrect.** Erythema infectiosum is viral exanthem occurring most often in children, also called “slapped cheek” disease or fifth disease due to the characteristic red cheeks the illness produces.

**Question 80**
What is the most likely reason for the clinical presentation?
A) Poxvirus infection- **Incorrect.** Poxviruses are a family of viruses whose genera cause diseases such as smallpox, molluscum contagiosum, milker’s nodule, and orf.
B) Coxsackie virus infection- **Correct.** Coxsackie virus A16 is the most common cause of hand-foot-mouth disease, with Coxsackie virus A6 implicated in atypically-presenting cases such as those occurring in adults or more clinically severe disease.
C) Parvovirus infection- **Incorrect.** Parvovirus B19 causes erythema infectiosum and is the most commonly implicated virus in papular-pruritic gloves and socks syndrome.
D) Mycoplasma pneumoniae infection – **Incorrect.** Mycoplasma infection can precipitate cases of erythema multiforme and Stevens Johnson syndrome but does not give rise to hand-foot-mouth disease.
E) Herpes simplex virus type 1 infection- **Incorrect.** HSV type 1 gives rise to herpetic dermatitis and can precipitate cases of erythema multiforme.

**Clinical Features**
Hand-foot-mouth disease is a self-limited viral illness. Most commonly, it occurs in young children, presenting as oral mucosal erosions and small vesicles on the palms and soles with accompanying fever. These cases are usually caused by Coxsackie virus serotype A16 and enterovirus type 71. More recently, outbreaks of Coxsackie virus type A6 have been described as causing an “atypical” form of hand-foot-mouth disease. These cases are more commonly seen...
in adult patients, may be widespread rather than limited in lesion distribution, are sometimes severe enough to require short hospitalizations, and may result in shedding of the nail (onychomadesis) during recovery. The term “eczema coxsackium” has been used to describe atypical hand-foot-mouth disease lesions preferentially involving the affected skin of patients with atopic dermatitis (in a manner similar to eczema herpeticum).

**Histopathologic Features**
- Intraepidermal vesicle/bullae with partial to total necrosis of the blister roof
- Reticular degeneration of keratinocytes
- Absence of specific viral cytopathic inclusions
- Mixed dermal inflammatory infiltrate
- Viral particles can be identified in skin lesions and blister fluid by electron microscopy

**References**
Diagnosis: Cystic Sebaceoma

This tumor presents as a nodule or plaque, typically on the face or scalp. The lesion is associated with the Muir-Torre syndrome as discussed in the section on sebaceous adenoma. Muir-Torre syndrome presents as multiple sebaceous neoplasms, multiple adenomatous polyps and improved survival despite the diagnosis of one or more visceral adenocarcinomas.

MICROSCOPIC FEATURES:

- Nodular or plate-like dermal proliferation of basaloid epithelial cells
- The tumor is surrounded by an eosinophilic fibrotic stroma
- The nodules are composed of a majority of basaloid cells and transitional cells with scattered aggregates of mature sebocytes
- In some cases, sheets of basaloid cells with multiple small vacuoles (immature sebocytes) may be seen
- Mitoses or central cysts with squamous metaplasia may be seen.
- Intra-epidermal benign sebaceous neoplasms have been described with abundant germinative and transitional cells (intra-epidermal sebaceoma or intra-epidermal sebaceous epithelioma).
- Transitions to areas with intra-epidermal neoplasms with more abundant sebocytes (intra-epidermal sebaceous adenoma) are seen
CASE #139 — SLIDE #139

Case Summary
A 56 year-old man presents to his general practitioner with a 1.5 cm solitary, circumscribed subcutaneous nodule on the back of his neck.

Question 87
What is the best diagnosis?
A. Superficial angiomyxoma - Incorrect. Superficial angiomyxoma shows spindled and stellate cells upon an often delicately and well-vascularized more basophilic matrix. In more than half of cases, an epithelial component (e.g. keratinous cysts, epithelial strands) may be seen.
B. Pleomorphic lipoma, fat-poor - Correct. A fibrous stroma containing uniform, evenly dispersed spindled cells makes up the majority of this lesion. The finding of scattered foci of more myxoid stroma containing enlarged floret-type cells is consistent with the fat-poor variant of pleomorphic lipoma. Some measure of atypia within enlarged floret-type cells is characteristic. Small clusters of mature adipocytes may be seen throughout the lesion.
C. Solitary fibrous tumor - Incorrect. Solitary fibrous tumor is a circumscribed lesion with alternating cellular and hypocellular regions. Tumor is composed of short spindled or ovoid cells arranged in a fascicular, storiform or more haphazard pattern. A hyalinized stroma containing prominent associated blood vessels is typically seen. Focal stromal myxoid change may be observed as well.
D. Dermatofibrosarcoma protuberans - Incorrect. DFSP typically arises in the dermis and is composed of a cellular monotonous population of cells often arranged in a more storiform pattern. Tumor growth characteristically spares adnexa and fat.
E. Low-grade myxofibrosarcoma - Incorrect. LG-MFS typically does not involve the upper trunk or head/neck area. Additionally, low-grade myxofibrosarcoma is purely myxoid and typically exhibits more diffuse nuclear atypia.

Question 88
What is the typical clinical course of this lesion?
A. Completely benign; rarely recurs if incompletely excised - Correct. This tumor is considered benign with only rare recurrences reported. Tumors do not dedifferentiate or metastasize.
B. Benign; high recurrence rate if incompletely excised - Incorrect. Although benign, this tumor recurs only very rarely.
C. Low-grade malignant; complete excision is required - Incorrect. Despite the observed atypia of scattered floret cells, this tumor is considered benign.
D. Low-grade malignant; complete excision with radiotherapy recommended - Incorrect. Once excised, there is typically no need for additional treatment.
E. Variable; complete excision is the recommended treatment - Incorrect. Despite a variable appearance which raises a broad differential diagnosis, this tumor is considered benign with only a rare risk of recurrence.

Clinical Features
Pleomorphic lipoma, considered a variant of spindle cell lipoma, typically presents as a dermal or subcutaneous solitary, circumscribed nodule or mass upon the upper back/posterior neck of middle-aged to elderly men. Other bodily sites are reported in a minority of cases (e.g. face, palm).
**Histopathologic Features**
Histologic sections show a fairly discrete lesion composed of eosinophilic fibrosis containing fairly uniform spindled cells with elongate nuclei and inconspicuous nucleoli. Foci of more myxoid stromal change with associated elongate spindled cells and scattered, enlarged floret-type giant cells are also seen. Scattered adipocytes, either singly or in small clusters, are observed typically at the lesion periphery. Despite the enlarged floret cells and some measure of atypia, mitoses are not identified.

Performed CD34 immunohistochemistry highlights both bland spindle-shaped cells, mesenchymal cells and more enlarged floret cells. S-100, desmin, smooth muscle actin and CD68 are negative in the spindled and floret cells. A Ki-67 proliferation index is low (< 1%).

**References:**
Diagnosis: Grover's disease, porokeratotic variant

In this 62-year old man who developed slightly pruritic, light pink, scaly flat-topped papules on the trunk, what is the most likely diagnosis?

A. Darier disease  
B. Eruptive verruca plana  
C. Pityriasis rosea  
D. Pityriasis rubra pilaris  
E. Porokeratotic variant of Grover disease

Answer: Grover disease, porokeratotic variant

Grover disease, or transient acantholytic dyskeratosis, usually presents as asymptomatic or pruritic pink papules on the trunk of middle-aged men. Exacerbating factors include heat and immobility, as may occur in the post-operative period. The microscopic features of Grover disease are varied. The most frequently observed feature is focal acantholytic dyskeratosis, with changes resembling those seen in Darier disease. Three other classical patterns include the spongiotic, pemphigus-like, and Hailey-Hailey disease-like changes. More recently reported microscopic variants include: porokeratotic, lentiginous, vesicular, lichenoid, dysmaturative, and epidermolytic hyperkeratosis variants. Approximately 1/3rd of cases contain more than one microscopic pattern. This particular case showed focal acantholytic dyskeratosis with numerous cornoid lamellae which, in combination with clinical findings, supported a diagnosis of Grover disease, porokeratotic variant. Treatment is optional but may include the use of topical corticosteroids, narrowband UVB phototherapy, and minimization of exacerbating factors. Accurate diagnosis requires careful clinicopathologic correlation.


CONTRIBUTED BY JULIA LEHMAN, MD
CASE #141 — SLIDE #141

**Diagnosis:** Hypertrophic Lichen Planus

This 87-year old woman developed multiple hyperkeratotic lesions on the bilateral lower extremities. The best diagnosis is:

- A. Extragenital lichen sclerosus
- B. Hypertrophic lupus erythematosus
- C. Hypertrophic lichen planus
- D. Pseudocarcinomatous hyperplasia
- E. Squamous cell carcinoma

**Answer:** Hypertrophic lichen planus

Lichen planus has many clinical and microscopic variants. Hypertrophic lichen planus usually presents as multiple hyperkeratotic nodules on the lower extremities. Microscopic features include lichenoid lymphohistiocytic inflammation with epidermal hyperplasia and hypergranulosis. Reactive squamous atypia is not uncommon. The lack of mucin deposition, basement membrane thickening, and superficial and deep perivascular lymphocytic inflammation may aid differentiation from hypertrophic lupus erythematosus. Direct immunofluorescence testing is optional but can show scattered and clumped cytoid bodies with multiple immune conjugates, as well as shaggy fibrinogen deposition along the basement membrane zone.

A challenging clinical scenario arises when patients develop atypical, proliferative lesions in the setting of lichen planus, since squamous cell carcinoma may arise in this context. One method of improving diagnostic accuracy in this scenario is for clinicians to treat hyperkeratotic lesions with high-potency topical corticosteroids under occlusion for a few weeks before pursuing biopsy. If the lesion regresses considerably with this treatment, continued observation may be reasonable. A persistent or growing lesion should be biopsied to exclude squamous cell carcinoma.

**Reference:**
CASE #142—SLIDE #142

Case Summary
A 14 year-old girl with presumed juvenile myoclonic epilepsy presents to her pediatrician reporting "break-through" seizures despite increased dosage of her anti-convulsant therapy. Her mother reports that her daughter is having difficulty in school with increasing deficits in attention-span and heightened somnolence. Close review of the patient's family history revealed similar problems in a paternal cousin. An axillary skin biopsy was performed.

Question 91
What is the best diagnosis?
A. Type IV glycogen storage disease (Andersen Disease) - Incorrect. Type IV GSD shows irregular accumulation of glycogen in muscle and liver cells.
B. Adult polyglucosan body disease - Incorrect. APBD shows 10-18 m, round to ovoid basophilic inclusions within apocrine gland myoepithelial cells.
C. Type I glycogen storage disease (von Gierke Disease) - Incorrect. Type I GSD may be confirmed per percutaneous liver biopsy which shows fibrosis, nuclear hyperglycogenation and fatty change.
D. LaFora Disease - Correct. The presence of numerous, 8-15 m rounded eosinophilic cytoplasmic inclusions within basilar glandular and myoepithelial cells - in conjunction with the prescribed clinical history - is consistent with a diagnosis of LaFora Disease.
E. Normal skin - Incorrect. The presence of numerous eosinophilic rounded inclusions within basilar apocrine gland epithelial and myoepithelial cells is an abnormal finding.

Question 92
Mutation in what gene is attributed to this disease?
A. GBE1 - Incorrect. Mutations in GBE1 are associated with type IV glycogen storage disease (Andersen disease) and adult polyglucosan body disease (APBD).
B. AGL - Incorrect. Mutations in AGL are associated with Type III glycogen storage disease (Cori disease).
C. G6PC - Incorrect. Mutations in G6PC are associated with type I glycogen storage disease (von Gierke Disease).
D. EPM2A - Correct. Mutations in EPM2A (Chr 6q24) are associated with LaFora disease. EMP2A encodes the protein laforin thought to play a critical role in nerve cell survival.
E. None - Incorrect.

Clinical Features
LaFora disease (aka LaFora Progressive Myoclonic Epilepsy) is an autosomal recessive disease which presents typically in the teen years. Patients with previously normal neural function exhibit resistant myoclonic seizures, myoclonus, generalized or focal occipital seizures, and often sensitivity to light. Patient cognitive and neurologic function continually deteriorates, to include dysarthria, ataxia and dementia. Most patients die within ten years of diagnosis due to complications related to degeneration of the nervous system. LaFora disease is caused by mutation in EPM2A or EPM2B/NHLRC1 genes which encode the proteins laforin and malin, respectively. These proteins are believed to play a critical role in nerve survival.

Histopathologic Features
Axillary skin biopsies from patients with LaFora disease reveal numerous round to oval 8 - 15 μm, PAS-positive, diastase resistant inclusions within both basilar secretory and myoepithelial cells of eccrine or apocrine cells (greater within apocrine cells).

References:

CONTRIBUTED BY G. PETER SARANTOPoulos, MD
CASE #143—SLIDE #143

**Diagnosis:** Syringocystadenoma papilliferum and verrucous cyst

This lesion was submitted for histopathologic evaluation with the clinical impression of “cyst”. The most likely diagnosis is:

A. Aggressive digital papillary adenocarcinoma
B. Hidradenoma papilliferum and trichilemal cyst
C. Hidradenoma papilliferum and verrucous cyst
D. Syringocystadenoma papilliferum and trichilemmal cyst
E. Syringocystadenoma papilliferum and verrucous cyst

Answer: E. Syringocystadenoma papilliferum and verrucous cyst

The specimen contains two distinct benign tumors, with one showing a convoluted adnexal neoplasm with ductular differentiation, papillary features, and a stromal lymphoplasmacytic infiltrate, and the other, showing a bland cystic structure with mild papillomatosis, acanthosis, and focal hypergranulosis within the cyst lining. The simultaneous occurrence of syringocystadenoma papilliferum and verrucous cyst in a single biopsy specimen has been reported in at least 4 cases previously.


CONTRIBUTED BY JULIA LEHMAN, MD
CASE #144 — SLIDE #144

**Diagnosis:** Elastosis perforans serpiginosa

In this 21-year old patient with Down syndrome, what is the most likely diagnosis?

A. Elastosis perforans serpiginosa
B. Neurotic excoriations
C. Perforating collagenosis
D. Perforating granuloma annulare
E. Pseudoxanthoma elasticum

Answer: A. Elastosis perforans serpiginosa

Elastosis perforans serpiginosa is characterized by keratotic inflamed papules that coalesce in a serpiginous configuration. EPS is associated with several conditions, including Down syndrome, penicillamine usage, Marfan syndrome, osteogenesis imperfecta, and Ehlers-Danlos syndrome.

Microscopic findings include an epidermal depression with transepidermal elimination of elastin. Overall density of elastin fibers in the superficial dermis is increased. Basophilic material is often present at the site of perforation. Elastin is more readily visualized when stained with a Verhoeff-van Gieson stain.

Diagnosis: Nipple adenoma

Which of the following is the most likely diagnosis?
A. Aggressive digital papillary adenocarcinoma
B. Apocrine cystadenoma
C. Hidradenoma papilliferum
D. Metastatic breast cancer
E. Nipple adenoma

Answer: E. Nipple adenoma

Nipple adenoma, or erosive nipple adenomatosis, is a benign proliferation of lactiferous ducts affecting the nipple-areola complex. Clinically, patients may be aware of a firm, retroareolar nodule deforming the nipple or associated with nipple discharge. While several microscopic variants have been described, consistent features include papillomatosis with ductal hyperplasia, showing a dual-cell layer with epithelial and myoepithelial cells. Accurate recognition of this entity, and differentiation from breast cancer, is essential.

CASE #146 — SLIDE #146

Case Summary
A 70 year-old man with a prior history of hypertension presented with a 3-month history of fatigue, anorexia with progressive weight loss and a painless plaque on the abdomen. Physical examination revealed a pale, ill-appearing male with stable vital signs, abdominal ascites and pitting edema in both lower extremities, but no lymphadenopathy. Skin exam revealed a poorly circumscribed, non-tender, slightly erythematous, indurated plaque at the periumbilical area.

Question 93
The best diagnosis is:
A. Folliculotropic mycosis fungoides — Incorrect. The tumor cells are large in size, entirely confined to the vessels, whereas folliculotropic mycosis fungoides is comprised of small-medium sized T-cells with folliculotropism.
B. Primary cutaneous T-cell lymphoma — Incorrect. The tumor cells in primary cutaneous T-cell lymphoma are not usually confined within the vessels and instead shows protean distribution throughout the skin and subcutaneous tissue.
C. Intravascular large B-cell lymphoma — Correct. Sections reveal the characteristic proliferation of large lymphocytes filling dilated blood vessels throughout the dermis and subcutaneous tissue.
D. Subcutaneous panniculitis-like T-cell lymphoma — Incorrect. The tumor cells in subcutaneous panniculitis-like T-cell lymphoma are typically small-medium in size, confined to the subcutaneous adipose tissue where they encircle adipocytes.
E. Hypersensitivity reaction to medication — Incorrect. Hypersensitivity reactions do not present with an atypical lymphoid infiltrate filling the vessels.

Question 94
Which of the following is the most common complication of this disease:
A. Central nervous system (CNS) Involvement — Correct. Although in theory, intravascular large B-cell lymphoma (IVLCL) can involve the vessels of any other organ, the most common site of involvement in patients from Western countries is the vasculature of the CNS, where it frequently causes neurologic symptoms.
B. Respiratory failure — Incorrect. Although the tumor cells can involve the blood vessels of the lung, IVLCL is not typically associated with respiratory failure.
C. Amyloidosis — Incorrect. Amyloid deposition is not a common feature of IVLCL.
D. Small bowel obstruction — Incorrect. Although the tumor cells can involve the blood vessels of the gastrointestinal tract, IVLCL is not typically associated with obstructive lesions.
E. Joint pain/swelling — Incorrect. Although the tumor cells can involve the blood vessels of the joints, IVLCL is not typically associated with joint pain.

Clinical features
Intravascular large B-cell lymphoma (IVLCL) exhibits protean clinical manifestations dependent upon which organs are involved and the geographic origin of the affected patient. In particular, IVLCL diagnosed in Western countries exhibit common CNS and cutaneous manifestations, whereas patients from Asian countries more frequently develop hemophagocytic syndrome and present with bone marrow involvement, fever,
hepatosplenomegaly and thrombocytopenia. Because IVLBCL can involve virtually any organ and is typically widely disseminated at the time it is diagnosed, it presents with a wide range of signs and symptoms, either generalized and nonspecific (such as fever, weight loss, cytopenias) or specifically related to the organ of involvement (including cutaneous lesions, neurologic deficits, hepatic or renal insufficiency). Although IVLBCL is most often disseminated (including common involvement of the central nervous system), the skin can be the only site of involvement, and this is more common in Western countries. Skin lesions show protean manifestations including one or multiple patches or plaques. Telangiectasias are occasionally seen.

**Histopathologic features**

Intravascular large B-cell lymphoma (IVLBCL) exhibits a characteristic proliferation of enlarged, discohesive mononuclear cells that fill and expand the blood vessels of the dermis and subcutaneous tissue; the tumor cells are characteristically confined to the intravascular spaces as demonstrated in the current case. Immunohistochemical studies reveal the tumor cells to be CD20+, CD79a+ B-cells that usually express Bcl-2 and Mum-1. Aberrant expression of CD5 has been described in some cases. Many hypotheses have been proffered to explain the mechanism underlying the predilection of the tumor cells for the vascular lumina. Immunohistochemical studies have demonstrated that IVLBCL cells lack certain cell adhesion molecules (CD29 [integrin B1]), CD54 (ICAM1), and CD11a) and certain matrix metalloproteinases (MMP) such as MMP-2 and MMP-9, which are important for vascular extravasation and parenchymal invasion by lymphocytes.

**References**


**CONTRIBUTED BY MICHAEL T. TETZLAFF, MD, PhD**
Diagnosis: Myxoid sarcoma

Myxoid sarcoma
Myxoid sarcoma tumors are typically composed of a lobulated mass with microscopic cords of polygonal, spindle, or stellate cells within myxoid stroma, morphologically reminiscent of extraskeletal myxoid chondrosarcoma. In a recent study of pulmonary myxoid sarcoma, nearly half of the 9 cases studied showed no or minimal atypia, 6 showed focal pleomorphism, and 5 had necrosis. Mitotic activity did not exceed 5/10 high-power fields. All cases demonstrated mild, chronic inflammation, which was predominantly lymphoplasmacytic with occasional eosinophils and foamy macrophages. Lymphoid aggregates with germinal centers were intermixed with or surrounded the tumor in 4 cases. Tumors were immunoreactive for vimentin and weakly focal for epithelial membrane antigen (EMA). Of 9 tumors, 7 were shown to harbor a specific EWSR1-CREB1 t(2;22)(q33;q12) similar to the translocation in conventional clear cell sarcoma (case #123), clear cell sarcoma involving the bowel, hyalinizing clear cell sarcoma of salivary gland and angiomatoid fibrous histiocytes (slide #130). EWSR1 is often referred to as promiscuous because translocations with it are found in Ewing sarcoma and similar (Ewing-like) small round cell sarcomas, desmoplastic small round cell tumor, myxoid liposarcoma, extraskeletal myxoid chondrosarcoma, extrasalivary myoepithelial tumors and sporadic examples of low-grade fibromyxoid sarcoma, sclerosing epithelioid fibrosarcoma and mesothelioma.


CONTRIBUTED BY RAJIV PATEL, MD AND DANIEL COHEN, MD, PHD
Diagnosis: Eccrine angiomatous hamartoma

Case Summary
A 44 year-old female presented with a 2 year history of an 8 x 15 cm red-brown plaque on the thigh.

The best diagnosis is:
A. Eccrine angiomatous hamartoma – Correct. This biopsy demonstrates both an increased number of normal appearing eccrine glands and an increase in small blood vessels which are the requisite components of eccrine angiomatous hamartoma.
B. Lupus Panniculitis – Incorrect. While this biopsy demonstrates some secondary inflammation in the subcutaneous tissue, lupus panniculitis is characterized by a lymphocytic lobular panniculitis with hyalinization of fat lobules in older lesions, without an increase in eccrine glands and small blood vessels.
C. Chronic erythema nodosum – Incorrect. Chronic erythema nodosum is a septal lobular panniculitis that often has septal radial granulomas and should not have increased eccrine glands or vessels.
D. Morphea profunda – Incorrect. While early morphea profunda may present as a septal lobular panniculitis with variable inflammation, it should not have increased eccrine glands or vessels.
E. Neutrophilic eccrine hidradenitis – Incorrect. The histologic hallmark of neutrophilic eccrine hidradenitis is neutrophilic inflammation surrounding and within eccrine secretory coils, often with necrosis of the secretory epithelium. There should not be an increase in numbers of eccrine glands or vessels.

Which of the following is characteristic of this lesion:
A. Associated with chemotherapeutic agents – Incorrect. Neutrophilic eccrine hidradenitis may be seen in association with induction chemotherapy. It is not associated with eccrine angiomatous hamartoma.
B. Involvement of fascia may be seen – Incorrect. In addition to subcutaneous septal sclerosis, morphea profunda may also involve the fascial layers. This is not a feature of eccrine angiomatous hamartoma.
C. Most commonly occurs on face and upper extremities – Incorrect. While lupus panniculitis is most commonly seen on the face and upper extremities, eccrine angiomatous hamartoma may occur anywhere, but most often on the lower extremities.
D. More commonly seen in pediatric age group – Correct. Eccrine angiomatous hamartoma is most commonly a congenital lesion or presents during childhood. Adult onset is less common, but may be seen.
E. Septal radial granulomas are characteristic – Incorrect. While there may be some secondary inflammation in the subcutaneous tissue in eccrine angiomatous hamartoma, septal radial granulomas are a histologic hallmark of erythema nodosum.
Clinical Features
Eccrine angiomatous hamartoma is a rare hamartomatous condition characterized by increased numbers of eccrine glands embedded in a mucinous stroma and increased small vessels. The classic clinical presentation is that of a solitary bluish-red nodule or plaque either present at birth or developing in childhood. Adult-onset lesions are less common, but may be seen. The lesions are generally asymptomatic. However, pain and/or hyperhidrosis have been reported as symptoms. The most common site of involvement is the lower extremity.

Histopathologic Features
In addition to the prerequisite increased eccrine coils and small blood vessels in the deep dermis, there may be increased mucin, fat, nerve fibers, or pilar structures, as well as background nonspecific inflammation.

References
Diagnosis: Fibroblastic rheumatism

Case Summary
A 6-year old boy with a history of juvenile idiopathic arthritis and a pericardial effusion presented with firm papules on thumb and digits.

The best diagnosis is:
A. Rheumatoid nodules – Incorrect. Palisaded granulomatous process with fibrinoid collagen degeneration is not identified.
B. Infantile digital fibromatosis – Incorrect. The lesion lacks the characteristic, brightly eosinophilic intracytoplasmic inclusions in fibrocytes.
C. Mucinosis – Incorrect. Mucin deposits are not identified.
D. Fibroblastic Rheumatism – Correct. There is a fibroblastic proliferation with complete loss of elastic fibers on elastic staining.
E. Granuloma annulare – Incorrect. Palisaded granulomas with mucinous collagen degeneration are not identified.

The condition most likely associated with this diagnosis is:
A. Scleroderma – Incorrect. Fibroblastic rheumatism has not been described in association with scleroderma.
B. Psoriasis – Incorrect. Fibroblastic rheumatism has not been described in association with psoriasis.
C. Polyarthritis – Correct. Fibroblastic rheumatism cases described thus far have a strong association with polyarthritis and flexion contractures of the hand.
D. Immunobullous disease – Incorrect. Fibroblastic rheumatism has not been described in association with immunobullous disease.
E. EBV infection – Incorrect. There is no known association between an EBV infection and fibroblastic rheumatism.

Clinical Features
- Cutaneous papules or nodules on digits and arthralgias
- Often occurring in the setting of polyarthritis and flexion contractures resulting in cutaneous nodules

Histopathologic Features
- Typically exophytic nodule with a fibroblastic proliferation in a collagenous stroma
- Fibroblast may form cellular fascicles or be arranged in a more pauci-cellular pattern in a background collagenous stroma
- Staining with elastic stain shows loss of elastic fibers
References
CASE #150 — SLIDE #150

Diagnosis: Frontal Fibrosing Alopecia

Case Summary
A 63-year old woman presented with hair loss across the frontal hairline.

The best diagnosis is:
A. Frontal fibrosing alopecia – Correct. Frontal fibrosing alopecia characteristically causes a recession of the frontal and preauricular hairline. Other forms of alopecia that can occur in this distribution are traction alopecia and alopecia areata
B. Ulerythema oophyrogenes – Incorrect. This typically affects the lateral eyebrows causing erythema and pitted scarring
C. Chronic cutaneous (discoid) lupus erythematosus – Incorrect. This typically affects the head and neck including the scalp
D. Folliculitis decalvans – Incorrect. This can affect any part of the scalp and does not typically affect the frontal hair line
E. Dissecting cellulitis of the scalp – Incorrect. This can affect any part of the scalp and early on resembles a follicular cyst

The histologic findings in frontal fibrosing alopecia most closely resemble those of which disease:
A. Chronic cutaneous (discoid) lupus erythematosus – Incorrect. While both diseases are examples of lymphocytic scarring alopecia, the histologic findings of frontal fibrosing alopecia are identical to lichen planopilaris
B. Lichen planopilaris – Correct. The histologic findings in frontal fibrosing alopecia are indistinguishable from lichen planopilaris
C. Traction alopecia – Incorrect. Traction alopecia is typically non-inflammatory, although follicular dropout can occur
D. Folliculitis decalvans – Incorrect. Folliculitis decalvans is classified as a neutrophilic scarring alopecia, and causes neutrophilic folliculitis, a neutrophilic infiltrate with admixed lymphocytes and plasma cells, and interfollicular fibrosis
E. Dissecting cellulitis of the scalp – Incorrect. Dissecting cellulitis is classified as a neutrophilic scarring alopecia, and causes a deep inflammatory infiltrate of neutrophils, lymphocytes and plasma cells, granulation tissue and formation of sinus tracts

Clinical Features
Frontal fibrosing alopecia is a recently described scarring alopecia that is being seen with increasing frequency, felt to be a variant of lichen planopilaris. It typically affects postmenopausal women, causing recession of the frontal and preauricular hairline. Loss of eyebrows occurs in over 50% of patients, and loss of body hair can occur as well. Hair loss at these sites can precede scalp loss. On close inspection some patients will exhibit perifollicular erythema and fine scale, especially when the disease is active, but this is not always present, especially in sites other than the scalp. Other clinical findings include individual hairs seeming to be on the forehead in front of a receded hairline (“lonely hairs”), a fine sandpaper-like rash on the temples, and glabellar red dots. The cause of frontal fibrosing alopecia is unknown.
**Histopathologic Features**

- There is often a decreased number of hair follicles, depending on how much scarring has occurred by the time of the biopsy
- Follicular size is normal
- Affected follicles exhibit loss of sebaceous glands, perifollicular fibrosis with admixed mucin, and a perifollicular lymphocytic infiltrate, especially at the level of the infundibulum
- Sometimes lymphocytes can be found within the follicular epithelium
- Vacuolar alteration of the follicular epithelium can be present
- In advanced cases, fibrosis replaces follicular units
- The disease can be focal, and sometimes there are normal follicular units admixed with affected follicles
- Biopsies of the face and body reveal similar but more subtle changes around smaller or vellus hair follicles

**References**

Diagnosis: Incontinentia Pigmenti

Case Summary
A 3-week old girl with papules and vesicles on all four limbs, blaschkoid in appearance.

The best diagnosis is:
A. Incontinentia pigmenti – Correct. The histologic findings of eosinophilic spongiosis and individually necrotic keratinocytes distributed in Blaschko’s lines are diagnostic of incontinentia pigmenti
B. Linear epidermal nevus – Incorrect. This could also be blaschkoid in distribution, is not preceded by vesicles and does not exhibit eosinophils
C. Hypomelanosis of Ito – Incorrect. This is also blaschkoid, but is not preceded by vesicles and does not exhibit eosinophils
D. Segmental Darier’s disease – Incorrect. This is also blaschkoid, but consists of scaly papules, not vesicles, and exhibits suprabasal acantholysis and dyskeratosis
E. Focal dermal hypoplasia (Goltz syndrome) – Incorrect. This is also blaschkoid, but consists of reticulate erythema with herniation of fat

A helpful histopathologic diagnostic clue to the late stage of this disease in adults is:
A. Lipodystrophy – Incorrect. This is not a feature of incontinentia pigmenti
B. Absent elastic fibers – Incorrect. Elastic fibers are normal in incontinentia pigmenti
C. Absence of hair follicles – Correct. Stage IV incontinentia pigmenti exhibits individually necrotic keratinocytes, slight epidermal atrophy, decreased pigment and number of melanocytes, slight thickening of the dermis, absent hair follicles and absent sweat glands
D. Increased dermal mucin – Incorrect. This is not a feature of incontinentia pigmenti in adults
E. A sparse neutrophilic infiltrate – Incorrect. This is not a feature of incontinentia pigmenti

Clinical Features
Incontinentia pigmenti (IP) is a rare, X-linked dominant genodermatosis which affects females and is lethal in utero in most males. It is caused by a mutation in the nuclear factor kappa B (NF-κB) signaling pathway, responsible for gene expression of many different cellular processes. The most frequent mutation is a deletion of exons 4-10 of NF-κB essential modulator (NEMO), recently renamed IKBKG (inhibitor of kappa B kinase gamma), on chromosome Xq28. Mosaicism accounts for the clinical phenotype, which is highly variable.

Most patients are diagnosed clinically, as the disease goes through 4 sequential stages starting in the neonatal period. Stage I consists of vesicles and pustules arranged along Blaschko’s lines. These become verrucous in Stage II, hyperpigmented in Stage III, and depigmented and scarred in Stage IV. All lesions after Stage I are alopecic, which can be a clue to the diagnosis. In adults the manifestations of IP can be very subtle. In a recent study half of patients were unaware of their diagnosis, and nearly one third did not report typical neonatal vesicles. Interestingly, Stage 1 lesions can be recurrent during adulthood.
Other manifestations of IP include abnormalities of dentition (including partial anodontia, conical incisors, and persistence of deciduous teeth), the eyes, central nervous system, and nipples.

**Histopathologic Features**

- Individually necrotic (apoptotic) keratinocytes are typical of all lesions
- Absent adnexae are typical of stage II-IV lesions
- The various findings in the Stages often overlap, and the typical findings of each Stage are listed
- Stage I lesions are characterized by spongiosis, spongiotic vesiculation, eosinophilic exocytosis, individually necrotic keratinocytes and a superficial perivascular lymphocytic and eosinophilic infiltrate
- Stage II lesions exhibit individually necrotic keratinocytes, absent adnexae and verrucous epidermal hyperplasia
- Stage III lesions exhibit individually necrotic keratinocytes, absent adnexae and numerous melanophages
- Stage IV lesions demonstrate individually necrotic keratinocytes, absent adnexae, epidermal atrophy, a marked decrease in basal keratinocyte pigmentation, a decreased number of melanocytes, slight thickening and homogenization of the dermis, and sometimes telangiectasia

**References**

Diagnosis: Myopericytoma

Case Summary
A 67 year old male presented to his general practitioner with a slowly enlarging mass on the right leg. Following consultation with a surgeon, the mass was removed.

The best diagnosis is:
A. Cellular neurothekeoma - Incorrect. Cellular neurothekeoma is a benign, nested, epithelioid cell proliferation with paley eosinophilic cytoplasm and occasional myxoid stroma.
B. Schwannoma - Incorrect. Schwannoma is a well-encapsulated proliferation of plump spindled cells growing in fascicles with alternating hypocellular and hypercellular regions.
C. Nodular fasciitis - Incorrect. Nodular fasciitis often shows myxoid stroma within which there is a loose proliferation of slender spindled cells and erythrocyte extravasation.
D. Myofibroma - Incorrect. Myofibroma is a biphasic tumor composed of short ovoid cells with branching vessels juxtaposed to a more slender spindle cell population showing myoid or pseudochondroid features.
E. Myopericytoma - Correct. Myopericytoma, while showing overlapping features with myofibroma, generally consists of a more uniform proliferation of the ovoid spindled cell population associated with branching vessels.

These tumors are most often positive for which immunomarker:
A. SMA - Correct. Myopericytoma often shows strong SMA expression as well as variable staining for h-caldesmon. Desmin stains approximately 10% of tumors.
B. Keratin AE1/AE3 - Incorrect. Myopericytic tumors are consistently negative for keratins.
C. S100P - Incorrect. Myopericytic tumors are consistently negative for S100P.
D. CD20 - Incorrect. Myopericytic tumors have not been reported to express CD20.
E. CD3 - Incorrect. Myopericytic tumors have not been reported to express CD3.

Clinical Features
• In adults, solitary tumors most commonly occur in the skin and/or subcutis of the distal extremities.
• Recurrence upon incomplete excision occurs in a minority of patients.

Histopathologic Features
• Well circumscribed, unencapsulated, often multinodular tumors.
• Ovoid to spindled cells associated with dilated branching vessels.
• Occasionally show glomoid features or myoid whorls.
• Cytomorphologic features are bland with rare mitotic figures.
References


CONTRIBUTED BY TRAVIS J. HOLLMAN, MD, PHD
Diagnosis: Agiokeratoma

Case Summary
A 10-day old generally healthy male was referred to Dermatology for evaluation of violaceous keratotic papules and plaques involving the right lower extremity, stable since birth.

The best diagnosis is:
A. Non-involuting congenital hemangioma – Incorrect. Lesions tend to progress and histopathologically consist of lobules of vessels with surrounding fibrosis and arteriovenous fistulae, without significant abnormalities in overlying epidermis.
B. Angiokeratoma – Correct. The pattern of dilated superficial dermal vessels under an acanthotic and hyperkeratotic epidermis favors this diagnosis.
C. Verrucous hemangioma – Incorrect. Verrucous hemangioma and angiokeratoma have similar clinical appearance and anatomic distribution, but verrucous hemangioma is distinguished by deep extension of vascular proliferation into the subcutis.
D. Tufted angioma – Incorrect. About 25% of tufted angiomas are congenital but are composed of multiple dermal capillary lobules in a “cannonball” pattern.
E. Eccrine angiomatous hamartoma – Incorrect. Although reported in association with angiokeratoma and verrucous hemangioma, eccrine angiomatous hamartoma is characterized by increased number of eccrine glands and sometimes of other normal-appearing structures.

Which of the following immunohistochemical stains is most helpful in the evaluation of vascular lesions of infants?
B. CD45RO – Incorrect. A T-cell marker, not expressed by vascular endothelium.
C. ERG – Incorrect. A vascular marker, not useful in differential diagnosis among vascular malformations and neoplasms.
D. WT1 – Correct. WT (Wilms tumor) 1 appears to be the best marker for differentiating vascular neoplasms from malformations.
E. GLUT-1 – Incorrect. GLUT1 is expressed by endothelial cells of infantile hemangioma but typically is negative or only focally positive in other vascular neoplasms and malformations.

Clinical Features
- Variants of angiokeratoma include Mibelli type mainly found on extensor extremities, Fordyce lesions of scrotum, solitary and multiple angiokeratomas usually of the lower extremities, angiokeratoma circumscriptum, and angiokeratoma corporis diffusum characteristically but not exclusively associated with Fabry disease.
- Congenital or acquired
- Dark violaceous keratotic papules and plaques
  - Solitary, multiple, linear, diffuse, discrete and/or coalescing
Histopathological Features

- Dilated superficial dermal vessels
  - Focal thrombosis
- Irregular epidermal acanthosis with elongated rete ridges between/around the ectatic vessels
- Hyperkeratosis

References
Diagnosis: Epitheloid Sarcoma

Case Summary
A 19-year-old male presented with an acquired slowly growing dermal nodule on the flexor side of his right forefinger.

The best diagnosis is:
A. Epithelioid melanoma – Incorrect. Although the present tumor (i.e. epithelioid sarcoma) imitates focal junctional activity there is no genuine involvement of the dermo-epidermal junction. There is no transepidermal ascent of melanocytic tumor cells. Tumor sheets are located exclusively in the dermis with a characteristic dense collagenous stroma. In contrast to epithelioid melanoma, this tumor is characterized by loosely aggregated tumor cells which quite often are separated from each other by collagenous fibers. There is no pigment.
B. Epithelioid angiosarcoma – Incorrect. The typical shrinkage clefts amidst densely packed epithelioid tumor cells of EAS are missing here. There are no pseudo-adenoid structures which are characteristic of EAS. Usually tumor cells of EAS are much bigger than the present rather small epithelioid tumor cells of ES. Intracytoplasmic vacuoles, which are a hallmark of both EAS and epithelioid hemangioendothelioma, are always missing in ES.
C. Epithelioid sarcoma – Correct. There are typical tumor sheets composed of small isomorphic epithelioid cells, often loosely arranged within a dense collagenous stroma. There is slight similarity with a cellular granuloma annulare, as tumor cells of ES morphologically imitate large histiocytes.
D. Granuloma annulare – Incorrect. The small epithelioid tumor cells of ES indeed imitate cellular granuloma annulare. This is a well-known pitfall. Quite misleading may be a large central tumor necrosis (“geographical necrosis”) which is typical of ES and might be mistaken for “necrobiosis” or a chronic granulomatous inflammation, e.g. granuloma annulare or rheumatoid nodule.
E. Epithelioid sarcoma-like hemangioendothelioma – Incorrect. Epithelioid sarcoma-like (pseudomyogenic) hemangioendothelioma is a distinctive endothelial neoplasm of intermediate malignant potential. The tumor cells are positive for cytokeratins and markers of vascular differentiation including such as ERG and CD31, but they are negative for CD34. Expression of SMARCB1 (INI-1) is retained in the nuclei of the lesional cells.

The characteristic immunophenotype of the forefinger tumor in the 19-year-old man is:
A. S100+, alpha smooth muscle actin+, p63+ - Incorrect. This is the immunophenotype of myoepithelioma, another imitator of ES. Remarkably, myoepithelial carcinoma may show lack of expression of INI1 which should not lead to the misdiagnosis of ES.
B. Fli1+, ERG+, INI1+ - Incorrect. This is the immunophenotype of either epithelioid angiosarcoma or epithelioid hemangioendothelioma. Endothelial markers are not expressed in ES. INI1-positivity is not observed in ES.
C. S100+, INI1+ - Incorrect. This is the immunophenotype of epithelioid malignant melanoma and other tumors, but not of ES which is both S100-negative and INI1-negative.
D. CD68+, Vimentin+ - Incorrect. This immunophenotype belongs to granuloma annulare and other necrobiotic histiocytic conditions. ES does not express CD68.
E. EMA+, Pan-Cytokeratin+, INI1-negative - Correct. Remarkable and paramount for diagnosis is the negativity for INI1. This is a hallmark of ES and quite unique among cutaneous tumors (with very few exceptions, e.g. malignant rhabdoid tumor, myoepithelial carcinoma).

Clinical Features
Epithelioid sarcoma ("distal-type") is a sarcoma characterized by a protracted clinical course, with late recurrences and metastases. It tends to propagate along fascial planes, tendons, and nerve sheaths, and therefore often requires radical surgery with wide excision or amputation as primary treatment. ES ("distal-type") shows a predilection for the distal extremities of young adults. Clinically, tumors frequently are misdiagnosed as deep infection, granuloma annulare, rheumatoid nodule or foreign body reaction.

Histopathologic Features
Histopathologically, there is a characteristic nodular growth pattern with central necrosis, which may superficially mimic a granulomatous process, or a palisading-granulomatous condition, e.g. granuloma annulare or rheumatoid nodule. The predominant cell type is a uniform epithelioid cell with mild nuclear atypia and eosinophilic cytoplasm. Tumor cells are arranged in confluent sheets, often in association with a sclerotic collagenous stroma. There is a characteristic immunophenotype: ES is diffusely positive for EMA, HMW & LMW keratins, and CD34 (50%). Loss of INI1 expression is a hallmark of ES ("proximal-type" and "distal-type") and of paramount importance for differential diagnosis as all other tumor entities in the differential diagnostic spectrum of ES are INI1-positive. In contrast to "distal-type" ES, "proximal-type" ES arises in the pelvis and perineum and shows large cell morphology with marked cytologic atypia. PT-ES usually is more aggressive than DT-ES. The marked loss of INI1 expression is the immunohistochemical hallmark of ES and is quite unique among cutaneous soft tissue tumors: all other relevant tumors are INI1-positive. Rare exceptions with INI1-negativity, apart from ES, are myoepithelial carcinomas and tumors with rhabdoid cell morphology, e.g. malignant rhabdoid tumor. The hSNF5/SMARCB1/INI1 tumor suppressor gene located at 22q11 is inactivated in both PT-ES and DT-ES.

References

CONTRIBUTED BY HEINZ KUTZNER, MD
CASE #155 — SLIDE #155

Diagnosis: Erythema elevatum diutinum (nodular)

Case Summary
An 81-year-old woman presented with multiple firm plantar nodules of long duration.

The best diagnosis is:
A. Superficial nodular fasciitis – Incorrect. The present condition is mostly fibrotic with interspersed leukocytoclastic vasculitis whereas nodular fasciitis is a loosely-textured smooth muscle actin-positive spindle cell proliferation with interspersed histiocytes, but without signs of leukocytoclastic vasculitis.
B. Bacillary angiomatosis – Incorrect. Bacillary angiomatosis in most cases presents either as a pyogenic granuloma-like or a granulation tissue-like richly vascularized lesion with an abundance of neutrophilic granulocytes and organisms (Bartonella quintana or B. henselae), but without fibrosis or sclerosis. Leukocytoclastic vasculitis is not a feature of bacillary angiomatosis.
C. Sclerotic fibroma – Incorrect. Sclerotic fibroma or plywood fibroma is a fibrosclerotic CD34-positive spindle cell proliferation without a significant inflammatory infiltrate. There are no signs of interspersed leukocytoclastic vasculitis.
D. Nodular erythema elevatum diutinum – Correct. Quite typical are the wiry collagen bundles sprinkled with foci of leukocytoclastic vasculitis.
E. Hyalinized leiomyoma – Incorrect. Late-stage piloleiomyoma may appear hyalinized, i.e. with homogeneous eosinophilic features (positive for smooth muscle actin and desmin) that markedly lack the pattern of wiry collagen bundles and superimposed leukocytoclastic vasculitis.

The present condition may show clinical and morphological overlap with
A. Juxtaarticular nodules of syphilis – Incorrect. There is neither association nor a histogenetic relationship or morphological overlap between syphilis and EED.
B. Periarticular nodules of borreliosis – Incorrect. There is no overlap between these two conditions. The etiopathogenesis of EED is unknown. An Arthus-type reaction is the most likely underlying pathogenetic mechanism. An infectious cause has been suggested, but so far could not be corroborated.
C. Extrafacial granuloma faciale – Correct. Although it is still hotly debated, a clinical and morphological overlap between extrafacial granuloma faciale and EED has been repeatedly reported. It remains a matter of debate whether these are two variants of the same disease or two diseases with the same morphological pattern.
D. Angiocentric eosinophilic fibrosis – Incorrect. Angiocentric eosinophilic fibrosis of the larynx and upper respiratory tract mucosa may be closely related with granuloma faciale. But so far an association with EED has not yet been reported.
E. Sweet syndrome – Incorrect. Although EED may be associated with a plethora of inflammatory conditions, a clinical and morphological overlap between EED and Sweet syndrome does not exist. EED is a leukocytoclastic long-standing vasculitis with a marked fibro-sclerotic response during late stages, while Sweet syndrome is a neutrophil-rich inflammatory condition with an accompanying lympho-histiocytic infiltrate but without any associated spindle cell proliferations, fibroplasia, or fibrosclerotic nodules.
Clinical Features
Erythema elevatum diutinum (EED) is a rare localized chronic fibrosing vasculitis of unknown cause first described by Hutchinson in 1888. Early lesions present as extrafacial plaques and small nodules. Advanced lesions manifest clinically as firm nodules of long duration.

Histopathologic Features
Early lesions display histopathologically features of leukocytoclastic vasculitis, similar to granuloma faciale. Overlap between extrafacial granuloma faciale and EED has been described. In advanced lesions of EED there is histopathologically a predominance of interweaving fascicles of wiry collagen bundles sprinkled with many neutrophils, few eosinophils, and lymphocytes. In general there is a predominance of neutrophilic granulocytes in conjunction with massive leukocytoclasis. Erythrocyte extravasation may be minimal. Plasma cells and histiocytes may be seen in resolving lesions of both granuloma faciale and erythema elevatum diutinum.

References

CONTRIBUTED BY HEINZ KUTZNER, MD
Diagnosis: Cutaneous Ewing sarcoma (large cell variant)

Case Summary
A 42 year old woman presented with a solitary lesion on the dorsal left foot, which developed 5 months previously and had been rapidly growing. The patient is otherwise healthy without any prior diagnosis of malignancy.

The best diagnosis is:
A. Myeloid leukemia cutis - Incorrect. The tumor cells are not immature myeloid cells or myeloblasts.
B. Metastatic melanoma - Incorrect. The tumor cells lack melanocytic differentiation.
C. Merkel cell carcinoma - Incorrect. The cells lack the characteristic salt and pepper chromatin pattern of Merkel cell carcinoma.
D. Cutaneous Ewing sarcoma, large cell variant - Correct. The biopsy shows a monomorphic intradermal neoplasm composed of cells with round nuclei, vesicular chromatin, and focally prominent nucleoli, arranged in sheets. The tumor cells are positive for an EWSR1 gene rearrangement by fluorescence in situ hybridization.
E. Epithelioid sarcoma - Incorrect. Although the acral location is good for epithelioid sarcoma, epithelioid sarcoma tends to show a less monomorphic population of tumor cells, with more abundant eosinophilic cytoplasm.

This lesion will most likely exhibit which immunophenotype:
A. S100 positive, MART-1 positive, keratin negative - Incorrect. This is the immunoprofile of melanoma.
B. S100 negative, focal keratin positivity, CD99 positive - Correct. Diffuse membranous CD99 staining is seen in the majority of Ewing sarcomas, and focal keratin positivity is seen in approximately 30 percent of cases.
C. CK20 positive (dot-like), synaptophysin positive, S100 negative - Incorrect. This is the immunoprofile of Merkel cell carcinoma.
D. CD34 positive, EMA positive, loss of INI1 - Incorrect. These markers are positive in epithelioid sarcoma.
E. Myeloperoxidase-positive, CD34-positive, CD117-positive, S100-negative, keratin negative - Incorrect. This immunoprofile fits with acute myeloid leukemia cutis.

Discussion
Ewing sarcoma/primitive neuroectodermal tumor (ES) can occur in the bone (most commonly), soft tissue, and rarely in the dermis and/or superficial subcutis (primary cutaneous Ewing sarcoma). ES is defined genetically by specific chromosomal translocations, resulting in a fusion of the EWSR1 gene with various members of the ETS family of transcription factors (including FL1, ERG, FEV, ETV1, and ETV4). ES is the second most common bone/soft tissue sarcoma in children, with a male predominance. While disease free and overall survival have improved significantly with current multimodality treatment approaches (particularly for localized disease at presentation) the overall 5 year survival rate is still approximately 60% for bone/soft tissue ES. In contrast, although the data are limited due to the rarity of primary cutaneous ES,
these superficially located ES appear to have an overall better prognosis than ES arising in bone or deep soft tissue, with a 91% 10 year survival probability in the largest meta analysis to date.

**Histopathologic Features**
Histopathologically, ES can be subdivided based on overall morphologic features into conventional/typical ES, peripheral neuroectodermal tumor (PNET) with neuroectodermal features and atypical ES (including large cell ES, clear cell ES, sclerosing ES, spindle cell ES, and adamantinoma-like ES). While conventional ES is composed of undifferentiated-appearing cells with fine chromatin, small nucleoli and scant cytoplasm, the less common large cell ES (of which this case is an example) is composed of larger cells with more abundant cytoplasm, and variably distinct nucleoli. Although not specific, membranous CD99 staining is a hallmark of all morphologic subtypes of ES, and can aid in the diagnosis. It is important to remember that up to 30% of ES are positive for keratins (often in a dot-like pattern), which can be a diagnostic pitfall. The diagnosis of ES is confirmed by identification of an EWSR1 gene rearrangement by FISH.

**References**

**CONTRIBUTED BY JULIE REIMANN, MD**
CASE #157 — SLIDE #157

**Diagnosis:** Foreign body granulomatous reaction to injectable poly-L-lactic acid (Sculptra)

**Case Summary:** A 76-year-old woman presented with a nodular lesion on the left eyebrow.

**Question**
What is the best diagnosis?

A. Ruptured epidermoid cyst *(Incorrect)* The well-circumscribed nodular pattern may raise the possibility of a ruptured cyst. However, the foreign material within giant cells is not keratin.
B. Ruptured dermoid cyst *(Incorrect)* The eyebrow location would raise the possibility of a dermoid cyst. However, the foreign material within giant cells is not keratin.
C. Reaction to hyaluronic acid *(Incorrect)* The histologic appearance of hyaluronic acid consists of extracellular basophilic amorphous material.
D. Reaction to poly-L-lactic acid *(Correct)* Foreign body granulomatous inflammatory infiltrate with numerous multinucleated giant cells around translucent particles of different sizes (oval, fusiform or spiky shape) and frequent asteroid bodies.
E. Reaction to calcium hydroxylapatite *(Incorrect)* The histologic appearance of calcium hydroxylapatite consists of bluish-gray, round to oval microspheres.

**Question**
Which of the following injectable soft tissue fillers is birefringent in polarized light examination?

A. Hyaluronic acid *(Incorrect)* Non-birefringent in polarized light
B. Poly-L-lactic acid *(Correct)* Birefringent in polarized light
C. Calcium hydroxylapatite *(Incorrect)* Non-birefringent in polarized light
D. Polymethyl-methacrylate microspheres *(Incorrect)* Non-birefringent in polarized light
E. Hydroxyethylmethacrylate/ethylmethacrylate *(Incorrect)* Non-birefringent in polarized light

**Clinical Features:**
Injectable poly-L-lactic acid (Sculptra, New-Fill) is a synthetic, resorbable soft tissue filler that has been used for facial cosmetic augmentation and to correct the signs of lipoatrophy in HIV patients. Nodules at the injection sites, which are palpable but generally not visible, may occur in up to 30% - 40% of patients, and without treatment tend to persist for months or years. Late-onset infections and foreign body granulomas have also been described.

**Histopathologic Features:**
Granulomatous adverse reactions at the sites of injection of poly-L-lactic acid may occur and reveal a foreign body granulomatous inflammatory infiltrate with numerous multinucleated giant cells around translucent particles of different sizes, most of them demonstrating an oval, fusiform or spiky shape (shorter and wider than cholesterol clefts). Asteroid bodies are frequently seen within the cytoplasm of multinucleated giant cells. Patchy lymphocytes are also seen. Poly-L-lactic acid is birefringent in polarized light examination.
Differential diagnoses
Hyaluronic acid (Restylane, Hylaform, Juvederm, Perlane, Macrolane): granulomatous foreign body reaction, with abundant multinucleated giant cells surrounding an extracellular basophilic amorphous material. Hyaluronic acid stains positively for Alcian blue at a pH of 2.7 and is negative when examined under polarized light.

Hyaluronic acid plus dextranomer microparticles (Matridex): suppurative granulomatous inflammatory infiltrate surrounding extracellular basophilic amorphous material (hyaluronic acid) and spherical dark bluish particles (dextranomer microparticles).

Calcium hydroxylapatite (Radiesse, Radiance): generally does not induce a foreign body reaction; however, granulomatous inflammation may occasionally occur. The microspheres of calcium hydroxylapatite are bluish-gray in color, 25 to 40 um in size, and round to oval in shape.

Polymethyl-methacrylate microspheres in bovine collagen (Artecoll, Arteplast, Artefill): nodular or diffuse granulomatous infiltrate surrounding round, sharply circumscribed, translucent, non-birefringent vacuoles of similar shape and size that resemble normal adipocytes within a sclerotic stroma.

Hydroxyethylmethacrylate/ethylmethacrylate fragments in hyaluronic acid (Dermalive, Dermadeep): nodular granulomatous infiltrates of macrophages and multinucleated giant cells with numerous pseudocystic structures of different sizes and shapes containing polygonal, pink, translucent, non-birefringent foreign bodies.

Bovine collagen (Zyderm, Zyplast): bovine collagen differs from native human collagen in being acellular, thicker and more eosinophilic.


Polyalkylimide gel (Bio-Alcamid): basophilic amorphous material with granular appearance surrounded by sparse epithelioid histiocytes, foreign body multinucleated giant cells, neutrophils, and red cells.

Silicone: variable histopathologic findings depending on the form of the injected silicone. Solid elastomer silicone induces an exuberant foreign body granulomatous reaction, while silicone oil and gel induce a sparser inflammatory response. Silicone particles appear as groups of round non-birefringent empty vacuoles of different sizes between collagen bundles or within macrophages. Polymerized silicone elastomer dispersed in polyvinylpyrrolidone (Bioplastique) reactions show granulomas with irregularly shaped cystic spaces containing translucent, jagged, popcorn-like, non-birefringent particles of varying size dispersed in a sclerotic stroma surrounded by abundant multinucleated foreign body giant cells, some of them containing asteroid bodies.
Paraffin: mostly lobular panniculitis, with the subcutaneous fat exhibiting a Swiss cheese appearance with cystic spaces of variable size and shape, surrounded by foamy histiocytes and multinucleated giant cells.

References
Case Summary
A 58 year-old man presented with a 3 mm hyperpigmented papule on his right nasal ala. The tumor cells exhibit strong, diffuse positivity for S100, but were negative with a pan-cytokeratin cocktail, MART-1, HMB-45, Sox-10, CD31 and p63.

Question 97
The best diagnosis is:
A. Langerhans cell histiocytosis — Correct. There is a nodular aggregate of epithelioid tumor cells in the dermis. The tumor cells exhibit increased cytoplasm and nuclear grooves with smooth chromatin and associated eosinophilic inflammation.
B. Granular cell tumor — Incorrect. The characteristic granular cytoplasm of the tumor cells and overlying pseudoepitheliomatous hyperplasia are not evident.
C. Intradermal melanocytic nevus — Incorrect. The tumor cells do not exhibit the classic nested morphology of a melanocytic nevus and lacks features of maturation, pigment. In addition, although the tumor cells are positive for S100, they lack expression of other melanocytic markers (MART-1, HMB-45, Sox-10).
D. Epithelioid angiosarcoma — Incorrect. The lesions lacks features of immature vascular formation with red blood cell extravasation at the periphery or an infiltrative pattern of growth by the tumor cells. Furthermore the tumor cells lack reactivity for the vascular marker CD31.
E. Juvenile xanthogranuloma (JXG) — Incorrect. The tumor cells lack the characteristic foamy cytoplasm and multinucleated Touton-type giant cells of xanthogranuloma and exhibit strong, diffuse positivity for S100 — both of which are against a diagnosis of JXG.

Question 98
The special stain likely to be most helpful in confirming the diagnosis is:
A. Acid fast/FITE — Incorrect. Since the cells are positive for S100, this lesion is unlikely to represent a mycobacterial infection.
B. MiTF — Incorrect. Given the negativity for numerous other melanocytic markers, an additional melanocytic marker is unlikely to be of high yield.
C. CD1a — Correct. Together with the morphology and the immunophenotypic findings already reported, this would confirm the diagnosis of Langerhans Cell Histiocytosis.
D. CD163 — Incorrect. CD163 is a non-specific fibrohistiocytic marker and is unlikely to be diagnostically informative in this context.
E. BRAF-V600E — Incorrect. Although Langerhans Cell Histiocytosis has been reported to carry mutations in BRAFV600E, other considerations in the differential diagnosis (including melanocytic lesions) also would carry this mutation and thus, it is unlikely to be informative.

Clinical features
Langerhans cell histiocytosis (LCH) can present a single lesion, as multiple lesions in one organ system or as disseminated disease with multi-system involvement. Although the most common site of single lesional disease is the bone, unilesional LCH (eosinophilic granuloma) can also involve the skin, lymph nodes and lung, and adults/older children are most commonly affected in that setting. Acute disseminated LCH (Abt-Letterer-Siwe disease) most commonly affects infants with variable combinations of fever, anemia, thrombocytopenia,
hepatosplenomegaly, lymphadenopathy and pulmonary infiltrates. Chronic multifocal LCH (Hand-Shuller-Christian disease) usually manifests with the classic triad of diabetes insipidus, exophthalmos and defects in bone (most often the skull); however, other organs (including the skin, liver, spleen, lungs, lymph nodes, or long bones) may also be affected. When the skin is involved, LCH presents as a variable number of red-brown papules.

**Histopathologic features**

Histopathologically, LCH displays a characteristic morphology regardless of the clinical scenario. Langerhans cells contain increased pale eosinophilic cytoplasm with enlarged, folded or grooved nuclei (often “kidney shaped”) with smooth chromatin and lacking conspicuous nucleoli. An additional characteristic feature of neoplastic Langerhans cells is their rounded oval quality—lacking the characteristic dendritic morphology of reactive Langerhans cell infiltrates—which is often best appreciated with immunohistochemical studies (CD1a). LCH lesions typically have an associated inflammatory infiltrate usually comprised of conspicuous eosinophils variably admixed with small lymphocytes, histiocytes, and neutrophils. Immunohistochemical studies are often necessary to confirm the diagnosis. LCH is characterized by positivity for S100, CD1a and Langerin (CD207). A subset of LCH has been shown to be positive for BRAF-V600E.

**References**


Diagnosis: Secondary cutaneous involvement by mantle cell lymphoma

Case Summary: A 78-year-old man presents with a violaceous nodule on the right shin. The immunophenotype seen here is: CD20+, CD79a+, CD5+, CD10-, CD23-, CD43+, BCL2+, and BCL6-.

Question
What is the best diagnosis?

A. Myeloid leukemia cutis (Incorrect) The immunophenotype seen here is B-cell, not myeloid.
B. Plasmablastic lymphoma. (Incorrect) The infiltrate seen here does not show plasmablastic morphologic features. This entity is generally CD20-.
C. Small lymphocytic lymphoma/chronic lymphocytic leukemia. (Incorrect) This entity generally shows CD5 and CD43 expression. However, the absence of CD23 and the presence of blastoid morphologic features would not be compatible with CLL/SLL.
D. Burkitt lymphoma. (Incorrect) While the high-grade B-cell pattern seen here would raise the possibility of Burkitt lymphoma, the immunophenotype is not supportive (lack of CD10, presence of BCL2, lack of BCL6).
E. Mantle cell lymphoma (Correct) The morphologic features and the immunophenotype seen here are consistent with mantle cell lymphoma.

Question
This condition is almost always associated with:

A. HIV infection. (Incorrect) Mantle cell lymphoma is not habitually associated with HIV infection.
B. HHV-8 infection. (Incorrect) Mantle cell lymphoma is not regularly associated with HHV-8 infection.
C. t(8;14). (Incorrect) This translocation is generally seen in Burkitt lymphoma.
D. t(11;14). (Correct) The (11;14) translocation involving CCND1 and IGH genes is characteristic of mantle cell lymphoma.
E. Indolent behavior. (Incorrect) Mantle cell lymphoma is associated with a poor prognosis and median survival of 3 - 5 years.

Clinical Features
Mantle cell lymphoma is a B-cell lymphoma generally composed of monomorphic small to medium-sized lymphocytes with irregular nuclear contours and expressing Cyclin D1. The (11;14)(q13;q32) translocation involving CCND1 and IGH genes is characteristic. The prognosis is generally poor, with a median survival of 3 - 5 years.

The most commonly involved site is lymph node. Other frequent sites are the spleen, gastrointestinal tract, and bone marrow (with or without peripheral blood involvement). Cutaneous lesions are uncommon but may represent the first manifestation of mantle cell lymphoma.
Histopathologic Features
Most cases of mantle cell lymphoma show an infiltrate of monomorphic small to medium-sized lymphocytes with variably irregular nuclear contours and inconspicuous nucleoli. Neoplastic large/transformed cells resembling centroblasts, immunoblasts or paraimmunoblasts are not seen. There is a spectrum of morphologic variants, including small cell (small round lymphocytes mimicking small lymphocytic lymphoma), blastoid (cells resembling lymphoblasts with dispersed chromatin and high mitotic rate) and pleomorphic (larger pleomorphic cells with oval to irregular nuclear contours and often prominent nucleoli). Most cases show a CD20+, CD5+, CD10-, CD23-, CD43+, BCL2+, BCL6-, FMC7 phenotype. Aberrant phenotypes are occasionally seen, including absence of CD5 and expression of CD10 or CD23. Almost all cases show nuclear expression of Cyclin D1.

References
Diagnosis: Primary cutaneous marginal zone B-cell lymphoma, plasmacytic variant

Case Summary:
A 68-year-old man presents with erythematous papules and nodules on the left upper arm and upper back. The vast majority of the plasma cells are immunoreactive with lambda immunoglobulin light chain stain. Only rare cells mark with kappa. A systemic work-up (including bone marrow examination, imaging studies, and serum/urine protein electrophoresis) is negative.

Question
What is the best diagnosis?
A. Secondary syphilis (Incorrect) While syphilis is often associated with plasma cell-rich infiltrates, the plasma cells should be polytypic.
B. Secondary cutaneous involvement by plasma cell myeloma (Incorrect) The presence of an atypical plasma cell-rich infiltrate with light chain restriction would raise the possibility of a plasma cell dyscrasia. However, the diagnosis of plasma cell myeloma requires additional clinical and pathologic findings, which are not present in this case.
C. Monoclonal gammopathy of undetermined significance (Incorrect) A monoclonal gammopathy is not present in this case.
D. Cutaneous plasmacytosis (Incorrect) While cutaneous plasmacytosis shows a plasma cell-rich dermal infiltrate, the plasma cells should be polytypic.
E. Cutaneous marginal zone B-cell lymphoma (Correct) The clinical and histopathologic findings are consistent with cutaneous marginal zone B-cell lymphoma. This diagnostic category currently includes cases previously labeled primary cutaneous plasmacytoma without underlying plasma cell myeloma (extramedullary plasmacytoma of the skin).

Question
This condition is almost always associated with:
A. Lytic bone lesions (Incorrect) This is not a feature of cutaneous marginal zone B-cell lymphoma.
B. Amyloidosis (Incorrect) Amyloidosis is not commonly seen in the setting of cutaneous marginal zone B-cell lymphoma.
C. Good prognosis. (Correct) Cutaneous marginal zone B-cell lymphoma is a very indolent entity.
D. HHV-8 infection (Incorrect) Some cases of extranodal marginal zone B-cell lymphomas may be associated with infections in certain sites (e.g., gastric Helicobacter pylori, ocular Chlamydia psittaci, intestinal Campylobacter jejuni, and cutaneous Borrelia burgdorferi). However, HHV-8 infection is not regularly seen in the setting of cutaneous marginal zone B-cell lymphoma.
E. Renal insufficiency (Incorrect) This may be seen in patients with plasma cell myeloma but is not a feature of cutaneous marginal zone B-cell lymphoma.
**Clinical Features**
Cutaneous marginal zone B-cell lymphoma is a very indolent lymphoma composed of small B cells, including marginal zone (centrocyte-like) cells, lymphoplasmacytoid cells, and plasma cells, admixed with small numbers of centroblast- or immunoblast-like cells and many reactive T-cells. Reactive germinal centers are frequently seen.

Patients generally present with red to violaceous papules, plaques and/or nodules on the trunk and/or extremities. Cutaneous recurrences are common, but dissemination to extracutaneous sites or large cell transformation is rare.

This category currently includes cases previously designated as:
- primary cutaneous immunocytoma
- cutaneous follicular lymphoid hyperplasia with monotypic plasma cells
- primary cutaneous plasmacytoma without underlying plasma cell myeloma (extramedullary plasmacytoma of the skin)

Cutaneous marginal zone B-cell lymphoma is considered part of the broad group of extranodal marginal zone B-cell lymphomas commonly involving mucosal sites, called MALT (mucosa-associated lymphoid tissue) lymphomas.

**Histopathologic Features**
The infiltrate is generally heterogeneous and is composed of a variable admixture of:
- Marginal zone B-cells: CD20+, CD79a+, BCL6-, BCL2+, low Ki-67
- Lymphoplasmacytoid and plasma cells: CD20-, CD79a+, monotypic kappa or lambda
- Many reactive small T-cells (may predominate): CD3+, CD20-
- Often with reactive germinal centers: CD20+, CD79a+, BCL6+, BCL2-, high Ki-67

**Pearls and pitfalls**
- A vertical orientation with periadnexal accentuation is a common pattern on low power magnification.
- Numerous plasma cells would be unusual in cutaneous follicle center lymphoma. If frequent plasma cells are present in a dense dermal infiltrate with lymphoid follicles, consider the possibility of cutaneous marginal zone lymphoma with reactive follicles.
- Cutaneous marginal zone lymphomas generally exhibit polymorphic infiltrates and may resemble cutaneous reactive lymphoid hyperplasia (pseudolymphoma). Kappa and lambda immunoglobulin light chain stains are usually helpful in this differential.
- Monotypic plasma cells are often located at the periphery of nodular infiltrates (semicircular arrangement) and in clusters near the papillary dermis.
- Reactive lymphoid follicles can be colonized by BCL2+ marginal zone B-cells and may mimic BCL2+ follicular lymphoma.
References

CONTRIBUTED BY ANTONIO SUBTIL, MD, MBA
CASE #161 — SLIDE #161

**Diagnosis:** Syphilis (Secondary)

**Case Summary:**
A 25-year-old man presents with a relatively generalized eruption.

**Question**
What is the best diagnosis?

A. Dermatomyositis (Incorrect) The features of dermatomyositis show mild vacuolar changes with scattered cytoid bodies and a sparse superficial perivascular infiltrate of lymphocytes. A variable amount of superficial dermal edema and mucin can be seen.

B. Lichen planus (Incorrect) Lichen planus has epidermal acanthosis, hypergranulosis, interface changes with “saw toothing” and cytoid body formation. Plasma cells are not common.

C. Lichenoid drug eruption (Incorrect) Similar findings to lichen planus, often with a perivascular infiltrate. Plasma cells can be seen but the lack of eosinophils makes this less likely.

D. Pityriasis rosea (Incorrect) Given the interface and non-spongiotic features of the inflammatory infiltrate, this diagnosis is not correct.

E. Secondary syphilis (Correct) Given the interface and non-spongiotic features of the inflammatory infiltrate, this diagnosis is not correct.

**Question**
The best additional stains or study for this lesion would include:

A. CD3, CD5, CD7, CD8 immunohistochemical studies (Incorrect) These T-cell markers are non-diagnostic in secondary syphilis.

B. Anti-spirochete immunohistochemical study (Correct) This stain will identify the thin, delicate 4-15 micron long spiral organisms in the intercellular spaces, as well as in macrophages, around blood vessels, endothelial cells and even plasma cells. Also a Warthin-Starry or Steiner stain can be used to identify the organisms.

C. Digested PAS stain (Incorrect) This stain for fungal organisms will be negative in secondary syphilis.

D. Direct immunofluorescence study (Incorrect) This study is non-diagnostic in secondary syphilis.

E. PAS stain (Incorrect) This stain for fungal organisms will be negative in secondary syphilis.
Discussion
Syphilis is an infectious disease that can easily be overlooked if one is not thinking about it clinically. Interface inflammation is typical and as such, several other diagnoses in the lichenoid or interface category can be considered. Recognizing the interface dermatitis and plasma cells within the infiltrate make this the correct diagnosis. Lichen planus may have similar changes but most often has epidermal acanthosis, hypergranulosis, interface changes with “saw toothing” and cytoid body formation. Plasma cells are not common in lichen planus not involving the mucous membranes. Warthin-Starry or Steiner stain can be used to identify the organisms. Anti-spirochete immunohistochemical stains are now available and will identify the thin, delicate 4-15 micron long spiral organisms in the intercellular spaces, as well as in macrophages, around blood vessels, endothelial cells and even plasma cells.

References

CASE #162—SLIDE #162

Diagnosis: Lichen Amyloidosis

Case Summary:
A 67-year-old woman complains of a pruritic eruption of the upper back.

Question
What is the best diagnosis?

A. Dermatomyositis (Incorrect) Although mild to focal interface changes can be seen, the characteristic eosinophilic globules seen in the papillary dermis seen in this biopsy are not noted in dermatomyositis.

B. Chronic and lichenified dermatitis (Incorrect) Irregular epidermal acanthosis with some compressed collagen and scattered dermal melanophages in the papillary dermis can be seen in a chronic dermatitis. The characteristic eosinophilic globules seen in this biopsy are not noted in a chronic and lichenified dermatitis.

C. Lichen amyloidosis (Correct) Focal interface changes with characteristic small eosinophilic globular deposits seen in the papillary dermis often with scattered dermal melanophages correctly identify this as lichen amyloidosis.

D. Lichenoid drug eruption (Incorrect) Similar findings to lichen planus consisting of a band-like lymphocytic infiltrate with interface changes. Plasma cells and eosinophils can be seen in the infiltrate which can also be perivascular.

E. Systemic amyloidosis with cutaneous involvement (Incorrect) Systemic amyloidosis with cutaneous involvement typically demonstrates pale eosinophilic deposition throughout the dermis but frequently around blood vessels.

Question
This lesion is often positive with which of the following stains:

A. Crystal violet (Correct) Multiple stains are positive in amyloidosis including crystal violet, Congo red, Thioflavin T, cotton dyes (Pagoda Red) and acid-orcein Giemsa.

B. Fontana (Incorrect) Stains melanin black.

C. Toluidine Blue (Incorrect) Stains mast cells.

D. von Gieson (Incorrect) Stains elastic fibers black.

E. von Kossa (Incorrect) Stains calcium black.

Discussion
Focal interface changes with characteristic small eosinophilic globular deposits seen in the papillary dermis often with scattered dermal melanophages correctly identify this as lichen amyloidosis. Irregular epidermal acanthosis with some compressed collagen and scattered dermal melanophages in the papillary dermis can also be seen in chronic dermatitis but the characteristic eosinophilic globules seen in this biopsy are not noted in a chronic and lichenified dermatitis. Melanin pigment incontinence can serve as a subtle clue and may draw one’s attention to the often faintly staining eosinophilic globules. Systemic amyloidosis with cutaneous involvement typically demonstrates pale eosinophilic deposition throughout the dermis but frequently around blood vessels and sometimes outlining adipocytes. Multiple
stains are positive in amyloidosis including crystal violet, Congo red, Thioflavin T, cotton dyes (Pagoda Red) and acid-orcein Giemsa. These superficial deposits in cutaneous amyloid may also stain with keratin stains, which will not highlight systemic forms of amyloid.

References

CONTRIBUTED BY DAVID MEHREGAN, MD
CASE #163 – SLIDE #163

**Diagnosis:** Lichen planopilaris

**Case Summary:**
A 55-year-old woman complains of a pruritic scalp and patchy hair loss.

**Question**
What is the best diagnosis?

A. Discoid lupus erythematous (**Incorrect**) The biopsy shows an interface dermatitis which is seen in DLE. The subtle differences which are not found in this biopsy for DLE include lack of interfollicular epidermal interface changes and lack of perivascular and periappendageal lymphocytic inflammation.

B. Folliculotrophic T-cell lymphoma (**Incorrect**) Although there is a perifollicular lymphoid infiltrate, there are no interface changes of the follicular epithelium and there are no cytologic atypical lymphocytes for cutaneous lymphoma.

C. Lichen planopilaris (**Correct**) The lack of both interfollicular epidermal interface changes and periappendageal and perivascular inflammation are consistent with LPP over DLE which usually has these features.

D. Secondary syphilis (**Incorrect**) Secondary syphilis of the scalp causing alopecia shows similar findings as cutaneous lesions with an interface dermatitis and plasma cells within the infiltrate.

E. Seborrheic dermatitis (**Incorrect**) Seborrheic dermatitis is either a spongiotic dermatitis or psoriasiform dermatitis and does not show follicular interface changes.

**Question**
A biopsy for direct immunofluorescence would typically show what features?

A. IgG staining along the dermal epidermal junction (**Incorrect**) Deposition of immunoglobulins particularly IgG and IgM are seen in 50-90% of cases of lupus erythematosus.

B. Linear homogeneous staining of C3 along the interfollicular epidermal basement membrane and dermo-epidermal junction (**Incorrect**) Deposition of linear, homogeneous of C3 along the basement membrane zone is seen in bullous pemphigoid.

C. Linear IgA along the follicular basement membrane (**Incorrect**) Deposition of linear IgA just along the follicular basement zone is non-diagnostic.

D. IgG and IgM staining of cytoid bodies (**Correct**) Cytoid bodies containing IgG and IgM in the dermis adjacent to the upper portion of the involved hair follicles is frequently seen in LLP.

E. No staining on direct immunofluorescence (**Incorrect**) Negative staining is usually not seen in lichen planopilaris except in lesions of long standing where the inflammatory component is lost and end staging cicatricial alopecia is found.
Discussion
Although there is a perifollicular lymphoid infiltrate, there are no interface changes of the follicular epithelium and there are no cytologic atypical lymphocytes seen in cutaneous lymphoma. The lack of both interfollicular epidermal interface changes and periappendageal and perivascular inflammation are consistent with LPP over DLE which usually has these features. The diagnosis can be made on both vertically and horizontally sectioned specimens, although the latter allow examination of a greater number of hair follicles. Biopsy from the involved skin where there is erythema and follicular plugging increases the specificity for the diagnosis as opposed to biopsies taken from completely scarred or alopecic skin. Biopsy for DIF may help differentiate from lupus erythematosus in more difficult cases.

References
CASE #164 — SLIDE #164

Diagnosis: Granular parakeratosis

Case Summary:
A 45-year-old woman presents with a slightly pruritic eruption in her inguinal folds.

Question
What is the best diagnosis?

A. Candidiasis (Incorrect) Candidiasis typically is spongiotic dermatitis with some accumulation of neutrophils in the stratum corneum. The unique changes seen in this biopsy of retention of keratohyaline granules and thickened basophilic stratum corneum is not seen.

B. Erythrasma (Incorrect) Minimal changes are seen in erythrasma. Occasional accumulation of coccobacilli may be found in the stratum corneum on Gram stain.

C. Granular parakeratosis (Correct) The thickened basophilic parakeratotic layer with characteristic retention of keratohyaline granules makes this the correct answer. The underlying epidermis may be normal, mild, atrophic or irregular acanthotic. Dermal inflammation is non specific and mostly lymphocytic.

D. Inverse psoriasis (Incorrect) Although some lesions of granular parakeratosis have a “psoriasiform acanthosis” the accumulation of neutrophils typically seen in psoriasis are not present. The unique changes seen in this biopsy of retention of keratohyaline granules and thickened basophilic stratum corneum are not seen in psoriasis.

E. Irritant/contact dermatitis (Incorrect) Typically both are spongiotic dermatitis with a perivascular infiltrate. The unique changes seen in this biopsy of retention of keratohyaline granules and thickened basophilic stratum corneum are not seen in an irritant or contact dermatitis.

Question
The basis of this disorder is best due to what etiology?

A. Absence of lamellar granules and accumulation of dense core granules (Incorrect) These are the electron microscopy findings seen in Harlequin fetus.

B. Defect in gene ATP2A2 encoding sarco/endoplasmic reticulum Ca-ATPase type 2 isoform (SERCA2) (Incorrect) This defect is seen in Darier’s disease.

C. Defect in crosslinkage of loricrin and involucrin and formation of cornified cell layer (Incorrect) This defect is seen in lamellar ichthyosis.

D. Defect in the processing of profilaggrin to filaggrin in keratinocytes (Correct) This is the proposed etiology of granular parakeratosis.

E. Deficiency of steroid sulfatase (Incorrect) This defect is seen in x-linked ichthyosis.
Discussion
This condition may be misdiagnosed clinically by those who are not familiar with it. Typical clinical diagnoses include inverse psoriasis, intertrigo, erythrasma and contact or irritant dermatitis. Although some lesions of granular parakeratosis have a “psoriasiform acanthosis” the accumulation of neutrophils typically seen in psoriasis are not present. The unique changes seen in this biopsy of retention of keratohyaline granules and thickened basophilic stratum corneum are not seen in psoriasis nor in dermatitis. The defect in maturation of profilaggrin to filaggrin is thought to be the cause of this distinct and recognizable entity.

References

CONTRIBUTED BY DAVID MEHREGAN, MD
CASE #165 — SLIDE #165

Diagnosis: Bullous systemic lupus erythematosus

Case Summary:
The patient is a 39-year-old white woman with a prior history of a positive ANA (titer 1:2560) and anti-dsDNA and anti-ssDNA. The patient presents with a two-month history of a papulovesicular eruption on the trunk and extremities.

Question
Which additional tool would aid in making the diagnosis?

A. Direct immunofluorescence (Correct) Direct immunofluorescence would show granular deposits of IgG, IgM, IgA, and C3 along the dermoepidermal junction.
B. Direct immunofluorescence on 1.0M NaCl-split skin (Correct) Direct immunofluorescence on salt-split skin would show linear deposits of IgG along the dermal side (floor) of the blister.
C. Electron or immunoelectron microscopy (Correct) EM or immune-EM would show cleavage and deposition of immunoglobulins on or beneath the lamina densa.
D. Western blot (Correct) By Western blot, there is detection of 290kD and 145kD autoantigens, which are components of type VII collagen.
E. All of the above (Correct)

Question
You are provided with a direct immunofluorescence which shows granular deposits of IgG, IgM, IgA, and C3 along the dermoepidermal junction. You are now able to make the diagnosis of:

A. Dermatitis herpetiformis (Incorrect) The DIF pattern would show granular deposits of IgA and C3 along the dermoepidermal junction, with localization and stippling at the tips of the dermal papilla.
B. Bullous systemic lupus erythematosus (Correct) Although all major classes of immunoglobulins may be present, IgG is almost always positive and IgA is positive twice as often as that seen in SLE without blisters. C3 is frequently positive and IgM is positive in about half of the patients. About 60% of cases show a granular pattern of deposits while 40% have a linear pattern. Both granular and linear patterns can be found in the same biopsy.
C. Bullous pemphigoid (Incorrect) The DIF pattern would show linear deposits of IgG and C3 along the basement membrane zone.
D. Linear IgA bullous dermatosis (Incorrect) The DIF pattern would show linear deposits of IgA and C3 along the basement membrane zone.
E. Sweet’s syndrome (Incorrect) While the presence of abundant neutrophils on the H&E may raise the possibility of Sweet’s syndrome, the DIF would be negative.
Clinical features
Bullous systemic lupus erythematosus is a rare subtype of systemic lupus erythematosus (SLE) associated with autoimmunity to type VII collagen, which occurs in less than 5% of patients with SLE. A vesiculobullous eruption may be the presenting manifestation of SLE, but more often occurs in those with a prior diagnosis of SLE. The eruption appears as large and tense or small and clustered clear to hemorrhagic vesicles or bulla arising on normal or inflamed skin. Lesions resolve, leaving behind hypopigmented, or less often, hyperpigmented macules without scarring. Sun exposed skin of the upper trunk, neck, supraclavicular region, axillary folds, and proximal extremities is most often affected. Mucous membranes, including nasal, oral, and vulvar, are also frequently involved. Original, then revised, diagnostic criteria for bullous SLE include: 1) diagnosis of SLE based on the American Rheumatism Association criteria, 2) vesicles and bulla arising upon, but not limited to, sun-exposed skin, 3) histopathology compatible with DH, 4) positive or negative indirect immunofluorescence for circulating basement membrane zone antibodies using separated skin as a substrate, and 5) DIF on lesional or non-lesional skin revealing linear or granular IgG and/or IgM and often IgA at the basement membrane zone. If there is a linear pattern of immunoglobulin deposition, immunoelectron microscopy should be done to demonstrate the immune reactants below the basal lamina. Unlike EBA, patients with bullous SLE show dramatic response to low dose dapsone with cessation of blister formation within 24 to 48 hours and complete clearance of the eruption within a week. In contrast to DH, taper or withdrawal of treatment does not always result in blister relapse. Differing from SLE without blisters, high dose corticosteroids and immunosuppressants that control visceral manifestations are usually not effective in clearing the vesiculobullous eruption. The course and onset of the vesiculobullous eruption does not necessarily parallel systemic disease activity and bullous SLE may resolve with no further recurrences, regardless of the systemic disease course.

Histological features
Histopathology:
- Subepidermal blister with fibrin and abundant neutrophils within the blister cavity
- Dense inflammatory infiltrate in the superficial dermis, predominately consisting of neutrophils, as well as lymphocytes and some eosinophils
- Neutrophil microabscesses within the tips of the dermal papilla
- +/- leukocytoclastic vasculitis and/or mucin deposition in the reticular dermis
- Epidermal atrophy, basovacuolar change, or basement membrane thickening are absent
DIF:
- Granular or linear deposits of IgG, IgA, IgM, and C3 along the basement membrane zone
DIF on salt-split skin:
- Linear deposits of IgG on the dermal side (floor) of the blister
Indirect immunofluorescence:
- Negative in those with a granular DIF pattern
- Positive in salt-split skin in those with a linear DIF pattern, showing IgG positivity along the dermal side (floor) of the blister
Immunoelectron microscopy:
- Cleavage and deposition of immunoglobulins on or beneath the lamina densa
Western blot:
- Detection of 290kD and 145kD autoantigens (components of type VII collagen)
References

CONTRIBUTED BY SARAH N. WALSH, MD
CASE #166 — SLIDE #166

Diagnosis: Adult-onset Still’s disease

Case Summary:
The patient is a 56-year-old black man with a clinical history of adult-onset Still’s disease and a non-pruritic non-edematous urticarial eruption on the trunk and proximal extremities, and occasionally elsewhere. The rash is intermittent and recurring and resolves spontaneously, lasting only one to several days. A punch biopsy is taken from a lesion on the right upper chest.

Question
The best diagnosis is:

A) Sweet syndrome (Incorrect) Pronounced papillary dermal edema is a classical feature of Sweet’s syndrome. In addition, in Sweet’s syndrome, the dermal neutrophilic infiltrate is usually much more dense.

B) Urticarial vasculitis (Incorrect) The presence of leukocytoclastic vasculitis is the hallmark feature in well-developed urticarial vasculitis. Early lesions may be more challenging, but show mild perivascular neutrophils with leukocytoclasia, as well as eosinophils, and subtle leukocytoclastic vasculitis with evidence of vascular damage, even if only focal.

C) Adult-onset Still’s disease (Correct) A variety of cutaneous eruptions can occur in adult-onset Still’s disease, most showing nonspecific subtle microscopic features including a mild superficial perivascular lymphocytic infiltrate with occasional scattered neutrophils. Persistent pruritic papules and plaques have a more characteristic histology with dyskeratosis confined to the upper layers of the epidermis, a sparse superficial dermal infiltrate with scattered neutrophils, and often an increase in dermal mucin deposition. Urticarial lesions of adult-onset Still’s disease usually show mild perivascular and interstitial superficial dermal neutrophilic inflammation without significant dermal edema, eosinophils, or vasculitis. These latter features, of no dermal edema, eosinophils, or vasculitis, are the main findings that allow distinction from classical urticaria or urticarial vasculitis.

D) Interstitial granulomatous dermatitis (palisading neutrophilic granulomatous dermatitis) (Incorrect) Interstitial granulomatous dermatitis is often associated with rheumatoid arthritis, and can show variable histological patterns, including interstitial and perivascular inflammatory infiltrates, predominately consisting of neutrophils, as well as neutrophilic debris, histiocytes, lymphocytes, and some eosinophils.

E) Bullous systemic lupus erythematosus (Incorrect) In addition to a subepidermal blister in bullous systemic lupus erythematosus, there is a dense inflammatory infiltrate in the superficial dermis, predominately consisting of neutrophils, as well as lymphocytes and some eosinophils.
**Question**

Cutaneous findings associated with this disease entity include:

The classical clinical rash of adult-onset Still’s disease is included as one of the four major diagnostic criteria and is characterized by an evanescent non-pruritic, non-scaly salmon-colored morbilliform eruption predominately on the trunk and extremities. However, other cutaneous eruptions have been described in association with adult-onset Still’s disease, the most common being persistent pruritic papules and plaques with scale and linear pigmentation, reported to occur, over time, in 65% of patients with the disease. Additional cutaneous manifestations seen in adult-onset Still’s disease include vesiculopustules on the hands and feet, acne-like lesions, purpura, persistent generalized erythema, generalized peau d’ orange-like lesions with diffuse cutaneous mucinosis, intermittent and recurrent urticaria-like eruption with non-pruritic erythematous macules or slightly elevated plaques, and a prurigo pigmentosa-like eruption.

A. Persistent pruritic papules and plaques with scale and linear pigmentation **(Correct)**
B. Evanescent non-pruritic non-scaly salmon-colored morbilliform eruption **(Correct)**
C. Intermittent and recurrent urticarial eruption with non-pruritic erythematous macules or slightly elevated plaques **(Correct)**
D. Generalized peau d’ orange-like lesions **(Correct)**
E. All of the above **(Correct)**

**Discussion**

Adult-onset Still’s disease is a rare systemic inflammatory disorder of unknown etiology that was first described by Eric Bywaters in 1971 in a report detailing 14 adult patients who presented with arthritis and systemic features similar to those seen in systemic juvenile-onset rheumatoid arthritis (systemic juvenile idiopathic arthritis- Still’s disease). There are no pathognomonic signs and symptoms of adult-onset Still’s disease and the clinical course is variable, often resulting in delay in diagnosis and treatment. Although several diagnostic criteria have been proposed, the most commonly used and best validated is the Yamaguchi classification which requires five or more criteria, including two or more major criteria and exclusion of infections, malignancies, and other rheumatic diseases. The major criteria in the Yamaguchi classification include fever of 39°C or higher lasting one week or longer, arthralgias lasting two weeks or longer, “typical” rash described as a macular or maculopapular non-pruritic salmon-pink eruption usually appearing during fever, leukocytosis (≥10x10^9/L) including 80% neutrophils, and minor criteria which include sore throat, lymphadenopathy and/or splenomegaly, abnormal liver function tests, particularly elevations in aspartate and alanine aminotransferases and lactate dehydrogenase concentrations, and negative rheumatoid factor and negative ANA. Although the non-scaly non-pruritic intermittent salmon-colored maculopapular rash is typically the initial cutaneous manifestation seen, there are a variety of other skin eruptions that can initially present or subsequently develop in adult-onset Still’s disease, as described above in question 2. Cutaneous eruptions have shown to change with ongoing disease with transition, most commonly, from the classical morbilliform salmon-colored rash to persistent hyperpigmented plaques with a rippled or linear appearance. Treatment includes initial trials with aspirin or non-steroidal anti-inflammatory drugs, followed by high dose corticosteroids and often additional disease modifying drugs, such as methotrexate, TNF-α, or anti-IL-1.

Histological features:
• Classical rash= subtle perivascular and interstitial inflammation in the superficial dermis consisting of lymphocytes and scattered neutrophils. The epidermis is unremarkable.
• Persistent pruritic papules and plaques= dyskeratotic keratinocytes within the upper stratum spinosum, stratum granulosum, and stratum corneum without basilar dyskeratosis. Dermal changes include a superficial perivascular infiltrate of lymphocytes and neutrophils and an increase in interstitial dermal mucin. Ortho- and parakeratotic hyperkeratosis is usually present. No vasculitis is seen.
• Urticarial eruption= perivascular and interstitial infiltrates, predominately of neutrophils, without eosinophils or evidence of vasculitis or significant dermal edema.

References

CONTRIBUTED BY SARAH N. WALSH, MD
**CASE #167 — SLIDE #167**

**Diagnosis:** Cellular blue nevus

**Case Summary:**
The patient is a 12-year-old girl with a mass on the buttock. The case is sent to you as a consultation. Provided immunohistochemical stains show the lesion to be positive for S100, HMB45, and Melan A and negative for CD34, actin, and myosin.

**Question**
The best diagnosis is:
A) Deep penetrating nevus (Incorrect) Deep penetrating nevi have a sharply demarcated, circumscribed, wedge-shaped architecture with a limited junctional component and epithelioid dermal melanocytes with abundant eosinophilic or amphophilic cytoplasm arranged in a plexiform pattern as loose nests and vertically oriented fascicles with discohesion at the periphery and base. The melanocytes extend down along adnexal structures into the deep dermis and subcutis and do not show obvious maturation. Perineural extension and involvement of the arrector pili muscles are frequently seen.
B) Melanoma (Incorrect) Features frequently seen in melanoma are listed in question 2 and include epithelioid cells with striking pleomorphism and large and/or multiple nucleoli, infiltrative borders, frequent associated inflammation, abundant (>3 /mm²) and/or atypical mitoses, necrosis, lymphovascular invasion, and often the presence of a junctional component.
C) Cellular neurothekeoma (Incorrect) Cellular neurothekeoma has an ill-defined plexiform or multi-lobular architecture and is composed of fascicles, nests, and whorls of epithelioid or spindled cells with ample eosinophilic cytoplasm and monomorphous nuclei. Immunohistochemical stains typically show positivity for NK1/C3, PGP9.5, CD68, CD57, +/- NSE or SMA, and negative staining with S100, Melan A, and HMB45.
D) Cellular blue nevus (Correct) Cellular blue nevus has a well circumscribed, nodular to dumb-bell shaped architecture with a biphasic pattern consisting of classic or common blue nevus areas and distinct hypercellular areas, particularly in the deeper portions of the lesion. The hypercellular areas form nests, nodules, fascicles, and alveolar patterns and are composed of spindled cells with monomorphous nuclei, even chromatin, inconspicuous nucleoli, and moderate amphophilic to lightly pigmented cytoplasm. Degenerative changes, including hemorrhage, cystic or myxoid areas, fibrosis, and stromal hyalinization are often present.
E) Angiosarcoma (Incorrect) Angiosarcomas are composed of irregular anastomosing blood vessels that dissect collagen bundles throughout the dermis. The neoplastic endothelial cells can be epithelioid and have multi-layering, nuclear pleomorphism, and mitoses. Areas with spindle cells arranged in bundles and fascicles can also be seen. An associated inflammatory infiltrate, extravasated red blood cells, and hemosiderin are usually present. Immunohistochemical stains are positive for CD31, CD34, and D2-40 and are negative for melanocytic markers.
Question
Histopathological features that support blue nevus-like melanoma over a cellular blue nevus:

The distinction between cellular blue nevus and blue nevus-like melanoma by light microscopy can be extremely difficult. In contrast to the features listed below, histopathological changes that support cellular blue nevus over melanoma include absent junctional activity, pushing well circumscribed borders with a nodular or dumb-bell shape architecture, absence of associated inflammation, biphasic pattern with areas of common blue nevus associated with areas of hypercellularity, fasciculation, spindled rather than epithelioid cytology, lack of significant cellular pleomorphism, rare and typical mitoses (1/mm²), single and small nucleoli, absence of necrosis, and infrequent ulceration.

A. Necrosis (Correct)
B. Atypical or abundant (>3/mm²) mitoses (Correct)
C. Epithelioid cells with marked nuclear pleomorphism (Correct)
D. Infiltrative borders (Correct)
E. All of the above (Correct)

Discussion
Cellular blue nevus was originally thought to be a variant of melanoma (so-called “melanosarcoma”), but Allen, in 1949, was the first to recognize it as a benign cellular variant of blue nevus. Cellular blue nevi predominately occur in Caucasian females between the ages of 10-40 years old, and are most commonly found on the buttock or sacrococcygeal region, scalp or face, proximal extremities, and trunk. Clinically, cellular blue nevi are blue, blue-black, or black firm to rubbery dome-shaped solitary nodules with smooth borders. Lesions are asymptomatic, non-ulcerated, and usually range in size from 1-3 cm.

Histological features:

- Well circumscribed symmetrical dermal melanocytic proliferation with an expansile pushing border and nodular to dumb-bell shaped outline, often extending into the subcutaneous tissue
- Lack of a junctional melanocytic component
- Biphasic pattern with areas of common blue nevus alternating with nodular and diffuse hypercellular areas
- Hypercellular areas are present in the deep portions of the lesion and form nests, whorls, fascicles, nodules, and alveolar patterns
- Spindle cells with monomorphic nuclei and finely stippled chromatin with inconspicuous nucleoli and moderate amphophilic to lightly pigmented cytoplasm
- Areas of hemorrhage, cystic degeneration, fibrosis, stromal hyalinization, and myxoid change often present
- Dilated vessels and hemosiderin can be scattered throughout the lesion
- Densely pigmented areas or pauci-pigmented areas with melanophages scattered in between cellular nests are present
- Lack of pronounced cellular pleomorphism, absent necrosis, and only rare typical mitoses
- + HMB45, Melan A, S100, and low proliferative index with Ki67
• Negative for chromosomal aberrations by FISH (blue nevus-like melanoma shows clonal aberrations in chromosome 6 by FISH)

References
Diagnosis: Pancreatic panniculitis

Case Summary:
The patient is a 59 year old man with a history of alcohol related cirrhosis and diabetes mellitus who presented to the emergency department complaining of tender nodules with increasing pain on the anterior lower extremities for approximately one month. The patient does not have a known history of pancreatitis or other pancreatic disorder. During his hospitalization, multiple cultures were taken from the subcutaneous lesions which were negative.

Question
Based on the histological findings, the best diagnosis is:

A) Pancreatic panniculitis, consistent with (Correct) Pancreatic panniculitis is a necrotizing lobular panniculitis with extensive enzymatic lobular fat necrosis. Anucleate ghost cell adipocytes have an eosinophilic rim and basophilic granular material with calcification due to saponification. Neutrophilic and/or mononuclear and granulomatous infiltrates within the lobules are present.

B) Erythema nodosum (Incorrect) Erythema nodosum is a septal panniculitis with mixed inflammation in the interlobular septa and Miescher’s granulomas. Fat necrosis is not a prominent feature.

C) Calciphylaxis (Incorrect) Calciphylaxis shows epidermal ulceration, dermal necrosis, and calcification within small and medium blood vessels and adipocytes within the subcutis.

D) Lipodermatosclerosis (Incorrect) Lipodermatosclerosis shows septal fibrosis, micro- and macro-pseudocyst formation, necrotic adipocytes, lipomembranous change, lipogranulomas, adipocyte and medium vessel calcification, and pseudoxanthoma elasticum-like septal elastosis with calcification.

E) Alpha-1 antitrypsin deficiency panniculitis (Incorrect) Alpha-1 antitrypsin deficiency panniculitis shows lobular neutrophilic infiltrates as well as infiltrates of both neutrophils and histiocytes within the septa. Lobular fat necrosis is often present. Liquefactive necrosis in the dermis and subcutaneous septa is characteristic of this form of panniculitis.

Question
Which of these statements, regarding this entity, is true?

A. Lesions only develop after a diagnosis of internal disease has been established (Incorrect) 40-45% of the time, cutaneous lesions are the initial manifestation and precede the diagnosis of pancreatic disease, usually by 1-7 months.

B. Lesions are most commonly present on the head and neck (Incorrect) Distal (usually lower and periarticular) extremities, thighs, buttock, and lower trunk are the sites most commonly affected in pancreatic panniculitis.

C. Complications, including arthritis of surrounding joints or gastrointestinal submucosal fat necrosis leading to gastrointestinal bleeding can occur (Correct) Distant foci of fat necrosis may be present in patients with pancreatic disease and include monoarticular or oligoarticular arthritis and gastrointestinal submucosal fat necrosis resulting in gastrointestinal bleeding.
D. This entity is always associated with a low morbidity and mortality (Incorrect) While there is complete spontaneous resolution of cutaneous lesions once the pancreatic inflammation subsides, pancreatic panniculitis with disseminated fat necrosis is associated with major morbidity and mortality. In one review of 27 patients with pancreatic panniculitis, all 8 with pancreatic carcinoma and 42% of the 19 of those with pancreatitis, died of their disease.

E. Young female patients are most commonly affected (Incorrect) In contrast to other forms of panniculitis, pancreatic panniculitis is more common in men than women (Male to Female ratio of 3:1), likely related to alcoholism. Affected patients are typically in their sixties with an age range of 21-75 years.

Discussion
Pancreatic panniculitis is characterized by necrosis of subcutaneous adipose lobules caused by circulating lipase, amylase, and trypsin. It occurs in 2-3% of patients with pancreatic disease, most commonly due to acute pancreatitis or pancreatic carcinoma, mainly acinar cell type. Males are more commonly affected than females, most likely due to a greater incidence of alcoholism in men, with a male to female ratio of 3:1. While there is a wide age range (21-75 years old) of patients with pancreatic panniculitis, it most commonly occurs in those in their sixties. Dermatological findings are the initial manifestation, and precede the diagnosis of pancreatic disease, 40-45% of the time, usually by 1-7 months. Cutaneous lesions can also be the initial manifestation of another internal malignancy, such as hepatocellular carcinoma, or metastatic disease to the pancreas originating from another primary carcinoma, such as from the stomach. Clinically, lesions are painful or asymptomatic erythematous, edematous subcutaneous nodules or indurated plaques on the distal (usually lower and periarticular) extremities, thighs, buttock, and lower trunk. In patients with underlying pancreatic carcinoma, there are typically more skin nodules which are not confined to the lower extremities or lower body, and show extensive spontaneous ulceration. The main complications associated with pancreatic panniculitis are arthritis of joints in the vicinity of active subcutaneous fat necrosis, and gastrointestinal submucosal fat necrosis resulting in gastrointestinal bleeding. As the pancreatic inflammation subsides, there is complete spontaneous resolution of the subcutaneous nodules, with residual lipoatrophy and hypopigmentation. Pancreatic panniculitis with disseminated fat necrosis, however, is associated with major morbidity and mortality.

Histopathological features:

- Lobular involvement with necrosis and neutrophilic and/or mononuclear and granulomatous inflammation
- Neutrophils attracted to areas of necrosis
- Anucleate “ghost cell” adipocytes have an eosinophilic rim and basophilic granular material with calcification arising from saponification of fat by pancreatic enzymes
References

CONTRIBUTED BY SARAH N. WALSH, MD
Diagnosis: Scabies
Scabies is caused by the mite *Sarcoptes scabiei hominis* that burrows in the superficial aspect of human skin and that can generate a cutaneous hypersensitivity response; mites are tiny arachnids belonging to the subclass Acari

Clinical features
- Anyone may be affected, with outbreaks not uncommon in schools, nursing homes, among the homeless, institutionalized patients, the immunocompromised, those living in close quarters, and health care workers
- Highly contagious
- Mite requires a human host, mates on human skin (with the male dying), and the female burrows into the skin to lay eggs

Presentation
- Pruritic burrows in finger-web and toe-web spaces, volar wrists, axillae, groin, scrotum, penis, buttocks, nipples
- Nocturnal pruritus characteristic
- Hypersensitivity response manifests as erythematos, edematous, few-millimeter to few-centimeter papules and nodules; in primary infections, hypersensitivity response that follows infestation occurs after 4 weeks’ latency
- In neonates, lesions may vesiculate and erythematos patches can coalesce to result in generalized erythroderma
- Pruritus and lesions may persist for over a week following eradication of actual scabetic organisms
- “Norwegian” scabies: exuberant response with crusted nodules, usually in the immunocompromised

Pathology:
- Hyperkeratosis and acanthosis
- Mites, scybala (feces), small oval pellets located within the stratum corneum
- Spongiosis
- Perivascular and/or interstitial lymphohistiocytic infiltrate with eosinophils; flame figures may be evident.

CONTRIBUTED BY JULIA LEHMAN, MD
Diagnosis: Lichen planus pigmentosus

Case Summary:
A 48-year-old East Indian man presented with a 2-year history of asymptomatic, progressive patches of hyperpigmentation of the face, neck, trunk and axillae.

Question
The best diagnosis in this case is
A. Dermatomyositis (Incorrect). Although epidermal atrophy and basal vacuolar degeneration are features of dermatomyositis, the band-like superficial dermal inflammation and heavy pigment incontinence, in addition to the clinical morphology, do not fit this diagnosis.
B. Erythema ab igne (Incorrect). Erythema ab igne presents as reticulate erythema with variable hyperpigmentation localized to sites subjected to prolonged or repeated heat. Histopathologic features of epidermal atrophy and mild basal vacuolar degeneration tend to be mild or absent, and pigment incontinence is less pronounced that in lichen planus pigmentosus (LPP).
C. Lichenoid drug reaction (Incorrect). The clinical history does not favor this diagnosis, although LPP and lichenoid drug eruptions may share histopathologic features.
D. Lichen planus pigmentosus (Correct). The clinical presentation in combination with histopathologic features of epidermal atrophy, basal vacuolar degeneration, mild interface and band-like inflammation and prominent pigment incontinence points to the diagnosis of LPP.
E. Mycosis fungoides (Incorrect). Early patch stage mycosis fungoides (MF) may resemble vacuolar interface dermatitis, but the lymphocytes appear small and banal in this case.

Question
Which of the following is most helpful in arriving at the correct diagnosis in this case?
A. Absence of eosinophils (Incorrect). Absence of eosinophils does not confirm the diagnosis of LPP or exclude other entities in the differential diagnosis, including lichenoid drug eruption.
B. Basal vacuolar degeneration (Incorrect). This feature does not narrow the differential diagnosis.
C. Clinical presentation (Correct). The clinical features are necessary to arrive at the correct diagnosis for this vacuolar interface dermatitis.
D. Epidermal atrophy (Incorrect). This feature does not narrow the differential diagnosis.
E. Lymphocyte morphology (Incorrect). This feature is helpful in excluding mycosis fungoides but does not further narrow the choices.

Discussion
Lichen planus pigmentosus (LPP) is considered to be an uncommon subset of lichen planus (LP). Whether LPP, ashy dermatosis and erythema dyschromicum perstans (EDP) are the same entity has been debated. Most reported cases of LPP have been in individuals from India, but the disorder also has been described in patients from Latin America, Middle Eastern countries, and other regions. Variants include LPP inversus as well as linear and Blaschkoid forms. Clinical presentation typically is with asymptomatic or mildly pruritic large dark brown or
slate-gray macules. Face and neck are the most common sites of onset, followed by the trunk and extremities; most patients eventually have bilateral, often symmetrical lesions involving multiple sites. Absence of erythematous borders is a feature considered to distinguish LPP from EDP. The histopathology of LPP includes epidermal atrophy, basal vacuolar degeneration, mild perivascular or superficial band-like and interface lymphocytic inflammation, prominent pigment incontinence with many dermal melanophages, and variable hyperkeratosis.

References

CONTRIBUTED BY MARGOT S. PETERS, MD
CASE #171 — SLIDE #171

Diagnosis: Folliculotropic BRAF-positive metastatic melanoma

Case Summary:
A 55-year-old man presented with a 2-mm papule of the scalp.

Question
The best diagnosis in this case is:
A. B-cell leukemia cutis (Incorrect). T-cell rather than B-cell malignancies involving the skin may exhibit folliculotropism, and the cellular morphology does not point to a lymphoproliferative malignancy.
B. Langerhans cell histiocytosis (Incorrect). Although Langerhans cell histiocytosis may involve the scalp and is epidermotropic, the clinical presentation with an isolated 2-mm papule, cellular morphology and folliculotropism are inconsistent with this diagnosis.
C. Metastatic adenocarcinoma from lung primary (Incorrect). The scalp is a common location of metastatic carcinoma, and there are areas of pseudoglandular formation in this tumor. However, the nested architecture and pigment fit better with metastatic melanoma. Metastatic adenocarcinoma is rarely epidermotropic and is not known to exhibit folliculotropism.
D. Metastatic melanoma (Correct). The dermal mass of densely packed tumor cells, with pigment, oriented about a follicle and with involvement of follicular epithelium, is most consistent with metastatic melanoma.
E. Mycosis fungoides (Incorrect). Mycosis fungoides may be folliculotropic, including with follicular mucinosis, but the cellular morphology in this lesion is not that of lymphocytes.

Question
Which immunohistochemical profile fits the correct diagnosis?
A. S100+ CD1a+ BRAF mutation+ (Incorrect). Langerhans cell histiocytosis is S100+ and CD1a+ and also may exhibit BRAF mutation.
B. S100- Cyclin D1+ BRAF mutation+ (Incorrect). Hairy cell leukemia is Cyclin D1+ and most cases have a BRAF mutation.
C. S100- Cyclin D1- BRAF mutation+ (Incorrect). Melanoma is usually S100+, may be Cyclin D1+ and may or may not have a BRAF mutation.
D. S100- CD1a- BRAF mutation+ (Incorrect). Metastatic adenocarcinoma from lung primary is S100- CD1a- and may show BRAF mutation.
E. S100+ CD1a- BRAF+ (Correct). This triad is consistent with metastatic melanoma.

Discussion
Primary cutaneous melanoma with folliculotropism has been reported in fewer than 10 cases. Folliculotropic metastatic melanoma is even more unusual and was first described in 2009, in a 70-year-old man who had a primary cutaneous melanoma of the abdomen and 2 cutaneous metastases; all 3 lesions had a folliculocentric pattern and a high mitotic index. Folliculotropic metastatic melanoma has been reported in two additional cases: one patient had multiple 1-2 mm black macules of the scalp (Davis et al) and another had widely distributed 1-2 mm cutaneous metastases, including 9 of 20 in a follicular distribution (Ishida and Okabe).
Our patient had a history of primary cutaneous melanoma (nodular type, Clark level IV, Breslow depth 3.4 mm) and metastatic melanoma of lymph node, liver and lung in addition to the isolated pigmented papule the scalp; after BRAF V600E mutation was documented in the scalp lesion, treatment with vemurafenib was started. In addition to primary cutaneous melanoma and cutaneous metastases of melanoma, BRAF gene mutation has been found in in metastatic melanoma of extracutaneous sites, Langerhans cell histiocytosis, hairy cell leukemia and also in carcinoma of thyroid, colon/rectum, lung, ovary, breast and liver.

References

CONTRIBUTED BY MARGOT S. PETERS, MD
Case Summary

A 45 year-old man presented with a papular brown lesion on abdomen.

Question 99

The best diagnosis is:

A. Langerhans cell histiocytosis—**Incorrect.** The classic morphology of Langerhans cells (large oval cells with increased pale pink cytoplasm and folded bland nuclei) is not evident.

B. Granular cell tumor—**Incorrect.** The tumor cells do not exhibit the characteristic granular cytoplasm, and pseudoepitheliomatous hyperplasia in the overlying epidermis (a common feature of granular cell tumors) is not present.

C. Congenital pattern nevus—**Incorrect.** The tumor cells are cells exhibit a bi-phasic appearance with centrally located epithelioid cells flanked by a more banal population of nevoid appearing melanocytes.

D. Combined melanocytic nevus with features of Spitz nevus and BAP1 loss—**Correct.** The lesion consists of melanocytes exhibit a bi-phasic appearance with centrally located epithelioid cells with a Spitzoid cytology flanked by a more banal population of nevoid appearing melanocytes.

E. Invasive melanoma—**Incorrect.** The pattern of growth (the melanocytes appear mostly well spaced), the uniform cytologic atypia of epithelioid cells, and the lack of other atypical features (dermal mitotic figures) argue against a diagnosis of melanoma.

Question 100

Which of the following markers is likely to also be positive in the large cells comprising the central aspect of the lesion:

A. BRAF-V600E—**Correct.** This is a classic example of a BAP-oma—a melanocytic nevus comprised of centrally located tumor cells lacking nuclear expression of BAP-1 and positive for BRAFV600E.

B. Ki-67—**Incorrect.** Ki-67 should not be prominently expressed in this lesion.

C. CD1a—**Incorrect.** This immunophenotype characterizes a Langerhans cell infiltrate.

D. CD163—**Incorrect.** CD163 is a marker of fibrohistiocytic lineage and would be negative in melanocytes.

E. p63—**Incorrect.** p63 would confirm an epithelial or myoepithelial lineage and would not be helpful in further classifying this tumor.
Clinical features

In a multi-institutional study, Wiesner et al. described a pair of families in which affected family members developed multiple papular melanocytic nevi, and some of the affected individuals also developed melanomas (uveal or cutaneous). They showed that alterations in the BAP1 gene (at the 3p21 locus) segregated with the phenotype. In addition, these authors and others have described melanocytic nevi with similar histopathologic features and clinical appearance arising sporadically. Tumors with BAP1 loss are typically homogeneous brown-tan-pink papules or nodules (or occasionally plaques) with a slightly translucent quality.

Histopathologic features

Histopathologically, tumors with BAP1 loss show a characteristic morphology. They are usually predominantly dermal-based tumors and contain a variable population of well-spaced tumor cells with a “Spitzoid” morphology (including increased amphophilic cytoplasm and enlarged epithelioid nuclei with occasionally conspicuous nucleoli). These cells are often associated with a variably dense lymphocytic infiltrate that is intimately associated with the epithelioid melanocytes. Some cases (similar to the current one) have been described to contain an associated banal nevus component. Immunohistochemical studies typically show loss of nuclear BAP-1 expression in the Spitzoid melanocytes; whereas if there is a banal component, these typically express BAP-1. So called “BAPomas” also frequently harbor BRAFV60E mutations. These melanocytic lesions lack features of typical Spitz nevi, such as epidermal hyperplasia, clefting, and Kamino bodies.

References


Diagnosis: Anaplastic CD30+ T-cell lymphoma

Case Summary:
A 68-year-old man with past history of malignant melanoma presents with a 1.5 cm nodule in the neck. The mass is excised. Immunohistochemical studies show the lesional cells to be negative for CD20 and CD34.

Question
The best diagnosis is:

A. Anaplastic large cell lymphoma (Correct)
B. Follicle center cell lymphoma (Incorrect) The lesional cells of follicle center cell lymphoma are CD20 positive B cells.
C. Merkel cell carcinoma (Incorrect) Merkel cell carcinoma cells are closely spaced and often arranged in a trabecular pattern.
D. Metastatic melanoma (Incorrect) Melanoma cells are typically epithelioid/spindled, contain abundant densely eosinophilic cytoplasm and vesicular nuclei with prominent eosinophilic nucleoli.
E. Myeloid sarcoma (Incorrect) Cells of myeloid sarcoma are typically positive for CD34.

Discussion
Sections show a dense diffuse infiltrate of large atypical cells involving the entire dermis and focally extending into the subcutaneous tissue. The cells have a moderate amount of pale cytoplasm and round to oval and occasionally indented nuclei with prominent nucleoli. Frequent mitotic figures including atypical forms are present. By initial immunohistochemical studies, the neoplastic cells are positive for CD3 and CD4 and negative for CD20 and ALK-1. These findings are consistent with primary cutaneous anaplastic large T-cell lymphoma. Follicle center cell lymphoma with a predominantly diffuse pattern and high grade morphology may be considered in the differential diagnosis. However, the lesional cells of follicle center cell lymphoma are CD20 positive B cells. Merkel cell carcinoma (cutaneous small-cell undifferentiated carcinoma) can show marked cytologic atypia and frequent mitotic figures similar to the index case. However, Merkel cell carcinoma cells are closely spaced and often arranged in a trabecular pattern. The cells contain scant cytoplasm, round and vesicular nuclei with a finely granular chromatin and inconspicuous nucleoli typical of neuroendocrine differentiation. Given the past history of melanoma, metastatic melanoma may be considered in the differential diagnosis. However, melanoma cells are typically epithelioid/spindled, contain abundant densely eosinophilic cytoplasm and vesicular nuclei with prominent eosinophilic nucleoli. In the differential diagnosis of anaplastic hematopoetic malignancies myeloid sarcoma (cutaneous involvement by a myeloid leukemia) may be considered. However, cells of myeloid sarcoma are typically positive for CD34.
Question
Which of the following immunohistochemical stains is/are most likely to be positive in the lesional cells?

A. CD19, BCL-6 (Incorrect)
B. CK20, Synaptophysin (Incorrect)
C. CD30 (Correct)
D. CD117, Myeloperoxidase (Incorrect)
E. Melan-A, HMB45 (Incorrect)

Anaplastic large cell lymphoma is **CD30 positive** and typically of the CD3+, CD4+, CD8- phenotype.

**CD19 and BCL-6** stains are positive in B-cell lymphoma of follicle center origin but not in anaplastic large T cell lymphoma. CD19, CD20 and CD79a are all B cell markers while BCL-6 is positive in cells of follicle center origin.  
**CK20 and synaptophysin** are positive in primary neuroendocrine (Merkel cell) carcinoma of skin but not in lymphoma.  
**CD117 and myeloperoxidase** stains can be positive in addition to CD34 in myeloid neoplasms but not in lymphoid neoplasms.  
**Melan-A and HMB45** stains are positive in malignant melanoma.

References
CASE #174 — SLIDE #174

Diagnosis: Lupus panniculitis

Case Summary: A 44-year-old woman presents with a 2-cm nodule on the right upper arm.

Question
The best diagnosis is:
A. Erythema nodosum (Incorrect)
B. Lipomembranous panniculitis (Incorrect)
C. Lupus panniculitis (Correct)
D. Pancreatic enzyme panniculitis (Incorrect)
B. Subcutaneous panniculitis-like T-cell lymphoma (Incorrect)

Discussion
Sections show a predominantly lobular pattern of panniculitis with lymphocytes and an admixture of plasma cells. Hyaline fat necrosis characterized by eosinophilic glassy degeneration of the adipocytes is present. Lymphocytic vasculitis of medium sized blood vessels can be seen. The overlying skin shows subtle vacuolar alteration of the basal cell layer that is also obscured by lymphocytes, a superficial and deep perivascular and perianexial lymphocytic infiltrate and interstitial mucin deposits. These findings are most characteristic of lupus panniculitis.

Erythema nodosum is predominantly a septal panniculitis characterized by a septal infiltrate of lymphocytes and neutrophils in early lesions and by widening of the septa with fibrosis and granulomatus inflammation in later lesions. Hyaline fat necrosis seen in the index case is not typical of erythema nodosum.

Lipomembranous panniculitis also known as lipodermatosclerosis shows a predominantly lobular panniculitis similar to the present case. In addition, there is degeneration and necrosis of fat with formation of pseudocysts that are lined by thin eosinophilic layer with feathery projections (lipomembrane). Hyaline fat necrosis is not present.

Pancreatic enzyme panniculitis is characterised fat necrosis with saponification and calcium deposits resulting in ghostlike appearance of the fat cells.

Subcutaneous panniculitis-like T-cell lymphoma is characterized by a dense, predominantly lobular infiltrate of lymphocytes similar to the present case. However, the lymphocytes in subcutaneous T-cell lymphoma are cytologically atypical and there is rimming of the adipocytes by these cells. Histiocytes containing lymphocytic nuclei (“bean bag” cells) can be seen.

Question
Which of the following findings is most likely in this patient?
A. Clonal T-cell receptor rearrangement (Incorrect)
B. Elevated serum amylase (Incorrect)
C. Positive ANAs on serology (Correct)
D. Positive bacterial cultures (Incorrect)
C. Severe stasis changes (Incorrect)

Correct answer: Positive ANAs on serology
Approximately 50% of the patients with lupus panniculitis have evidence of mild systemic lupus erythematosus and elevated ANAs while 70% also have other lesions typical of discoid lupus. Positive immunofluorescence at the dermoepidermal junction can be also seen in more than 50% of patients with lupus panniculitis.

**Clonal T-cell receptor rearrangement** is seen in T cell lymphomas including subcutaneous panniculitis-like T cell lymphoma.

**Elevated serum amylase** and lipase are seen in pancreatic enzyme panniculitis.

**Positive bacterial cultures** imply an infectious etiology and therefore not expected in this patient.

**Severe stasis changes** and obesity are typically seen in lipodermatosclerosis.

**References**
Diagnosis: Pseudomonas vasculitis/septicemia

Case Summary:
A 31-year old man with past history of aplastic anemia and chronic renal failure presents with a rapidly darkening lesion with erythematous borders on left leg. An excisional biopsy is performed.

Question
The best diagnosis is:

A. Calciphylaxis (Incorrect)
B. Coumarin necrosis (Incorrect)
C. Ecchymosis (Incorrect)
D. Leukocytoclastic vasculitis (Incorrect)
E. Pseudomonas vasculitis/septicemia (Correct)

Discussion
Sections show early ischemic changes of the epidermis, abundant extravased red cells and scant inflammatory cell infiltrate in the dermis. There is extensive necrotizing vasculitis involving the vessels of the dermis and subcutaneous fat. There is fibrin in the vascular walls and occasional thrombi in the lumina but no significant neutrophilic infiltration or neutrophilic nuclear dust. There is widespread bacillary infiltration of the perivascular region and media and adventia of the vessels with relative sparing of the intima and lumina. These findings are typical of pseudomonas vasculitis/septicemia, also known as ecthyma gangrenosum.

Calciphylaxis is small vessel vasculopathy that occurs as an uncommon complication of renal failure. Cutaneous involvement by painful violaceous lesions that rapidly progress to ulcers and gangrene can occur. Histological sections show fibrin thrombi and associated ischemic changes of the skin similar to the index case. However, instead of the bacillary infiltration there is calcification of the small arteries and soft tissue.

Coumarin necrosis shows the dermal hemorrhage and ischemic changes seen in this case. However, coumarin necrosis is characterized by prominent thrombotic occlusion of the vascular lumina without significant inflammatory cell infiltrate or bacteria.

Ecchymosis is characterized by dermal hemorrhage without significant vascular damage, fibrin thrombi or bacteria.

Leukocytoclastic vasculitis involves the small blood vessels of the dermis and is typically associated with neutrophils and neutrophilic nuclear dust in addition to fibrin deposits and extravasated red cells seen in this case.
Question
Which of the following is most helpful in confirmation of the diagnosis?

A. Bacterial cultures (Correct)
D. Direct immunofluorescence studies (Incorrect)
E. Platelet count (Incorrect)
F. Protein C levels (Incorrect)
E. Serum calcium and phosphorous (Incorrect)

Discussion
Microbiologic cultures of the blood and/or skin lesions grow pseudomonas aeroginasa, a gram negative bacillus. Bacterial cultures are important not only to confirm the diagnosis but also for antibiotic sensitivity testing.

Direct immunofluorescence studies of skin biopsy are of utility in evaluation of leukocytoclastic vasculitis but not septicemia.

Platelet count can be helpful in the diagnosis of thrombocytopenia causing an ecchymosis.

Acquired protein C deficiency can be seen in coumarin necrosis and sepsis. Measurement of protein C levels will not help in confirming the diagnosis in this case.

Serum calcium and phosphorous product may be elevated in calciphylaxis.

References

CONTRIBUTED BY VIJAYA B. REDDY, MD, MBA
CASE #176—SLIDE #176

Diagnosis: Perineurioma

Case Summary:
A 45-year-old woman presented with a 1.5-cm nodule on the distal digit of her right index finger.

Question
The best diagnosis is:

A. Cutaneous myxoma (Incorrect)
B. Dermatofibrosarcoma protuberans (Incorrect)
C. Digital Fibromyxoma (Incorrect)
D. Low-grade fibromyxoid sarcoma (Incorrect)
E. Peineurioma (Correct)

Discussion
Sections show a fairly well circumscribed nodule surrounded by a thin capsule of fibrous tissue and composed predominantly of slender spindled cells with oval to wavy nuclei and elongated cytoplasmic processes. In some areas, there are plumper spindled to ovoid cells and some are arranged as fascicles. The stroma is predominantly myxoid and contains thin-walled blood vessels. These findings are consistent with perineurioma. Soft tissue perineuriomas occur most commonly in the subcutis of the extremities and show a morphologic spectrum ranging from hypercellular lesions with collagenous stroma to hypocellular tumors with myxoid stroma necessitating the use of immunohistochemical stains (S-100, CD34, SMA, desmin, EMA, Claudin-1) for confirmation of the diagnosis.

Cutaneous myxoma is a well circumscribed, sparsely cellular dermal lesion composed of stellate and spindled fibroblasts in a myxoid matrix.

Dermatofibrosarcoma protuberans can have a myxoid pattern. However, it is typically poorly circumscribed, involves the deep dermis and infiltrates into the subcutaneous fat in a “honey comb” pattern.

Digital fibromyxoma (superficial acral fibromyxoma) occurs preferentially in the subungual or periungual region and often poorly circumscribed. It is composed of spindled or stellate shaped cells with a vaguely storiform arrangement. Alternating areas of myxoid and fibrous stroma are present.

Low grade fibromyxoid sarcoma arises most commonly in deep soft tissue of the proximal extremities and is characterized by uniform spindled cells in alternating zones of collagenous and myxoid stroma. Thin walled blood vessels with a branching pattern can be present.
Question
Which of the following immunohistochemical stains is most useful in confirming the diagnosis?

A. CD34 (Incorrect)
B. Desmin (Incorrect)
C. Epithelial membrane antigen (EMA) (Correct)
D. Smooth muscle actin (SMA) (Incorrect)
E. S-100 protein (Incorrect)

Correct answer: Epithelial membrane antigen (EMA)
All perineuriomas are positive for EMA making it an essential stain in confirming the diagnosis and excluding other entities in the differential diagnosis. The phenotype of perineurioma parallels that of normal perineural cell (EMA+/S-100- ). In addition, perineuriomas have been shown to be positive for Claudin-1. CD34 can be positive in perineurioma but not helpful in differentiating it from other tumors including dermatofibrosarcoma protuberans. Uniform positivity for CD34 favors a diagnosis of dermatofibrosarcoma protuberans.
Desmin is generally negative in perineurioma.
Smooth muscle actin (SMA) is positive in some perineuriomas but not helpful in confirming the diagnosis.
S-100 protein is typically negative in perineurioma and therefore can be helpful in differentiating it from neurofibroma.

References

CONTRIBUTED BY VIJAYA B. REDDY, MD, MBA
Diagnosis: Acanthamoebiasis

Case Summary:
A 44-year-old man with AIDS presents with multiple violaceous papules on the extremities.

Question
The best diagnosis is:

A. Acanthamebiasis (Correct)
B. Atypical mycobacterial infection (Incorrect)
C. Cytomegalovirus infection (Incorrect)
D. Herpes virus infection (Incorrect)
E. Pyoderma gangrenosum (Incorrect)

Discussion
Sections show epidermal necrosis, diffuse dermal infiltrate of neutrophils, nuclear dust, lymphocytes and histiocytes. There is damage of the small blood vessels with fibrinoid change and fibrin thrombi. Admixed with the inflammatory cell infiltrate are round trophozoites with vacuolated cytoplasm, central nucleus and a single prominent nucleolus characteristic of Acanthamoeba spp.

Atypical mycobacterial infection can be considered in the differential diagnosis in the context of an immunocompromised host and if the trophozoites of acanthamoeba are mistaken for histiocytes. The central nucleus with single prominent nucleolus differentiates Acanthamoeba from histiocytes.

Cytomegalovirus infection typically involves endothelial cells of the dermal blood vessels. The affected cells contain large hyperchromatic, basophilic intranuclear inclusions. Some of the inclusions are surrounded by a halo.

Herpes virus infection can show epidermal necrosis and underlying vasculitis similar to that seen in this case. However, multinucleated giant cells with viral cytopathic effects are typically seen in the epidermis in herpes infection.

Pyoderma gangrenosum can show epidermal necrosis/ulceration, a dense dermal neutrophilic infiltrate with nuclear dust and vascular damage. The recognition of the trophozoites of acanthamoeba is crucial in the differential diagnosis.

Question
For which of the following is this patient at greatest risk?

A. Chronic keratitis (Incorrect)
B. Eczema herpeticum (Incorrect)
C. Granulomatous encephalitis (Correct)
D. Inflammatory bowel disease (Incorrect)
E. Interstitial pneumonia (Incorrect)

Correct answer: Granulomatous encephalitis
Immunocompromised patients with disseminated acanthamoebiasis are at risk for developing often fatal **granulomatous encephalitis.**

**Chronic keratitis** caused by acanthamoeba is typically seen in non-immune compromised individuals who wear soft contact lenses.

**Eczema herpeticum** is a disseminated herpes virus infection occurring on previous skin disease such as atopic dermatitis.

**Inflammatory bowel disease** may be associated with pyoderma gangrenosum.

**Interstitial pneumonia** can be caused by viral infections including CMV and herpes infection.

**References**

**CONTRIBUTED BY VIJAYA B. REDDY, MD, MBA**
CASE #178 — SLIDE #178

Diagnosis: HTLV-1 associated adult T cell leukemia/lymphoma

Case Summary:
An 80-year-old man from Japan presents with plaques in his axilla, atypical cells in his blood, and elevated calcium. A biopsy from the axilla was performed.

Question
The best diagnosis is:

A. Chronic active dermatitis (Incorrect) Cells are too atypical, no spongiosis.
B. Pagetoid Reticulosis (Incorrect) History not consistent with this diagnosis, not enough epidermotropism.
C. HTLV-1 associated adult T cell lymphoma/leukemia (Correct) Histology is consistent with CTCL, and hypercalcemia and history of living in Japan, should raise suspicion for HTLV-1 associated leukemia/lymphoma.
D. Atypical drug eruption (Incorrect) Cells are too atypical, no eosinophils.
E. Paget’s Disease (Incorrect) Cells in the epidermis are lymphocytes.

Question
The cells in the epidermis are most likely to express which phenotype?

A. CD3+/CD8+/CD7- (Incorrect) While some cases of ATL are CD8 predominant, most patients have a CD4+ phenotype.
B. CK7+/CK20- (Incorrect) The cells are lymphoid, not epithelial.
C. CD3+/CD4+/CD7+ (Incorrect) There is loss of the mature T cell marker CD7 in ATL.
D. CD3+/CD4+/CD7- (Correct)
E. CD30+/CD4+/CD7- (Incorrect) This is not transformed mycoses fungoides, or ALCL.

Discussion
HTLV-1 associated adult T cell leukemia/lymphoma (ATL) is a rare, multisystem, aggressive lymphoma/leukemia caused by the human T-lymphotropic retrovirus type I (HTLV-I). ATL has been reported in every area where HTLV-1 is common, including the Caribbean and parts of Japan, West Africa, the Middle East, South America, and Pacific Melanesia. People who acquire the infection early in life are thought to be at higher risk than those who are infected later. In Japan, men seem to be at greater risk than women; the virus is transmitted through breast milk (mother to child), sexually, and through blood. Patients may present with maculopapular eruptions, nodules, or plaques, and the skin is the most common secondary organ involved. The histology can be non-specific, but in most cases, the histology mimics that of cutaneous T cell lymphoma, mycoses fungoides type. In the present case, the history provided some clues that the patient had ATL—hypercalcemia, atypical cells in the blood, and skin lesions that mimicked mycoses fungoides. HTLV-1 is also a causal factor in tropical spastic paraparesis and HTLV-1 associated myelopathy. The normal T cell counter part are peripheral CD4+ cells, probably the CD4+ CD25+ FOXP3+ regulatory T cells. Hypercalcemia is present in 50% of patients.
References

CONTRIBUTED BY GLYNIS SCOTT, MD
CASE #179 — SLIDE #179

**Diagnosis:** Atypical mycobacterial infection in a tattoo

**Case Summary:**
A 38-year-old man presented with red papules on his arm.

**Question**
What stains should you order?

A. Alcian blue (Incorrect) While there are some histiocytes in the infiltrate, there is no collagen degradation suggestive of granuloma annulare.
B. Iron (Incorrect) The pigment in the dermis is too dark to be iron.
C. Acid fast and fungal stain (Correct) The reaction pattern suggests the possibility of infection.
D. Melanin stain (Incorrect) The pigment is too fine and too black for melanin.
E. Brown and Brenn (Incorrect) The reaction pattern is not typical for a bacterial infection.

**Question**
What is your best diagnosis?

A. Granulomatous interstitial allergic reaction to a drug (Incorrect) There is pigment, typical for a tattoo, in the dermis. There are no eosinophils.
B. Granuloma annulare (Incorrect) No palisading, no mucin, presence of tattoo pigment.
C. Argyria (Incorrect) While the color of the pigment is good for argyria, it is not distributed around eccrine glands/vessels, and the presence of inflammation is unusual for argyria.
D. Granulomatous reaction to a tattoo, suspicious for infection (Correct) the presence of tattoo pigment, and the presence of histiocytes, is most consistent with an infected tattoo.
E. Granulomatous variant of mycoses fungoides (Incorrect) Lymphocytes are not atypical, no epidermotropism.

**Discussion**
Cutaneous infections following tattoos are uncommon, but are a risk. This patient represents a cluster of >18 patients in the Rochester area who were tattooed with grey pigment that was contaminated with *Mycobacterium chelonae*. All patients had papules, nodules and plaques overlying their tattoos within 2 weeks of the procedure. Culture grew out *Mycobacterium chelonae*. Of the 18 patients, only one had a positive AFB stain, indicating that the absence of organisms on sections does not preclude the diagnosis. Infection of tattoos may be overlooked clinically; many patients receive alternate diagnoses before mycobacterial infection is identified. The clinical appearance includes papules, plaques, and lichenoid papules. The histology is straightforward and includes the presence of tattoo pigment associated with a lymphohistiocytic inflammatory cell infiltrate. Granulomas may be seen, but may be absent. Other reported Mycobacterium identified in tattoos causes of infection include M. haemophilum and M. immunogenenum.
References

CASE #180 — SLIDE #180

Diagnosis: Vasculitis/coagulopathy induced by Levamisole-tainted cocaine

Case Summary: A 38-year-old woman presented to the emergency room with necrotic lesions on her face and ears. No fever, no chills. She has a history of using crack cocaine recently.

Question
What is your best diagnosis?

A. Sepsis (Incorrect) Although the presence of intravascular thrombi is consistent with sepsis, the clinical history does not support that diagnosis.

B. Levamisole-associated skin necrosis due to contaminated crack cocaine (Correct) the presence of thrombi and skin necrosis in this clinical setting raises the possibility of levamisole-associated skin necrosis.

C. Sweets syndrome (Incorrect) Lack of a neutrophil predominant infiltrate, presence of thrombi, excludes neutrophilic dermatosis.

D. Granuloma fasciale (Incorrect) The presence of thrombi does not support that diagnosis.

E. Erythema elevatum diutinum (Incorrect) Location is poor, lack of onion skinning of the vessels/fibrosis, and presence of thrombi, are not consistent with EED.

Question
If you could perform just one test, what would it be?

A. Serum cryoglobulin levels (Correct) This histology would also be typical for skin lesions associated with cryoglobulinemia.

B. Cardiac Echo (Incorrect) While thrombi are a feature of marantic endocarditis, the location of the lesions is not typical.

C. Bone marrow biopsy (Incorrect) Skin changes are not consistent with neutrophilic dermatosis, therefore leukemia is unlikely.

D. Hepatitis C serology (Incorrect) The findings are primarily thrombotic, and not leukocytoclastic, which would be more typical for Hepatitis C associated skin necrosis.

E. None of the above (Incorrect)

Discussion
Levamisole is used in veterinary medicine and is currently approved for use in cattle, sheep and swine as an anti-parasitic agent. Although it was once used in human medicine in the past for treating autoimmune diseases and cancer, it is no longer an approved drug for human use. In 2009 a nation wide alert was sent out warning of effects of levamisole-laced cocaine, including the presence of skin changes. Levamisole is used as a cutting agent for cocaine, and is present in 80% of street cocaine. Ingesting cocaine mixed with levamisole can seriously reduce a person's white blood cells, suppressing immune function and the body's ability to fight off even minor infections. People who snort, smoke, or inject crack or powder cocaine contaminated by levamisole can experience overwhelming, rapidly-developing, life threatening infections. Other serious side effects can also occur. Skin changes consist of necrosis, usually of the head and neck areas, with the ears particularly affected. The histology consists of coagulopathy, vasculitis, or both. Neutropenia may precede the onset of the skin necrosis. The presence of intravascular
thrombi raises a broad differential diagnosis, including cryoglobulinemia, sepsis, disorders of clotting factors such as Protein C, protein S, and anti-phospholipid syndrome. Levamisole-laced cocaine should be added to the list of disorders that result in vasculitis and intravascular thrombi. Levamisole causes a typical clinical picture characterized by bilateral necrosis of the ears; serology may show positive perinuclear anti-neutrophil cytoplasmic antibodies, anticardiolipin antibodies, and lupus anticoagulant.

**References**


Diagnosis: Scleromyxedema

Case Summary: A 59-year-old female presented with dozens of flesh-colored, firm 2-mm papules over the dorsal hands, thighs, posterior neck and face.

Question
The best diagnosis is:
A. Scleromyxedema – **Correct.** The biopsy shows typical findings including superficial dermal mucin and fibroblasts in the setting of a supportive clinical presentation.
B. Nephrogenic systemic fibrosis – **Incorrect.** Induration of the extremities would be a more typical clinical presentation, and the histopathologic findings typically include deeper dermal and subcutaneous fibrosis.
C. Reticular erythematous mucinosis – **Incorrect.** This diagnosis is often classified as tumid lupus. Dermal mucin can be present, but this presents with a perivascular lymphocytic infiltrate (similar to tumid LE). Clinically, it presents with erythematous plaques on the chest.
D. Scleredema – **Incorrect.** Scleredema would present with diffuse cutaneous induration. The histopathology would show large collagen bundles separated by mucin *without* increased fibroblasts.
E. Myxedema – **Incorrect.** The histopathology would show large diffuse mucin deposition without increased fibroblasts.

Question
The most likely associated finding is:
A. Elevated fasting glucose – **Incorrect.** This finding is associated with scleredema.
B. IgA monoclonal gammopathy – **Incorrect.** IgG monoclonal gammopathy most typically observed. IgA monoclonal gammopathy can be seen with other cutaneous conditions, including erythema elevatum diutinum.
C. Abnormal TSH – **Incorrect.** This would be seen in pretibial or localized myxedema associated with Grave’s disease or in generalized myxedema associated with severe hypothyroidism.
D. IgG lambda monoclonal gammopathy – **Correct.** Paraproteinemia (typically IgG lambda) is seen in over 80% of patients with scleromyxedema.
E. HIV positive – **Incorrect.** This has been observed in localized variants of lichen myxedematous.

Clinical Features
Scleromyxedema (or generalized and sclerodermoid variant of lichen myxedematosus) is characterized by a widespread eruption of multiple, firm papules that most commonly affect the face, neck, upper extremities, hands, and thighs. They may be arranged linearly and are not typically pruritic. Serious systemic manifestations can occur including esophageal dysmotility, numerous central and peripheral nervous system abnormalities, and pulmonary involvement. Attempts at treatment include targeting the underlying paraproteinemia (including melphalan, steroids, and chemotherapy).
Histopathologic Features
- Diffuse mucin deposition with the upper and mid dermis
- Irregularly arranged fibroblasts
- May have atrophic epidermis and/or mild perivascular lymphoplasmacytic infiltrate

References

CONTRIBUTED BY CARILYN N. WIELAND, MD
Diagnosis: Acquired Epidermodysplasia Verruciformis

Case Summary: An 11-year-old male with HIV presented with hypopigmented flat-topped papules and plaques on the neck.

Question
The best diagnosis is:
A. Acquired epidermodysplasia verruciformis – Correct. The biopsy shows enlarged keratinocytes with a blue-gray pallor typical for epidermodysplasia verruciformis. The history of immunosuppression would be consistent with the acquired form.
B. Tinea versicolor – Incorrect. The clinical description could be suggestive for tinea versicolor, but intracorneal hyphae are not seen.
C. Verruca vulgaris – Incorrect. Common warts are often seen in the setting of immunosuppression, but typically have more parakeratosis and papillomatosis with koilocytes.
D. Bowenoid papulosis – Incorrect. There is not significant atypia or increased mitoses.
E. Confluent and reticulated papillomatosis – Incorrect. The specimen shows acanthosis and increased pigment (associated with the patient’s darker skin type), but the other epidermal changes are not consistent with this diagnosis.

Question
The most likely detected finding would include:
A. HPV types 1 & 4 – Incorrect. These HPV types are typical for common warts.
B. HPV types 6 & 11 – Incorrect. These HPV types are associated with genital warts.
C. HPV types 5 & 8 – Correct. As with inherited epidermodysplasia verruciformis, HPV types 5 & 8 are most common in the setting of immunosuppression with EV-like skin changes.
D. HPV types 16 & 18 – Incorrect. These HPV types are associated with Bowenoid papulosis, genital warts, and cervical dysplasia.
E. None of the above – Incorrect.

Clinical Features
Epidermodysplasia verruciformis is an inherited condition in which individuals are susceptible to verrucae, especially with HPV types 5 & 8. An epidermodysplasia verruciformis-like condition has been reported in patients with immunosuppression secondary to numerous causes including organ transplant, lymphoma, and HIV. These patients present with numerous, recalcitrant verrucae that are similar to flat warts. However, while typical flat warts are associated with HPV types 3 & 10, HPV types 5 & 8 are most frequently detected acquired epidermodysplasia verruciformis-like disease.

Histopathologic Features
- Hyperkeratosis, hypergranulosis, and acanthosis
- Keratinocytes are enlarged and have a distinctive grey-blue pallor
- Perinuclear halos and vacuolation may be present
- Disordered maturation of keratinocytes
References

CONTRIBUTED BY CARILYN N. WIELAND, MD
Diagnosis: Lupus miliaris disseminatus faciei

Case Summary:
A 30 year-old female presented with a several month history of reddish-orange papules on the central face and axillae.

Question
A. Granuloma annulare – Incorrect. This would typically present with more palisading granulomas with central necrobiosis and mucin deposition.
B. Sarcoidosis – Incorrect. In contrast to the case presented, sarcoidosis can be distinguished by non-caseating granulomas.
C. Hidradenitis suppurativa – Incorrect. This can also show follicular-associated changes, but should typically include deeper changes with more suppurative inflammation, fibrosis, broken hair shafts, and granulomatous inflammation in association with keratin.
D. Rheumatoid nodule - Incorrect. These lesions present at sites of pressure, such as the extensor surfaces. Rheumatoid nodules consist of palisading histiocytes surrounding necrobiosis and fibrin and tend to be in the deep dermis to subcutaneous tissue.
E. Lupus miliaris disseminatus faciei – Correct. The biopsy shows follicular-associated granulomatous inflammation with central caseating necrosis. This, in conjunction with the clinical presentation, is most consistent with lupus miliaris disseminatus faciei.

Question
The most common location for this entity to present is the:
A. Nose – Incorrect. Based on the above diagnoses, this location would be more common for cutaneous sarcoidosis, particularly the type referred to as lupus pernio.
B. Eyelids/periorbital area – Correct. The most typical area of involvement for lupus miliaris disseminatus faciei is the in the periocular areas.
C. Elbows/forearm – Incorrect. This location would be typical for rheumatoid nodule.
D. Distal extremities – Incorrect. This location would be a common location for granuloma annulare.
E. Axilla – Incorrect. This location would be more common for hidradenitis suppurativa. Axillary involvement of lupus miliaris disseminatus faciei can occur, but it is not the most typical presentation.

Clinical Features
Lupus miliaris disseminatus faciei (acne agminata) is a rare condition that is not well understood. Despite histopathologic features suggestive for tuberculosis, bacilli have not been identified with this entity. Due to the presence of granulomas and the clinical presentation of yellowish-red papules often on the central face, this entity has sometimes been lumped with granulomatous rosacea or perioral dermatitis. However, unlike rosacea, lupus miliaris disseminatus faciei does not present with facial flushing or telangiectasias. It does not respond to treatments typical for rosacea. Lesions tend to regress over time and may resolve with scarring. Given the distinctive clinical presentation, histopathology, and absence of known infectious etiology, an alternative name for the disease has been proposed: facial idiopathic granulomata with regressive evolution (F.I.G.U.R.E.).
Histopathologic Features
- Granulomatous inflammation surrounding a well-defined area of caseating necrosis
- Necrosis may be in association with hair follicles
- Stains and cultures for mycobacteria are negative

References
CASE #184 — SLIDE #184

Diagnosis: Circinate balanitis in reactive arthritis (Reiter’s syndrome)

Case Summary:
A 52-year-old male presented with a penile rash.

Question
A. Fixed drug eruption – Incorrect. The genitalia are a common location for a fixed drug eruption, but histopathological features should include lichenoid interface dermatitis with eosinophils.
B. Scabies – Incorrect. The location would be common for scabies infestation, but mite parts evidence for a hypersensitivity reaction (including eosinophils) are absent.
C. Lichen sclerosus – Incorrect. Lichen sclerosus would show epidermal atrophy, dermal edema, and homogenized collagen.
D. Lichen planus – Incorrect. As with fixed drug eruption, this should present with lichenoid interface dermatitis.
E. Circinate balanitis – Correct. The psoriasiform hyperplasia with numerous pustules is consistent with circinate balanitis.

Question
A. Hepatitis C – Incorrect. This would be more commonly associated with lichen planus.
B. Intense pruritus – Incorrect. Significant pruritus would be most likely with scabies infestation.
C. Squamous cell carcinoma – Incorrect. This is more likely to be seen in association with lichen sclerosus.
D. Phimosis – Incorrect. Phimosis (inability to retract the foreskin) is a side effect of lichen sclerosus due to scarring.
E. Arthritis – Correct. Circinate balanitis is a common presentation with reactive arthritis, a seronegative spondyloarthropathy associated with HLAB-27 that can occur after urogenital or gastrointestinal infection.

Clinical Features
Reactive arthritis (Reiter’s syndrome) includes the triad of conjunctivitis, urethritis, and arthritis that can occur following a urogenital or gastrointestinal infection. It can present with numerous dermatologic manifestations, including keratoderma blennorrhagicum, circinate balanitis, ulcerative vulvitis, nail changes, and oral lesions. Circinate balanitis is the most common dermatologic manifestation occurring in up to 50% of patients with reactive arthritis. It presents as annular, hyperkeratotic plaques typically on the glans penis. Keratoderma blennorrhagicum presents with hyperkeratotic to pustular lesions on the plantar surface. Clinically, the nail and mucosal changes may mimic psoriasis with nail pitting, onycholysis, and geographic tongue. Histopathologic features of these mucocutaneous manifestations are essentially indistinguishable from pustular psoriasis.
Histopathologic Features
- Psoriasiform hyperplasia with regular elongation of rete ridges
- Thinning of the suprapapillary plates
- Subcorneal pustules, intraepithelial neutrophils and microabscesses
- Overall, features are similar to pustular psoriasis

References
Case summary
70 year-old-female presented with a small nodule on the right buttock. There was previous history of anal canal cancer and malignancy was suspected.

Question 125
The best diagnosis is:
A. Squamous cell carcinoma in situ – Incorrect. There is no keratinocytic atypia.
B. Verruca vulgaris – Incorrect. There is no papillomatosis or areas of hypergranulosis.
C. Porokeratosis – Correct. Characteristic cornoid lamellae are present.
D. Epidermolytic hyperkeratosis – Incorrect. The characteristic granular and vacuolar degeneration of the cells in the spinous and granular layer is not seen.
E. Pseudoepitheliomatous hyperplasia – Incorrect. There is no hyperplasia of the squamous epithelium to a degree that would evoke the diagnosis of squamous cell carcinoma

Question 126
The diagnostic morphological feature seen in the slide is:
B. Cornoid lamella – Correct. The cornoid lamella is a thin column of parakeratotic cells with absent or decreased underlying granular zone and vacuolated or dyskeratotic cells in the spinous layer. It is the key histopathological feature of porokeratosis.
C. Viral cytopathic effect – Incorrect. Not present.
D. Vacuolar degeneration of cells in the spinous and granular layer – Incorrect – not present.
E. Basket-weave keratin layer – Incorrect. Present over non-lesional skin.

Clinical Features:
Porokeratosis is a disorder of keratinization, characterized clinically by hyperkeratotic papules or plaques with a thread-like elevated border. Common clinical variants include: classic porokeratosis of Mibelli, disseminated superficial porokeratosis, porokeratosis palmaris et plantaris disseminata, linear porokeratosis and punctate porokeratosis. Rarely, it may involve the perianal area. This was first described in 1995 by Lucker et al. The authors used the Greek words ptyche (fold) and trope (a turning) to depict the flexural distribution of this condition. Usually it is a solitary lesion but may occur with other forms of porokeratosis.

Histopathologic Features:
The typical diagnostic histopathologic feature of porokeratosis is the cornoid lamellae. The cornoid lamella is a thin column of parakeratotic cells with absent or decreased underlying granular zone and vacuolated or dyskeratotic cells in the spinous layer.

References:
Diagnosis: Rosai-Dorfman disease

Case Summary:
A 39-year-old man presents with a two-year history of an asymptomatic, red-brown 1.3-x 1.0-cm nodule on the cheek.

Question
The best diagnosis is:
A. Cutaneous plasmacytoma (Incorrect) Primary and secondary forms of cutaneous plasmacytoma are circumscribed, non-encapsulated infiltrates of plasma cells within the reticular dermis. The plasma cells show variable maturation with some binucleate forms and occasional mitoses. Plasmacytoma lacks the histiocytic component present in this case.
B. Eruptive xanthoma (Incorrect) The cellular infiltrate depends upon the age of the lesion in eruptive xanthoma. Neutrophils and lymphocytes generally accompany small histiocytes in early lesions. Established lesions have more lipidized foam cells. Extracellular lipid may form lace-like deposits between collagen bundles. Emperipolesis is not present. The histiocytes are immunoreactive for CD68 but are negative for S-100 protein.
C. Juvenile xanthogranuloma (Incorrect) JXG consists of a nodular or diffuse infiltrate of histiocytes, lymphocytes, eosinophils and a small number of plasma cells. The histiocytes may include a variety of forms, often with a component of xanthomatized (foamy) and Touton multinucleate cells. The histiocytes show immunoreactivity for CD68 but are negative for S-100 protein and CD1a.
D. Langerhans cell histiocytosis (Incorrect) Tumor cells in Langerhans cell histiocytosis are smaller than those present in this case and have reniform (coffee bean) vesicular nucleus with inconspicuous nucleolus and moderately abundant, light eosinophilic cytoplasm. The cells may show epidermotropism. There is a variable admixture of inflammatory cells, often with numerous eosinophils. The lesional cells show immunoreactivity for S-100 protein but are also positive for CD1a and langerin.
E. Rosai-Dorfman disease (Correct) Characteristic histologic features include sheets of very large histiocytes with abundant feathery cytoplasm, few multinucleate cells, numerous plasma cells, and nodular aggregates of lymphocytes. There is emperipolesis. The histiocytes show immunoreactivity for S-100 protein and CD68 but are negative for factor X111A, CD1a, and langerin.

Question
Which of the following features is often seen in this disorder?
A. Birbeck granules (Incorrect) These granules are cytoplasmic organelles that characterize Langerhans cells.
B. Emperipolesis (Correct) Intracytoplasmic inflammatory cells. The histiocytes in Rosai-Dorfman disease show variable emperipolesis.
C. Epidermotropism (Incorrect) Spread of cells into the epidermis from a dermal or subcutaneous pathology. Mycosis fungoides and Langerhans cell histiocytosis typically have this feature. Rosai-Dorfman disease does not show this feature.
D. Extracellular lipid (Incorrect) Extracellular lipid is a finding in some types of xanthoma, including eruptive xanthoma. Small numbers of xanthomatous histiocytes may be present in Rosai-Dorfman disease but there is no extracellular lipid deposition.

E. Monoclonal population of plasma cells (Incorrect) The majority of cutaneous plasmacytomas are monoclonal. Although there is a prominent plasma cell component in Rosai-Dorfman disease, the plasma cells are polyclonal.

Clinical Features
Rosai-Dorfman disease (RDD) is a rare, benign condition characterized by a proliferation of reactive histiocytes. Also referred to as sinus histiocytosis with massive lymphadenopathy, it commonly involves the lymph nodes with secondary skin involvement. These cases present with prominent bilateral cervical lymphadenopathy accompanied by fever, malaise, night sweats, and weight loss. Skin lesions may be solitary or multiple and may present as papules or nodules that are dermal or subcutaneous. They may be xanthomatous or red-brown to orange-yellow. There is no site predilection. Cutaneous findings of RDD may be present without lymph node involvement. There are no distinguishing clinical or histologic features to differentiate purely cutaneous RDD from systemic disease. Purely cutaneous disease is not associated with systemic symptoms and does not evolve to systemic disease even with long-term follow-up. Cutaneous RDD occurs in a somewhat older age group and is more frequent in females compared to the classic nodal form. The clinical course is variable, with most lesions resolving spontaneously over weeks to months. Others may persist for years and recur after excision. Treatment is generally by excision.

Histopathologic Features
- Dense cellular infiltrate involving dermis and sometimes subcutis
- Sheets of histiocytes characterized by abundant pale-staining cytoplasm with feathery cytoplasmic borders, central vesicular nucleus
  - Histiocytes are S-100 protein (+), CD68 (+), CD1a (-), Factor XIIIa (-)
- Histiocytes show emperipolesis (engulfed inflammatory cells)
- Background of lymphocytes, plasma cells, neutrophils, and variable eosinophils

References

CONTRIBUTED BY DEBORAH L. COOK, MD
Diagnosis: Merkel Cell carcinoma
Merkel Cell Carcinoma (MCC) is an aggressive high grade neuroendocrine carcinoma (NEC) in the dermis from sun exposed sites that often has an epidermal connection. Histologically, MCC is very similar to other small cell neuroendocrine carcinomas from the lung, pancreas and prostate. Morphology and immunophenotype are used for diagnosis and differentiation from NEC of other sites. Most notable for the CK20 dot-like positivity, this pattern is also seen with Cam5.2. Any CK20 staining with confident small cell neuroendocrine morphologic diagnosis is sufficient to diagnose MCC, however confirming neuroendocrine origin, preferably by two of synaptophysin, chromogranin and/or CD56 and demonstrating the absence of pulmonary primary by TTF-1 negativity is valuable. In 2008 Merkel Cell polyomavirus virus (MCPyV) was discovered in the large majority of MCC most importantly with integration of the viral genome and truncation-activation mutation of the Large T protein (also called LT antigen). Highly sensitive PCR can detect integrated MCPyV, however integration, contamination or coincidence viral nucleic acid detection cannot be distinguished in basic direct PCR assays. Lung NEC and normal skin biopsies can be MCPyV PCR positive. Antibodies CMB4 show promise to identify LT antigen-positive MCC. Serologic studies for MCC have shown prognostic value (Paulson 2010, Asgari 2014). Intratumoral immune responses and T-cell repertoire (CD8, CD4, T-reg) are under investigation in MCC (Paulson 2014).


CASE #188 — SLIDE #188

Diagnosis: Malignant melanoma, small cell variant

Case Summary:
A 71-year-old man presents with a 15-cm scaly plaque on the anterior lower leg.

Question
The best diagnosis is:

A. Lymphoblastic B-cell lymphoma (Incorrect) Characterized by a monotonous, diffuse or nodular dermal infiltrate separated from the epidermis by a grenz zone. The cells have little cytoplasm and round to oval nuclei with finely disperse chromatin and inconspicuous nucleoli. Mitotic figures are frequent. Tumor cells dissect collagen bundles, as in this case, but perineural invasion is not a usual feature. Tumor cells are positive for CD20, CD19, CD79a, and TdT. This is generally a tumor of children and young adults.

B. Malignant melanoma, small cell variant (Correct) The neoplasm is composed of relatively monotonous small cells with scant cytoplasm and hyperchromatic nuclei. Mitotic figures are frequent and there is abundant apoptotic debris. There is a vague nested pattern superficially with a subtle intraepidermal component. Tumor cells are positive for S-100 protein, Mart-1, and HMB45.

C. Merkel cell carcinoma (Incorrect) Merkel cell carcinoma can have a variety of histologic patterns. It most commonly presents as nodules or diffuse sheets of basophilic cells with granular (“salt and pepper”) chromatin pattern. There is scant cytoplasm and often nuclear molding is evident. Mitoses are numerous and there may be extensive karyorrhectic debris. The tumor cells dissect the collagen bundles, as in this case, and lymphovascular invasion is often present. Tumor cells are positive for neuroendocrine markers, low molecular weight cytokeratins, and CK20 in perinuclear dot-like pattern.

D. Metastatic small cell carcinoma (Incorrect) Characterized by sheets, ribbons, or rosettes of small to medium-sized round-oval cells with minimal cytoplasm, salt and pepper chromatin, indistinct nucleoli, nuclear molding, smudging, and frequent mitotic figures. Necrosis and apoptotic debris are common. Generally spares the epidermis. Tumor cells are positive for cytokeratin in dot-like pattern, neuroendocrine markers, and TTF-1.

E. Peripheral primitive neuroectodermal tumor (Incorrect) Like this case, peripheral primitive neuroectodermal tumor is composed of relatively uniform small cells with round nuclei, finely distributed chromatin, and minimal cytoplasm. The tumors have a lobular or trabecular growth pattern with highly vascular stroma. The tumor cells are positive for CD99 and neuroendocrine markers with patchy immunoreactivity for S-100 protein. This is generally a tumor of children and young adults.

CONTRIBUTED BY DEBORAH L. COOK, MD
CASE #189 – SLIDE #189

**Diagnosis:** Dendritic cell neurofibroma with pseudorosettes

**Case Summary:**
A 68-year-old female presents with an enlarging growth on the left inner thigh. The clinical differential diagnosis is cyst versus lipoma.

**Question**
The best diagnosis is:
A. Dendritic cell neurofibroma with pseudorosettes (Correct) The neoplasm forms nodules within the dermis that are composed of two cell types. Type I cells are small, dark cells with slightly irregular nucleus and scant cytoplasm. Type II cells are larger with pale-staining vesicular nuclei and abundant light eosinophilic cytoplasm. Type I cells are arranged concentrically around Type II cells forming pseudorosettes.

B. Neuroblastoma-like neurilemmoma (Incorrect) Neuroblastoma-like neurilemmoma is characterized by a proliferation of cells with round to oval nuclei, indistinct nucleoli, and scant cytoplasm. Lesional cells tend to form rosette-like structures around blood vessels or collagenous cores.

C. Palisaded encapsulated neuroma (Incorrect) Palisaded encapsulated neuroma consists of a well circumscribed dermal nodule with incomplete encapsulation. It is composed of pale staining spindle cells arranged in short fascicles separated by artifactual clefting. The nuclei may be arranged in a palisaded fashion but pseudorosette formation is not present.

D. Plexiform neurofibroma (Incorrect) Plexiform neurofibroma nodules consist of distended nerve portions that are much larger than the nodules in this case. There often is extensive myxoid change. Pseudorosette formation and dendritic cells are not present.

E. Plexiform schwannoma (Incorrect) Plexiform schwannoma consists of multiple nodules within the dermis, as in this case. However, the nodules are generally composed of Antoni A type tissue with spindle-shaped Schwann cells arranged in interlacing fascicles. There may be Verocay body formation but pseudorosette formation is not present.

**Question**
Which of the following histopathologic features characterizes this lesion?

A. Homer-Wright rosettes (Incorrect) Homer–Wright rosettes, seen most often in neuroblastomas or peripheral neuroepitheliomas, contain a central solid core of neurofibrillary material. This case has pseudorosettes filled with type II cells and a dense network of dendritic extensions.

B. Presence of intralesional axons (Incorrect) Lesional axons are seen in palisaded encapsulated neuroma

C. Pseudorosette formation by type I and type II cells (Correct) The pseudorosettes in the dendritic cell neurofibroma are formed by small type I cells grouped concentrically around large type II cells and a dense network of dendritic extensions.

D. Verocay body formation (Incorrect) Verocay bodies are seen in schwannomas

E. Wagner-Meissner bodies (Incorrect) Wagner-Meissner bodies are seen in neurofibromas and schwannomas. They are a characteristic feature of the diffuse variant of neurofibroma.
Clinical Features
Dendritic cell neurofibroma with pseudorosettes was first described in 2001 as a distinct variant of neurofibroma. It generally presents as a solitary superficial cutaneous nodule. It is found primarily in adults without sex predilection. The lesions are well circumscribed, dome shaped, and measure less than 2 cm. Of the original series of 18 patients, none was associated with neurofibromatosis. However, a subsequent case associated with neurofibromatosis has been described. Dendritic cell neurofibroma appears to be benign and cases have not shown evidence of recurrence, malignant transformation, or metastasis.

Histopathologic Features
- Distinctive variant of neurofibroma with nodular growth pattern and two cell types
- Small round, dark lymphocyte-like cells (type I) surround larger cells (type II)
- Larger cells have vesicular nuclei, frequent intranuclear inclusions and abundant pale cytoplasm
- Two cell pattern results in pseudorosette appearance
  - Pseudorosettes do not have collagenous cores
- Both cell types are positive for S-100 protein and CD57

References

CONTRIBUTED BY DEBORAH L. COOK, MD
CASE #190 — SLIDE #190

Diagnosis: Histoplasmosis

Case Summary:
A 65-year-old woman with polymyalgia rheumatica presents with a red plaque on the face.

Question
The most likely diagnosis is:

A. Histoplasmosis (Correct) in the skin may be caused by two related fungi, Histoplasma
capsulatum var. capsulatum and Histoplasma capsulatum var. duboisii. The most common
histopathologic pattern is diffuse aggregates of macrophages, some multinucleated,
containing small basophilic round or ovoid yeast surrounded by a clear halo. Occasionally
well-formed granulomas are seen. Disseminated disease is uncommon but is seen in
immunocompromised patients, especially those with HIV/ AIDS. Cutaneous lesions are
rare (fewer than 10% of cases) and their clinical appearance varies markedly. This patient
was immunocompromised and also had lesions on the lip, tongue, and posterior pharyngeal
wall. Serological tests confirmed the diagnosis of histoplasmosis.

B. Lepromatous leprosy (Incorrect) may also demonstrate infiltration of the dermis by
macrophages with foamy appearing cytoplasm. Mycobacterium leprae bacilli are often
evident within the cytoplasm and may form large aggregates (globi). Fite stain (or Wade-
Fite stain, a modified Ziehl-Neelsen stain) is best for highlighting organisms.

C. Leishmaniasis (Incorrect) may present with diffuse histiocytic infiltrates of the dermis rather
than with discrete granulomas. The organisms (amastigotes referred to Donovan bodies) are
found within the histiocytes. Amastigotes have round basophilic nuclei and small basophilic
rolike kinteoplast. A Giemsa stain should highlight the organisms (purple or red and
purple).

D. Rosai-Dorfman disease (Incorrect) involving the skin may present with a diffuse dermal
infiltrate of histiocytoid cells with abundant cytoplasm, but these cells express S100 protein
and typically exhibit emperipolesis, the presence of lymphocytes or other inflammatory cells
surrounded by a clear ‘halo’ within the cytoplasm.

E. Xanthogranulomas (Incorrect) contain macrophages with abundant foamy appearing
cytoplasm (xanthoma cells) and multinucleated cells in which the nuclei form a concentric
ring surrounded by a rim of vacuolated cytoplasm. They typically contain other
inflammatory cells as well.
**Question**

The majority of the infiltrating cells will likely:

A. Express S100 protein and CD1a. **(Incorrect)** Expression of S100 and CD1a is characteristic of Langerhans cells (the histiocytoid cells of Rosai-Dorfman express S100, but not CD1a).

B. Contain microorganisms that stain with Grocott methenamine silver (GMS) but not periodic acid Schiff (PAS) **(Correct)** In Histoplasmosis the organisms usually stain strongly with GMS, while PAS is often negative or only weakly positive. If Histoplasmosis is suspected, a PAS stain alone is not sufficient.

C. Contain microorganisms that can be highlighted with a Fite stain. **(Incorrect)** The Fite stain (or Wade-Fite stain, a modified Ziehl-Neelsen stain) is best for highlighting the *Mycobacterium leprae* bacilli and would not stain the causative the fungi of Histoplasmosis.

D. Express Factor XIIIa and CD68 **(Incorrect)** Factor XIIIa is usually expressed by the xanthoma cells of xanthogranulomas.

E. Contain organisms that can be highlighted with a Giemsa stain. **(Incorrect)** The amastigotes of Leishmaniasis have round basophilic nuclei and small basophilic rod-like kinteoplasts that are purple or slightly red on Giemsa stains.

**References**


CASE #191 — SLIDE #191

Diagnosis: Acneiform Eruption due to Trametinib Treatment

Sudden onset of acneiform papulopustules of the face and upper trunk typically occurs within 1-2 weeks after initiation of the MEK inhibitor trametinib for treatment of metastatic melanoma. Trametinib does not appear to be as effective alone as are BRAF inhibitors in the treatment of metastatic melanoma. Almost 80% of patients treated with trametinib alone develop an acneiform eruption but only 10% of patients treated with the combination of the BRAF-inhibitor dabrafenib and trametinib. There is limited data on the histopathology of acneiform eruptions associated with MEK-inhibitors, but features may include ruptured folliculitis with follicular and perifollicular mixed inflammation including neutrophils, lymphocytes, histiocytes, focal perifollicular granulomas, as well as follicular plugging and necrosis. Epidermal growth factor receptor (EGFR)-inhibitor induced acne appears to be follicular but not comedonal. Acneiform papulopustular eruptions are a characteristic dose-dependent effect of EGFR inhibitors (erlotinib, cetuximab, gefitinib) and a marker of therapeutic anti-cancer benefit.

References

CONTRIBUTED BY MARGOT S. PETERS, MD
Diagnosis: Panfolliculoma

Case Summary:
A 4-year-old woman presented with a skin-toned nodule on her flank.

The best diagnosis is:
A. Panfolliculoma (Correct) This is an example of a cystic panfolliculoma, which is exceedingly rare. Some panfolliculomata may display smaller cysts as part of differentiation towards the infundibulum. Panfolliculoma contains all patterns of follicular differentiation, which this proliferation demonstrates, including, infundibular, isthmic, inner and outer root sheath, and matrical.
B. Trichofolliculoma (Incorrect) This is the most difficult entity in the differential diagnosis. However, trichofolliculoma is often cystic, but fully formed small hair follicles emanate from the periphery of the patulous/cystic portion. The cystic contents usually contain multiple hair shafts, resulting in a tuft of hair often evident in the orifice of the lesion clinically.
C. Trichoblastoma (Incorrect) This nodular basaloid tumor is composed mainly of follicular germinative elements, and does not generally display a connection to the epidermis. On occasion, small cystic elements may be present. It is usually associated with abundant fibrocellular stroma, which may be separated by clefts from the adjacent stroma.
D. Trichoepithelioma (Incorrect) Considered by many to be a more mature subset of trichoblastoma, it often displays advanced follicular germinative differentiation. It is also lobular and associated with a fibrocellular stroma. It may display small cysts, which rupture forming small granulomata, and this is also true in the desmoplastic variant.
E. Trichilemmoma (Incorrect) Outer root sheath differentiation with pallid keratinocytes is the hallmark of this tumor, which is often small, lobular to papillated, and displays peripheral palisading of nuclei and a thickened basement membrane.

This tumor labels with:
A. EMA (Incorrect) This particular case does not display sebaceous differentiation, although sebaceous features have been reported in one recent case.
B. Ber-EP4 (Correct) This marker labels many tumors with follicular features. In panfolliculoma, it labels the germinative cells but not the follicular papillae.
C. CD117 (Incorrect) Only scattered mast cells label in the stroma of this tumor. CD117 can be observed in another basaloid tumor, adenoid cystic carcinoma.
D. CEA (Incorrect) This tumor does not display ductal differentiation.
E. SOX-10 (Incorrect) This melanocytic/neural marker would not be expected to be positive in this tumor.

Clinical features
Panfolliculoma may present as a skin-toned to red, dermal or cystic-appearing nodule, often on the head or trunk, in patients from the 2nd to 6th decades.
Histopathologic features
Panfolliculoma was first described in 1993 and since then roughly 16 cases have been reported. This benign follicular tumor displays differentiation towards all elements of the hair follicle, including infundibular, isthmic, inner and outer root sheath, and matrix. As such, infundibular cysts, follicular germs, trichohyaline granules, pallid keratinocytes, matrical cells and shadow cells may be encountered in varying amounts in such tumors, and in a variable arrangement. It may display a lobular contour, and in rare cases such as this one, may be cystic. An epidermal variant has also been described, in which all follicular elements are present in a papillated epidermis in a more plaque-like configuration.

References

CONTRIBUTED BY BETH S. RUBEN, MD
**CASE #193 — SLIDE #193**

**Diagnosis:** Solitary fibrous tumor

**Case Summary:**
A 39-year-old woman presented with an axillary mass. A fine needle aspiration diagnosis was made. When the patient presented for complete excision, the lesion was noted to be a deep subcutaneous lesion with no dermal connection, mimicking a lymph node.

The best diagnosis is:
A. Dermatofibroma **(Incorrect)** While this proliferation is also composed of spindle cells, other cells such as foamy siderophages may be present. It assumes a nodular contour in the dermis that blends into the dermis amongst thickened collagen bundles. It may also display associated epidermal hyperplasia, basilar pigmentation, and many other variable features, such as hemorrhage and folliculosebaceous induction.

B. Solitary fibrous tumor (SFT) **(Correct)** These tumors are often well-circumscribed, and composed of fairly monomorphous bland spindle cells, with irregular vascular channels.

C. Schwannoma **(Incorrect)** These are also circumscribed tumors, but a zonal pattern is usually present, with cellular areas that may contain palisaded nuclei enclosing Verocay bodies (Antoni A), and less cellular areas containing a loose stroma with foamy cells (Antoni B). A capsule is often visible.

D. Spindle cell lipoma (“low fat” variant) **(Incorrect)** This tumor may or may not be circumscribed, and while also containing spindled cells, there are usually admixed adipocytes and some myxoid changes, as well as interspersed ropey collagen.

E. DFSP **(Incorrect)** This is the closest mimic of SFT, and in a partial biopsy, distinguishing these two entities in routine sections may be impossible. In a representative sample, this tumor typically displays a storiform pattern, is infiltrative, effacing normal adipose tissue around adnexa, and involves the subcutis in a “honeycomb” pattern. A number of variants also exist. In difficult cases, examining tissue for the characteristic translocation t(17;22) forming a COL1A-PDFGR fusion protein can be essential.

This tumor labels with:
A. S-100 protein **(Incorrect)** Schwannoma is in the differential diagnosis, and would label with this marker, as would some other neural tumors one might consider.

B. EMA **(Incorrect)** This marker may label some neural neoplasms, including schwannoma and perineurioma, which might also be considered in the differential diagnosis, but not SFT.

C. bcl-2 **(Correct)** CD34 staining is the most well-known result in SFT, but bcl-2 and CD99 also label this tumor.

D. SOX-10 **(Incorrect)** This marker would label some neural (as above) and melanocytic entities in the differential diagnosis. In a partial biopsy, spindle cell melanoma is sometimes considered.

E. Factor XIIIa **(Incorrect)** This labels dermatofibroma, but not SFT.
Clinical features
This is an uncommon neoplasm, usually found in the pleura, and less commonly at other sites (liver, kidney, thyroid, CNS, adrenal gland, head and neck, soft tissue, skin). These are considered biologically “borderline” neoplasms, with some cases of local recurrence, distant metastasis, rarely, at non-cutaneous sites. It may be identical to hemangiopericytoma (also referred to as cellular SFT in WHO 2002 classification).
In 1997, Okamura et al described the first cutaneous case. From 1997-2007 Only 11 additional cases were described, one “malignant” (invasive to bone, dura). In 2007 Erdag et al reported 10 additional cases. This tumor when found in the skin, occurs mainly in adults, with rare pediatric cases. The most common cutaneous sites are the head and neck. A dermal or subcutaneous nodule or plaque is often described, with the size not well-documented. There are rare reports of recurrence. No skin tumors have resulted in metastasis or death. Nonetheless, because of some lingering uncertainties as to the biologic behavior of this tumor, the recommended treatment is complete excision.

Histologic features
This spindle cell proliferation often assumes a so-called “patternless pattern”, and may contain irregular vessels (“staghorn”). Variants more often described in the pleural tumors, but sometimes seen in skin tumors, include solid-spindle cell, diffuse sclerosing, fascicular, storiform, herringbone, angiofibromatous, epithelioid, hemangiopericytoid, synovial sarcoma-like, and palisading. The tumor labels with CD34, CD99, bcl-2, and vimentin. There is no consistent cytogenetic profile.

References

CONTRIBUTED BY BETH S. RUBEN, MD
Slide 194 Intravascular sheath material

Endovascular procedures are common, and multiple devices and coatings are used to assist with insertion of sheaths, catheters, and guide wires. Many such devices contain hydrophilic polymer gel coatings that help to limit vascular spasm and increase maneuverability. Introduction of foreign material into the vasculature carries a risk of embolization and ischemic sequelae. Iatrogenic embolization of hydrophilic polymer coating has been reported, with complications ranging from pulmonary infarction, stroke, and gangrene to death. Hydrophilic polymer gel has a characteristic appearance on immunohistochemical staining and has been identified in biopsy samples and autopsy tissues from various organs. Cutaneous lesions are usually unilateral, involving most commonly lower extremities. Clinical presentations include asymptomatic livedo racemosa and purpura, usually occurring several hours postoperatively. Rare cases have later onset of lesion which occur 2-9 days after the procedure. Tenderness was occasionally reported. Histologically, diagnosis can be confirmed by pauci-inflammatory occlusion of small superficial and mid-dermal vessels with pale basophilic to lavender lamellated material and dermal hemorrhage, consistent with the morphology of hydrophilic gel polymer emboli. Colloidal iron staining can highlight the foreign material in biopsy specimens. The cutaneous lesions can occur with or without internal organ involvement, and the skin lesions usually resolve spontaneously.

Reference:


CONTRIBUTED BY MICHAEL J. CAMILLERI, MD
CASE #195 — SLIDE #195

Diagnosis: Pilomatrix carcinoma

Case Summary
A 55 year old male presented with a 20 year history of a mass on his right arm which had recently increased significantly in size. An MRI revealed a 6 centimeters soft tissue mass with calcifications.

The best diagnosis is:
A. Spiradenocarcinoma - Incorrect. Spiradenocarcinoma does not show features of matrical differentiation, such as shadow cells.
B. Squamous cell carcinoma - Incorrect. Squamous cell carcinoma does not show features of matrical differentiation, such as shadow cells.
C. Pilomatricoma - Incorrect. While pilomatricoma can show numerous mitotic figures, the widespread pleomorphism, diffuse infiltration and necrosis do not fit with a benign diagnosis.
D. Pilomatrix carcinoma - Correct. Pilomatrix carcinoma often shows shadow cells, matrical differentiation, mitotic activity, pleomorphism and diffuse infiltration.
E. Porocarcinoma - Incorrect. Porocarcinoma does not show features of matrical differentiation, such as shadow cells.

Nuclear and cytoplasmic labeling of which protein is typical of pilomatrix tumors?
A. MITF - Incorrect. Pilomatrix tumors do not label for MITF.
B. WT1 - Incorrect. Pilomatrix tumors do not label for WT1.
C. Beta-Catenin - Correct. Nuclear and cytoplasmic labeling for Beta-Catenin is typical of pilomatrix tumors. This is related to a mutation of the CTNNB1 gene on chromosome 3p21, which encodes the Beta-Catenin protein.
D. ERG - Incorrect. Pilomatrix tumors are negative for ERG.

Clinical Features
• Most commonly tumors of the elderly. However, occasional cases have been reported in children.
• Most tumors occur on the scalp and face.
• Recurrences are common with occasional metastasis.

Histopathologic Features
• Poorly circumscribed, dermal and/or subcutaneous tumor with infiltration.
• Proliferation of pleomorphic, highly atypical basalog cells with frequent mitotic figures and prominent nuclei.
• Necrosis and shadow cells are often seen.
• Characteristically immunoreactive for β-catenin.
References

CONTRIBUTED BY TRAVIS J. HOLLMAN, MD, PHD
**CASE #196 — SLIDE #196**

**Diagnosis:** Mucha-Habermann disease (PLEVA)

**Case Summary:**
A 7-year-old boy presented with a five-week history of an erythematous ulcerated eruption on the trunk, neck, axillae, groin, penis and lips, sparing the palms, soles and remaining mucosal surfaces.

Which of the following is the most likely diagnosis:

A. While erythema multiforme (Incorrect) Frequently demonstrates vacuolar alteration and epidermal necrosis, it usually lacks mounds of parakeratosis with neutrophils or as deeply extending an infiltrate. Also, the current case does not feature typical targetoid lesions involving acral surfaces.

B. Fixed drug eruption (Incorrect) Demonstrates larger erythematous to dusky plaques, or in the generalized form, exfoliating erythema, and on biopsy contains vacuolar change and dyskeratosis (without spongiosis) and a mixed infiltrate of neutrophils and eosinophils.

C. Hand-foot-mouth disease (Incorrect) Typically an exanthem caused by coxsackievirus A16, presents with fever and vesicles involving the anterior parts of the mouth, as well as the hands and feet. On biopsy, these lesions demonstrate intraepidermal vesicles with reticular degeneration and ballooned cells.

D. Mucha-Habermann disease (Correct) This condition has been termed febrile ulceronecrotic Mucha-Habermann disease, a rare, fulminant variant of the more common classic eruption (pityriasis lichenoides et varioliformis acuta, or PLEVA). Like conventional PLEVA, it commonly involves children and young adults, although it presents with fever as well as generalized, ulcerated and necrotic papules, sometimes with mucosal involvement. On biopsy, one sees typical features of PLEVA, including mounds of parakeratosis, sometimes with neutrophils, foci of both spongiosis and vacuolar alteration, dyskeratosis, and a superficial and deep predominantly lymphocytic infiltrate with extravasated red cells. The ulceronecrotic variant frequently has a greater degree of both epidermal necrosis as well as ulceration compared with the more conventional type.

E. Primary varicella infection (Incorrect) Presents with intraepidermal vesicles demonstrating acantholysis, multinucleated keratinocytes, peripheral margination of chromatin, and a slate-gray cytoplasmic color.

The next best step in evaluation/management would be:

A. Acyclovir (Incorrect) While a preceding viral infection is frequently suspected as a trigger of Mucha-Habermann disease, antiviral treatments such as acyclovir have not been shown to be consistently therapeutic.

B. Mycoplasma titer. (Incorrect) Mycoplasma infection is sometimes associated with more severe forms of erythema multiforme / Stevens-Johnson syndrome, rather than Mucha-Habermann disease.

C. Discontinue the offending medication. (Incorrect) Medication hypersensitivity can be associated with either fixed drug eruption or severe forms of erythema multiforme/Stevens-Johnson syndrome, but is not a typical trigger of Mucha-Habermann disease.

D. Methotrexate (Correct) While a variety of treatments have been reportedly effective in Mucha-Habermann disease, including tetracycline-type antibiotics and UV light therapy,
among others, the high morbidity of this variant necessitates immunosuppressive treatment, commonly with either oral methotrexate or systemic steroids.

E. Broad spectrum antibiotic coverage. (Incorrect) While tetracycline-type antibiotics have been used in the treatment of conventional Mucha-Habermann disease, this condition is not felt to be related to an acute bacterial infection, and thus broad spectrum antibiotic therapy would not be appropriate.

References
1. Weedon, D. Weedon’s Skin Pathology, Churchill Livingstone, 2010

CONTRIBUTED BY KEVIN WHITE, MD
**CASE #197 — SLIDE #197**

**Diagnosis:** Kaposiform Hemangioendothelioma

Unifocal, purpuric cutaneous lesion in early infancy, kaposiform hemangioendothelioma (KHE) is a deeply invested lymphovascular tumor that is highly associated with thrombocytopenia, bleeding and Kaschelbach-Merrit phenomenon (platelet trapping within lesion) with high mortality (10% to 24%) in deeply seated tumors particularly in children under 6 months of age (O’Regan et al 2009). Tumor growth occurs primarily as more defined, rounded confluent nodules that histologically show “cannon balls” with glomeruloid foci and microthrombi. Additionally a “vascular pattern” of KHE in neonates is observed to have a high proliferative rate (50% MIB) and transforms to lobules in older patients with lower proliferative rate (5-10% MIB). In the differential diagnosis is infantile hemangioma and tufted angioma (TA) (see table below). Infantile hemangioma is GLUT1 positive while KHE is GLUT1 negative. While TA focally may show very similar cannon ball histomorphology, KHE involves all tissue planes and is thought to be on a spectrum with TA. KHE and TA are almost exclusively associated with Kaschelbach-Merrit phenomenon. The lesion of KHE/TA are believed to be of intermediate malignant potential—will not transform to high grade sarcoma, but will progressively invade surrounding tissue and cause major deformity.

**Vascular tumor/ malformation in children: abbreviated differential diagnosis**

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<td><strong>Infantile hemangioma</strong></td>
<td>Skin and/or subcutaneous; early postnatal period. Rapidly grows and slowly involutes over 1 to 2 years. Lobules of poorly canalized capillaries with mitotically active endothelium and prominent pericytes. Late lesions: canalized vessels and multilayered basement membrane. <strong>Endothelium is GLUT1 positive.</strong></td>
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<tr>
<td><strong>Kaposiform hemangioendothelioma (KHE)</strong></td>
<td>Congenital or acquired lesion of skin or deep tissues. Most common cause of KMP secondary to platelet trapping. Progressive growth and rare local metastasis. Does not involute. Kaposi sarcoma (KS, Chang 1994) is unlikely in children. Irregular cannon ball nodules infiltrating tissues composed of slit-like vessels circumscribing glomeruloid vessels containing fibrin thrombi. <strong>Endothelium express early lymphatic markers (LYVE 1, PROX1) but not GLUT1.</strong> Focal D240 positive. Unlike Kaposi sarcoma, <strong>HHV8-IHC is negative.</strong></td>
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**CONTRIBUTED BY LAWRENCE GIBSON, MD and DANIEL COHEN MD, PHD**
Diagnosis: Plasmacytosis

Case Summary
A 68 year-old man presented with brown patches.

The best diagnosis is:
A. Mycosis fungoides – Incorrect. The lack of an epitheliotropic infiltrate and predominance of B-cells argue against cutaneous T-cell lymphoma.
B. Plasmacytosis – Correct. The presence of persistent patches, a polyclonal plasma cell-rich dermal inflammatory cell infiltrate, and lack of identifiable infectious etiology support the diagnosis of cutaneous plasmacytosis.
C. Immunocytoma – Incorrect. Immunocytoma is a variant of cutaneous marginal zone B-cell lymphoma with many plasma cells. It is characterized by light chain restriction.
D. Myeloma – Incorrect. Cutaneous involvement by multiple myeloma usually occurs in the setting of known myeloma. The clinical presentation of patches would be unusual. Multiple myeloma usually presents as nodules or plaques. In multiple myeloma the plasmacytoid infiltrate is clonal and the neoplastic cells are cytologically more atypical.
E. Syphilis – Incorrect. Although syphilis may be associated with many plasma cells, the lack of identifiable organisms and negative serology argues against syphilis.

The following statement about the disease is correct:
A. It is characterized by frequent rapid progression to a high grade lymphoma – Incorrect. Progression to lymphoma is rare.
B. The rash responds well to antibiotics – Incorrect. The disease is not known to respond to antibiotics.
C. The disease is characterized by a chronic course with potential progression to systemic disease – Correct. The process is usually persistent and gradually progressive with spread to extracutaneous sites.
D. The disease preferentially affects individuals of Scandinavian origin – Incorrect. Most cases have been reported in Japan.
E. Spontaneous resolution within months – Incorrect. The lesions usually persist.

Clinical Features
- Persistent brown patches and plaques.
- May be associated with systemic symptoms.
- Usually associated with polyclonal gammopathy
- Usually associated with elevated IL6

Histopathological Features
- Mixed plasma cell-rich inflammatory cell infiltrate, often perivascular
- No evidence of light chain restriction or B-cell clonality
- Negative modified Steiner stain; negative IHC for T. pallidum
References

CONTRIBUTED BY KLAUS BUSAM, MD
CASE #199 — SLIDE #199

Slide 199 Angiomatoid chronic GVHD

Graft-versus-host disease (GVHD) represents a complex multisystem major complication of organ transplantation, usually bone marrow that particularly affects the skin, intestine, and liver. It develops when transplanted immunocompetent donor T lymphocytes are activated, proliferate, and respond to foreign host major histocompatibility complex (MHC)-histoincompatible antigens in a background of recipient immunosuppression. GVHD is a very serious complication of allogeneic bone marrow transplantation and morbidity and mortality is very high. Historically, GVHD was conventionally subdivided into two subgroups by time after transplantation: acute (<3 months) and chronic (>3 months). Although distinctive, the cutaneous manifestations of chronic GVHD (cGVHD) are more diverse and frequently pose a treatment challenge as effective therapies are limited. Manifestations of cGVHD range from superficial cutaneous involvement including dyspigmentation and lichenoid disease to deep involvement including dermal or fascial fibrosis resembling systemic sclerosis and eosinophilic fasciitis, respectively. An uncommon cutaneous presentation of cGVHD is “eruptive angiomas,” a manifestation that is rarely reported, poorly understood, and challenging to treat. Vascular proliferations were first documented a median of 44 months after transplantation and were exclusively within areas of sclerosis. Lesions developed on the lower extremities in 7 of 11 (73%) patients and trunk in 5 of 11 (45%) patients. Lower extremity edema was a complicating symptom of 6 of 11 (55%) patients. In general, vascular proliferations were nontender and most often presented as asymptomatic papules, nodules, and tumors; however, bleeding and ulceration occurred in several lesions, primarily on the lower extremities. Histologically, it is characterized by extensive endoluminal proliferations in the papillary dermis. Diffuse dermal angiomatosis with multifocality and sclerotic background presents with ulcerating plaques and nodules primarily on the extremities, breasts, and abdominal pannus of patients with atherosclerosis or other chronic hypoxic conditions. Other benign vascular neoplasms in the differential diagnosis including pyogenic granuloma, cavernous hemangioma, and acquired tufted angioma. Because it is now believed these cases represent spectrum of reactive angiomatosis associated with sclerotic chronic GVHD, the term “graft-versus-host disease-associated angiomatosis” has been proposed.

Reference:

CONTRIBUTED BY JULIA S. LEHMAN, MD
The malignant atrophic papulosis (Köhlmeier-Degos disease; MAP) was initially described by Köhlmeier in 1941 and documented as a separate entity by Degos et al. in 1942. It is a rare entity with less than 200 cases have been described in the literature. The first manifestation of MAP usually occurs between the third and fourth decades of life. A genetic predisposition with an autosomal dominant trait has been suggested. The diagnosis of MAP is based on the pathognomonic skin lesions, 0.5-1 cm papules with an atrophic porcelain-white center and an erythematous, telangiectatic rim mostly occurring on the trunk and the upper extremities. Palms, soles, scalp and face are usually spared. Internal organ involvement, with multiple limited infarcts of the intestine and/or the central nervous system as well as of other organs, such as the lungs (presenting as pleuritis and/or pericarditis) and the eyes also occurs. The classical histology shows a wedge-shaped connective tissue necrosis, due to thrombotic occlusion of small arteries. However, early lesions demonstrate a superficial and deep perivascular lymphocytic infiltrate, with distinct mucin deposition. The fully developed lesions had more prominent changes in the dermoepidermal junction, with atrophy of the epidermis and an area of sclerosis in the papillary dermis. The late lesions showed a wedge-shaped necrosis, sparse lymphocytes and markedly less mucin deposition in comparison to the early and fully developed lesions.

Reference:

CONTRIBUTED BY CARILYN N. WIELAND, MD