DERMPATH ON DEMAND

Digital Board Review

Answer Key

COCKERELL DERMATOPATHOLOGY™

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Answer Key

Slide 1: Porokeratosis

- Cornoid lamellae—bilateral columns of trailing parakeratosis oriented 45 degrees to epidermis with hypogranulosis and/or dyskeratotic keratinocytes below.
- Epidermis in the central part of the lesion may be normal, hyperplastic, or atrophic.
- Lichenoid reactions are common.
- DDx: DLE— thin epidermis, parakeratosis, follicular plugging, thick BMZ, mucin in the dermis, superficial and deep perivascular and periadnexal infiltrate; Benign lichenoid keratosis—lichenoid interface dermatitis, solar lentigo commonly present at the margin; AK—may have cornoid lamellae, but has atypical keratinocytes.

Slide 2: Hypertrophic lichen planus

- Pseudoepitheliomatous hyperplasia.
- Hyperkeratosis and wedge-shaped hypergranulosis.
- Lichenoid lymphocytes in the papillary dermis with liquefaction degeneration.
- Colloid bodies and melanin pigment incontinence.
- DDx: Invasive squamous cell carcinoma—keratinocyte atypia with infiltrative growth pattern; Chromomycosis—pseudoepitheliomatous hyperplasia, suppurative granulomatous inflammation, presence of copper pennies; Lichenoid AK—band-like lymphocytic inflammation, distinguished from hypertrophic LP by the keratinocytic atypia; Secondary syphilis—psoriasiform lichenoid dermatitis with plasma cells.

Slide 3: Pityriasis lichenoides

- Superficial and deep wedge-shaped infiltrate.
- Vacuolar interface with lymphocyte exocytosis and focal necrotic keratinocytes.
- Extravasation of erythrocytes.
- Parakeratotic neutrophilic scale crust.
- DDx: Erythema multiforme—vacuolar interface, sparse perivascular lymphocytes, basket-weave stratum corneum; Lymphomatoid papulosis—wedge-shaped infiltrate with large atypical lymphocytes associated with eosinophils and neutrophils; Pityriasis rosea—spongiosis, mounds of parakeratosis, superficial perivascular lymphocytic infiltrate, no prominent interface changes; Arthropod bite—wedge-shaped infiltrate with eosinophils.

Slide 4: Fixed drug eruption

- Interface dermititis with scattered single or clustered necrotic keratinocytes.
- Mixed superficial perivascular infiltrate with eosinophils, lymphocytes, histioctyes, and neutrophils.
- Melanophages and fibrosis in the papillary dermis with chronicity.
- DDx: Erythema multiforme—vacuolar interface, sparse perivascular lymphocytes (no eosinophils), basket-weave stratum corneum; Erythema dyschromicum perstans—vacuolization of basal layer, perivascular infiltrate of lymphocytes, melanophages; Post-inflammatory hyperpigmentation— melanophages in the papillary dermis; Toxic epidermal necrolysis—full thickness epidermal necrosis, basket-weave stratum corneum, sparse inflammation.

Slide 5: Pityriasis rubra pilaris (PRP)

- **Pityriasis rubra pilaris can cause erythroderma. Clinical findings are characterized by follicular keratotic papules, salmon-colored plaques with islands of sparing, and palmoplantar keratoderma.**
- Alternating orthokeratosis and parakeratosis, both vertically and horizontally, "checkerboard pattern".
- Irregular psoriasiform hyperplasia and follicular plugging.
- Sparse superficial perivascular lymphocytes.
- DDx (Clinical-Erythroderma): Psoriasis—regular psoriasiform hyperplasia, confluent parakeratosis, no follicular plugging; Sezary syndrome—dense infiltrate of atypical lymphocytes, frequent loss of pan T cell markers; DRESS— perivascular infiltrate (lymphocytes and eosinophils) in the papillary dermis.

Slide 6: Nutritional deficiency

- Psoriasiform epidermal hyperplasia.
- Pallor and vacuolization of mid to upper epidermis.
- May have focal or confluent necrosis of the upper epidermis.
- Overlying confluent parakeratosis.
- DDx: Toxic epidermal necrolysis— full thickness epidermal necrosis, basket-weave stratum corneum, sparse inflammation; Erythema multiforme— vacuolar interface, sparse superficial inflammation, basket-weave stratum corneum; Psoriasis—psoriasiform hyperplasia, confluent parakeratosis, no pallor in the upper epidermis, no necrotic keratinocytes; Herpes simplex virus infection—intraepidermal acantholytic vesicle, multinucleated giant cells, keratinocytes with steel-gray nuclei.

Slide 7: Psoriasis

- Psoriasiform epidermal hyperplasia (regular acanthosis) with thinning of the suprapapillary plates.
- Confluent parakeratosis wth hypogranulosis.
- Neutrophil aggregates in stratum corneum (microabscess of Munro).
- Neutrophils aggregates in stratum spinosum (spongiform pustule of Kojog).
- Hypervascular edematous dermal papillae.
- DDx: Cutaneous candidiasis—scale crust with neutrophils, yeast, and pseudohyphae; Nutritional deficiency—psoriasiform hyperplasia with pallor of the upper epidermis; Tinea corporis—epidermal spongiosis, hyphae seen between an upper basket-weave layer and a lower compact orthokeratotic or parakeratotic layer ("sandwich" sign); Seborrheic dermatitis—spongiosis with overlying scale crust containing neutrophils centered on a follicle.

Slide 8: Alopecia areata (AA)

- Autoimmune non-scarring alopecia.
- Increased number of telogen and catagen follicles.
- Peribulbar inflammatory infiltrate ("swarm of bees") in acute phase.
- DDx: Telogen effluvium—increase in the number of telogen hairs, no inflammation; Lichen planopilaris—scarring alopecia, lichenoid inflammation in the infundibulum and isthmus, follicular plugging; Trichotillomania—trichomalacia, pigmented hair casts, hemorrhage, increased number of catagen hairs; Androgenetic alopecia—increased number of miniaturized hair follicles.

Slide 9: Sweet's syndrome (acute febrile neutrophilic dermatosis)

- **10-40% of cases are associated with hematological malignancy such as leukemia, myelodysplasia, lymphoma, and multiple myeloma.**
- Nodular diffuse infiltrate of neutrophils with karyorrhexis (leukocytoclasia –nuclear dust).
- Marked papillary dermal edema.
- No true vasculitis!
- DDx: Leukocytoclastic vasculitis—nuclear dust with prominent fibrinoid vascular change; Erythema elevatum diutinum—leukocytoclastic vasculitis with onion skin fibrosis; Pyoderma gangrenosum—clinically, presence of large ulcers helps distinguish pyoderma gangrenosum from Sweet's syndrome. Also, pyoderma gangrenosum does not usually show the same degree of karyorrhexis as seen in Sweet's.

Slide 10: Leukocytoclastic vasculitis (LCV)

- Infiltration of post-capillary venules with neutrophils inducing vascular damage including endothelial swelling and fibrin deposition (fibrinoid necrosis in chronic well-developed lesion).
- Perivascular infiltrate with neutrophils and karyorrhexis (leukocytoclasia—nuclear dust).
- Erythrocyte extravasation.
- DDx: Pigmented purpuric dermatosis—lymphocytic inflammation surrounding capillaries and erythrocyte extravasation; Sweet's syndrome—diffuse neutrophilic infiltrate with marked papillary dermal edema; Livedoid vasculopathy—hyalinized vessel walls, thrombi, cannonball tufting of vessels in the superficial dermis (stasis change); Septic vasculitis—involves postcapillary venules and larger deeper vessels, endothelial cell necrosis and thrombi are common, neutrophilic debris common.

Slide 11: Bowen's (clear cell variant)

- **Bowen's is positive for p63; p63 is also useful to distinguish primary cutaneous spindle SCC (+) from mesenchymal spindle cell tumors (-).**
- Full-thickness squamous dysplasia with loss of maturation ("wind blown" appearance).
- Mitoses in all levels of epidermis with aytpical forms.
- Pale keratinocytes contain glycogen.
- Diminished or absent granular layer.
- Parakeratosis, hyperkeratosis, acanthosis.
- DDx: Paget's disease—pale cells with intracytoplasmic mucin, basal cells are often compressed, stains with CEA, EMA, CK7, and GCDFP-15; Melanoma in situ—S-100, HMB-45, MART-1 and SOX-10 positive; Mycosis fungoides—Pautrier microabscesses, positive for CD45 (leukocyte common antigen), also CD4+ and CD3+, diminished CD7 expression; Langerhans cell histiocytosis—malignant Langerhans cells, kidney-shaped nuclei, CD1a and S-100 positive.

Slide 12: Warty dyskeratoma

- Comedo-like invagination of the epidermis filled with hyperkeratosis and parakeratotic, acantholytic, and dyskeratotic keratinocytes (corp ronds and grains).
- Dermal papillae lined by basal cells may project up into the invagination (resembling villi).
- DDx: Darier's disease—does not have deeply penetrating crateriform lesions with villus formation; Keratoacanthoma, acantholytic AK, acantholytic SCC—have cytologic atypia.

Slide 13: Hailey-Hailey disease

- Acanthosis with full thickness diffuse acantholysis and clefting ("delapidated brick wall") with sparing of adnexal epithelium.
- Varible acute and chronic inflammation.
- Occasional dyskeratosis.
- DDx: Acantholytic actinic keratosis—has cytologic atypia; Grover's disease—less extensive, focal involvement; Darier's disease—more dyskeratosis, less acantholysis than Hailey-Hailey disease, has corp ronds and grains; Pemphigus vulgaris—involves the hair follicles, DIF is positive (intercellular epidermal deposition of IgG and C3).

Slide 14: Dermatitis herpetiformis (DH)

- **Potassium iodide can cause flaring of dermatitis herpetiformis.**
- Neutrophilic microabscesses at dermal papillae tips forming small subepidermal vesicles.
- In older lesions, vesicles coalesce forming larger subepidermal bullae.
- DDx: Bullous pemphigoid—subepidermal vesicle with eosinophils; EBA—subepidermal blister with scant inflammatory infiltrate, neutrophil-rich or eosinophil-rich; Bullous SLE—subepidermal blister with abundant neutrophils (indistinguishable from DH); Linear IgA Bullous Dermatosis (LABD)—subepidermal blister with neutrophils (indistinguishable from DH).

Slide 15: Accessory tragus

- Pedunculated papule containing numerous vellus hairs and often hyaline cartilage.
- Central fibrovascular core with abundant adipose tissue.
- DDx: Fibroepithelial polyp—pedunculated papule with acanthosis and papillomatosis, dermis has loose connective tissue, no vellus hairs; Acquired digital fibrokeratoma—acral lesion with massive orthokeratosis, thickened collagen in the dermis oriented parallel to the long axis; Supernumerary nipple—epidermis with papillomatosis and hyperpigmentation, increased smooth muscle bundles, mammary glands and ducts in the dermis and subcutaneous fat.

Slide 16: Pseudoxanthoma elasticum (PXE)

- **Autosomal dominant inheritance, ABCC6 (chromosome 16p13.11) encoding a transmembrane ATP-binding cassette transporter.**
- Clumped elastic fiber fragments in deep dermis associated with dystrophic calcifications.
- Positive for elastic fiber stains (VVG).
- Positive for calcium stains (von Kossa, alizarin red).
- DDx: Dystrophic calcinosis cutis—more focal (less diffuse) involving areas of damaged tissue and not specifically elastic fibers; Periumbilical perforating calcific elastosis—may represent an acquired localized variant of PXE or a separate distinct entity (jury is out), usually affects multiparous African American females, histologic features are identifical to PXE with transepidermal elimination.

Slide 17: Lichen sclerosus (LS)

- **Less than 4% of patients with vulvar LS develop SCC; in males→ 4-8%; 32-50% of penile SCC excisions have associated LS changes.**
- Hyperkeratosis with follicular plugging.
- Atrophy of spinous layer.
- Early—Lichenoid infiltrate at DE junction with interface change.
- Late—lichenoid band moves to mid dermis beneath edematous homogenized (hyalinized) superficial dermis.
- DDx: Chronic radiation dermatitis – hyalinization of dermis more diffuse, atypical fibroblasts, telangiectasia with thrombi sometimes; Morphea/scleroderma– dense sclerotic collagen extends to and involving subQ, perivacular and perieccrine chronic

lymphoctyic infiltrate +/- plasma cells; early lesions overlap with LS; Atrophic lichen planus – sawtoothing less pronounced, interface changes associated with colloid bodies and pigment incontinence, lacks edematous hyalinized dermis.

Slide 18: Balloon cell nevus

- >50% balloon cells within a compound or intradermal nevus.
    - Round/oval cells with abundant foamy pale staining or clear cytoplasm
    - Central hyperchromatic or vesicular nucleus with conspicous nucleolus
    - Mitotic activity absent
    - More obvious ordinary melanocytic features sometimes evident at periphery
- DDx: Balloon cell melanoma—nuclear pelomorphism and mitotic acivity lacking in nevus counterpart; Clear cell sarcoma (melanoma of soft parts)—deeper mass with nested pattern separated by fibrous septa, cytoplasm clear to eosinophilic (as opposed to just clear), 60% contain variable amounts of melanin pigment; Xanthoma—cytoplasm tends to be relatively more foamy (finely vacuolated), lacks prominent nucleoli, CD68 (+) for confirmation if needed. Metastatic renal cell carcioma—highly vascular stroma with prominent thin delicate anastomizing vessels surrounding tumor lobules. RBC extravasation/hemorrhage and hemosiderin deposition. Positive for CK, CD10, and RCC marker.

Slide 19: Necrobiosis lipoidica diabeticorum (NLD)

- **11% of patients with NLD have diabetes mellitus and a further 11% develop the disease or altered glucose tolerance on follow-up.**
- Horizontally-oriented necrobiosis involving deep dermis.
- Alternating horizontal layers of palisading granulomatous inflammation (“layered cake”).
- Superficial and deep lymphocytic infiltrate with plasma cells.
- DDx: Granuloma annulare—palisading granulomas surrounding central necrobiosis and mucin, usually superficial and mid dermis; Necrobiotic xanthogranuloma—palisading granulomas with touton giant cells and cholesterol clefts, absence of mucin; Rheumatoid nodule—large areas of necrobiosis with fibrin deposition in deep dermis and subQ, palisading lymphs and histioctyes, multinucleated cells not prominent feature; Infectious granulomas—plasma cells and neutrophils prominent in infiltrate, more suppurative, i.e. frank necrosis rather than necrobiosis (acellular degeneration of collagen).

Slide 20: Eruptive xanthoma

- **The intracytoplasmic lipid is predominately triglycerides (in contrast to other xanthomata which contains mostly cholesterol).**
- Diffuse and interstitial proliferation of large pale staining foamy histioctyes with intracellular and extracellular lipid.
- Scattered lymphocytes and neutrophils in early lesions.
- DDx: Xanthelasma—identical histologic features without extracellular contents or inflammation; Tuberous xanthoma—fibrotic nodules with xanthomatous foamy cells. Verruciform xanthoma—oral mucosa with verruca architecture and pale foam cells in dermal papillae; Granular cell tumor—abundant eosinophilic granular cytoplasm, indistinct cell borders, pustulo-ovoid bodies, overlying epidermal hyperplasia.

Slide 21: Interstitial granuloma annulare

- Classic pattern of GA is palisading granulomas surrounding central areas of necrobiosis (degenerated collagen debris) with mucin deposition.
- Less common, interstitial pattern shows histiocytes dissecting through collagen accompanied by mucin deposition ("busy dermis" on low power).
- CD68 and CD163 may confirm presence of histiocytes, especially in subtle cases.
- DDX: Necrobiosis lipoidica—larger horizontal layers of necrobiosis alternating with parallel aggregates of histiocytes and giant cells, plasma cells, no mucin. Necrobiotic xanthogranuloma—palisading granulomas with touton giant cells and cholesterol clefts, absence of mucin; rheumatoid nodule—large areas of necrobiosis with fibrin deposition in deep dermis and subQ, palisading lymphs and histioctyes, multinucleated cells not prominent feature; Infectious granulomas—plasma cells and neutrophils prominent in infiltrate, more suppurative, i.e. frank necrosis rather than necrobiosis (acellular degeneration of collagen).

Slide 22: Erythema nodosum

- **Most common associations is streptococcal infection, inflammatory bowel disease, sarcoidosis, Sweet's syndrome, Behcets disease, cat scratch disease, pregnancy, estrogens, oral contraceptives, and various drugs (bromides, sulfonamides, etc.)**
- Classic septal panniculitis with septal thickening containig lymphohistiocytic infiltrate.
- Multinucleated giant cells in older lesions.
- Limited lobular involvement at periphery.
- "Miescher's radial granuloma"—nodular spindled/radially arranged histiocytes around central cleft .
- DDx: most other panniculiutis are predominately lobular (+/- septal involvement) including: lupus panniculitis—lymphoid follicles adjacent to septae, plasma cells, epidermal and dermal changes c/w lupus; erythema induratum—caseation necrosis with with neutrophilic vasculitis in fat; Lipomembranous panniculitis—associated with stasis changes, arabesque pattern of fat necrosis, sclerosis, and foamy macrophages. Infection-related panniculitis—granulomatous with neutrophils and necrosis, consider special stains/cultures.

Slide 23: Mucocele (mucous escape phenomenon)

- **Due to distal obstruction of a minor salivary gland duct causing rupture and spillage of mucin into the interstitium.**
- Most common location is lower labial mucosa (59-73%).
- Pseudocyst-like cavity in dermis of oral mucosa filled with large pools of sialomucin, scattered muciphages, and variable mixed inflammation.
- No true epithelial lining. Condensed granulation tissue at the periphery.
- Salivary glands may be present in the biopsy.
- Sialomucin is amorophous, slightly eosinophilic/amphophilic material. Positive for PAS (+/- diastase), Alcian blue, and colloidal iron.
- DDX: Cannot be confused with anything else!

Slide 24: Langerhans cell histiocytosis (Histiocytosis X)

- **Positive for S-100, Cd1a, and Langerin (CD207), and CD4.**
- Diffuse dermal +/- subcutaneous infiltrate of Langerhans cells (abundant pink cytoplasm with indented "coffee/kidney bean" nuclei containg longitudinal grooves
- Eosinophilic infiltrate (particularly eosinophilic granuloma variant)
- Epidermotropism common with Langerhans cell microabscesses (+/- ulceration)
- Birbeck granules on EM (pentilaminar tennis racket organelle)—now superceded by IHC.
- DDx: Langerhans cell sarcoma—overt cytologic atypia, high mitotic index, less prominent inflammatory background; Indeterminate dendritic cell tumor—histologically

identifical, but lack of epidermotropism and no Birbeck granules on EM; Melanoma—always needs to be excluded, typically lacks nuclear indentations and grooves characteristic of Langerhans cells, more cytologic atypia, cytoplasm less eosinophilic and more “smokey gray”; Allergic contact dermatitis/eczema—may have focal Langerhans cell microabscesses, but is not a prominent feature and no dermal infiltrate. Juvenile xanthogranuloma—Tuton giant cells, no epidermotropism.

Slide 25: Merkel cell carcinoma

- **Approximately 80% of Merkel cell carcinomas show integration of Merkel cell polyomavirus (MCV or MCPyV); viral DNA first described in January 2008.**
- Small round blue cell tumor with neuroendocrine features: hyperchromatic nuclei with coarse “salt and pepper” chromatin, nuclear molding, and crush artifact (Azzopardi phenomenon).
- Numerous mitoses and apoptotic bodies.
- Positive for CK20 (paranuclear dot-like pattern), synaptophysin, chromogranin, NSE, and CM2B4 (Merkel cell polyoma virus marker).
- Ddx: Metastatic small cell carcinoma—identical histology, but positive for TTF-1, CK7 and lacks CK20 staining pattern; small cell melanoma—commonly mistaken for MCC, nucleoli more prominent, look for possible melanin pigment or junctional activity; lymphoma—lacks nuclear molding, positive for LCA and B or T cell markers.

Slide 26: Reticulohistiocytoma (reticulohistiocytic granuloma)

- **Multicentric reticulohistiocytosis is associated with systemic symptoms, particularly a mutilating arthritis affecting the interphalangeal joints of the hands most frequently causing ‘opera house deformity’ and ‘main en lorgnette’.**
- Dense dermal infiltrate of large mononuclear and multinucleated histiocytes with abundant dense eosinophilic “ground glass” cytoplasm.
- Bizarre polygonal multinucleated giant cell forms with irregularly distributed nuceli seen in older lesions.
- DDx: Xanthogranuloma—cytoplasm more foamy, Tuton giant cells; Epithelioid cell histiocytoma—variant of DF, cells not so large, collagen trapping at periphery; Dermal Spitz nevus— lacks multinucleation and polygonal shape, may display slight eosinophilic cytoplasm, but not ground glass quality.

Slide 27: Nodular amyloidosis

- Single or numerous large waxy nodules of pale eosinophilic amorphous deposition in dermis and SubQ.
- Deposition of amyloid light chain (AL) seen in many cases.
- Plasma cells often present.
- Ddx**:** Colloid milium—fissures and clefts in amorphous material comprised of degenerated elastic fibers, adjacent solar elastosis, Grenz zone; Lipoid proteinosis—eosinophilic PAS+ pale staining material initially around capillaries and sweat ducts, later vertically oriented dermal deposition, negative for amyloid stains (congo red, thioflavine-T, etc.); Cutaneous macroglobulinosis—cutenous involvement of Waldenstroms, nodular deposits of homogenous eosinophilic material due to IgM deposition, PAS+/Congo red negative; Porphyria—cell poor subepi blister with hyalinized superficial papillary dermal vessels and lower epidermis linear caterpillar bodies due to IgG and C3 deposition, DIF+.

Slide 28: Gout

- **Brown needle-shaped crystals, preserved and polarizable (negative birefrigence) in alcohol-fixed tissue.**
- Amorphous eosinophilic "cotton candy" swirling dermal depositon (formalin fixed tissue).
- Surrounding granulomatous inflammation.
- DDx: Pseudogout (calcium pyrophosphate)—rhomboid and rod shaped, weak positive birefrigence; Calciosis cutis—fractured deposition, specimens treated with decalification solution removes purple crystalline granules leaving pale basophilic amorphous material; Cutaneous oxalosis (calcium oxalate)—yellow-brown bipyramidal crystals with strong positive birefringence, caused by metabolic defects, renal disease, and ethylene glycol ingestion.

Slide 29: Pilomatricoma (calcifying epithelioma of Malherbe)

- **Associated with myotonic dystrophy, Gardner's syndrome, MYH-associated poylposis, Turner's syndrome, trisomy 9, Rubinstein-Taybi, Soto's syndrome, and spina bifida.**
- Well circumscribed cyst-like dermal nodule with three components (outside→in):
    - Peripheral basaloid cells.
    - Tansitional cells with small pkynotic nuclei and eosinophlic cytoplasm.
    - Loss of nuclei results in "ghost" or "shadow" cells—nonviable keratinous debris.
- Calcification and ossification common in older lesions.
- Granulomatous reaction with foreign body multinucleated giant cells.
- DDx Pilomatrix carcinoma—rare malignant counterpart, poorly circumscribed with infiltrative pattern, atypical basaloid cells with atypical and increased mitotic activity, areas of geographic necrosis; Osteoma cutis—metaplastic trabecular bone; Basal cell carcinoma—can display matrical differentiation, but lacks shadow cells.

Slide 30: Dermatofibrosarcoma protuberans (DFSP)

- Dermal proliferation of bland spindle cells (**CD34+**) with little atypia and storiform architecture.
- Uninvolved epidermis and Grenz zone.
- Extension into SubQ in a "honeycomb" pattern—obliteration and replacement of fat with residual small groups of or individual adipocytes.
- DDx: Cellular dermatofibroma— collagen trapping at periphery, lacks storiform architecture, can have overlying epidermal changes (acanthosis, tabling of rete ridges, hyperpigmentation of basal layer, etc.), can extend into superficial subQ without dissection, CD34 (-) Factor XIIIa (+); Fibrosarcoma—deeper subQ mass, herringbone pattern; Plaque-like CD34 + dermal fibroma (medallion-like dermal dendrocyte hamartoma)—rare, young children, superfical tumor cells arranged vertically to epidermis, deep cells have horizontal orientation, subQ extension not typical.

Slide 31: Angiolipoma

- Encapsulated proliferation of small capillary sized vessels admixed with mature fat.
- Intravascular fibrin microthombi often seen, especially at the periphery.
- Occasionally, adipocyte component can be sparse—cellular angiolipoma.
- Ddx: **Repeated evalution has shown no chromosomal aberations in angiolipoma**. In normal lipomas, rearrangement of HMGA2 is typically seen. Pleomorphic and spindle cell lipomas commonly have monosomy or partial loss of chromosome 13 and 16. Well differentiated liposarcoma is associated with amplification of MDM2 at chromosome 12 and 15. Loss of chromosome 9p is the most common finding in melanoma. 9p21.3 is the location of CDKN2A gene that encodes p16 (an important tumor suppresion gene).

Slide 32: Sebaceous adenoma

- Proliferation of well-differentiated and well-circumscribed sebaceous lobules.
- Immature basaloid cells at periphery and mature sebocytes (bubbly cytoplasm) centrally.
- Mature sebocytes predominate (>50% of tumor).
- Minimal cytologic atypia (although focal mitoses may be seen).
- Frequent connection to epidermis, sometimes opening into it.
- DDx: Sebaceous hyperplasia—>90% mature sebocytes with 1-2 cell layer rim of basaloid cells at periphery; Sebaceoma–more germinative basaloid cells comprising over 50% of the lesion; Sebaceous carcinoma–-large, deep, and asymmetrical with mitotic activity; necrosis may be present. BCC–-can have focal sebaceous differentiation but would have other characteristic features of BCC; Trichilemmoma-–often has clear cell change (but are not sebocytes), peripheral rim of palisading basophilic cells surrounding by thickened PAS+ basement membrane.

Slide 33: Intravascular papillary endothelial hyperplasia (IPEH, Masson's tumor)

- **Reactive proliferative changes of recanalizing thrombus within normal vessel (typically vein) or vascular tumor/malformation (esp. cavernous hemangioma).**
- An associated adjacent organizing thrombus frequently present.
- Multiple small papillary fronds with acellular collagenous hyalinized cores lined by flattened endothelial cells.
- No atypia, pleomorphism, necrosis, or mitotic activity.
- DDx: Angiosarcoma (main mimic!)–not intravascular, commonly has frank malignant features: pleomorphism, mitotic activity, necrosis, endothelial cell multilayering, can be associated with chronic lymphedema; Kaposi's Sarcoma – tumor stage→dense proliferating spindled cells, slit like vascular spaces, extravasated RBCs, promontory sign, HHV-8 positive; Epitheloid hemangioma (angiolympoid hyperplasia with eosinophilia)—central thick-walled vessels with hobnail cells, nodular lymphoid aggregates and/or follicles with numerous eosinophils, frequently seen around the ear; Bacillary angiomatosis (cat scratch dz)—necrotizing granulomatous mixed inflammation, smudgy amphophilic areas = gram + *B. henselae*.

Slide 34: Glomangioma

- Uniformily spaced dark blue round monomorphic cells, often single filing.
- Represent modified smooth muscle cells (SMA+, desmin +) arising from Sucquet-Hoyer canal acting as thermoregulatory receptors.
- Glomus cells surround proliferation of prominent large dilated blood vessels.
- Stroma often pale and loose.
- DDx: Glomus tumor—glomus component overshadows inconspicous vessels they surround; Angiolipoma— SubQ encapsulated variant of lipoma, small capillary sized vessels admixed with mature fat, fibrin microthombi; Arteriovenous hemangioma—hemangioma with thick walled arteriole and venules; Eccrine spiradenoma—well circumscribed dermal nodule of basaloid cells "blue balls", two cell types: smaller cells forming rosettes and cells with larger pale nucleus, scattered small sweat ducts and droplets of eosinophilic basement membrane material.

Slide 35: Kaposi's Sarcoma, patch stage

- Most difficult stage to recognize (can be subtle).
- Proliferation of slit-like vascular spaces dissecting through dermis arranged mainly parallel to epidermis.
- Minimal cytologic atypia of endothelial cells (focally swollen and hyperchromatic).
- Focal extravasated erythrocytes, siderophages, lymphocytes and plasma cells.
- HHV-8+
- DDx: Microvenular hemangioma—slowly growing and usually <1 cm, irregularly branching but uniform slit-like vessels with collapsed lumina, HHV-8 negative; Acroangiodermatitis—lobular proliferation of thick-walled, stasis associated blood vessels. Angiosarcoma—broad, diffuse poorly circumscribed neoplasm with much atypia; Aneurysmal benign fibrous histiocystoma—sclerosing hemangioma variant of dermatofibroma; numerous blood vessels, histiocytes, siderophages.

Slide 36: Angioleiomyoma

- Well-circumscribed deep dermal or subQ nodule derived from vascular smooth muscle.
- Fasicles of smooth muscles cells with blunt "cigar" shaped nuclei and small perinuclear vacoules seen on cross section.
- Varying dilated and compressed small slit-like vessels embedded within smooth muscle.
- DDx: Palisaded encapuslated neuroma (PEN)— solitary dermal nodule, fasicles of neural cells (mostly Schwann) with wavy tapering nuclei, clefts can occur; Leiomyosarcoma—malignant features present→infiltrative borders, cytologic atypia, mitotic activity, necrosis; Myofibroma—biphasic tumor of myofibroblasts and more primitive smaller rounder and spindle cells with scant cytoplasm, containing vessels with hemangiopericytoma-like pattern, paucicellular areas may have hyalinized pseudochonroid appearance; Rheumatoid nodule—deep dermal/subQ nodule of palisading granuomas surrounding large area of necrobiosis and fibrin deposition.

Slide 37: Syringoma, clear cell type

- Well circumscribed proliferation of small ecrine ducts (two layers of flattened cuboidal cells) with comma shaped tails ("tadpole" or "paisley tie" pattern).
- Clear cell variant due to glyogen accumulation.
- Eosinophilic intraluminal material→ ductal secretion "sweat"
- Dense fibrotic stroma; may have horn cysts or milia.
- DDx: Metastatic renal cell carcinoma (vs. clear cell variant)—nested pattern with prominent vascular component, no ducts; Microcytic adnexal carcinoma (MAC)—can have little cytologic atypia, superficially can be difficult to tell apart, more infiltrative and extends deep, mitoses, often perineural invasion. Morpheaform BCC—also infiltrative, no ducts, hyperchromatic basaloid cells with atypia, mitoses, apoptotic bodies, stromal retraction; Desmoplastic trichoepithelioma—no sweat ducts, more horn cysts, papillary mesenchymal bodies.

Slide 38: Sebaceous carcinoma

- **Muir-Torre patients have an increased risk of sebaceous neoplasms including sebaceous adenomas (most specific marker for syndrome) as well as sebaceous carcinomas (ocular and extracocular).**
- Infiltrative lobules of immature atypical sebocytes, basaloid cells, and squamoid cells often extending into SubQ.
- Sebocytes often with vacuolated cytoplasm (bubbly in mature seboctyes)—may be sparse component of tumor.
- Prominent nucleoli, mitoses, and often necrosis.
- EMA+ (strong), adipophilin+, CAM 5.2 (low molecular weight keratin).
- Oil-red-O and Sudan black stains for lipids (on frozen sections).
- Pagetoid epidermal sebocytes overlying tumor may be seen.

- DDx:. Sebecaous adenoma/sebaceoma—lacks atypia and infiltrative pattern; BCC with sebaceous differentiation— features of BCC with <30% mature sebocytes (typically only focal); Clear cell SCC—negative for CAM 5.2; Balloon cell melanoma—will be positive for S-100, SOX-10, Melan-A, or HMB-45.

Slide 39: Schwannoma (neurilemmoma)
Neurilemmomas (schwannomas) can be incidental, but are associated with NF type II which is also associated with acoustic neuromas.

- Deep dermal or subcutaneous neural Schwann cell tumor with perineural capsule.
- Attachment to a peripheral nerve root may be seen (compression causes pain).
- Schwann cells are bland and fusiform with tapered, wavy nuclei.
    - Antoni A—cellular areas containing Verocay bodies, parallel rows of nuclei separated by acellular centers.
    - Antoni B—hypocellular areas with loose myxoid stroma
- Strongly S-100+
- Ddx: Palisaded encapsulated neuroma—smaller more superficial lesions, fascicles with clefting, axons present, no Verocay bodies; Neurofibroma— has axons, mucinous stroma, mast cells, no Verocay bodies; Leiomyoma—more superficial, cigar shaped nuclei with\ blunt ends, perinuclear vacuoles on cross section.

Slide 40: Chondrodermatitis nodularis chronica helicis

- Overlying epidermis—pseudoepitheliomatous hyperplasia, hyperkeratosis/parakeratosis.
- Often focal ulceration
- Underlying degenerating hyaline cartilage.
- Fibrosis, granulation tissue, and solar elastosis in between.
- DDx: Squamous cell carcinoma—more cytologic atypia and mitotic activity; Relapsing polychondritis—- perichondral inflammation, loss of basophilia of hyaline cartilage (loss of chondroitin sulfate), vacuolization of chondrocytes, adjacent granulation tissue and fibrosis in older lesions; Weathering nodule—fibrosis and degenerating elastic tissue +/- cartilage, not painful; Fibrous papule—on nose, dome shaped with ectatic vessels and fibrotic stroma .

Slide 41: Proliferating trichilemmal cyst

- Arises from trichilemmal (pilar) cyst with multilobulated solid and cystic architecture.
- Trichilemmal keratinization—absent granular layer and compact homogenized keratin.
- Peripheral palisading of basaloid cells.
- Prominent epithelial infoldings “rolls and scrolls”.
- Squamous eddies and pearls sometimes.
- May have clear cells sometimes.
- Few if any mitotic figures, minimal cytologic atypia.
  DDx: Trichilemmal carcinoma—more infiltrative, significant cytologic atypia and mitotic activity; SCC —more obvious connection to overlying epidermis with more cytologic atypia and mitotic activity. Pseudoepitheliomatous hyperplasia—reactive epidermal changes mimicking SCC, not a dermal cystic neoplasm; Trichilemmoma—Endophytic epidermal lobular growth pattern, clear glycogenated cells, peripheral rim of palisading basal cells, thickened basement membrane.

Slide 42: Dermal leiomyosarcoma

- Ill-defined diffuse and hypercellular proliferation of smooth muscle with blunt-ended, cigar shaped nuclei, perinuclear vacoules on cross section, and eosinophilic cytoplasm.
- Varying degrees of cytologic atypia with high N/C ratios, nuclear pleomorphism and hyperchromasia.
- Dermal variant generally has less atypia than subcutaneous or metastatic variants.
- Increased mitotic activity (>10/10HPFs).
- Necrosis may be present.
- Arises from arrector pili muscle.
- SMA+, desmin+, h-caldesmon+
- DDx (for immunostains): Spindle cell melanoma—SOX-10+, S-100+ (negative for HMB-45 and Melan-A); Atypical fibroxanthoma (AFX)—CD68+, CD10+, PC-1 (procollagen 1)+; spindle cell squamous cell carcinoma—CK, CK5/6, p63; Dermatofibroma—Factor XIIIa+, CD31 highlights background vessels.

Slide 43: Cutaneous endometriosis

- Glandular spaces embedded in fibromyxoid stroma, often with red blood cells and hemosiderin in the stroma.
- DDx: Omphalomesenteric duct polyp—surface epithelium adjacent to tumor with sharp transition, gastrointestinal columnar epithelium with goblet cells, ulceration; Hidrocystoma—eyelids or periorbital skin, unilocular/multilocular cyst lined by1-2 cell layers of cuboidal or columnar epithelium, classically has apocrine decapitation secretion, intraluminal pigmented secretion (sweat) not uncommon; Median raphe cyst—men ventral midline along anogenital raphe, highly variable lining, stroma has delicate collagen and randomly arranged smooth muscle; Cutaneous ciliated cyst—on lower extremities of women, ciliated columnar or cuboidal epithelium, no goblet cells.

Slide 44: Irritated seborrheic keratosis

- Typical features of an SK (proliferation of basaloid keratinoctyes, horn psueodcysts, increased melanin, flattened base “string sign”, etc.)
- Squamous eddies—spherical aggregates of swirling spindled eosinophilic keratinocytes, focal parakeratosis, and +/- chronic inflammation are features of chronic irritation.
- Inverted follicular keratosis (IFK) = irritated SK with endophytic growth pattern downward along a follicle.
- DDx: Poroma—connected to acanthotic epidermis, endophytic growth pattern of uniform cuboidal basaloid “poroid” eccrine cells, scattered ducts may contain sweat secretion; Verruca—papillomatosis, acanthosis, hyergranulosis +/- koilocytes, hyperkeratosis with columns of parakeratosis above projecting dermal papillae, intracorneal hemorrhage, intowing of the rete ridges; Squamous cell carcinoma—atypical nuclei, mitoses, lacks uniformity, keratin pearls. Prurigo nodularis—marked irregular acanthosis, hyperkeratosis with focal parakeratosis, hypergranulosis, thickened and vertically oriented collagen in dermal papillae.

Slide 45: **Granular cell tumor**

- Usually solitary, 10% multiple; 40% involve the tongue.
- Dermal sheets of polygonal cells with abundant eosinophilic granular cytoplasm
- PAS+ (diastase resistant) and S-100+
- Pustulo-ovoid bodies of Milian= larger intracytoplasmic granules.
- May have overlying pseudoepitheliomatous hyperplasia (especially mucosal lesions)
- DDx: SCC—overlying pseudoepitheliomatous hyperplasia can be mistaken for SCC; Xanthoma—less granularity and more foamy, less distinct cell boundaries, positive for lipid stains, S-100 and PAS negative; Rare granular cell changes and variants have been reported in a wide range of neoplasms including renal cell carcinoma,

dermatofibroma, leiomyoma, BCC, melanoma, etc. Awareness of this fact and other histological features +/- appropriate stains can help confirm diagnosis.

Slide 46: Mucinous eccrine carcinoma (primary mucinous carcinoma)

- Small islands of ductal epithelium in pools of abundant mucin, separated by thin fibrous septae.
- DDx: Metastatic mucinous carcinoma of GI tract or breast—can have identical histology, may require history and/or imaging; Focal cutaneous mucinosis—solitary localized papule of dermal mucin accumulation, collarete of epidermal rete may be present, lacks malignant epithelial ductal component; Digital mucous cyst—resembles focal mucinosis but associated with dorsal proximal nail fold of a digit; Mucocele— usually occurs in lower labial mucosa (nonkeratinizing squamous mucosa), pseudocyst filled with mucin due to obstruction of minor salivary gland (may be present in biopsy); Granuloma annulare—doesn't produce this degree of mucin, scattered discohesive histiocytes in dermis.

Slide 47: Chromoblastomycosis (chromomycosis)

- Pseudocarcinomatous hyperplasia with a dense suppurative granulomatous mixed dermal infiltrate and intraepithelial neutrophilic microabscesses.
- Sclerotic bodies (medlar bodies or "copper pennies") are dark brown, thick walled, ovoid or round spores (6-12 μm)
- Pigmented fungi: *Philalophora verrucosa, Fonsacea pedrosoi, Fonsacea compactum, Exophiala dermatitidis, Cladosporium carrionii*
- Organisms found within giant cells, neutrophilic abscesses, or free in tissue.
- DDx: Blastomycosis—broad based budding, unpigmented yeast; Sporotrichosis—clinically an ascending lymphangitis, non-pigmented yeast; Paracoccidioidomycosis, coccidioidomycosis—multiple small organisms within macrophages, not pigmented; Keratoacanthoma—no fungal forms, cup-shaped crateriform squamous neoplasm.

Slide 48: Orf/Milker's nodule (farmyard pox)

- Acral skin; orf—solitary lesion from contact of infected sheep; milker's nodule—multiple lesions from cows.
- Symmetrical acanthotic nodule with delicate finger-like projections into the dermis.
- Ballooning vacuolization of superficial epidermis with loss of granular cell layer, fibrin deposition, spingiosis, and epidermal necrosis.
- Early lesion, small intracytoplasmic eosinophilic viral inclusions (3-5 μm) in keratinocytes.
- Marked dermal capillary proliferation and dilatation with edema and mixed inflammation.
- DDx: Hand foot and mouth—vesicular degeneration of epidermis without viral inclusions or multinucleated giant cells; Herpes— homogenous large intranuclear inclusions & "the 3 M's" (margination of chromatin, multinucleation, and nuclear molding); Erythema multiforme—interface changes with necrotic keratinocytes, no viral inclusions.

Slide 49: Paget's Disease

- Intraepidermal proliferation of large atypical pale cells (may contain intracytoplasmic mucin) in variable sized nests or single cells.
- Can appear multifocal with skip areas within same biopsy.
- Flattening of the basal cells by neoplastic nests.
- Dyskeratosis is uncommon.
- Mammary Paget's—nearly 100% underlying ductal carcinoma.
- Extramammary Paget's—50% chance of underlying carcinoma.
- Typically stain with CEA, EMA, CAM 5.2 (low molecular weight cytokeratin), CK7; PAS, mucicarmine, & Alcian blue (stains mucin)

- DDx: Bowen's (clear cell variant)—dyskeratosis, negative for CEA, EMA, PAS, mucicarmine; Melanoma in situ—lower tumor cell burden in the dermis, more single cell "pagetoid" spread, positive for melanoma markers, negative for all Paget's markers.

Slide 50: Leishmaniasis

- Diffuse dermal mixed granulomatous infiltrate.
- Caseation and necrosis can occur.
- Amastigotes within histiocytes visible on H&E, PAS+, Giemsa+ (best).
    - 2-3 μm with 1 μm nucleus and small adjacent rod-shaped kinetoplast.
    - Can be arranged peripherally ("marquee sign").
- DDx: Histoplasmosis—similar size, no kinetoplast, "Marquee sign" arrangement not typical, pseudocapsule, GMS positive, Giemsa negative; Granuloma inguinale—limited to groin, gram negative bacilli within histiocytes, also Giemsa and Warthin-Starry positive with bipolar "safety pin" staining; Malakoplakia—cutaneous lesions limited to genitalia and perineum, reactive repsonse to bacterial infection (usually E. coli) in immunosuppressed patients, confluent sheets of histiocytes with slighlty eosinophilic granular cytoplasm, Michaelis-Gutman bodies—calcified laminated basophilic intracytoplasmic structures (von Kossa +).

Slide 51: Nevus of Ito (nevus fuscoceruleus acromiondeltoideus)

- Spindle shaped and dendritic melanocytes in superficial to mid dermis with fine melanin granules; most oriented parallel to skin surface or may be seen encircling appendages.
- Epidermis uninvolved—no junctional activity.
- Melanophages generally absent.
- DDx: Nevus of Ota—identical histology, located around eye, forehead, cheek; Blue nevus—increased cellularity, small, well defined darkly pigmented lesion; Dermal melanosis—comprised of melanophages.

Slide 52: Coccidioidomycosis

- Pseudoepitheliomatous hyperplasia with focal intraepidermal microabscesses.
- Diffuse dermal granulomatous and mixed inflammatory infiltrate.
- Large thick-walled spores(10-80 microns) which contain multiple endospores (2-10 microns); contained within giant cells and free in interstitium.
- Often visibile on H&E but can be highlighted with PAS or GMS stains.
- *Coccidioides immitis* is endemic in the southwestern desert states.
- DDx: Cryptococcus—thick capsule stains with mucicarmine, cell wall with PAS; Blastomycosis—broad based budding; Histoplasmosis—smaller spores (2-4microns) without endospores.

Slide 53: Deep penetrating nevus (Seab's nevus)

- Dermal melanocytic neoplasm with a a upper broad base and vertically oriented, sharply demarcated bulbous extensions into the deep dermis or subcutis.
- Deep extensions contain predominantly spindled melanocytes and typically follow hair follicles and neurovascular bundles.
- Can have increased cellularity, some nuclear pleomorphism, hyperchromasia, and melanophages.
- Lacks significant mitotic activity.
- DDx: Cellular blue nevus—dense collections of plump melanocytes without focal extensions into the deep tissues; Melanoma—will have atypia and mitotic activity; Spitz's nevus—epithelioid to spindled cells, without deep extension.

Slide 54: Syringocystadenoma papilliferum (SCAP)

- Epidermal papillomatosis and acanthosis with epidermal connection to underlying tumor.
- Papillary projections extend into a cystic space.
- Cystic space lined by squamous epithelium superficially and sweat gland epithelium deeper.
- Apocrine (decapitate) secretion is generally present.
- Plasma cell infiltrate in papillary cores and around the tumor.
- Commonly present within nevus sebaceous (which are associated with: trichoblastomas, basal cell carcinoma, & rarely squamous cell carcinoma).
- Malignant counterpart (syringocystadenocarcinoma papilliferum) can develop from SCAP
- DDx: Hidradenoma papilliferum—almost always on vulva, maze-like glandular spaces, no connection to epidermis, minimal inflammation; Nipple adenoma—located on nipple.

Slide 55: Histoplasmosis

- ***Histoplasma* capsulatum is endemic in Mississippi and Ohio river valleys & associated with bat guano (feces).**
- Diffuse mixed granulomatous dermal infiltrate with occassional tuberculoid giant cells and foci of necrosis.
- Parasitized macrophages containing numerous small (2-4 micron) spores with surrounding pseudocapsule.
- Fungal elements are highlighted with PAS, GMS, and Giemsa stains.
- DDx: Leishmaniasis—Geimsa positive, GMS negative, has kinetoplast, organisms arranged peripherally within histiocyte ("Marquee sign"); Blastomycoses—broad based budding; Cryptococcosis—large mucicarmine positive gelatinous capsule, PAS positive cell wall.

Slide 56: Metastatic renal cell carcinoma

- Skin-colored or violaceous nodule, may resemble a pyogenic granuloma clinically.
- More common in males with a predilection for the head and neck area.
- Intradermal nodule composed of large clear cells (contains glycogen and lipid) in a lobular pattern.
- Stroma is vascular with extravasated red blood cells/hemorrhage and hemosiderin.
- DDx: Nodular hidradenoma—multilobular, vascular stroma absent, presence of ductal structures; Clear cell sarcoma—clear cells, often multinucleated cells present, melanin, common on foot; Balloon cell melanoma—nests of "balloon cell" melanocytes, sometimes junctional component, vascular stroma absent; Pyogenic granuloma—lobule composed of granulation tissue (vascular proliferation with an inflammatory cell infiltrate composed of lymphocytes and neutrophils).

Slide 57: Cryptococcus

- Impaired immunity is a significant risk factor for systemic infection and poor outcome.
- Round yeast (4-20 microns) with thick polysaccharide capsule (mucicarmine positive).
- PAS stains cell wall (central portion); narrow based budding.
- Intra and extra cellular organisms can be seen.
- Mixed inflammatory cell infiltrate with variable PMNs, plasmas, lymphocytes, histiocytes; granulomatous reaction in some cases, necrosis can be present.
- Definitive diagnosis with cryptococcal antigen test (performed on serum or CSF).
- DDx: Histoplasma—no capsule with mucicarmine, intracellular organisms only; Blastomyces dermatitidis—no capsule with mucicarmine, broad based budding.

Slide 58: Chondroid syringoma (mixed tumor of the skin)

- Well circumscribed, lobulated mass: the epithelial component contains polygonal cells with plump nuclei and eosinophilic cytoplasm arranged in nests, chords, and singly.
- Chondromyxoid stroma.
- Cystic dilation and apocrine “decapitate” secretion are variably present.
- Tubuloalveolar components may indicate differentiation toward eccrine coil and contain an outer layer of myoepithelial cells.
- Squamous differentiation, keratinaceous cysts, clear cell change, mucinous, columnar, and osseous metaplasia of the epithelial component can occur.
- Mitosis, atypia, and necrosis are notably absent.
- DDx: Adenoid cystic carcinoma—lacks chondroid stroma; Hidrocystoma—lacks chondroid stroma and myoepithelial cell layer around epithelial components.

Slide 59: **Lepromatous leprosy (Hansen’s disease)**

- Foamy or vacuolated histiocytes (full of mycobacterial bacilli—globi) diffusely in dermis and subcutis, minimal associated lymphocytic infiltrate.
- Grenz zone.
- Bacilli are also present in association with nerves, arrector pili muscles, within vascular walls, eccrine ductal, and secretory structures.
- Can be highlighted with acid fast stains (Fite).
- DDx: Granuloma annulare—has necrobiotic collagen and lacks bacilli-filled histiocytes; Tuberculoid leprosy—granulomatous reaction with few-to-no mycobacterial bacilli present.

Slide 60: Nodular melanoma

- Lacks radial growth phase.
- Atypical melanocytes with mitotic activity.
- Rapid growth frequently results in a consumed (thin or atrophic) overlying epidermis.
- Epidermotropism beyond the extent of the dermal mass is uncommon and limited to a just few rete on either side.
- S-100, SOX-10, Melan-A/Mart1 or HMB45 positive.
- DDx: Metastatic melanoma—infrequently has overlying epidermal involvement, often as wide as it is deep, may be difficult to differentiate if history of prior melanoma is lacking; Atypical fibroxanthoma—will be S-100/SOX-10 negative; Merkel cell carcinoma—rarely involves epidermis, usually poorly differentiated basaloid cells without architectural organization, S-100/SOX-10 negative; neuroendocrine markers (Synaptophysin, chromogranin, NSE) variably positive, CK20 positive (perinuclear dot-pattern).