ASDP
48TH
ANNUAL
MEETING

The American Society of
Dermatopathology

2011

Board Review Course

48th Annual Meeting
October 20-23, 2011
Sheraton Seattle
Seattle, Washington

2011 Board Review
The American Society of Dermatopathology

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COURSE OBJECTIVES

Upon completion of this course, participants should be able to:

- Identify board examination requirements.
- Utilize new technology to assist with various diagnoses and treatment methods.

Structure and Function of the Skin

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Structure and Function of the Epidermis

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I. *Functions*

A. Protection
B. Sensory reception
C. Thermal regulation
D. Nutrient (Vitamin D) metabolism
E. Immunologic surveillance
    1.Keratinocytes produce interleukins, colony stimulating factors, tumor necrosis factors, transforming growth factors and growth
F. Repair

II. *Epidermis*

A. Derived from ectoderm
B. Keratinizing stratified squamous epithelium from which arise cutaneous appendages (sebaceous glands, nails and apocrine and eccrine sweat glands)
    1. Rete
    2. Dermal papillae
C. Comprises the following layers
    a) Stratum germinativum (Basal cell layer)
    b) Stratum spinosum (Spinous Cell layer)
    c) Stratum granulosum (Granular layer)
    d) Stratum corneum (Horny cell layer)
    e) Stratum lucidum present in areas where the stratum corneum is thickest, such as the palms and soles.
D. Types of cells that comprise the epidermis
    1. Keratinocytes comprise over 80% of the epidermal cells.
        a) Larger ample stainable cytoplasm with intercellular bridges
        b) Epidermal
        c) Adnexal
            (1) Acrotrichial (intraepidermal hair follicle)
            (2) Acrosytingeal (Intraepidermal sweat duct)
    3. Nonkeratinocytes comprise less than 20% of epidermal cells.
        a) Dendritic cells or clear cells
            (1) Melanocytes
            (2) Langerhans cells
            (3) Indeterminate dendritic cells
        b) Merkel cells (neuroendocrine)
E. Specialized cuboidal epithelial that forms the acrosyringia of eccrine sweat ducts.
F. Cells program for possible adnexal/glandular differential
    1. Toker cells found in the nipple epidermis in about 10%

III. *Keratinocyte*

A. Differentiation of the epidermis is expressed in the form of keratinization.

1. Differentiation is a genetically programmed, highly regulated series of evens that occurs in postmitotic keratinocytes.
2. As they differentiated into cornified keratinocytes, the keratinocytes migrate upward through the layers of the epidermis, which are defined by the position, shape, polarity, morphology and state of differentiation of the keratinocytes.
3. Structure of the keratinocyte correlates with its position within the epidermis and its state of differentiation. Structure, in turn, correlates with and reflects the function.
    a) The structure has been well investigated over several decades using routine methods for histology and ultrastructure but the interpretation of structure in terms of function is continually being refined by new knowledge of the composition of the keratinocyte gained from biochemical and molecular analyses.
4. At each stage of differentiation, the keratinocyte becomes more specialized and restricted in cell structure and function in order to focus on synthesis and modification of proteins and lipids required for keratinization.
5. To become a terminally differentiated or cornified keratinocyte, characterized by keratin filaments and matrix protein, and a protein-reinforced plasma membrane with surface-associated lipids, keratinocytes proceed through the following steps:
    a) Become larger and flatter
    b) Progressively increase their number of tonofibrils and thicken their tonofilaments.
    c) Rearrange preexisting organelles and acquire new organelles
    d) Alter their surface antigens and receptors
    e) Lose their nuclei and organelles
    f) Lose 45-86% of their dry weight
    g) Acquire thick cell membranes
6. Keratinocytes at the intermediate stage between the granular and first cornified layer are called transitional cells.
7. The transit time from the basal layer to the stratum corneum is 26-42 days.
    a) This time increased to 3-4 days in psoriasis, after stripping adhesive tape and when peeling after a sunburn.
8. An additional 14 days is spent in transit through the stratum corneum until the keratinocytes desquamate.
9. The total epidermal renewal time is 45-75 days.

B. All keratinocytes contain keratin intermediate filaments in their cytoplasm and form desmosomes or hemidesmosomes with adjacent cells (except the outermost stratum corneum cells, where they are cleaved as the cornified cells are shed).

1. Desmosomes (maculae adherens)

a) Provide firm mechanical attachment between adjacent cells but break and reform during the process of keratinocyte migration and maturation.

(1) The cleavage between desmosomes in the cornified layer results in invisible shedding of cornified keratinocytes.

b) Structure of each desmosome:

(1) Two electron-dense plaques located in the cytoplasm of the adjacent keratinocytes.

(2) Next to each attachment plaque lies the trilaminar plasma membrane of the two keratinocytes.

(3) Keratin intermediate filaments insert on each plaque.

(4) Glycocalx formed by the extracellular domain of the transmembrane glycoproteins in the center of the desmosomes allows for cohesion between cells as well as opening of the desmosomes and cell movement.

c) Contain two classes of transmembrane glucoproteins which are members of the cadherin calcium-dependent cell adhesion molecules:

(1) Desmocollins (Dsc 1-3)-IgA pemphigus antigens

(2) Desmogleins (Dsg 1-3)-pemphigus foliaceous (Dsg-1), pemphigus vulgaris (Dsg-3), and drug-induced pemphigus (Dsg-1 or Dsg-3) antigens

(3) Dsg1 and Dsc1 are preferentially expressed in the superficial layers of the epidermis whereas Dsg3 and Dsc3 show greater expression in basal keratinocytes

d) There are several non-glycosylated proteins present in the plaque which forms a link between the glycoproteins and the keratin intermediate filaments.

(1) Plakins

(a) Desmoplakins (DP) – paraneoplastic pemphigus antigens (DP-I and DP-II

(b) Plakoglobin – associated with pemphigus foliaceous and pemphigus vulgaris antigens

(2) Armadillo family of nuclear and junctional proteins

(a) Plakophilin,

(b) Envoplakin, periplakin

e) Diseases can result from abnormal desmosomal structures or disruption of desmosomes characterized by acantholysis and blister formation leading to exfoliation.

C. Gap junctions or metabolically-coupled cells, adherens junctions and tight junctions also connect keratinocytes

1. Gap junctions increase as the keratinocytes become more differentiated.
   (a) Clusters of intercellular channels, known as connexons
2. Adherens junctions contain classic cadherins as transmembrane

glycoproteins. In the plaque, α-, ß-, and γ- catenins are found. ß- catenin is associated most tightly with the cytoplasmic domain of class cadherins. α-catenin, is required for binding of classic cadherins to actin filaments.

3. Tight junctions are the major regulators of permeability and skin barrier integrity

D. The cytoskeleton of the keratinocyte is also composed of microfilaments and microtubules.

E. The keratinocyte contains the „house-keeping organelles" such as rough endoplasmic reticulum, Golgi complex, ribosomes and mitochondria whose density varies depending on the cell layer.

F. Nucleus is oval and the heterochromatin varies in amount according to the cell layer.

G. A large nucleolus is typical.

H. Keratinocyte integrins

1. Superfamily of cell-surface glycoproteins forming receptors, which mediate adhesion, in both intercellular and cell-substrate interactions

IV. Stratum Germinativum or Basalis (basal cell layer)

A. Single layer of low columnar to cuboidal cells with deeply basophilic cytoplasm and round to oval nuclei arranged perpendicular to he basement membrane.

B. Connected to each other and to overlying keratinocytes by desmosomes.

1. These relationships impart polarity on the cells.

C. Connected to the basement membrane zone or epidermal dermal junction by hemidesmosomes.

1. Possessing only one intracytoplasmic attachment plaque to which tonofilaments from the interior of the basal cell attach, hemidesmosomes are situated at regular intervals along the plasma membrane of basal cells and anchor the epidermis to basal lamina (comprised of lamina lucida and lamina densa) via anchoring filaments.

2. This association is important for the physical and mechanical integration of the epidermis, as well as regulatory signal to restrain or to trigger differentiation.

D. Ultrastructurally, possess a well-defined highly convoluted membrane, microfilaments (assist in upward cell migration), microtubules and keratin intermediate filaments (tonafilaments) K5 and K14 (form the developing cytoskeleton), membrane-bound vacuoles that contain melanosomes, organelles of synthesis and replication, including Golgi complex, rough endoplasmic reticulum, mitochondria, ribosomes (impart basophilia to hematoxylin-eosin stained specimens), centrioles and prominent nucleoli.

E. Most of the mitotic activity in the epidermis occurs in the basal cell layer. 3-5% of the basal cells are synthesizing DNA at any given time, but only 1/1000 is in mitosis.

F. Basal cell division occurs every 19 days.

G. Basal cell DNA synthesis takes 16 hours.

H. Approximately 50% of the daughter cell from each division will move outward.

I. There are three subpopulations of basal cells

1. Stem cells – clonogenic cells which have a long life span, short S phase and cycle slowly. These cells reside at the tip of the rete ridges.
2. Transient amplifying cells – rapidly dividing to produce postmitotic cells
3. Postmitotic cells – cells that move upward toward the surface and terminally differentiate. Transient amplifying and postmitotic cells are referred to as the epidermal proliferation unit.

V. Stratum Spinosum or squamous cell layer

A. Usually 5-10 layers thigh

B. Spine-like appearance at margins of cells that form desmosomes.

1. The spines correspond to the bundles of keratin that insert into the desmosomal plaques of adjacent cells.

C. Suprabasal keratinocytes are polyhedral with oval, vesicular nuclei and eosinophilic cytoplasm, but they flatten toward the upper layers with their long axis parallel to the skin surface.

D. Intercellular spaces between keratinocytes contain glycoproteins (neutral mucopolysaccharides and acid mucopolysaccharides/glycosaminoglycans) and lipids which mediate cell adhesion. Hyaluronic acid is the most important component of the glycosaminoglycans.

E. Lamellar granules, new organelles, are first evident in the cytoplasm of the upper most spinous layers.

F. Newly synthesized differentiation specific keratin filaments, K1 and K10 are added to the K5/K14 already present when the cells moved out o the basal and into the spinous layers increasing the quantity and diversity of keratin protein.

1. In epidermolytic hyperkeratosis, also known as bullous congenital ichthyosiform erythroderma, mutation of keratin 1 and keratin 10 may affect K1/K10 heterodimer formation resulting in clumping of the tonofilaments in the suprabasal keratinocytes with suprabasal blistering and ridge-like hyperkeratosis primarily affecting the flexural areas of the skin.
2. In hyperproliferative conditions such as psoriasis, actinic keratoses and wound healing, suprabasal keratinocytes downregulate K1/K10 synthesis and upregulate K6/K16 synthesis.

VI. Stratum Granulosum (Granular layer)

A. Most highly differentiated cells of the viable epidermis.

B. Involved in both synthetic and degradative events.

1. Engaged in synthesis of new structural proteins (proteins of the cornified cell membrane, profilaggrin), lipids, cell surface receptors and antigens and plays a role in its own programmed differentiation.

C. Thickness can vary from 1 to 10 layers depending on the thickness of the stratum corneum.
D. Flattened or diamond-shaped keratinocytes with course, irregular, basophilic keratohyalin granules.
E. In the process of keratinization, keratohyalin granules form two structures; Filaggrin of the interfibrillary matrix and the inner lying of the stratum corneum or marginal band.

1. Composition of keratohyalin granules includes:
    a. Profilaggrin
        (1) electron-dense, high molecular mass, histidine rich, phosphorylated intermediate filament-associated protein composed of filaggrin monomers linked by small peptides.
        (2) Converted to filaggrin, which functions to cement the keratin filaments together by proteolysis and dephosphorylation.
    b. Keratin intermediate filaments
        (1) Modification of K1 to K2 and K10 to K11
    c. Loricrin – a protein also found in the cornified cell envelope
    d. Keratohyalin has a high sulfur protein content.
2. Keratohyalin granules become progressively larger as the keratinocytes move into the outermost granular layer wher,e in some cells, they form interconnecting masses that appear to involve the majority of the keratin filaments.

F. Lysosomal enzymes are present diffusely throughout the cytoplasm in preparation for degradation of organelles and nuclei.
G. Odland bodies (lamellar granules, keratinosomes, membrane-coating lamellar granules) are oval, 300-500 nm, membrane bound, lamellated organelles that contain a series of disk-like lipid bilayers discharged into the intercellular space.

1. Found intracellularly in the granular layer keratinocytes and extracellularly at the junction between the stratum granulosum and stratum corneum.
2. Contain carbohydrates and lipids complexed to lipids and proteins, hydrolytic enzymes, sugars and free sterols.
3. Provide lipids that establish a barrier to water loss and mediate stratum corneum cohesion/desquamation.

H. Granular cells synthesize and cross-like a number of structural proteins that will form the cornified cell envelope of the stratum corneum.
I. Associated Diseases

1. Filaggrin is absent in ichthyosis vulgaris, characterized by fine, whitish scaling, sparing of flexures and increased palmoplantar skin markings with hyperkeratosis.
2. Harlequin ichthyosis, an autosomal recessive disorder lethal within the first few days of birth, is characterized by plate-like sheets of scale separated by deep fissures. Lamellar granules are abnormal and fail to form intercellular lamellae. It may also be associated with lack of K1/K10 and profilaggrin.

VII. Stratum Lucidum

A. Gray-blue layer between the stratum corneum and stratum granulosum on acral skin such as the palms and soles.

B. Rich in protein-bound lipids contained in Odland bodies.

VIII. Stratum Corneum

A. Multilayered zone of terminally differentiated keratinocytes suspended in extracellular lipid; series of "bricks" (keratinocytes) bonded by "mortar" (lipid).

B. Largest cells of the epidermis

1. Single cell of stratum corneum is 30-40 μm in diameter compared with 6-8 μm diameter basal cells; 1 corneocyte is equivalent in area of 25 basal cells.

C. Most cell layers of the epidermis vary in thickness from 15 years on the face, 25 layers on the arms and over 100 on the palms and soles.

D. Flat, polyhedral, anuclear, eosinophilic cornified cells.

E. On electron microscopy, the cell contains electron-lucent, keratin filaments surrounded by electron-dense filaggrin, remnants of organelles, enzymes for remodeling of lipids, promotion of desquamations, and alternation of lipids bound covalently to the surface of the cornified cell envelope.

1. Filaggrin, which acts as the matrix protein that embeds and promotes the aggregation and disulfide bonding of keratin filaments to provide stability and integrity to this layer, undergoes final proteolysis to free amino acids in the outer layers of the stratum corneum.

2. Cornified cell envelope, deposited beneath the plasma membrane is synthesized in the spinous and granular layers.

a. Composed of lipids and proteins incorporated into the marginal band (involucrin, loricrin, keratolinin, pancornulins) cross-linked by calcium-requiring transglutaminase enzyme.

F. The keratinocytes of the stratum corneum differ substantially in structure (thickness, organization of keratin filaments and filaggrin-containing interfilamentous matrix, cell-to-cell attachment mechanisms and nature and quantity of intercellular material) depending upon their position relative to the granular layer and the skin surface.

1. Cells of the deeper layer of the strtum corneum (stratum compactum) are thicker and have more densely packed, organized parallel arrays of keratin filaments, a more fragile cornified cell envelopes and greater modifications for cell-to-cell attachments (modified desmosomes, overlapping margins and superior-inferior interlocking ridges and villi) compared w the outer cornified layers (stratum dysjunctum).

2. Cells of the mid and upper cornified layers are less well fortified structurally to remain attached to each other and lose their internal density as keratin filaments become more randomly oriented, which is thought to correspond biochemically to the stepwise breakdown of filaggrin into its component amino acids and correlate with enhanced water holding capacity.

3. Cornified cell envelope is structurally identical to the stratum corneum even though it is soft in the stratum compactum, permitting greater pliability of the cell, and hard in the cells of the stratum disjunctum.

4. Desmosomes undergo proteolytic degradation in the outer most stratum corneum to promote desquamation.

G. Associated diseases

1. In X-linked ichthyosis, a steroid sulfatase deficiency may produce a retention hyperkeratosis because of a lack of elimination of cholesterol sulfate which is essential for the cohesion of cells in the stratum corneum. It is characterized by brown, adherent scales, involving the flexures and sparing the palms and soles.

IX. Melanocyte

A Dendritic cells that synthesize and secrete melanin.

B. Derived from neural crest.

C. Located between the basal layer and constitute approximately 10% of epidermal cells.

D. Ratio of melanocytes to basal keratinocytes varies from approximately 1:4 on the cheek to 1:10 on the trunk or limbs

E. The number of melanocytes in the epidermis is the same regardless of race or sex.

1. Differences in skin color are the results of the number, size and packaging of melanosomes.

F. On light microscopy, have a pale cytoplasm with a smaller and more basophilic nucleus in comparison to the keratinocytes.

1. Clear space is a fixation artifact due to collapse of the cytoplasm around the nucleus.

G. The basal layer is most heavily pigmented, but melanin pigment can be found in all epidermal layers.

H. On electron microscopy, possess the following features:

1. Large mitochondria, rough endoplasmic reticulum and a prominent Golgi complex for protein synthesis

2. No desmosomes or hemidesmosomes

3. Vimentin intermediate filaments

4. Melanosomes-spherical or ellipsoid, membrane-bound, lamellar melanin-producing organelles.

I. Once melanin is formed, it is transferred from the melanocytes into keratinocytes by apocopation. Once transferred to the keratinocyte, the melanosomes are partially degraded by lysosomal enzymes and shed along with the cornified cells.

1. There is one melanocyte for every 36 surrounding keratinocytes (epidermal melanin unit).

J. The principle function of melanin in skin is protection from ultraviolet radiation by absorbing and scattering their radiant energy.

K. Certain pigment disorders can arise from the alterations in melanosome formation, melanization, transfer and degradation.

1. In melasma, there is an increase in the formation, melanization and transfer of melanosomes to the epidermis.
2. In tinea versicolor, there appears to be defective melanosome maturation and transfer block.

X. Langerhans Cell

A. Derived from precursor monocyte-macrophage cells in the bone marrow.
B. Constitutes 3-5% of epidermal cells.
C. Found in basal, spinous and granular layers but show preference for the suprabasal location.
1. Also found in other squamous epithelia, lymphoid organs and normal dermis.
D. Do not form desmosomes or hemidesmosomes
E. On light microscopy are dendritic cells with pale cytoplasm and convoluted nucleus.
F. Ultrastructurally, cytoplasm contains vimentin intermediate filaments, phagolysosomes, and Langerhans cell granules or Birbeck granules.
1. Birbeck granules are formed by endocytosis of membrane-bound and appear "tennis racket" shaped.
G. Express ATPase, HLA-DR antigen, Fc and C3 receptors, CD4 antigen, CD1a antigen, leukocyte common antigen and S-100.
H. Involved in recognition, uptake, processing and presentation of antigen to sensitized T lymphocytes, induction of graft rejection, contact hypersensitivity and immunosurveillance.
1. Decreased in the epidermis with repeated UV light exposure and in certain skin diseases such as psoriasis, contact dermatitis and sarcoidosis.

XI. Merkel Cell

A. There is considerable controversy about the origin of this cell.
1. Currently, believed to derive from a primitive epidermal stem cell that is capable of differentiating towards both neuroendocrine cells and keratinocytes.
B. Found in glabrous skin of fingertips, lip, gingiva and nail bed and outer root sheath of hair-bearing cells where they function as slow-adapting type I mechanoreceptors.
C. On light microscopy, appear as large, oval, clear cells in the basal layers of the epidermis with their long axis parallel to the skin surface.
D. On electron microscopy, show lobulated nucleus with occasional intranuclear rodlets and an electron-lucent cytoplasm rich in organelles including a prominent Golgi complex with free ribosomes, which give rise to small, 80-120 nm, membrane-bound neurosecretory-type core granules.
E. Form connections with neighboring keratinocytes via desmosomes and extend cytoplasmic projections containing microfilaments that impinge on neighboring cells.
F. Possess immunohistochemical properties of both epithelial and neuroendocrine cells.

1. Stain with antibodies to low-molecular weight cytokeratins 8, 18, 19 and 20 as well as desmoplakins but not to prekeratins.
2. Express neuroendocrine markers such as neuron-specific enolase, chromogranin and synaptophysin.
    a. Labeling for vimentin, desmin glial fibrillary acidic protein and neurofilaments is negative.
3. Putative neurotransmitters localized to the cytoplasmic dense core granules include vasoactive intestinal polypeptide and met-enkephalin, but not substance P, CGRP or serotonin.
4. Cytokeratin 20 is a highly specific marker for cells.

NOTES

NOTES

Genodermatoses

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Dermatopathology fellowship Board Review

GENODERMATOSES
OCTOBER 2011

DARIUS MEHREGAN, M.D.
HERMANN PINKUS CHAIRMAN
WAYNE STATE UNIVERSITY

Icthyosis vulgaris

- Autosomal dominant unknown genetic locus
- Defect in profillagrin
- Associated with atopic dermatitis and keratosis pilaris
- Histologic findings: decreased granular cell layer , average epidermal thickness, hyperkeratosis, follicular plugging
- Electron microscopy small keratohyalin granules
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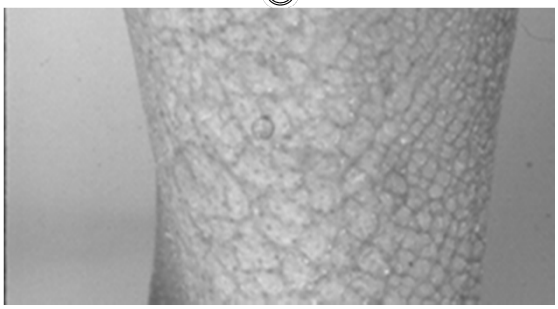
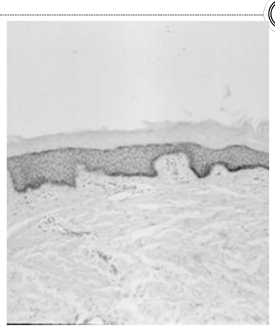
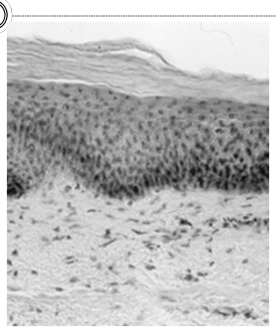
Icthyosis vulgaris



Icthyosis vulgaris

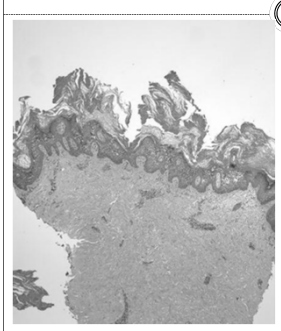


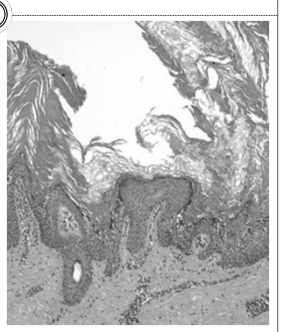


Epidermolytic hyperkeratosis

- "Bullous congenital icthyosiform erythroderma"
- Autosomal dominant mutations in keratin-1 (12a) and keratin-10 genes (17a)
- Skin biopsy shows extensive perinuclear clearing in granular cells with large irregular keratohyalin granules
- Epidermal nevi may reflect somatic mosaicism for k-1/k-10 mutations

Epidermolytic Hyperkeratosis

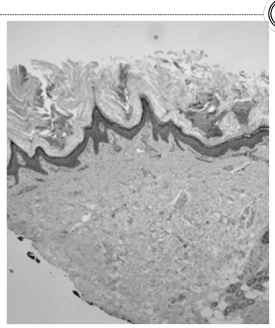
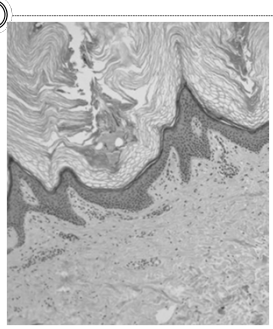




Lamellar Icthyosis

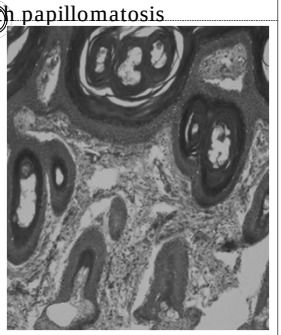
- Autosomal recessive defect in transglutaminase-1 gene on 14-q 11
- Histologic findings hyperkeratosis without parakeratosis
-

Lamellar Icthyosis

Harlequin fetus

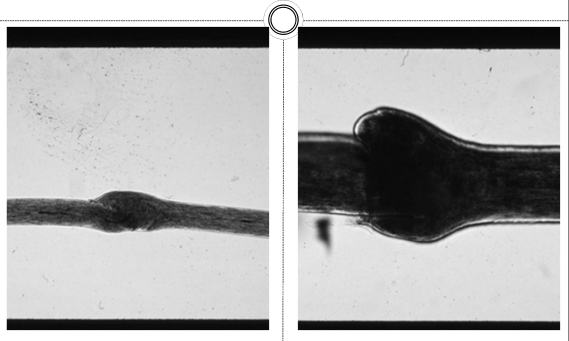
Hyperkeratosis with papillomatosis

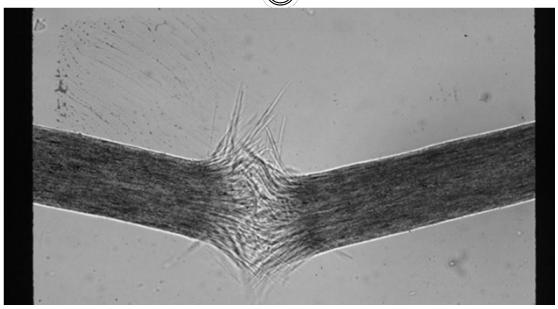
Nethertons

- Autosomal recessive defect in the SPINK-5 gene
- Codes LEKT-1 serine protease inhibitor
- Associated with atopy and food allergies
- Migratory polycyclic serpiginous plaques with double-edge scale along the margins
- Associated with trichorrhexis invaginata, pili torti and trichorrhexis nodosa
- Histologic findings variable with ortho/parakeratosis, spongiosis, acanthosis

Trichorhexis invaginata



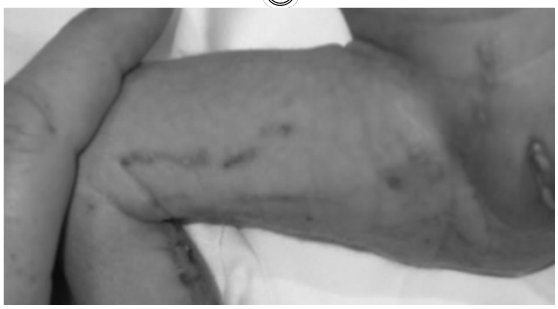
Trichorhexis nodosa



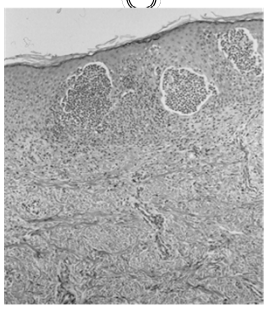
Incontinentia pigmenti
Bloch Sulzberger disease

- X-linked dominant caused by mutation in NEMO gene on chromosome X q-28
- Male survivors are mosaic or Klinefelters
- Mutation in NEMO (nf-kappa B essential modulator) gene which leads to defective nf-kappa B activation
-
- Stage I vesicular stage: Intraepidermal eosinophilic spongiosis
- Stage II verrucous stage intraepidermal whorled dyskeratotic cells
- Stage III hyperpigmented stage: Dermal macrophagic pigmentation
- Stage IV hypopigmented stage: Epidermal hypopigmentation

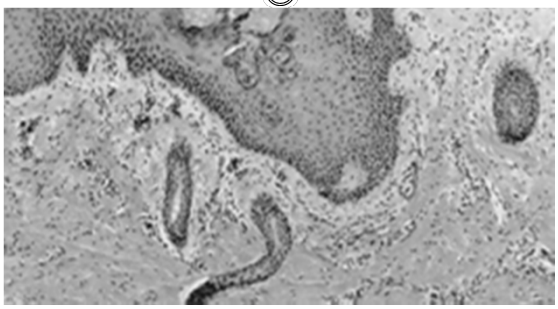
Incontinentia pigmenti



Incontinentia pigmenti



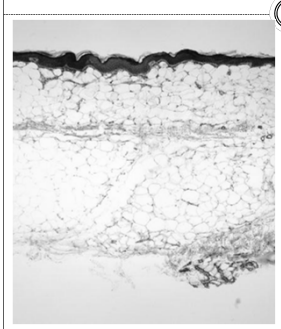
Incontinentia pigmenti

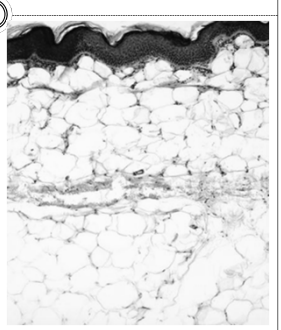


Focal dermal hypoplasia

- Goltz syndrome
- X-linked dominant, X-p11.23 (PORCN gene involved in Wnt signalling)
- Asymmetric atrophic telangiectatic linear streaks
- Follow Blaschko's lines of trunk and extremities
- Soft yellow nodules (fat herniations)
- Ulcers at sites of congenital absence of skin that heal with atrophy
- Abnormalities of hair, nails, eyes, teeth, bones and central nervous system , osteopathia striata
- Histologic findings marked thinning of the dermis

Focal dermal hypoplasia

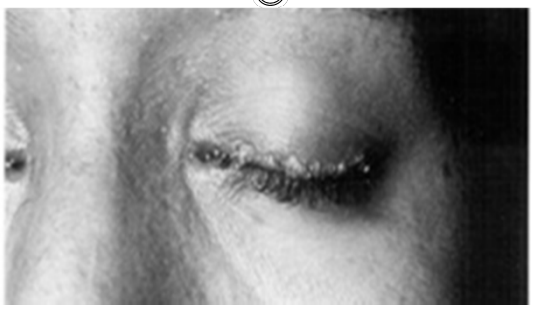




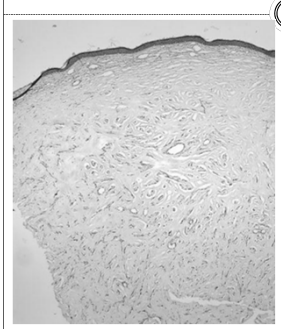
Hyalinosis cutis et mucosae: Lipoid Protienosis

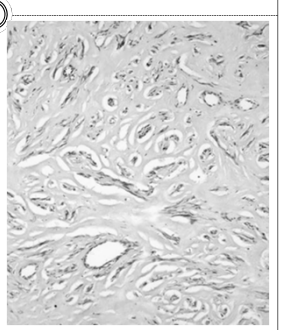
Urbach-Wiethe disease
Autosomal recessive extracellular matrix protein-1 (ecm-1) gene on chromosome 1-q21 (glycoprotein)
Bullae heal with residual atrophic scarring on the face, neck and extremities
Yellowish papules and nodules on the face, neck, extremities and eyelids with eyelids "string of pearls"
Verrucous nodules on elbows, knees and hands
Infiltration of mucous membranes and vocal cords, presents in infancy with hoarseness
Histologic findings: Eosinophilic hyalin material distributed in a perivascular pattern, which is PAS positive and Congo red negative

Lipoid Protienosis Kuchabal et al



Lipoid Protienosis

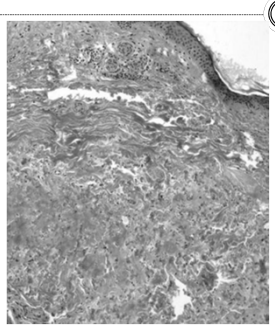
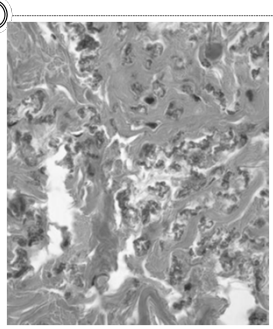




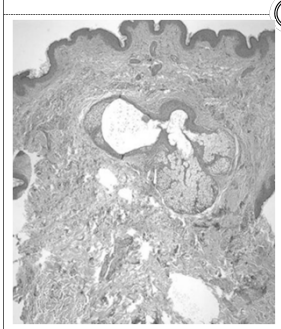
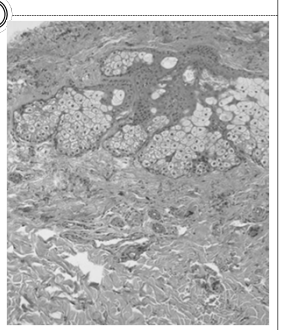
Pseudoxanthoma elasticum

- Inheritance autosomal recessive more common than autosomal dominant mutation in ABCC6 gene, which is a transmembrane transporter gene
- Yellow papules coallesing to plaques overlying redundant skin with skin folds on the side of the neck and intertriginous areas
- Yellow papules on mucosa, angoid streaks secondary to elastic fiber defects in the Bruch's membrane and defects in weakened arteries leading to hemorrhage
- Histologic findings fragmented and curled elastic fibers with calcification of elastic fibers
-

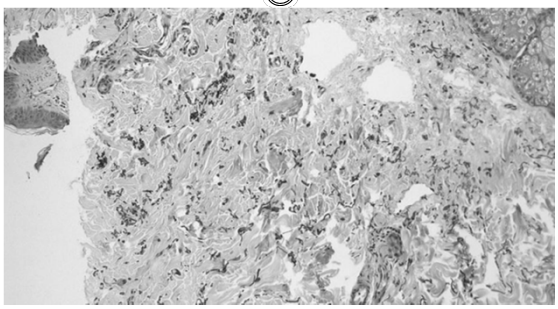
Pseudoxanthoma elasticum

Psuedoxanthoma elasticum

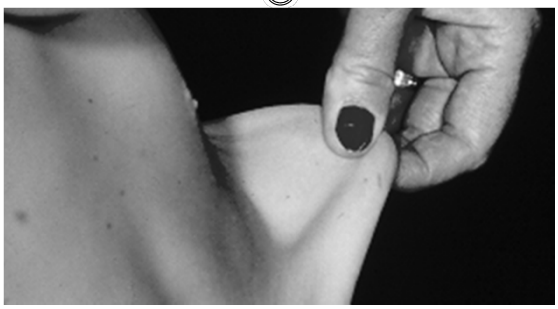
Pseudoxanthoma elasticum



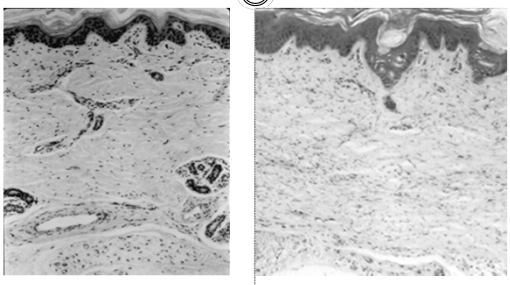
Cutis laxa

- Autosomal recessive: Fibulin-5$^{(FBLN5)}$ gene on 14-q 32 or 5-q 23-31
- Autosomal dominant elastin gene on 7-q 11 and fibulin-5 on 14-q 32
- X-linked recessive ATP7a on x-q 12-13
- Loose redundant pendulous skin folds with hound dog face and premature aged appearance
- Emphysema, gastrointestinal diverticula
- Hernias and bladder diverticula
- Skin biopsy shows decreased and fragmented elastic fibers
-

Cutis laxa



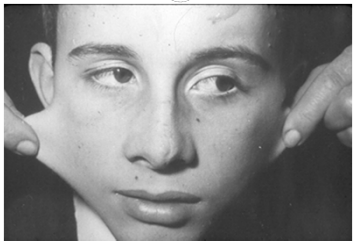
Cutis laxa



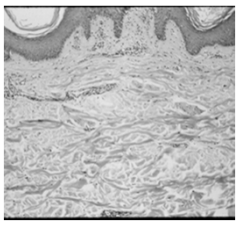
Ehlers danlos

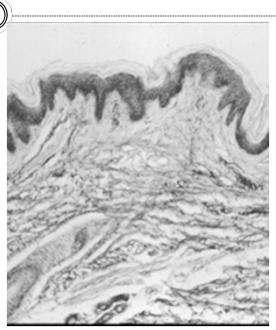
Classical types 1 & 2 is autosomal dominant associated with deficient type-5 collagen
Type 3 hypermobile is autosomal dominant
Type 4 vascular is autosomal dominant associated with decreased type 3 collagen
Type 5 arthrochalasia associated with type 1 collagen (col1-a1 and col1a-2) gene
Type 6 Kyphoscoliosis
Hyperextensible skin, gapping wounds from minimal trauma, cigarette paper scars, molluscoid pseudotumors and calcified subcutaneous nodules
Hypermobile joints
Histologic findings normal,areas of scar, calcifications

Ehlers danlos



Ehlers danlos





Cowden Syndrome
International CS Consortium operational criteria

- Muco-cutaneous lesions
- Trichilemmomas
- Acral keratoses
- Oral papillomatoses

- Mutation in PTEN gene on 10q23

Cowden Syndrome
International CS Consortium operational criteria

- Major Criteria
  - Breast, Endometrial, non Medullary Thyroid Carcinoma(esp follicular thyroid carcinoma)
  - Macrocephaly
  - Lhermitte-duclos disease (Dysplastic gangliocytoma of cerebellum)
- Minor Criteria
  - Other thyroid lesions
  - Mental retardation
  - GI hamartomas
  - Fibrocystic disease of the breast
  - Lipomas, Fibromas
  - GU tumors

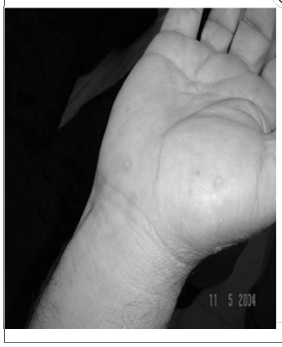
Cowden Syndome
International CS Consortium operational criteria

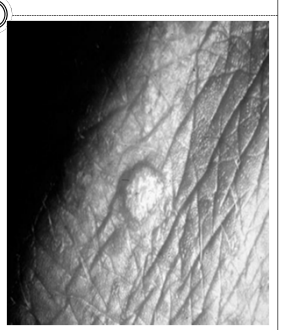
- Diagnosis in an individual
  - Mucocutaneous lesions including 6 or more trichilemmomas, or 3 trichilemmomas and oral papillomatosis or oral papillomatosis and acral keratoses
  - 2 Major criteria including macrocephaly or LDD
  - 1 major and 3 minor criteria
  - 4 Minor criteria
  - If family history present
    - Mucocutaneous lesions
    - Any major criterion
    - 2 minor criteria

International CS Consortium operational criteria

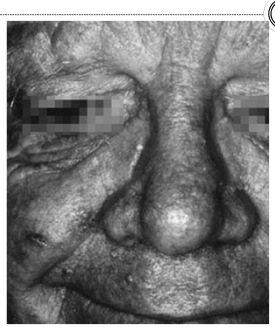
- Family history Aut Dom with variable expression and
  - Mucocutaneous lesions
  - 1 Major criteria
  - 2 Minor criteria

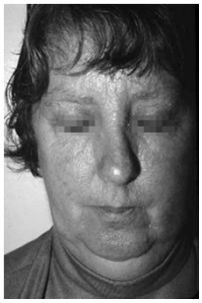
Acral Keratoses





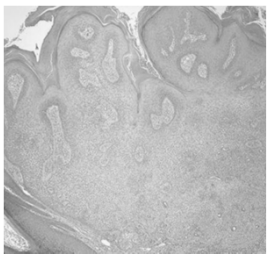
Trichilemmoma



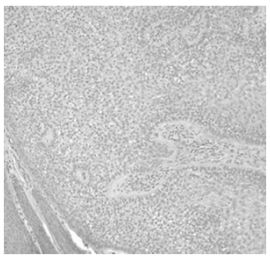


Trichilemmomas

Exo-endophytic growth with hair follicle outer root sheath differentiation



Pale staining cells with peripheral palisading at base.



Oral Papillomas

- Give the lips , gingiva and tongue a cobblestone appearance
- Histologically an oral fibroma

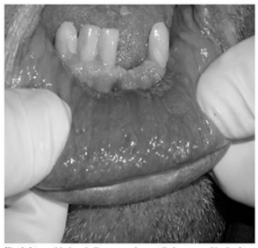
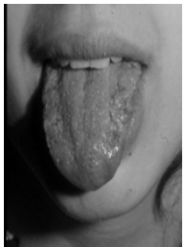
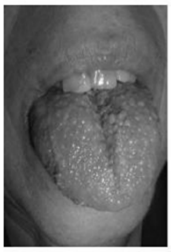


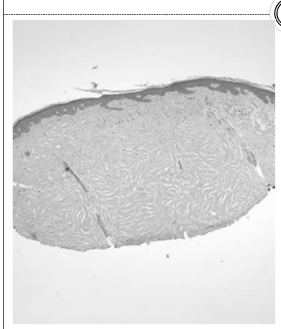
Fig. 2. Intraoral lesions in lip mucosa, low vestibular gum and back of tongue.

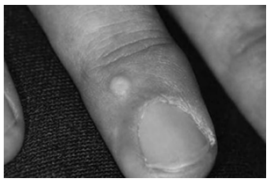
Oral Papillomas





Sclerotic fibromas





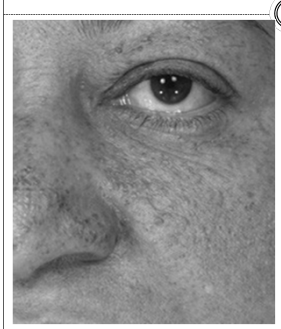
Birt Hogg Dube

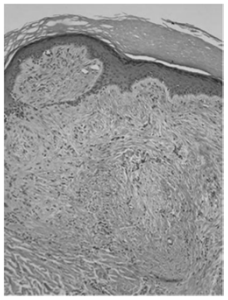
- Autosomal Dominant
- Follicular hamartomas (Perifollicular fibromas, trichodiscomas) and acrochordons
- Renal tumors
  - Oncocytoma, chromophobe and clear cell CA
- Pulmonary symptoms
  - Emphysema, cysts, spontaneous pneumothoraces
  - Less frequently thyroid CA

Birt Hogg Dube

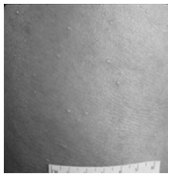
- Mutation in folliculin (FCLN) on 17p 11.2
- Thought to be a tumor suppressor acting as a regulator of mTOR pathway
- Encodes 579 aa protein

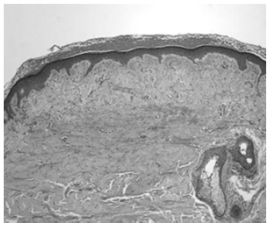
Birt Hogg Dube



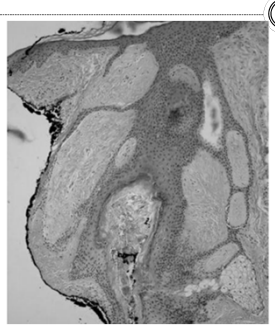


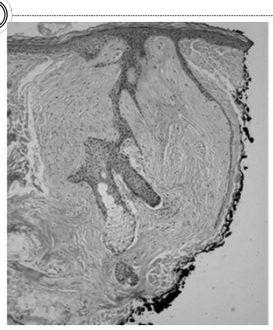
Trichodiscomas





Birt Hogg Dube

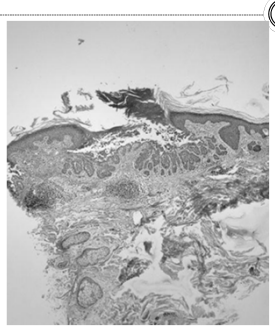


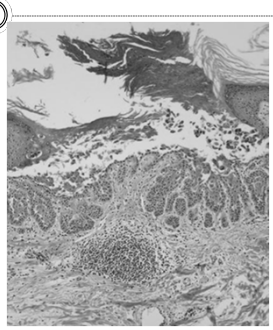


Darier's (keratosis follicularis)

- Autosomal dominant
- ATP2A2 encodes SERCA2 calcium ATPase
- Hyperkeratotic papules and warty plaques in seborrheic distribution
- Verrucous papules on dorsal hands (acrokeratosis verruciformis)
- Palmoplantar punctuate keratoses
- Red and white longitudinal nail bands with v-shaped nick distally
- Cobblestone papules in mucosae
- Intraepidermal acantholysis with extensive dyskeratosis
- Eosinophilic corp ronds and parakeratotic grains
- Epidermal acanthosis and papillomatosis

Darier's

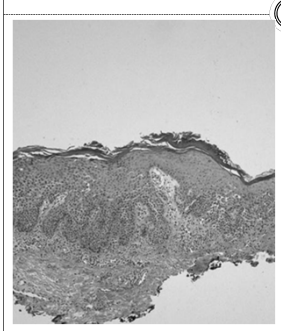


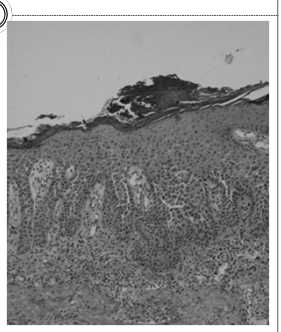


Hailey Hailey (benign familial pemphigus)

- Autosomal dominant
- ATP2C1 encodes hSPCA1 Calcium ATPase
- Blisters and erosions predominantly in skin folds
- Intraepidermal acantholysis is suprabasilar and more pronounced than Darier's
- Acantholytic cells clump together in lacunae leading to dilapidated brickwall appearance, due to preservation of few intercellular bridges
- Minimal dyskeratosis

Hailey Hailey





Wayne State University

Vasculitis, Panniculitis and Connective Tissue Diseases

Margot S. Peters, MD
Mayo Clinic, Rochester

CONNECTIVE TISSUE DISEASES

Lichenoid - Interface Reaction

Basal layer vacuolar degeneration – dominates the histology of lupus erythematosus (LE) (especially acute SLE) and dermatomyositis (DM)
Cell death (apoptosis or necrosis) **–** Civatte (epidermal), colloid (papillary dermal) bodies
Interface and/or dermal mainly lymphocytic inflammation – evaluate location and extent
Pigment incontinence – poikilodermas, lichenoid reactions of Fitzpatrick type V-VI skin

Lupus erythematosus - systemic, discoid, subacute cutaneous, neonatal

Basal vacuolar degeneration, Civatte/colloid bodies
Epidermal atrophy, follicular plugging, BMZ thickening, dermal mucin
Superficial and deep perivascular and periadnexal lymphocytic inflammation

Drug-induced lupus – implicated drugs include thiazide diuretics, calcium channel blockers, ACE inhibitors, terbinafine; anti–TNF-α therapy-induced lupus-like syndrome
Tumid LE / Jessner's lymphocytic infiltrate – papules/plaques, eyelid erythema, edema
Superficial and deep dermal lymphocytic inflammation and mucin
Absent/minimal vacuolar degeneration
Bullous LE – dermatitis herpetiformis-like infiltrate of neutrophils
Rowell's syndrome – LE + erythema multiforme
Chilblain/pernio – vacuolar change, perivascular lymphocytic inflammation, edema

Dermatomyositis – acute LE-like pattern with prominent vacuolar degeneration
Dermal inflammation more superficial and mild than in LE
Epidermal atrophy, few Civatte/colloid bodies, dermal mucin, edema, poikiloderma
Drug-induced DM – implicated drugs include statins, penicillamine, terbinafine
DM-like hydroxyurea-induced / DM-LE hydroxyurea dermopathy

Differential Diagnosis

Lichen planus – band-like lymphocytic inflammation hugging epidermis, perifollicular in LPP
Orthokeratosis (not parakeratosis), granular layer intact or increased, many colloid bodies
Pigment incontinence in erythema dyschromicum perstans
Lichenoid drug reaction – parakeratosis, mixed inflammation including eosinophils
Fixed drug reaction – cell death above basal layer, pigment incontinence
GVHD – basal vacuolar degeneration, prominent apoptosis with satellite cell necrosis
Poikilodermas – telangiectasias, pigment incontinence, mild basal vacuolar degeneration
Rothmund–Thomson syndrome (poikiloderma congenitale), Bloom's syndrome (congenital telangiectatic erythema, LE-like facial rash), dyskeratosis congenita, Kindler's syndrome (EB subtype, acral blisters), early mycosis fungoides

Other Lichenoid - Interface Dermatoses

Erythema multiforme, lichenoid purpura, LP-like keratosis (benign lichenoid keratosis), pityriasis lichenoides, lichen sclerosus, lichenoid contact dermatitis, eruption of lymphocyte recovery, AIDS interface dermatitis

Direct Immunofluorescence

LE (lupus band): granular IgM + C3 and/or IgG +/- IgA BMZ deposition
DM: C5b-9 (membrane attack complex, MAC) vascular deposition in setting of negative lupus band and negative serum Ro, La, RNP
+/- C5b-9 BMZ deposition (C5b-9 BMZ deposition also may be seen in LE)
LP: Many IgM-positive cytoids + shaggy fibrinogen BMZ deposition
Pattern not specific for LP, seen in other lichenoid dermatoses including LE, DM

Bullous LE: Linear-granular IgG +/- IgM +/- IgA + C3 BMZ deposition
Deposits represent anti-type VII collagen / anti-BPA / other

Immunohistochemistry – plasmacytoid dendritic cells (PDCs) (CD123+)
PDCs in LE > DM: mainly dermal in LE, epidermal/junctional in DM
Perivascular and periadnexal clusters in LE and Jessner's infiltrate/tumid LE
Single/scattered PDCs in dermal/subepidermal infiltrate in other entities

PCR - Parvovirus B19 association with LE, DM, scleroderma
Borrelia association with morphea / lichen sclerosus

Morphea / Scleroderma
Hyaline sclerosis (rather than fibrosis) - square biopsy
Thickened collagen bundles in mid-deep dermis +/- subcutis, reduced peri-adnexal fat
Limited inflammation of mainly plasma cells and lymphocytes, small vessel hyalinization
No vacuolar interface reaction versus lichen sclerosus / sclerodermoid GVHD
No atypical stellate fibroblasts in post-radiation morphea versus radiation-related dermatitis

PANNICULITIS

Clinical Context
Age, gender, anatomic site of lesions (above or below knees), duration
Background – immunosuppression, metabolic/other systemic disease, trauma/injection
Morphology – nodules, ulcers, drainage, lipoatrophy, induration/sclerosis, scars

Histology
Cellular infiltrate – neutrophils, lymphocytes, histiocytes, granulomas
Deposits – gout, calcium, polarizable foreign material
Hyaline sclerosis versus fibrosis
Lipocyte morphology – cell size variation, microcysts
Necrosis – hyaline versus basophilic
Vessel abnormalities – necrotizing vasculitis versus vascular inflammation

Mostly Septal Panniculitis
Erythema nodosum – nodules of anterior legs, granulomatous panniculitis without necrosis
Morphea profundus / scleroderma /eosinophilic fasciitis – hyaline sclerosis
Limited inflammation of plasma cells and lymphocytes +/- few eosinophils

Mostly Lobular Panniculitis
Lupus panniculitis/profundus – hyaline necrosis, lymphoid nodules, mucin, +/- calcification
Pancreatic panniculitis – saponification, ghost-like lipocytes, basophilic necrosis
Alpha-1-anti-trypsin panniculitis – draining ulcers, trunk and proximal extremities
Suppurative inflammation, lobular and perilobular necrosis
Erythema induratum – nodules of posterior legs, vasculitis and panniculitis with necrosis
Gouty panniculitis – nodules, arthritis, polarizable brown urate crystal deposits, necrosis
Traumatic/factitial panniculitis – including sclerosing lipogranuloma/paraffinoma
Infectious panniculitis – suppurative/granulomatous, fungal, mycobacterial, bacterial
Neonates/Infants
Sclerema neonatorum – needle-shaped radial crystals in fat cells, minimal inflammation
Subcutaneous fat necrosis of newborn – radial crystals in fat cells, mixed inflammation
Non-infectious granulomatous panniculitis – necrobiotic xanthogranuloma, GA, sarcoid
Eosinophilic panniculitis – various settings including parasites, erythema nodosum, Wells
Lipodermatosclerosis – stasis changes, lipomembranous fat necrosis, frosty lipocytes, microcysts

Cold panniculitis – infants/children, including Popsicle panniculitis, equestrian panniculitis
Lymphocytes and histiocytes in fat, superficial perivascular dermal inflammation
Post steroid panniculitis – after withdrawal of high dose systemic steroids
Mixed inflammation with giant cells, lymphocytes, needle-shaped clefts
Connective tissue panniculitis – lymphohistiocytic panniculitis with limited necrosis
Lipoatrophy – absence or decreased fat +/- mild lymphohistiocytic inflammation
Involutional lipoatrophy – localized, lobules of small lipocytes with prominent capillaries
Cutaneous polyarteritis nodosa – nodule of legs, vasculitis with panniculitis
Cytophagic panniculitis – fever, hepatosplenomegaly, lymphadenopathy, pancytopenia
Cytophagic histiocytes (bean-bag cells), lymphohistiocytic inflammation
Panniculitis-like subcutaneous T-cell lymphoma – atypical lymphocytes rimming lipocytes

VASCULITIS /VASCULOPATHY

Clinical morphology – purpura, nodules, livedo, ulcers, urticaria, hemorrhagic bullae
Histology – involvement of vessels in/across size categories - superficial/mid-deep dermis/subcutis
Endothelial swelling, fibrinoid necrosis, thrombosis
Vascular and perivascular inflammation
Neutrophils, leukocytoclasis, lymphocytes, eosinophils, granulomatous
DIF: IgM/IgG/C3 vascular deposition, IgA in HSP/adult IgA vasculitis/other settings

Large Size Vessels
Giant cell (temporal) arteritis – granulomatous vasculitis, polymyalgia rheumatica
Takayasu's arteritis – aortic arch syndrome, granulomatous vasculitis

Medium Size Vessels
Cutaneous polyarteritis nodosa – painful/tender nodules of legs, livedo, ulceration
Neuropathy – mononeuropathy/mononeuropathy multiplex
Necrotizing vasculitis of deep dermis and/or subcutis, +/- panniculitis
IgM antiphosphatidylserine–prothrombin complex
Systemic polyarteritis nodosa – renal disease, hypertension
Kawasaki's disease – cutaneous biopsies typically noncontributory
Nodular vasculitis – vasculitis with panniculitis, posterior rather than anterior legs

Small Size Vessels
Leukocytoclastic (hypersensitivity) vasculitis (LCV) (cutaneous leukocytoclastic angiitis)
Palpable purpura of lower extremities
Drugs, infection (especially Strep), autoimmune CTD, malignancy, other causes/idiopathic
cANCA-associated vasculitis [PR3 (proteinase 3)-ANCA]
Wegener's granulomatosis (granulomatosis with polyangiitis) – respiratory, renal disease
LCV +/- granulomatous vasculitis, extravascular palisading granulomatous infiltrate with central necrosis and neutrophils
pANCA-associated vasculitis [MPO (myeloperoxidase)-ANCA]
Churg-Strauss Syndrome – papules/nodules of elbows and knees, asthma
LCV and extravascular palisading granulomas with central necrosis and eosinophils +/- flame figures, peripheral eosinophilia
Microscopic polyangiitis – palpable purpura, livedo, LCV
Systemic disease, especially renal
Henoch-Schönlein purpura (IgA vasculitis) – palpable purpura, LCV
Preceding upper respiratory infection, arthritis, abdominal pain, glomerulonephritis
IgA vasculitis associated with inflammatory bowel disease/malignancy/other disorders

Acute hemorrhagic edema of infancy (Finkelstein disease, acute benign cutaneous LCV of infancy)
Preceding infection, symmetrical palpable purpuric lesions, edema, no internal disease
IgA/other Ig + C3 vascular deposition
Urticarial vasculitis – urticaria + vasculitis, lesions > 24 hours duration, hypocomplementemia
Cryoglobulinemic vasculitis (mixed cryoglobulinemia, types II and III)
Association with hepatitis C, autoimmune disease, or essential
Septic vasculitis – thrombosis + necrosis, meningococcemia, gonococcemia, pseudomonas/other
Eosinophilic vasculitis – eosinophil-dominant necrotizing vasculitis
Rheumatoid vasculitis – small-medium size vessels, palpable purpura, ulcers
Granuloma faciale – LCV with eosinophils, extravascular fibrosis, not granulomatous
Chronic asymmetrical red-brown papules-plaques of face and/or ears
Erythema elevatum diutinum – LCV, extravascular fibrosis (> in granuloma faciale)
Chronic symmetrical red-brown papules-nodules of elbows and knees
Extraintestinal Crohn's disease – granulomatous vasculitis, papules-nodules, ulcers
Post herpes-zoster – granulomatous vasculitis of small-medium sized vessels

Occlusive vasculopathy
Thrombotic disorders/coagulopathies – absent/minimal inflammation
Cryoglobulinemia (monoclonal IgG/IgM, type I, with myeloproliferative disease or essential), antiphospholipid syndrome/lupus anticoagulant, DIC/purpura fulminans, Protein C and S deficiencies, Sneddon's syndrome (livedo reticularis and cerebrovascular ischemia), warfarin necrosis, cholesterol emboli, others
Livedo/livedoid vasculopathy (atrophie blanche) – thrombosis, hyalinized vessels
Livedo reticularis, punched out ulcers of ankles
Degos disease (malignant atrophic papulosis) – papules with porcelain white atrophic centers
GI and CNS involvement; occlusive vasculopathy, perivascular lymphocytic inflammation
Cocaine-related retiform purpura – levamisole (adulterant) induced vasculopathy
Microvascular thrombosis +/- LCV, + anti-human neutrophil elastase (HNE) antibodies

Lymphocytic vasculitis – variety of dermatoses, including pernio/chilblains

Thrombophlebitis – inflammation of vein, with/without thrombosis
Behçet's disease – aphthae, EN-like nodules, pathergic pustules, thrombophlebitis
Buerger's disease (thromboangiitis obliterans) – male smoker, peripheral vascular disease
Inflammation, thrombosis, +/- intramural abscesses

Hemorrhage - RBC extravasation, limited/no inflammation
Senile/solar purpura, pigmented purpuric dermatoses
Scurvy – petechiae, perifollicular hemorrhage, follicular hyperkeratosis

Neutrophilic urticaria – vascular-perivascular neutrophils
Absence of leukocytoclasia, fibrinoid necrosis or hemorrhage

Neutrophilic urticarial dermatoses (NUD)
Vascular-perivascular and interstitial neutrophils and leukocytoclasia
Schnitzler's syndrome – urticarial eruption, monoclonal IgM/IgG gammopathy, fevers, arthralgias/arthritis, bone pain, lymphadenopathy, hepatosplenomegaly, leukocytosis, increased ESR
Adult Still's disease – episodic macular rash with fevers, arthropathy, leukocytosis
Cryopyrin-associated periodic syndromes (and other autoinflammatory syndromes)
Urticaria, arthropathy, neurological abnormalities, fevers
NUD with perieccrine inflammation

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Immunohistochemistry as an Aid in the Diagnosis of Adnexal Neoplasms

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Immunohistochemistry as an Aid in the Diagnosis of Some Adnexal Neoplasms

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I. Sebaceous neoplasms and relationship to Muir-Torre syndrome (MTS)

a. When is the diagnosis of a sebaceous neoplasm an indication for search for an associated visceral malignancy (i.e. MTS). In other words, what is the role of the dermatopathologist in raising suspicion for MTS.

b. MTS is caused by germline mutations in one copy of DNA mismatch repair (MMR) genes, most frequently MSH-2 (more than 90%) and MLH-1.

c. The above genes code for microsatellite instability enzymes, an abnormality of which may be detected by genetic testing on peripheral blood, hence raising suspicion for MTS.

d. Alternatively, immunohistochemistry may be used (and is being used more frequently than genetic testing) with cutaneous and/or visceral neoplasms.

e. Neoplastic cells of cutaneous or visceral neoplasms in patients with MTS do not express the protein product of the MMR genes.

f. Positive predictive value (PPV) for MTS depends on the number and type of MMR proteins that are lost.

   i. PPV for MTS in neoplasms demonstrating loss of MSH-2, MLH-1 and MSH-6 is 100%.
   ii. PPV for MTS in neoplasms demonstrating loss of MLH-1 and MSH-6 is 100%.
   iii. PPV for MTS in neoplasms demonstrating loss of MSH-2 and MSH-6 is 55%

g. Recommendations/suggestions:

   i. IHC for MMR proteins should be obtained in all non-SGH sebaceous neoplasms, especially if the histopathology is atypical/unusual.
   ii. 20% of MTS patients, however, do not have detectable loss of MMR proteins, i.e. testing is highly specific, but less sensitive.
   iii. Hence, evaluation for visceral neoplasm has been recommended in

1. All patients with multiple sebaceous neoplasms (non-SGH), especially those with atypical features, and
2. In cases occurring below the head and neck, in patients less than 50 years of age, especially if family history is positive for sebaceous or visceral neoplasms.

II. Sebaceous adenoma vs. sebaceous carcinoma in a superficial biopsy specimen

a. Sporadic sebaceous carcinoma has a higher frequency of p53 and Ki-67 expression and lower frequency of bcl-2 expression compared to sebaceous adenoma.

b. Complete excision is still required for further microscopic evaluation

III. Differentiation between microcystic adnexal carcinoma (MAC) vs. infiltrating BCC vs. trichoepithelioma (TE) vs. infiltrating SCC, especially in partial excisional specimens.

a. There are multiple studies that address this area

b. Most studies address 2 or 3 different neoplasms together rather than all.

c. Results vary, occasionally dramatically, among studies. The following is an "overview" of the literature

d. Overview of antibodies specificity:

   i. Oncogenes:
      1. p63
      2. p21/p53
      3. bcl-2
   ii. Hematopoeitic:
      1. CD34
      2. CD23
   iii. Hematopoeitic & epithelial:
      1. CD10
   iv. Epithelial:
      1. CKs
      2. Ber-EP4 (epithelial CAM)

e. bcl-2 and CD34 in differentiating infiltrating BCC and TE:

i. bcl-2 staining has been reported to be positive and limited to the peripheral cells of TE in contrast to diffuse staining among cells of BCC.
ii. BCC stroma was reported to be CD34 positive while TE stroma was negative.
iii. Other authors could not confirm the above findings.

f. CD10 expression in BCC, TE and SCC:

i. In one study, CD10 expression was positive in all types of BCC, including sclerosing BCC. There was absence of stromal reactivity.
ii. In another study, CD10 expression was limited to stromal cells, but negative in tumor cells of sclerosing BCC.
iii. CD10 was negative in epithelial cells of TE, but positive in stromal cells and papilla cells.
iv. CD10 was negative in SCC tumor cells, but positive in stromal cells.

g. Ber-EP4 in infiltrating/sclerosing BCC, MAC and TE:

i. Most studies indicate that Ber-BP4 is negative in MAC (one study, however, revealed positivity in 38% of cases).
ii. Ber-BP4 is positive in the superficial and deep components of infiltrating and sclerosing BCC.
iii. Epithelial cells of TE are positive for Ber-EP4.

h. CD23 in the differentiation between MAC and sclerosing BCC:

i. Some cases of MAC revealed CD23 positivity in the glandular component.
ii. Sclerosing BCC was negative in epithelial cells.

i. CK15 and CK7 in the differentiation between MAC, TE, BCC, and SCC:

i. CK15 is a HF bulge stem cell CK and is almost universally expressed in MAC and desmoplastic TE and is universally negative in infiltrating BCC and SCC.
ii. CK7 was not a useful marker

	MAC	(D)TE	iBCC	iSCC
CD10	31%	-	60%	-
Ber-EP4	0-38%	57%	100%	38%
CD23	42%		-	
CK15	92%	100%	-	-
CK7	15%	-	40%	-
CEA	30%	-	-	-

IV. Primary cutaneous sweat gland neoplasms (PCSGN) (and SCC) vs. metastatic carcinoma

a. Clinical history is important. PCSGN whether benign or malignant is usually a single lesion that is stable while metastatic carcinoma may be multiple and is usually progressive.

b. Using a panel of four antibodies, p63 and CK5/6 expression is relatively sensitive and specific and strongly favors PCSGN over metastatic carcinoma.

c. CK7 is positive in metastatic carcinoma.

d. In other studies, CK7 differentiated strongly between metastatic carcinoma(+) and primary skin carcinoma(-)

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Melanoma and Merkel Cell Carcinoma

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DESMOPLASTIC MELANOMA

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SUMMARY

Desmoplastic melanoma (DM) is a sclerosing usually amelanotic variant of melanoma that can be difficult to diagnose clinically and histopathologically. DM differs from conventional melanoma is several ways. Immunohistochemically, it usually only stains for S100 protein and not for other melanocyte differentiation antigens. Clinically, they are characterized by propensity for local recurrence if only narrowly excised. Regional lymph node involvement is uncommon. Sentinel lymph node mapping is unnecessary.

INTRODUCTION

Desmoplastic melanoma is characterized by the association of invasive melanoma with a prominent stromal fibrosis. Conley, Orr and Lattes introduced the term desmoplastic melanoma (DM) in 1971, describing a "variant of spindle cell melanoma which produces or elicits the production of abundant collagen"[1]. In the words of Reed and Leonard, DMs are "fibrous tumors whose individual spindle cells are isolated in a dense fibrous matrix"[2].

DM is uncommon, representing less than 4 % of melanomas seen at large cancer centers[3]. Familiarity with DM is relevant for clinicians and pathologists, because, for the

unwary, this tumor may represent a diagnostic pitfall and lead to confusion with benign lesions including fibrosing lesions and scars[4].

CLINICAL FEATURES

DM is most commonly found on chronically sun-damaged skin on the head and neck region of elderly males over the age of 60, but can occur also at a younger age[5-8]. The male to female ratio is around 1.7:1. The median age at diagnosis of DM is approximately 10 years later than for conventional melanoma. This is likely related to both delays in diagnosis (DM is more difficult to recognize clinically in its early stage than conventional melanoma) and an inherent difference in the biology of the lesion (association of DM with lentigo maligna and chronic sun-damage). DM most often affects the head and neck region, but it can occur anywhere, including acral and mucosal sites[5-10]. In the US, approximately 20% of DM are found on the torso, 20% on the extremities and the rest on the head and neck. The vast majority of DM affects Caucasians, but a rare tumor may also be found in individuals of dark skin color at acral and non-acral sites.

DM usually presents as a firm papule, nodule or plaque. It is often associated with a lentigo maligna, which is why it is advisable to palpate the skin overlying or surrounding a lentigo maligna or excision sites thereof to better detect a dermal tumor. However, DM may develop in the absence of a clinically detectable precursor lesion. Pigmentation is often lacking but shades of tan or erythema may be present. Due to the lack of characteristic clinical features correct identification of DM by a clinician is uncommon and the tumor is rarely diagnosed at an early stage[11]. The clinical impression

of lesions that ultimately prove to be DM, typically includes a scar, fibroma or cyst. Seborrheic keratosis, eczema, or melanocytic nevus may also be considered. Occasionally the differential diagnosis will include malignant lesions such as basal cell carcinoma, squamous cell carcinoma, sarcoma or amelanotic melanoma.

MICROSCOPIC FEATURES

Most DMs are fibrosing spindle cell melanomas. Rarely, an epithelioid cell melanoma shows prominent intratumoral fibrosis. Classic DM presents as a pauci-cellular scar-like tumor[5]. Because of the abundance of fibrous tissue, DM has at scanning magnification a “pink” appearance. Most DMs display a diffusely infiltrative pattern with expansion of subcutaneous fibrous septae and eventual replacement of the fat lobules by tumor and its desmoplastic stroma. Lymphocytic aggregates are often present. Superficially, an associated in situ melanoma component is identified in 80-85% of cases[5,12].

Cytologic atypia of tumor cells in DM can be quite variable ranging from a fairly bland appearance to marked nuclear pleomorphism[5]. If the cytology is overall bland and the tumor cells have a fibroblast-like appearance there is potential confusion with a scar. If the tumor cells differentiate along Schwannian lines, the features of the tumor cells may at times mimic the cells of a neurofibroma, neurotized melanocytic nevus, or nerve sheath myxoma. Bland cytology is rarely uniform throughout the entire tumor and presents a diagnostic problem usually only on partial biopsies. When DM is frankly pleomorphic, it is readily recognized as malignant, but in the absence of melanin pigment and in situ melanoma, may be confused with a sarcoma or sarcomatoid carcinoma.

A subset of DM has a myxoid material[13-15], which may lead to potential confusion with other myxoid soft tissue tumors[16] (especially of fibrous or nerve sheath origin) or sclerosing mucinous melanocytic nevi[17].

DIFFERENTIAL DIAGNOSIS

1. *Desmoplastic melanoma versus a sclerosing melanocytic nevus*

Desmoplasia may also be associated with benign melanocytic nevi, such as pauci- or amelanotic sclerosing variants of blue nevus, Spitz nevus, or other nevi[17]and lead to potential confusion with DM (Tab.1).

Sclerosing nevi often occur in patients younger than the average age of diagnosis for DM, and are less commonly found in markedly sun-damaged skin[18-20]. Histologically, they display a benign circumscribed silhouette. Cytologic atypia and mitotic figures are usually absent. In contrast, DMs tend to be asymmetric, infiltrative and poorly circumscribed. The majority of DM is associated with in situ melanoma. If a sclerosing nevus is has a junctional melanocytic proliferation, it has features of a benign nevus.

Immunohistochemistry can be helpful for the distinction of sclerosing nevus from melanoma[21]. Most sclerosing nevi are immunoreactive for Melan-A or other differentiation markers, while DMs tend to be negative.

2. Desmoplastic melanoma versus a non-melanocytic spindle cell proliferation

2A. Distinction from dermal scar or benign soft tissue tumor

In the absence of associated intraepidermal melanoma, recognition of a dermal spindle cell tumor as melanoma can be difficult. DM may be mistaken for a scar[22,23],

fibroma[19], or other soft tissue tumors, such as desmoplastic cellular neuroethekeoma. Scars are best distinguished from invasive DM by examining the growth pattern of the spindle cells, their cytology and by analysis of associated features, such as vascularity and lymphocytic aggregates. In scars, the fibroblasts are typically oriented parallel to the skin surface, while the blood vessels often run perpendicular to it. In dermatofibromas, the spindle cells tend to wrap around collagen bundles. In DM, the spindle cells are often oriented vertically or diagonally to the surface. DM frequently displays some degree of nuclear atypia, most often in the form of elongated hyperchromatic nuclei.

If a distinction of a scar or fibroma by morphologic criteria is difficult (e.g., pleomorphic fibroma vs DM), immunohistochemistry should clarify the diagnosis. Although scars and fibromas may contain scattered isolated S-100 protein-positive cells, they are typically negative for S-100 protein. In contrast, DM is typically strongly and diffusely positive for S100 protein[24,25].

While desmoplastic cellular neurothekeoma (CNTK) can in part simulate the appearance of a desmoplastic melanoma, usually, desmoplasia is only partial and associated with more classic areas of CNTK. If those are not seen, immunohistochemical studies will provide clarity: by definition, cellular neurothekeoma is negative for S100 protein, in contrast to DM.

2B. Distinction from sarcoma or sarcomatoid carcinoma

Pleomorphic variants of DM need to be distinguished from fibrosarcoma, desmoplastic leiomyosarcoma and sclerosing sarcomatoid squamous cell carcinoma[5,26,27] (Tab.3). Immunohistochemical studies are critical in this regard. Sensitive markers for the

diagnosis of sarcomatoid carcinoma are 34BE12, CK5/6 and 4A4/p63. Melanomas should be negative for these markers. The distinction from fibrosarcoma or leiomyosarcoma rarely poses a challenge, because these tumors are negative for S-100 protein. However, caution must be used in interpreting immunostains for fibroblastic (CD34, CD10), myofibroblastic, or smooth muscle tumors (SMA, desmin, CMA), since DM may stain with any of these markers[28,29].

Neurotropic melanomas can be difficult to distinguish from a malignant peripheral nerve sheath tumor (MPNST). Melanomas tend to be diffusely and strongly positive for S-100 protein, while MPNSTs usually only stain focally, but there are exceptions. Clinical and histologic context are important. For example, if a malignant spindle cell tumor occurs in a patient with neurofibromatosis and/or in association with neurofibroma, the diagnosis of MPNST is straightforward.

DIAGNOSIS

A diagnosis of DM can readily be established if an in situ melanoma component is associated with a fibrosing malignant spindle cell tumor. In the absence of a detectable in situ melanoma, strong diffuse immunoreactivity of the malignant dermal spindle cell tumor for S100 protein (and lack of staining for epithelial markers) supports the diagnosis. Immunohistochemistry for the melanocyte differentiation antigens Melan-A, tyrosinase, gp100 or microphthalmia transcription factor is usually negative in DM[24,25]. If the staining for S100 protein is weak, labeling for NGF-R may be helpful[30].

Due to the prominent fibrous stroma separating the tumor cells, the typical DM is overall pauci-cellular throughout the entire lesion. Small foci of higher cell density are

not uncommon, but usually constitute a minor component of the tumor. In some tumors, dense cellular aggregates without significant or any intra-tumoral fibrosis may represent a significant part of the entire invasive tumor. There is no consensus as to the extent to which typical, i.e., pauci-cellular fibrosing features of DM need to be present for a tumor to qualify as DM. Most series of DM fail to precisely define the histologic criteria necessary for a diagnosis of DM. Recent data from MSKCC have highlighted the importance of strict criteria for DM[5,8]. A separation of pure from combined or mixed forms of DM was proposed. Pure DMs were defined as melanomas, in which 90% of the invasive tumor was desmoplastic with a pauci-cellular fibrosing appearance[5,8]. In combined DM, typical features of DM are mixed with dense cellular tumor foci without fibrosis. A number of subsequent studies have supported the value of distinguishing pure from mixed tumors: pure DM tend to have a much lower incidence of positive SLN than mixed tumors (see below)[31,32].

A subset of DMs show neurotropism. Reed and Leonard have first drawn attention to a group of melanomas characterized by “neuroma-like” growth patterns and prominent infiltration of peripheral nerves[2]. They designated neurotropic melanoma (NM) as a variant of DM, classifying them as desmoplastic neurotropic melanomas (DNM)[3]. However, it needs to be emphasized that not all neurotropic melanomas are desmoplastic. May of them would fall into the category of mixed DM.

Additional subtypes of DNM have been described. In one variant, the invasive component closely simulates the growth pattern and cytologic appearance of a nerve sheath tumor (neurofibroma, if cytologically bland or “neurosarcoma”/malignant peripheral nerve sheath tumor, if the cytologic features are pleomorphic). This

phenomenon has been described as so-called "neural transformation" [33,34]. In another rare variant, the tumor is totally neurotropic in the sense that it is entirely confined to within the nerve and nerve sheath, leading to grossly visible nerve enlargement and thereby mimicking a primary nerve sheath tumor. This latter form of DNM has been termed "nerve-centered" DM[33].

PROGNOSIS

There is controversy with regard to the prognosis of DM[8]. In Conley et al.'s series of melanomas with desmoplasia, the tumors were described as "highly malignant stubbornly recurring and often metastasizing neoplasms" [1]. This characterization has contributed to the perception in the years thereafter that DM may be associated with worse clinical outcome than melanomas of the more usual type.

The perception of DM began to change, when in 1988, Walsh et al.[35] suggested that DM may be associated with a more favorable outcome. The majority of subsequent studies supported this notion by reporting longer survival of patients with DM compared to those with conventional melanomas of similar thickness[6,12,36], the verdict was not unanimous[3,37]. However, the failure of some studies to detect differences between DM and conventional melanoma[3,37] may in part be attributable to the fact that they contained many more thin or intermediate thickness DM than others. The favorable prognostic impact of desmoplasia is best appreciated in deeply infiltrating melanomas, when additional Breslow thickness above and beyond 4 mm looses its prognostic strength. This hypothesis is supported by a study by Spatz et al. who compared the histologic features of thick (> 5 mm) melanomas from patients with at least 10-year survival to control cases of

patients who died within 3 years of diagnosis[38]. Seven of 42 patients with long-term survival had a DM. None of the thick tumors from 42 patients with short term survival was desmoplastic[38].

Another reason for conflicting results in the literature about clinical behavior of DM is heterogeneity among melanomas classified as desmoplastic[8]. Some reports suggest that the participating pathologists included tumors with variable degrees of desmoplasia, even if stromal fibrosis involved only a partial component of an otherwise conventional melanoma (equivalent to the term mixed or combined DM used herein)[8].

There is emerging consensus, however, from most melanoma programs, that DM is associated with a lower incidence of positive SLNs than conventional melanomas. The difference is most striking if strict criteria are applied for the diagnosis of DM, i.e., pure DM are less likely to metastasize to the regional node than mixed DM[31,32,39-41].

MOLECULAR FINDINGS

Some variants of melanoma have been closely associated with distinct mutations. Superficial spreading melanomas, for example, tend to carry B-Raf mutations. Acral melanomas may harbor c-kit mutations. No distinct mutations have yet been associated with desmoplastic melanoma.

Desmoplastic melanomas have a gene expression profile different from conventional melanomas. One of the genes overexpressed in DM is clusterin. However, available data from such studies are limited due to small sample size and possible contamination by non-tumorous stromal tissue.

Cytogenetic studies suggest that DM like conventional melanomas tend to be associated with gains and/or losses, but no unique profile has emerged to date.

Application of the four-probe fluorescence in situ hybridization assay has shown that a significant number of tumors are FISH negative. It is unclear whether this is related to technical issues (thin elongated nuclei) or a reflection of the intrinsic biology (less common aberrations at chromosomes 6 and 11).

Table 1

Desmoplastic Melanoma versus Desmoplastic Melanocytic Nevus

	Desmoplastic Melanoma	Desmoplastic Nevus
Silhouette	Asymmetric	Symmetric
Growth pattern	Irregular and Infiltrative	Circumscribed (“orderly”)
Maturation	Absent	Present
Atypia	Usually present; often moderate	Usually absent, except for sclerosing Spitz’s nevi
Mitoses	Variable	Usually absent
In situ melanoma	Often present	Absent
Junctional nevus	Absent	May be present
Lymphocytic aggregates	Common	Rare
Replacement of fat	Common	Absent, except for congenital nevi with sclerosis
Immunophenotype	Negative or minimally positive for MDA; MIB-labeling variable (low or clearly increased); p16 labeling variable (often negative, may be focally or strongly positive)	Usually positive for MDA MIB-1 labeling index variable (low or absent); p16 usually strongly positive

MDA: Melanocytic differentiation antigens (Melan-A/Mart-1, tyrosinase, gp100, microphthalmia transcription factor)

Table 2

Differential Diagnosis of DM on H&E-stained biopsy sections

Benign Lesions

- Sclerosing melanocytic nevus
- Dermal scar
- Dermatofibroma
- Neurofibroma
- Pleomorphic fibroma
- Desmoplastic cellular neurothekeoma

Malignant Tumors

- Sarcomatoid carcinoma
    - Sclerosing spindle cell squamous cell carcinoma
    - Sclerosing myoepithelial carcinoma

- Sarcoma
    - Spindle cell variant of atypical fibroxanthoma
    - Desmoplastic spindle cell sarcoma (sarcoma, NOS; "MFH")
    - Desmoplastic leiomyosarcoma
    - Malignant Peripheral Nerve Sheath Tumor (MPNST)

Table 3

Immunohistochemical Studies for S100 P to distinguish DM from its Mimics

Tumors **excluded** by strong staining for S100 protein:

Benign lesions

- Desmoplastic cellular neurothekeoma

- Dermatofibroma

Malignant tumors

- Squamous cell carcinoma

- Leiomyosarcoma

- Dermatofibrosarcoma protruberans

- Fibrosarcoma

- Spindle cell variant of MPNST (usually only focally positive)

Tumors **not excluded** by strong staining for S100 protein:

Benign:

- Neurofibroma

Malignant:

- Spindle cell myoepithelial carcinomas

- Dendritic cell tumor/sarcoma

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Cutaneous Neuroendocrine (Merkel Cell) Carcinoma

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Definition

Merkel cell carcinoma (MCC) is the eponyom for primary neuroendocrine carcinoma of the skin and/or subcutis.

Histologic Findings

MCC typically presents under the microscope as a "blue" nodule in the dermis and/or subcutis. It may be fairly circumscribed, but more often shows an infiltrative growth pattern at its periphery. The "blue" appearance relates to the composition of the tumor nodules of cells with minimal cytoplasm. A spectrum from small to intermediate and large cells has been described based on the nuclear size, the intermediate cell type being most common. The cytology of the tumor cells is characterized by nuclei with finely granular ("salt and pepper") chromatin pattern. Dense hyperchromatic cells may be present, but the nuclei are often pale ("see through nuclei"). Nuclear molding is not uncommon. On rare occasion, one may see rosettes. An Azzopardi phenomenon (crushed nuclei) may also be found. Mitotic figures and apoptotic bodies tend to be numerous. Lymphatic tumor emboli are commonly identified at the periphery of many tumors. There may or may not be an associated lymphocytic inflammatory cell infiltrate of variable density.

A trabecular "organoid" growth pattern may be present, but most often the tumor cells are dispersed as sheets lacking a distinct architectural arrangement. Cellular discohesion may be marked and give rise to a diffusely infiltrative lymphoma-like appearance.

While most MCC are entirely dermal or subcutaneous, some of them have an intraepidermal component ("epidermotropic MCC"). Others tend to surround adnexal structures. The majority of MCCs develop de novo. A subset of MCCs, however, is found in association with other non-neuroendocrine carcinomas, most often squamous cell carcinomas, rarely basal cell carcinoma or other adnexal tumors. Although collision lesions may occur, the intimate admixture of conventional squamous cell carcinomas and Merkel cell carcinoma and presence of transition areas indicate that at least a subset of MCCs represent biphenotypic (combined) carcinomas. Some may indeed arise from squamous cell carcinomas, when the formation of neuroendocrine carcinoma is preceded squamous cell carcinoma at the same anatomic site and transition areas are still found once MCC is detected.

Ancillary Studies

Immunohistochemistry

The tumor cells express epithelial markers (cytokeratins, such as CAM5.2., AE1:AE3, CK20, 34BE12, and EMA) and neuroendocrine markers (chromogranin, synaptophysin, CD56). Antibodies to CK20 have been found to be particularly useful for

diagnosis. The majority of MCCs (75-90% of cases) are at least focally positive for CK20, typically, but not always, in a paranuclear dot-like pattern. Not uncommonly the staining is mixed paranulcear dot-like is some cells and diffuse cytoplasmic in others. Rarely seen. MCC may also be positive for CD99 or CD117. In contrast to the majority of pulmonary and a subset of extrapulmonary (non-cutaneous) neuroendocrine carcinomas, MCC are usually negative for TTF-1.

Electron Microscopy

MCC is characterized by the presence of membrane bound, 80-120 nm, dense core granules located in the cytoplasm at the periphery of the cells. Round groups of intermediate filaments may be observed adjacent to the nucleus. While EM has been useful historically, it is nowadays no longer necessary for diagnosis.

Histologic Differential Diagnosis

MCC may be confused with other primary cutaneous tumors, such as carcinomas with basaloid or small cell features (BCC, small cell/basaloid variant of sweat gland carcinoma, pilomatrix carcinoma), small cell variant of melanoma, cutaneous Ewing's sarcoma and lymphoma. The distinction may on occasion be difficult on a small biopsy sample, but attention to the presence or absence of the characteristic nuclear features associated with MCC and the use of immunohistochemical markers should lead to the correct diagnosis.

The distinction of cutaneous Ewing's sarcoma from MCC can be particularly difficult, since both tumors may express cytokeratins, neuroendocrine markers and CD99. Molecular studies (FISH for Ewing's translocation or PCR studies for EWS-Fli-1 fusion product) can be decisive for this problem.

MCC may also be confused with neuroendocrine carcinomas metastatic to the skin, especially metastatic small cell carcinoma. If there is no known history of an extracutaneous neuroendocrine carcinoma, and the tumor presents in the superficial dermis of sun-damaged skin with the characteristic light microscopic finding of intermediate sized pale ("see through") nuclei with fine salt and pepper chromatin pattern, the diagnosis of MCC is almost certain, since other neuroendocrine carcinomas with the exception of those of salivary gland origin rarely show this feature. However, if a tumor shows cytologic features similar to small cell carcinomas of the lung, a definitive diagnosis requires immunohistochemical studies. Typically, pulmonary small cell carcinomas are positive for CK7 and TTF-1, while MCCs are usually positive for CK20 and negative for TTF-1.

However, exceptions exist. Some pulmonary and extrapulmonary non-cutaneous small cell carcinomas may also be positive for CK20. Furthermore, not all lung tumors stain for TTF-1, and TTF-1 expression is not restricted to lung tumors, but can also be seen in extrapulmonary neuroendocrine carcinomas. It also needs to be emphasized that not all MCCs are CK20-positive. One can accept a CK20-negative tumor as MCC, if the histology and marker studies (positive staining for other keratins and neuroendocrine markers) support a neuroendocrine carcinoma and the clinical setting is consistent with a primary cutaneous origin. Thus, a diagnosis on the most likely origin of a neuroendocrine carcinoma should not be based alone on immunohistochemical results. Correlation with histologic and clinical findings is paramount.

On occasion primary MCC needs to be distinguished from metastatic MCC to the skin. Clinical history is essential here. There are few histologic features, which can help, such as the presence of an associated squamous cell carcinoma or a dense lymphocytic infiltrate, both of which would favor a primary tumor.

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NOTES

NOTES

Spindle Cell Neoplasms

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2011 ASDP Board Review
Spindle Cell Tumors

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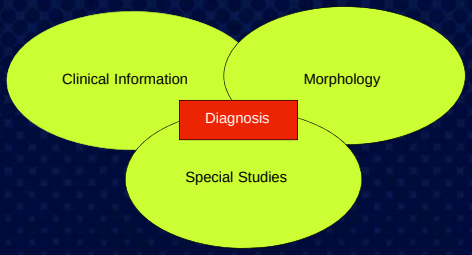
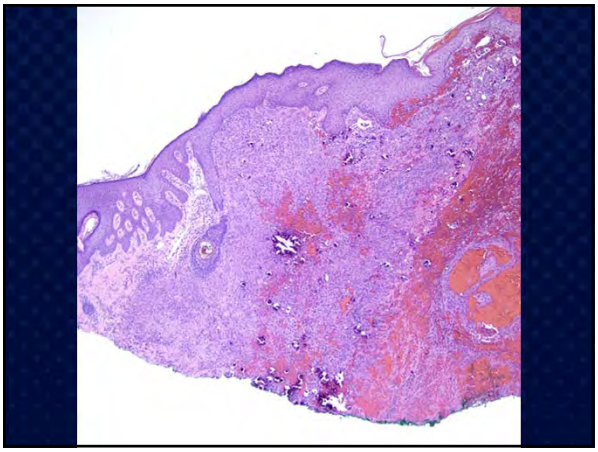
DEPARTMENT OF PATHOLOGY

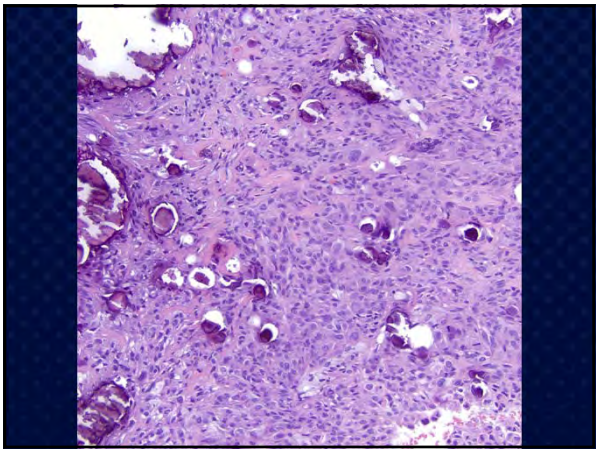
Integrated Approach

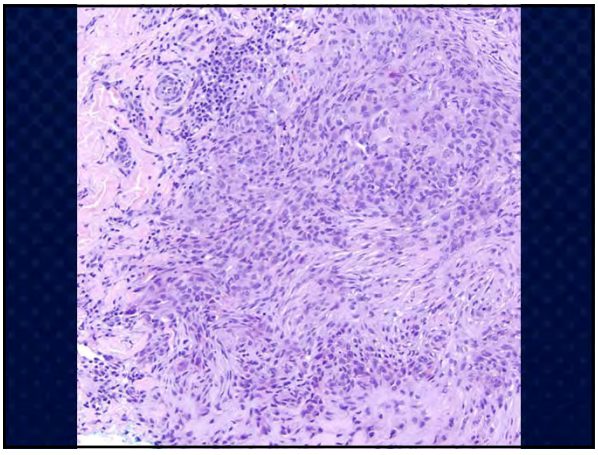


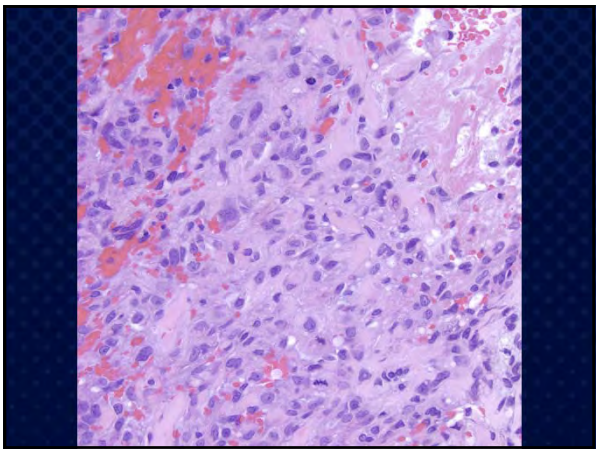
Epithelioid Sarcoma

- Adolescents and young adults
- Hands, fingers and lower arm
- Superficial with involvement of tendons and aponeuroses, often dermis
- Ulcerated firm nodules, single or multiple
- Usually <3cm





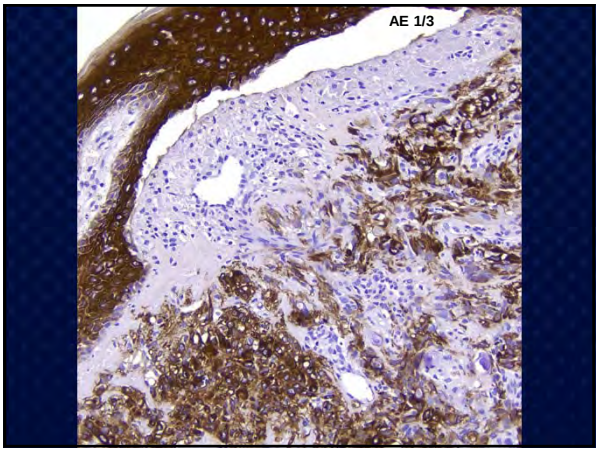


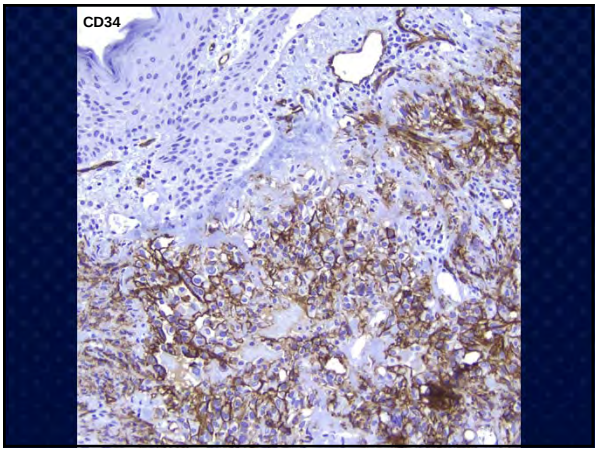


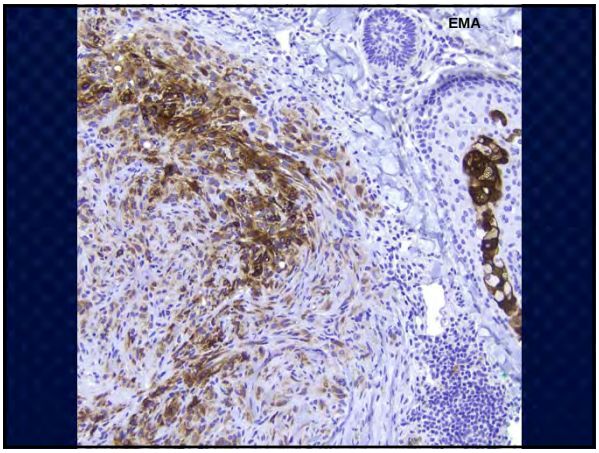
IHC Epithelioid Neoplasms

Antigen	CA	Melanoma/ EMPNST	Lymphoma	ES	EAS
CK	+	+/- melanoma, - EMPNST	-	+	+/-
S-100	-	+	-	-	-
CD45	-	-	+ conventional B & T-cell lymphoma, - most ALCL	-	-
CD30	-	-	- most conventional B & T-cell lymphoma, + ALCL	-	-
CD31	-	-	-	-	+

ALCL, anaplastic large cell lymphoma; EAS, epithelioid angiosarcoma; CA, carcinoma; CK, cytokeratin; EMPNST, epithelioid malignant peripheral nerve sheath tumor







Histopathology

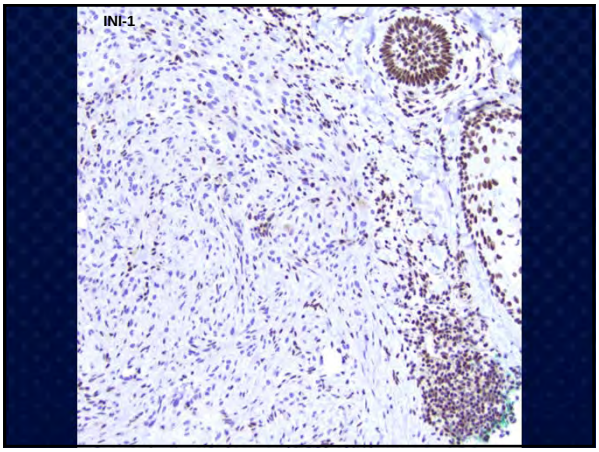
- Nodular, vaguely circumscribed but infiltrative
- Garland-like appearance with central necrosis
- Bland epithelioid cells, dense eosinophilic cytoplasm
- Epithelioid to spindled areas
- Sheet-like growth, pleomorphic rhabdoid cells in proximal variant

Immunohistochemistry

- CK and vimentin co-expression
- Low and high MW cytokeratins as well as EMA
- CD34 50-60%
- CD31, Fli-1, CK5/6 negative
- May be factor XIIIa positive
- >90% loss of INI-1 expression

INI-1

- hSNF51/INI1/SMARCB1/BAF47 gene
- Tumor suppressor
- Loss of expression hallmark of pediatric rhabdoid tumors and atypical teratoid rhabdoid tumors of CNS
- Loss in >90% of epitheliod sarcomas, but not in almost all other sarcomas and carcinomas

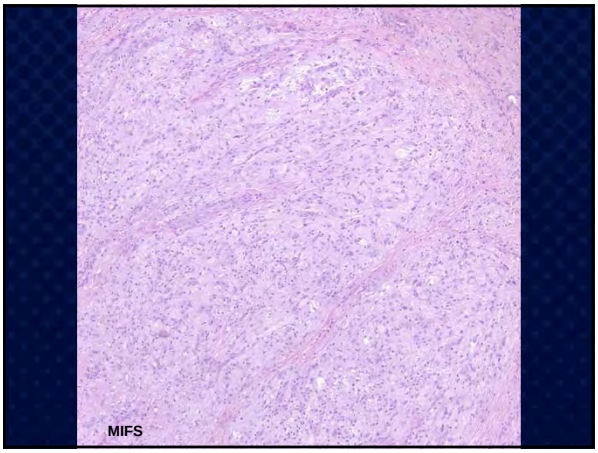


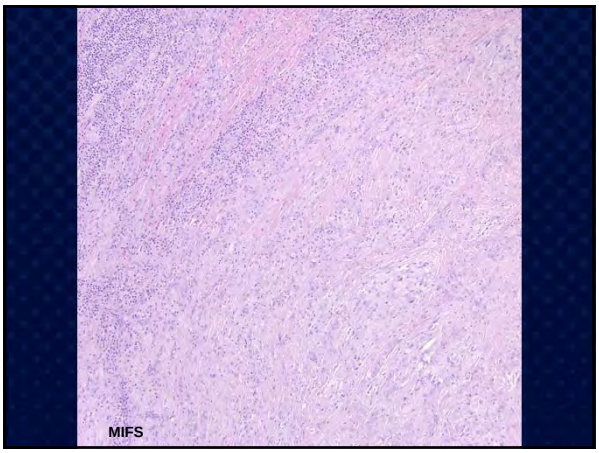
Differential

- Necrobiotic granulomas
- Cutaneous CA (SCC & adnexal)
- Metastatic CA
- BFH/DF (fibroma-like)
- Epithelioid vascular tumors
- Cutaneous meningioma

Myxoinflammatory Fibroblastic Sarcoma

- Distal extremities (hands and feet)
- Multinodular; spindle, epithelioid, lipoblast-like and ganglion-like cells in myxoid back
- ground, prominent inflammation
- Up to 67% local recurrence, rare metastases
- Vimentin +, CD34, CD68 +/-

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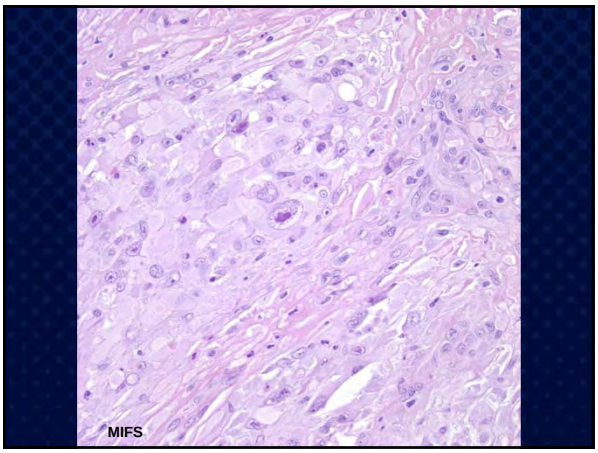
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(Am J Surg Pathol 2007;31:1103–1114)

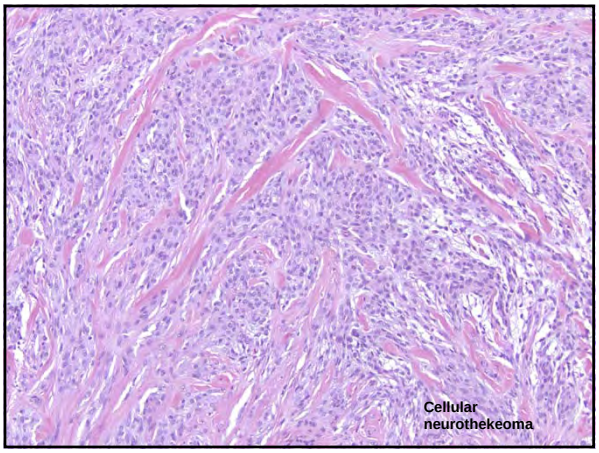
ORIGINAL ARTICLE

Neurothekeoma: An Analysis of 178 Tumors With Detailed Immunohistochemical Data and Long-term Patient Follow-up Information

John F. Fetsch, MD,* William B. Laskin, MD,† James R. Hallman, MD,‡ George P. Lupton, MD,‡ and Markku Miettinen, MD*

Cellular Neurothekeoma

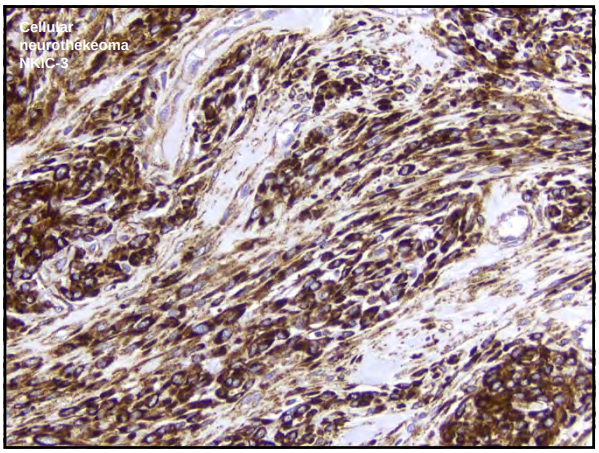
- Benign
- Head and neck, proximal extremities of young adults
- Painless papules or nodules
- Distinctly nested to fascicular with subtle whorling
- May have atypical features (mitoses, atypia, large size), still benign


Cellular neurothekeoma

Immunohistochemistry

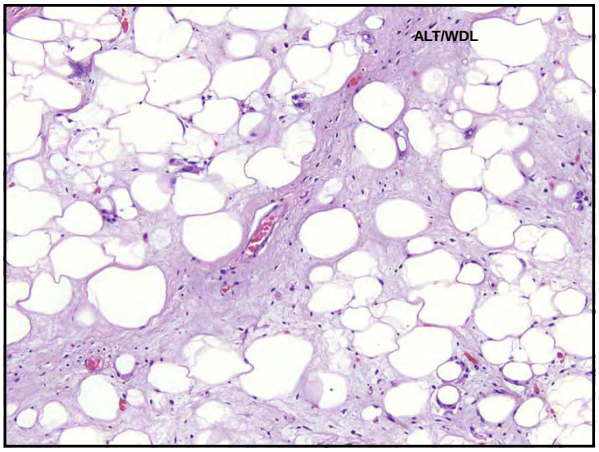
- Positive:
- NKIC3
- MiTF
- PGP9.5
- NSE
- S100A6
- Vimentin
- 40-60% SMA

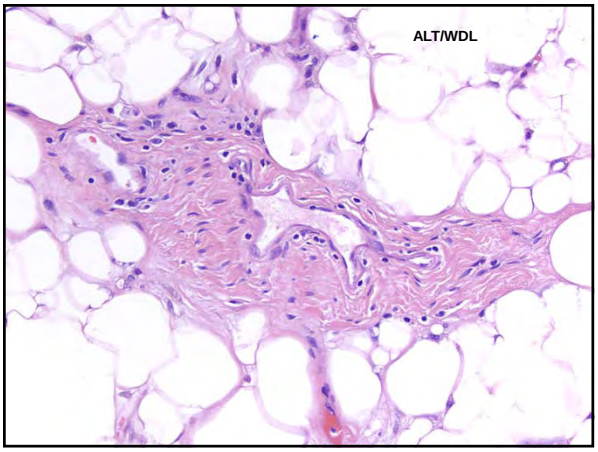
- Negative:
- S100
- CD34
- EMA
- HMB45
- MelanA
- CK



Well-Differentiated Liposarcoma/Atypical Lipomatous Tumor

- M>F peak incidence 6th decade
- Slow-growing painless mass
- Retroperitoneum, limbs, spermatic cord, mediastinum
- Anatomic location main prognostic factor
- Mature adipocytic differentiation, nuclear atypia in stromal and/or fat
- Variable lipoblasts



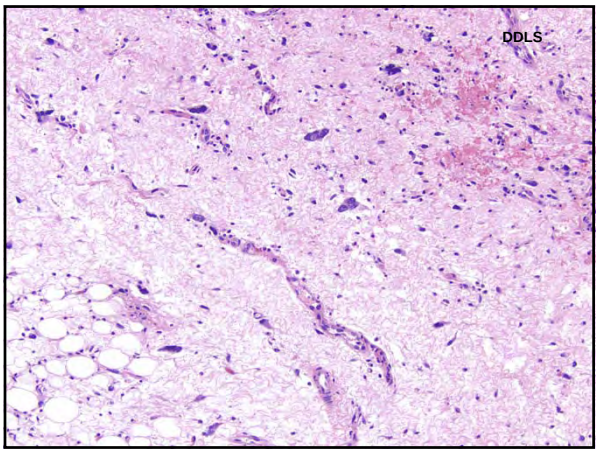


Ancillary Studies

- Ring & giant marker chromosomes
- Amplification 12q12-15 region
- Lipogenic areas S-100 +
- Nuclear expression of MDM2 & CDK4

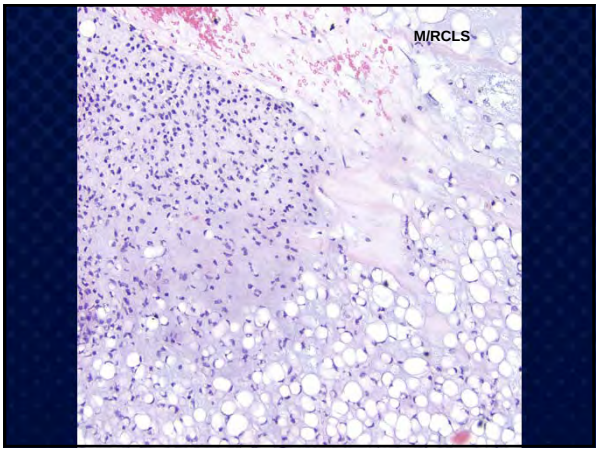
Dedifferentiated Liposarcoma

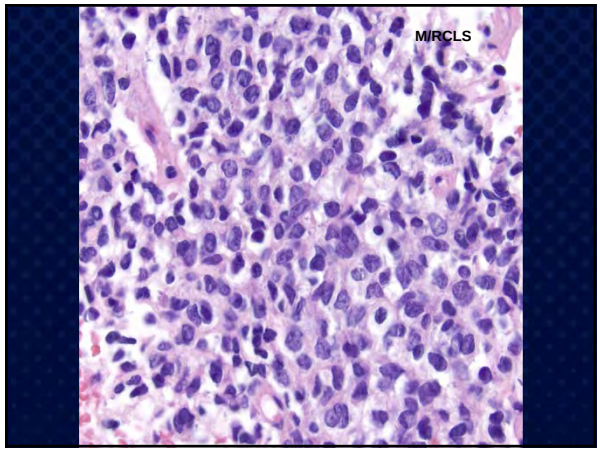
- Transition of WDL to high-grade nonlipogenic sarcoma (also low-grade DD)
- Retroperitoneum > limbs
- Metastatic rate < 20%; overall survival at 5yrs: 60-70%
- Heterologous differentiation
- Ring & giant marker chromosome



Myxoid-Round Cell Liposarcoma

- Plexiform vasculature, myxoid, spindled or round cells
- 30% liposarcoma; 10% of all sarcomas
- Deep soft tissues of limbs
- M=F; peak incidence 4th decade
- 90% overall 5 yr survival purely myxoid, 40% high-grade "round cell"



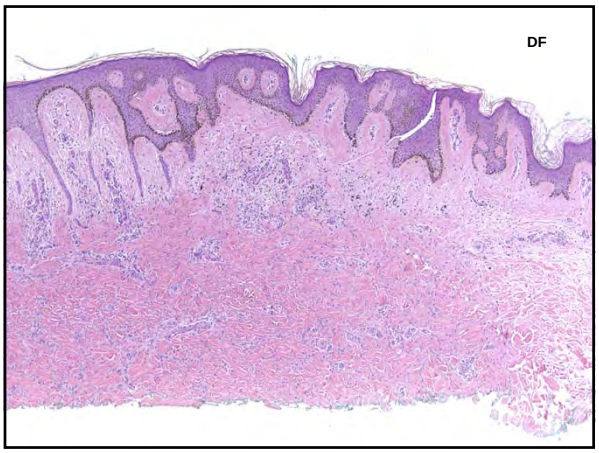


Ancillary Studies

- S-100 protein +
- t(12;16)(q13;p11) fusing *DDIT3* with *TLS*
- t(12;22)(q13;q11) fusing *DDIT3* and *EWS*

Cellular Fibrous Histiocytoma

- Dermatofibroma (BFH) variant
- BFH most common cutaneous soft tissue tumor
- Proximal extremities, head & neck
- Clinical: basal cell carcinoma, epidermoid cyst, pyogenic granuloma
- "Hero with a thousand faces"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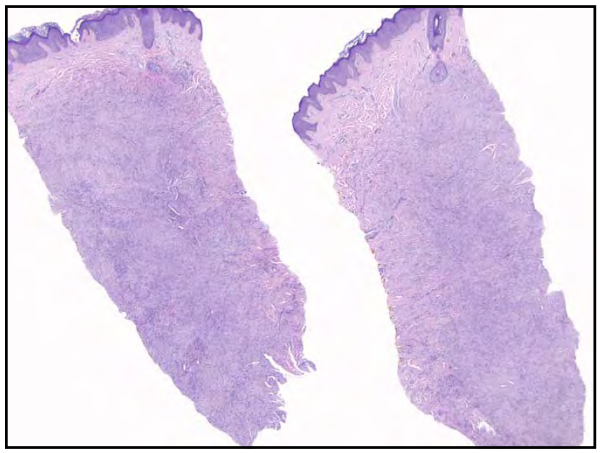
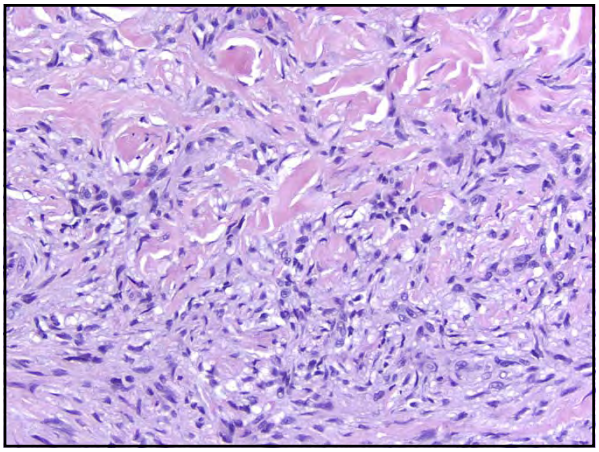
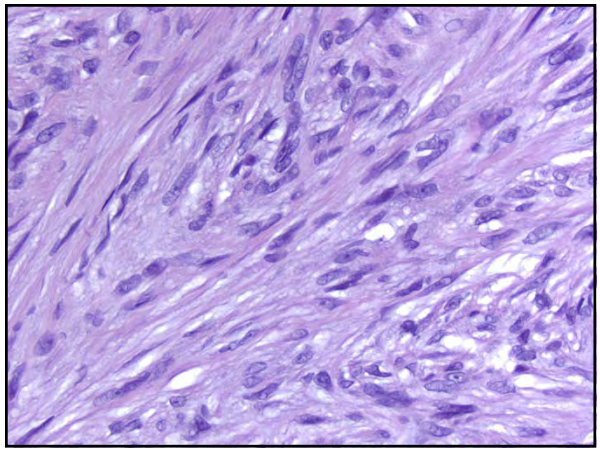
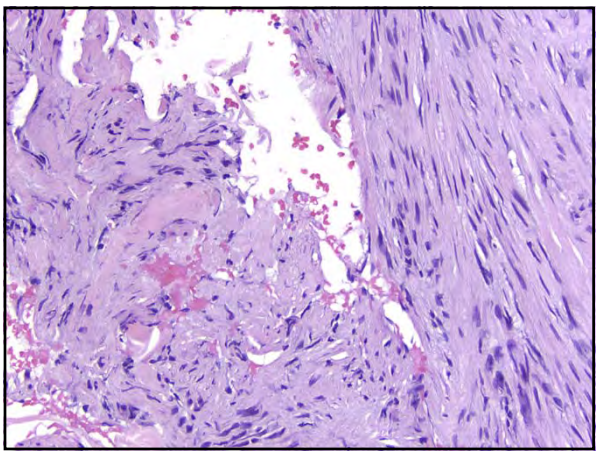
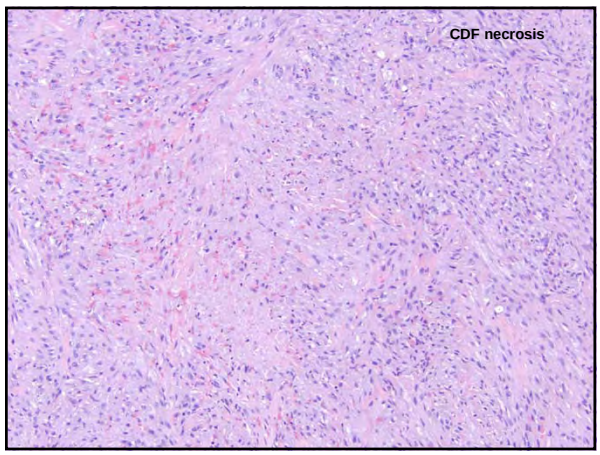









CDF necrosis

Cutaneous Spindle Cell Tumor Panel

Basic Panel
- Cytokeratin 34βE12 or MNF116
- Possibly CK5/6
- S100 protein
- SMA
- Desmin

Secondary markers
(AS/KS)
- CD31/CD34 (also DFSP)
- HHV-8 LANA

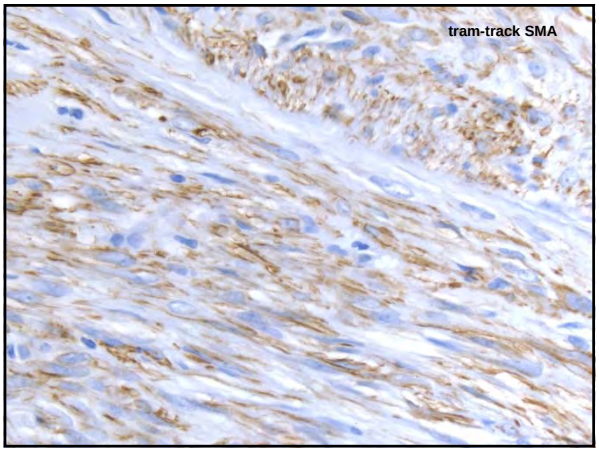
(SSCC)
- p63

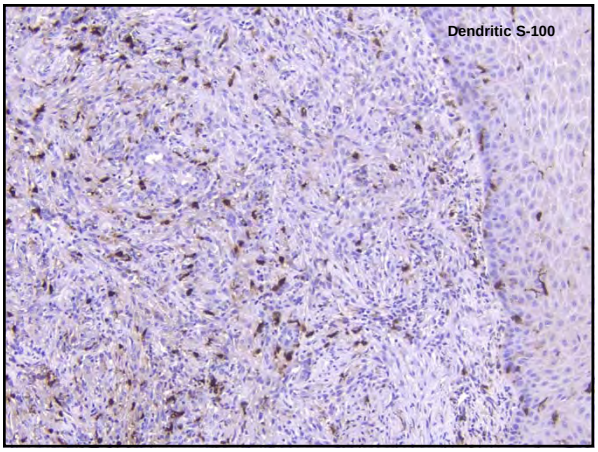
(Melanoma)
- Melan-A, HMB45, MiTF

(BFH)
- XIIIa

Immunohistochemistry

- Factor XIIIa usually negative
- Tram-track smooth muscle actin, desmin negative
- Entrapped S-100 positive dermal dendrocytes
- Entrapped or peripheral CD34 positive cells
- Most useful to exclude other tumors



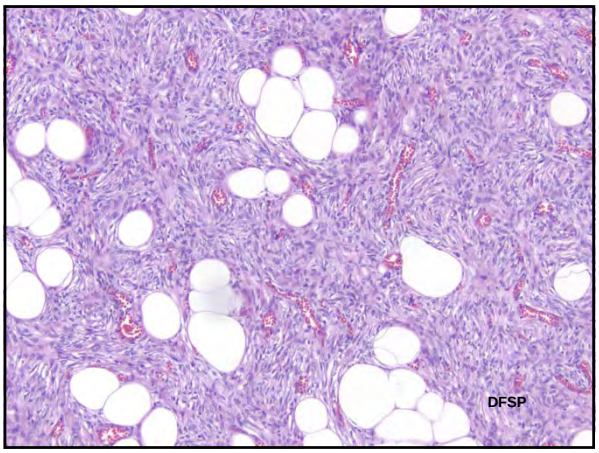


CFH: Histopathology

- Circumscription
- Epidermal hyperplasia
- Collagen trapping
- 1/3 focal subcutaneous extension
- Cellular fascicular growth of only eosinophilic spindle cells, lack atypia
- Mitoses up to 10/10hpf, no atypical forms,
- 10% Central necrosis

Differential Diangosis

- Dermatofibrosarcoma protuberans
- Leiomyosarcoma
- Nodular fasciitis
- Spindled variant of epithelioid sarcoma



Dermatofibrosarcoma Protuberans

- Young to middle aged adults most common- may occur in infants & children
- Trunk and proximal extremities
- Plaque progressing to uni/multinodular mass

Histopathology

- Storiform and sometimes fascicular growth (particularly in sarcomatous transformation)
- Monotonous bland spindle cells
- "Honeycomb" subcutaneous extension
- Few mitoses, no secondary elements
- Nearly always strongly CD34+
- Usually negative for S-100 protein, actin, desmin

Variants

- Fibrosarcomatous
- Myxoid
- Giant cell fibroblastoma
- Bednar tumor (pigmented)
- Myoid nodules
- Atrophic

Genetics

- Supernumerary ring chromosomes
- t(17;22)(q22;q13.1)
- COL1A1/PDGF-β fusion gene
- Block PDGF-β receptor with imatinib mesylate (Gleevec)
- Identical molecular abnormalities in giant cell fibroblastoma

Cellular Fibrous Histiocytoma vs. Dermatofibrosarcoma Protuberans

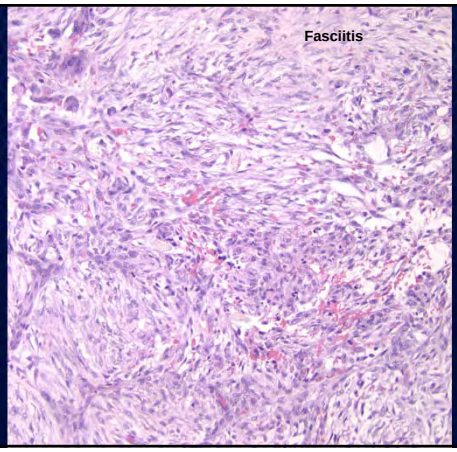
	CFH	DFSP
Circumscription	Relatively circumscribed	Infiltrative
Epidermal hyperplasia	Often	Absent
Subcutaneous extension	Limited	Extensive
Collagen trapping	Present	Absent
Growth pattern	Fascicular to storiform	Storiform
Secondary elements	Often present	Absent
Immunophenotype	Factor XIIIa -/+; CD34-	Factor XIIa -; CD34+

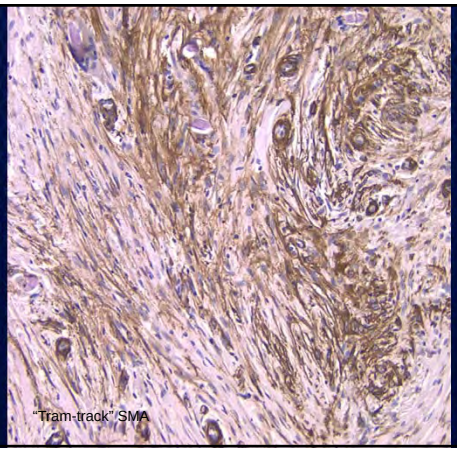
Reactive Process?

- Often superficial
- Zonal quality
- "Tissue culture quality"
- Mitoses-no atypical forms
- Lack of pleomorphic nuclear atypia

Nodular Fasciitis

- Recent small superficial mass in young patient- often history of trauma
- Dermis or subcutis
- Random short fascicles of normochromatic myofibroblasts
- Frequent mitoses





NF of the Head & Neck Region

- 13-20% of cases
- Commonly not considered in this location
- Incompletely excised = additional Dx challenges
- Typical histologic features

Weinreb I, Shaw AJ Ordonez BP, et al. J Cutaneous Pathol. 2009 Nov;36(11):1168-73.

NF DDx: CFH vs DFSP

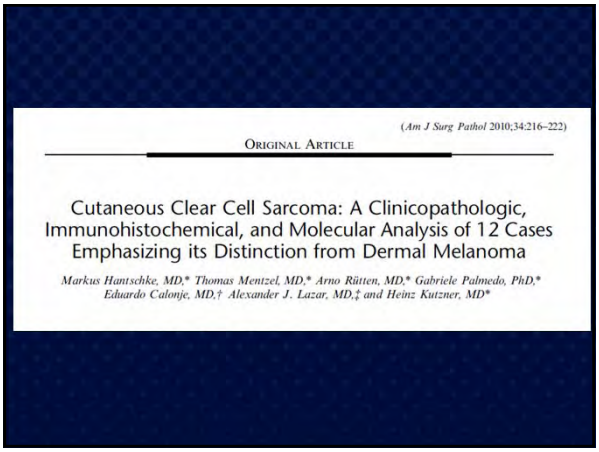
	CFH	DFSP
Circumscribed	+	-
Epi hyperplasia	+/-	-
Collagen trapping	+	-
Secondary elements	Focal	-
Fat infiltration	Limited	Diffuse
IHC	XIIIa -/+;CD34-	XIIIa -;CD34+

NF DDx: Other Considerations

- LMS
  - Cigar-shaped nuclei, SMA & desmin+, atypia, mitoses +/- abnormal forms
- KS
  - Hyaline globules, sieve-like, HHV8+
- ES, spindle cell variant
  - Young, distal extremities, CK, EMA, CD34 (50%) +

Clear Cell Sarcoma

- Slowly enlarging painful mass
- Adolescents and young adults 20-40 yrs
- Most common sarcoma of foot and ankle (50%)
- Also knee, thigh, hand, neck and trunk
- Associated with tendons and aponeuroses

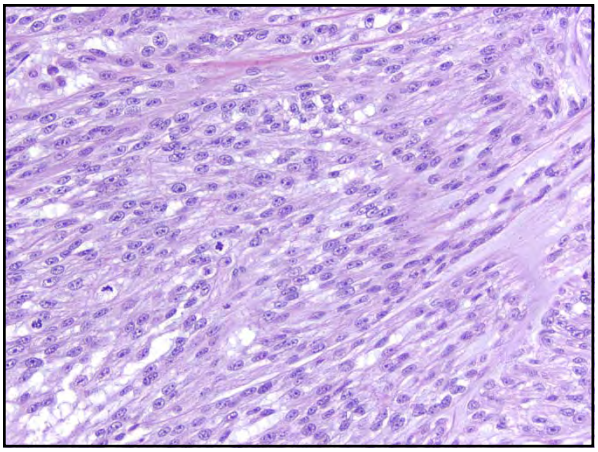


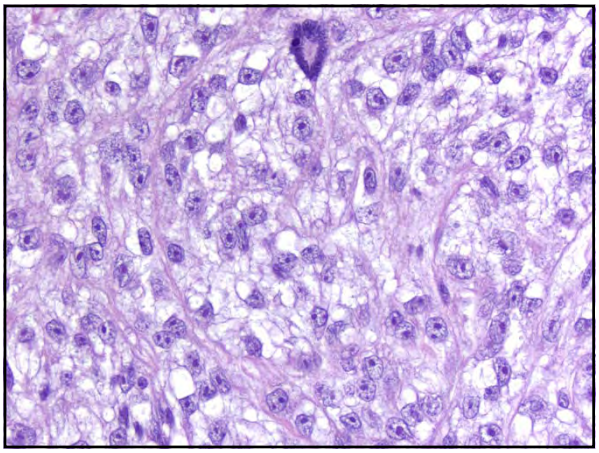
(*Am J Surg Pathol* 2010;34:216–222)

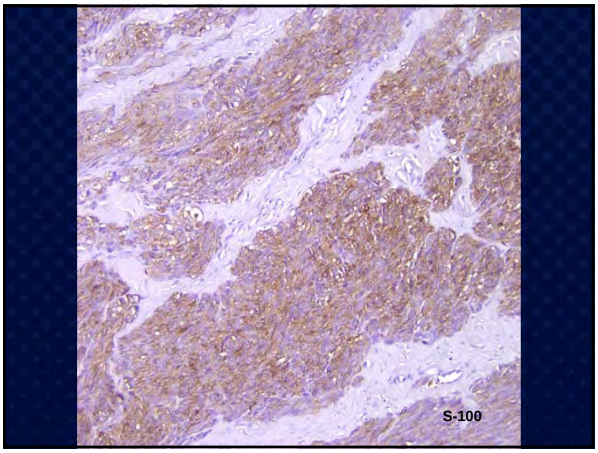
ORIGINAL ARTICLE

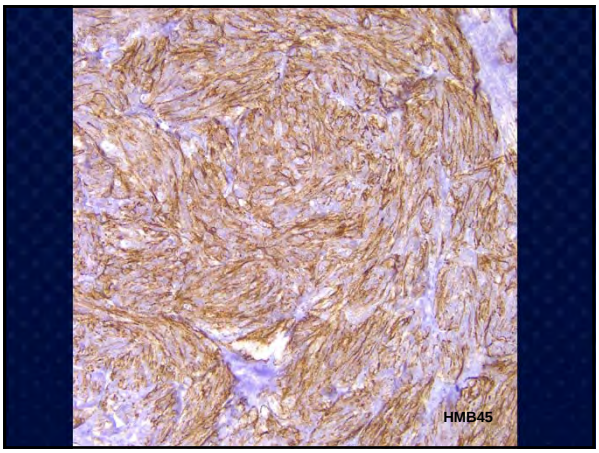
Cutaneous Clear Cell Sarcoma: A Clinicopathologic, Immunohistochemical, and Molecular Analysis of 12 Cases Emphasizing its Distinction from Dermal Melanoma

Markus Hantschke, MD, Thomas Menzel, MD,* Arno Rütten, MD,* Gabriele Palmedo, PhD,* Eduardo Calonje, MD,† Alexander J. Lazar, MD,‡ and Heinz Kutzner, MD**







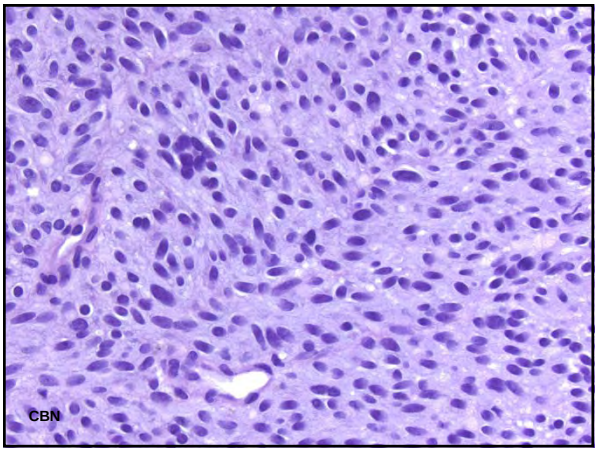


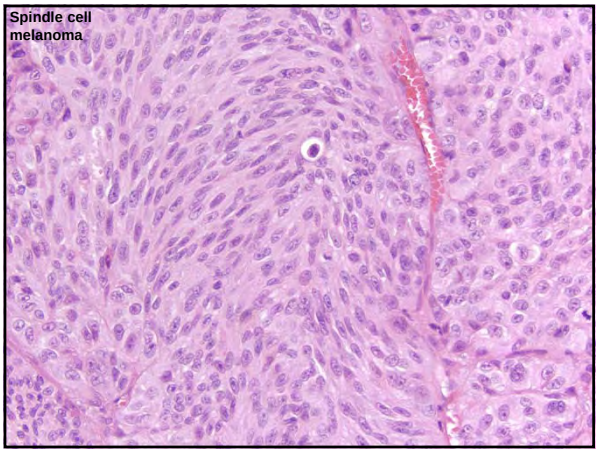
Histopathology

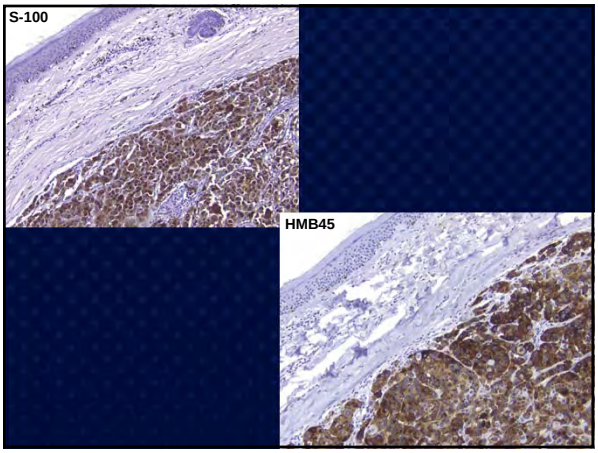
- Spindled to epithelioid tumor in nests and sheets, infiltrates fibroconnective tissue
- Clear to pale eosinophilic cytoplasm, vesicular nuclei, prominent eosinophilic nucleoli
- Touton-type tumor giant cells
- Tumor separated by variable thick fibrous bands

CCS-Differential Diagnosis

- CBN
- Conventional melanoma
- Epithelioid MPNST
- Epithelioid sarcoma-spindle cell type







Ancillary Studies

- S-100 protein +
- HMB45, Melan-A, tyrosinase, MiTF
- Melanocytic markers may be stronger than S-100 protein (similar to CBN)
- t(12;22)(q13;q12)
- EWS-ATF1 fusion transcript, not found in melanoma

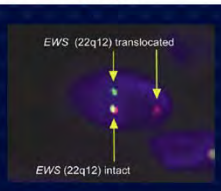
Dual-color, break-apart fluorescence *in situ* hybridization for *EWS* gene rearrangement distinguishes clear cell sarcoma of soft tissue from malignant melanoma

Rajiv M Patel[1], Erinn Downs-Kelly[2], Sharon W Weiss[1], Andrew L Folpe[1], Raymond R Tubbs[2], Ralph J Tuthill[2], John R Goldblum[2] and Marek Skacel[2]

[1]*Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA and* [2]*Division of Pathology and Laboratory Medicine, The Cleveland Clinic Foundation, Cleveland, OH, USA*

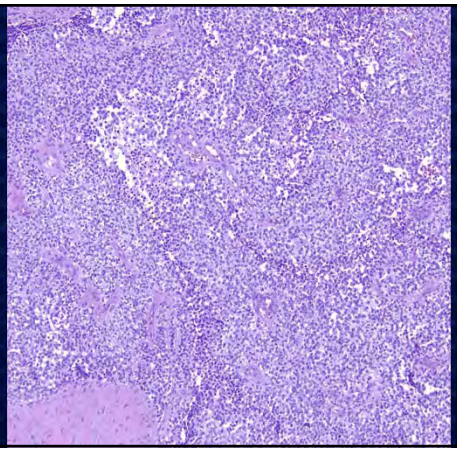
Table 1 *EWS* gene rearrangement by diagnosis

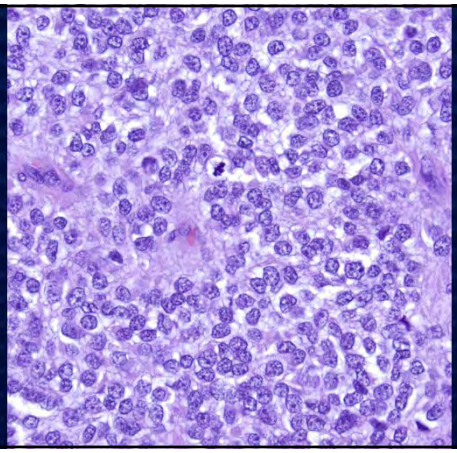
Diagnosis	*EWS (22q12) gene rearrangement*
Clear cell sarcoma	7/10 (70%) (range 60–95% cells per case)
Malignant melanoma	0/32 (range 0–4% cells per core)



Ewing Sarcoma/PNET

- Rare highly malignant SRBCT of bone or ST
- Most common in children & adolescents, but occurs at any age
- 10-year SR 60% with multimodality Tx

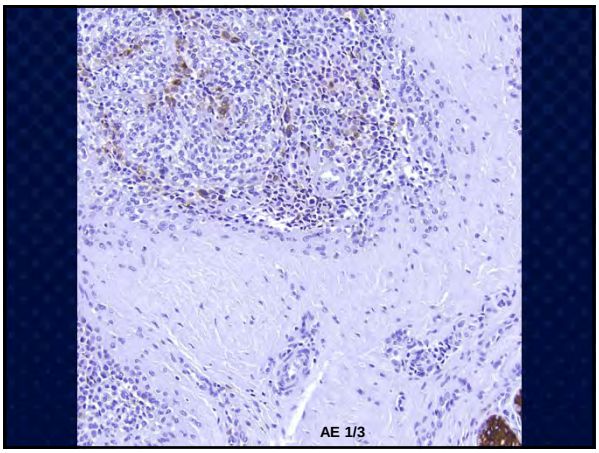


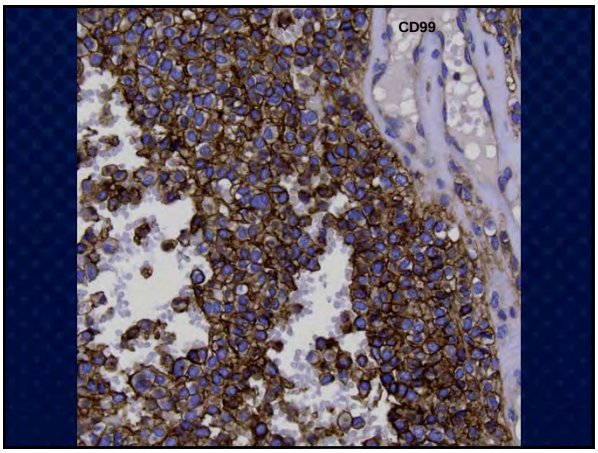


Small Round Blue Cell Tumor IHC

AB	SCCA	MM	ML	Ewing-PNET	RMS	PDSS	DRCT
PANK	+	+/-	-	+/-	Rare	+	+
S-100	-	+	-	+/-	Rare	+/-	-
CD45	-	-	+	-	-	-	-
TdT	-	-	+	-	-	-	-
Desmin	-	+/-	-	Rare	+	-	+
CD99	-	-	+/-	+	+/-	+	Rare

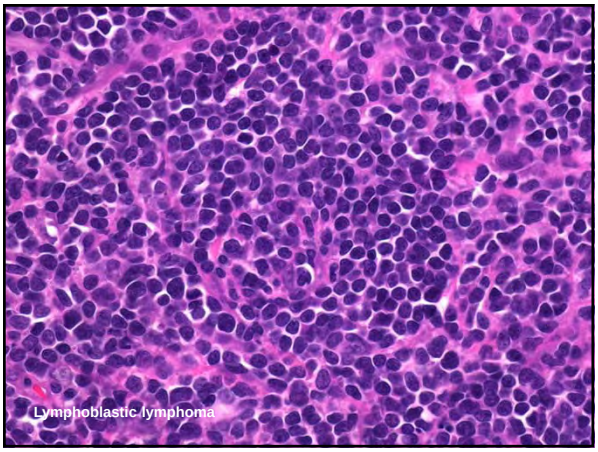
AB, antibody; SCCA, small cell carinoma; MM, melanoma; ML, lymphoma; PNET, primitive neuroectodermal tumor; RMS, rhabdomyosarcoma; PDSS, poorly differentiated synovial sarcoma; DRCT, desmoplastic small round cell tumor



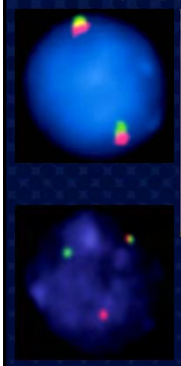


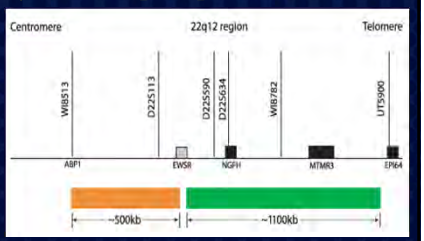
SRBCT in Young Patients

- Ewing sarcoma/PNET
- Alveolar rhabdomyosarcoma
- Neuroblastoma
- Desmoplastic small round cell tumor
- Mesenchymal chondrosarcoma
- Lymphoblastic lymphoma
- Small cell osteosarcoma



EWS (22q12) **Break-apart probe**





t(11;22), t(21;22) – EWS/PNET (FLI1/EWS, ERG/EWS)
t(11;22), t(21;22) - DSRCT (WT-1/EWS, ERG/EWS)
t(12;22) – Clear Cell Sarcoma (ATF1/EWS)
t(9;22) – ES Myxoid Chondrosarcoma (CHN/EWS)
t(16;22) – Myxoid/Round Cell Liposarcoma (CHOP/EWS)

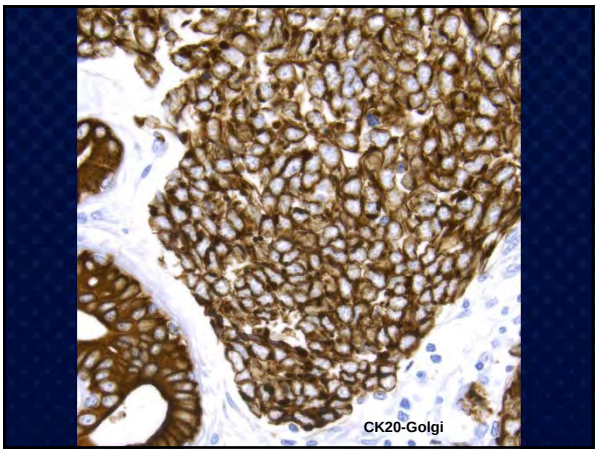
SRBCT in Older Patients

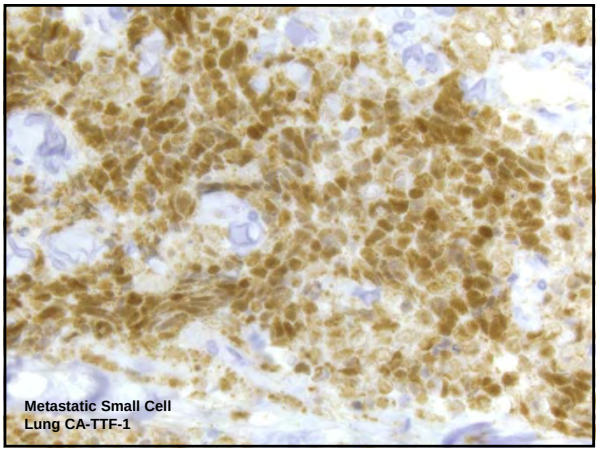
- Primary cutaneous neuroendocrine carcinoma (Merkel cell carcinoma)
- Metastatic small cell carcinoma
- Small cell melanoma
- Poorly differentiated adnexal carcinoma (malignant eccrine spiradenoma)
- Poorly differentiated SCC

Is it a Merkel cell carcinoma?

Primary markers
- CK20 (dot-like pattern)
  - 1-5% neg
  - 1-3% small cell ca +
- Chromogranin >75%
- Synaptophysin >75%
- TTF-1
  - 0% Merkel cell ca
  - 75-95% lung adeno and small cell ca

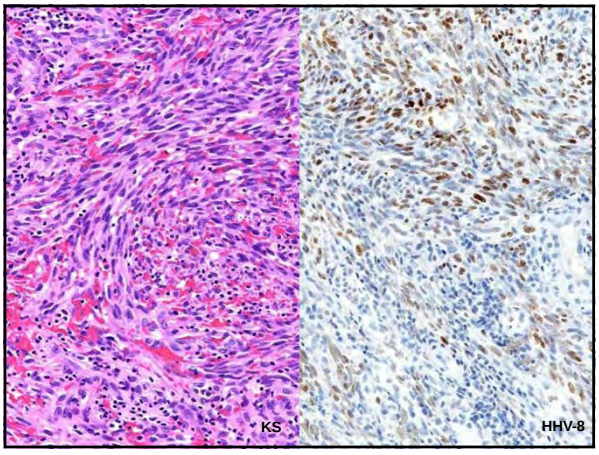
Secondary markers
- Neurofilament 50-90%
- CD45RB (LCA)
  - Exclude lymphoma
- S100
  - Exclude melanoma
- NSE
  - Lacks specificity



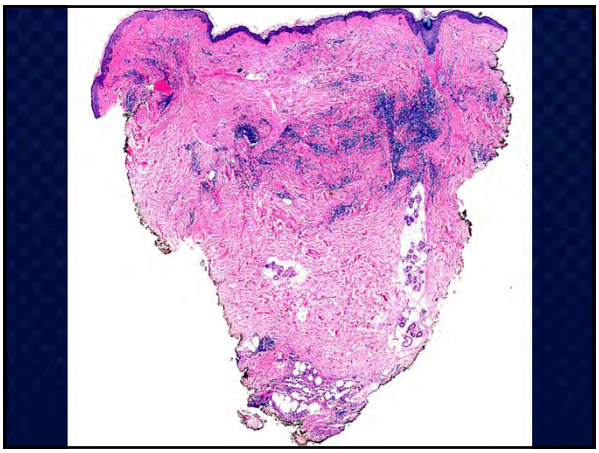


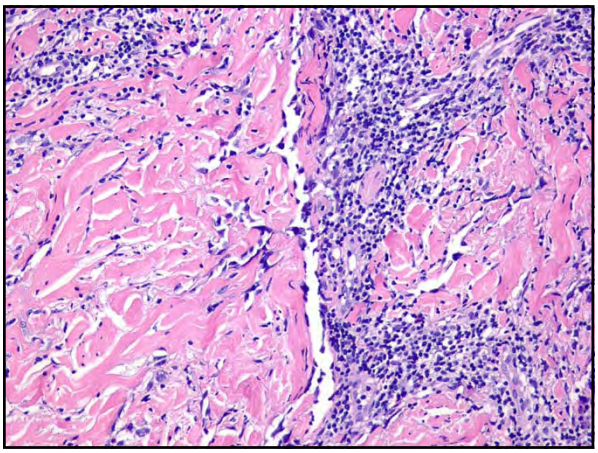
Kaposi Sarcoma

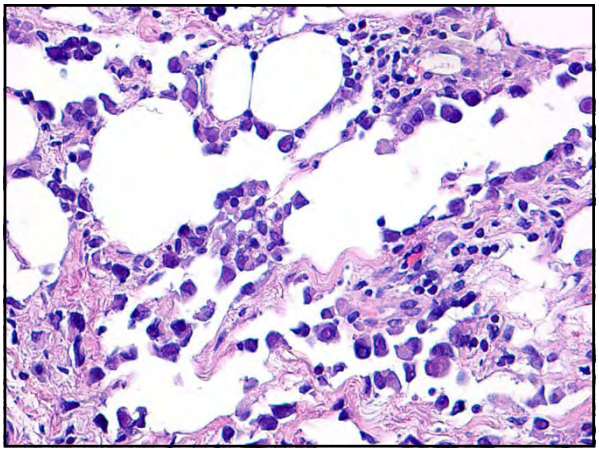
- Classic, endemic, epidemic (AIDS), iatrogenic
- Violaceous patch, plaque, macule, papule or tumor
- Promontory sign, increased bland myoid spindle cells, sieve-like vascular channels, extravasated RBC, hyaline globules
- Good prognosis in immunocompetent

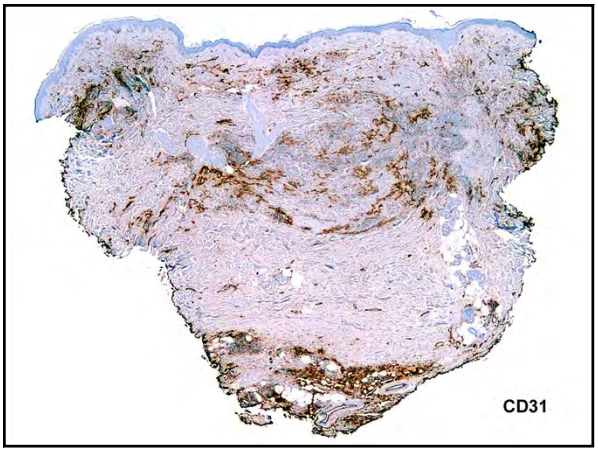


Cutaneous Postradiation Angiosarcoma





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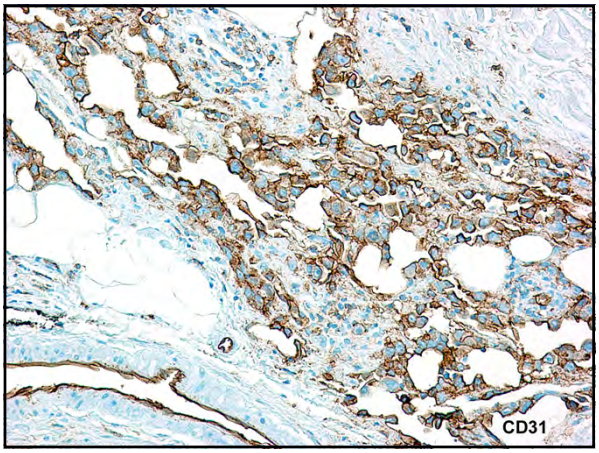
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NOTES

NOTES

Lymphoma
and
Lymphoproliferative Diseases

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Cutaneous Hematolymphoid Neoplasms

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Introduction

The diagnosis of cutaneous hematolymphoid neoplasms can be hard. A seemingly endless array of lymphomas and leukemias can show up in skin. Complicated immunohistochemical panels and molecular tests may be necessary to differentiate them. Even then, a firm diagnosis usually requires clinical and laboratory data. Moreover, the understanding of hematolymphoid neoplasms is rapidly evolving, resulting in reclassification every few years. And, unlike most of their counterparts within blood and lymph nodes, many skin hematolymphoid tumors are composed of just a few neoplastic cells that are easily obscured by the much denser 'background' inflammatory cell infiltrate. As a result, simply telling benign from malignant may be difficult or even impossible in some situations. Nevertheless, a few basic principles can simplify things dramatically.

1) Use pattern analysis. Most texts and classification systems group hematolymphoid neoplasms by lineage (e.g. B-cell vs. T-cell). Unfortunately, this assumes that you already know the lineage. Few of us can subtype lymphocytes on H&E, of course, and rather than endure the time-consuming study of the H&E, many pathologists reflexively order a 'standard' IHC panel at the mere sight of round blue cells. This is understandable, but often produces a differential diagnosis that is too limited and excludes entire categories of neoplasms. Instead, try assigning infiltrates to one of a few basic patterns, as explained in the lecture. This prompts consideration of a broader differential diagnosis and usually a more prudent choice of immunohistochemical stains.
2) Remember the mimics. The most common cutaneous lymphomas have more benign simulators than any other type of tumor. Earlymycosis fungoides, CD30+ lymphomas, and others share so many features with benign inflammatory dermatoses that distinction is simply not possible in some cases. Even dense collections of large, atypical-appearing cells can be caused by viral infections or drugs. Thus, never make a diagnosis of lymphoma without carefully excluding a benign simulator. If you cannot, simply state the differential in your report. There is nothing more embarrassing than hearing that the 'lymphoma' you diagnosed was cured by permethrin cream -*After* the entire ICU staff developed scabies.
3) Insist on clinical information. Mycosis fungoides, for example, cannot be diagnosed without knowledge of the clinical course. In fact, MF is defined in part by its clinical course, and definitive diagnosis requires evidence that lesions are progressing or have progressed in the typical fashion (i.e. from patches to plaques to tumors).

4) Don't overreach. Even with a thorough clinical history, not every case can be diagnosed on a single biopsy. When this happens, a diagnosis of "atypical lymphocytic infiltrate" or simply "lymphoma" accompanied by a comment that explains the differential is better than pretending to know something with certainty when you don't.

Abbreviations Used

MF = Mycosis Fungoides

SPTL = Subcutaneous panniculitis-like T-cell lymphoma

γ/δ T-cell lymphoma = Gamma / delta T-cell lymphoma

BPCDN = Blasticplasmacytoid dendritic cell neoplasm (formerly CD4+/cd56+ Hematodermic Neoplasm)

PCMZL = Primary cutaneous marginal zone lymphoma

PCFCCL = Primary cutaneous follicle center cell lymphoma (follicular lymphoma)

LyP = Lymphomatoidpapulosis

ALCL = Anaplastic large cell lymphoma

CD30+ LPD = CD30+ lymphoproliferative disorders (i.e. LyP and ALCL)

UP / MPCM = Urticaria pigmentosa / Maculopapular cutaneous mastocytosis

Part I. The Epidermotropic / Adnexotropic Pattern

T-Cell Pseudolymphomas

Diagnostic Criteria

- A cutaneous infiltrate composed predominantly of T-lymphocytes that simulates lymphoma clinically and histopathologically but proves to be reactive rather than neoplastic

Differential Diagnosis

- T-cell lymphomas
- T-cell dermatoses (e.g actinic reticuloid, lichen planus, lichen sclerosus, etc)
- Drug eruptions, insect bite reactions, viral infections

Pitfalls

- Some T-cell pseudolymphomas contain clonal T-cell populations
- Cause is not always identifiable; many are due to viruses, drugs, or insect bites

Pearls

- Features favoring pseudolymphoma over genuine lymphoma
    - Mixed infiltrate (T-cells, B-cells, eosinophils, neutrophils, macrophages, etc)
    - B-cell aggregates surrounded by T-cells (recapitulating lymphoid follicles)
    - Onset within days to months of new medication(s)
- Look carefully for viral cytopathic effect as a clue to a viral induced pseudolymphoma
- No clear-cut diagnostic criteria exist for T-cell pseudolymphomas; diagnosis requires clinical correlation
- Occasionally definitive diagnosis is only possible by excluding other entities, which may require months or occasionally even years

Mycosis Fungoides

Diagnostic Criteria

- Indolent course; slow progression from patches to plaques to tumors
- Lichenoid infiltrate of benign lymphocytes with scattered neoplastic T-lymphocytes in epidermis, particularly in basal layer
- Skin-limited for a protracted period
- Lymph nodes and viscera involved later in course; bone marrow involvement rare
- CD2 / CD3 / CD4 / CLA +
- CD7 - often
- CD8 -
- CD30 + (usually large cell transformation)

Differential Diangosis

- Inflammatory interface dermatoses, such as lichen planus, lichen sclerosus, contact dermatitis, and lichenoid drug eruptions
- Sezary syndrome
- 'Parapsoriasis'
- LyP (Type B)
- CD8+ Epidermotropic lymphomas (especially CD8+ variant of MF)
- ATLL

Pitfalls

- Rare CD8+ / CD4- cases of MF exist; they are otherwise typical of conventional MF
- Differentiation of CD8+ MF from CD8+ Aggressive Epidermotropic Lymphoma is based on clinical course; histopathologic differences cannot reliably differentiate them
- MF may affect children and adolescents (one of very few primary cutaneous T-cell lymphomas that do so); CD8 positivity is more frequent in these cases
- Rarely, erythroderma develops early in MF and may mimic Sezary syndrome (SS); such cases must be shown to lack the other diagnostic criteria of SS (see below)
- "Loss of CD7" often touted as a clue to MF, but is unreliable by IHC in patch stage MF
- Clonal TCR rearrangement may not be detectable in early lesions
- Benign dermatoses that simulate MF Clonal TCR
- Large cell transformation of MF may be CD30+, requiring differentiation from other CD30+ lymphomas

Pearls

- *By definition,* diagnosis requires clinical correlation
- Extent of disease is most important prognostic factor
- Limited disease has an excellent prognosis (survival similar to that of age-matched persons without MF)
- Extracutaneous dissemination indicates poor prognosis
- Other adverse prognostic factors: Age > 60 yrs, elevated LDH; large cell transformation
- Large cell transformation defined as > 25% large cells
- Evidence –based criteria for diagnosis of early / patch stage MF exist (see Table)

Variants of Mycosis Fungoides

Folliculotropic / Adnexotropic Variant

- Neoplastic infiltrate centered on follicular epithelium or (less commonly) other adnexal epithelium with relative sparing of epidermis
- Follicular mucinosis common but not invariably present
- Other features similar to conventional MF
- Less responsive to most therapies than conventional MF
- Benign forms of follicular mucinosis occur, and must be excluded

Pagetoid Reticulosis Variant

- Histopathologic features similar to conventional MF but only one or several lesions are present and there is no progression
- Predilection for breast skin

Granulomatous Slack Skin Variant

- Patients develop folds of lax skin in axilla or groin that contain numerous macrophages and multinucleated giant cells in addition to neoplastic T-cells with the immunophenotype of conventional MF

Sezary Sydrome

Diagnostic Criteria

Classic triad

1. Erythroderma
2. Generalized lymphadenopathy
3. Clonal T-cell population with cerebriform nuclei

+

One or more of the following secondary criteria:

- 1000/ mm3 absolute Sezary cell count
- CD_4:CD_8 ratio > 10 (by Flow cytometry)
- Abnormal phenotype (Loss of one or more T-cell antigens CD_2, CD_3, CD_4, CD_5, CD_7, CD_{26})

Differential Diagnosis

- MF (although SS tends to be less epidermotropic)
- Other causes of erythroderma (correlation with clinical data, peripheral blood findings, and other criteria necessary)

Pitfalls

- Histopathologic features are nonspecific in > 30% of skin biopsies
- Cannot be differentiated from MF without clinical data and peripheral blood criteria

Pearls

- Adults exclusively, usually age 60+
- Onychodystrophy, pruritus, ectropion, alopecia, palmoplantar hyperkeratosis common
- Loss of CD_7 and CD_{26} characteristic of Sezary syndrome
- Aggressive; 5 year survival = 10-20%
- Opportunistic infections are most common cause of death

Adult T-Cell Leukemia / Lymphoma

DIAGNOSTIC CRITERIA

- A clonal T-cell population with monoclonal integration of HTLV-1 virus
- **CD25** / CD2 / CD3 / CD5 +
- CD7 -
- CD30 - / +
- Commonly CD4+ / CD8-
- Rarely CD4- / CD8+
- Rarely CD4+ / CD8+

VARIANTS

1. Acute: Leukemia with markedly elevated WBC count, generalized lymphadenopathy, generalized erythema, papules, or nodules, hypercalcemia, constitutional symptoms, elevated LDH, eosinophilia; opportunistic infections common
2. Chronic: Exfoliative rash; mildly elevated WBC count; no hypercalcemia
3. Smoldering: Rash or papules, lung involvement, normal WBC count, no hypercalcemia

DIFFERENTIAL DIAGNOSIS

- Broad differential diagnosis since three variants exist, each with different clinical and histopathologic features
- Various other types of T-cell lymphoma and inflammatory processes should be considered in the differential

PITFALLS

- Skin lesions can vary so much in clinical appearance that lymphoma may not be in the clinical differential
- Histopathologic variability among variants; for example, the cells are usually medium to large and pleomorphic in the acute type, but small cells predominate occasionally, even in acute type
- Epidermotropism with microabscess formation can be identical to MF
- Atypical EBV-positive B-cell proliferations (some mimicking Hodgkin lymphoma) may occur (secondary to immunodeficiency resulting from T-cell dysfunction)
- Histopathologic features often nonspecific in 'smoldering' type

PEARLS

- Most patients from endemic regions: Southwest Japan, Caribbean Islands, South America, Central Africa
- CD25 positivity is a key feature
- Skin lesions are most common site of extranodal involvement and are present in more than 50% of cases
- Widely disseminated nature of disease allows differentiation from indolent primary cutaneous lymphomas
- BUT a smoldering variant limited to skin may exist

Aggressive CD8+ Epidermotropic Lymphoma

DIAGNOSTIC CRITERIA

- **Aggressive course**
- Ulcerated plaques and tumors at onset
- No history of MF or CD8+ LyP
- CD8+ cytotoxic T-cells, usually epidermotropic but also nodular and diffuse dermal aggregates
- βF1 / CD3 / CD7 / CD8 / TIA1 +
- CD4 -

DIFFERENTIAL DIAGNOSIS

- γ/δ T-cell lymphoma (see below)
- **CD8+ variant of MF**
- CD8+ variant of LyP
- Actinic reticuloid
- SPTL

PITFALLS

- May be difficult or impossible to differentiate from γ/δ T-cell lymphoma, and the two may represent variants of the same disease
- βF1 occasionally negative (neoplastic cells may lose expression)

PEARLS

- Diagnosis requires clinical correlation (to exclude MF and LyP)
- Mucosal involvement common

Part II. The Dermal + / - Subcutaneous Pattern

CD30+ Lymphomas / Lymphoproliferative Disorders

DIAGNOSTIC CRITERIA

- Infiltrate of CD30+ lymphocytes that are large and pleomorphic or immunoblastic-like
- Indolent course
- CD_4 +
- CD_3, CD_5 - / +
- CLA + (unlike systemic ALCL)
- ALK - (unlike many systemic ALCL)
- CD15 - (unlike Hodgkin's lymphoma)
- CD_{56} - / +
- IRF_4 translocation -/+

- Clinical features differentiateLyP from ALCL:

LYP

- Crops of numerous centrally necrotic, crusted papules that regress spontaneous and then recur at another site

ALCL

- One or several grouped plaques or tumors that persist (occasionally regress)

DIFFERENTIAL DIAGNOSIS

LYP

- Pityriasislichenoides
- Insect bite reactions / scabies
- Viral infections

ALCL

- CD30+ pseudolymphomas (same as LyP)
- Melanoma, sarcoma, carcinoma, metastatic tumors
- Secondary skin involvement by systemic variant of ALCL
- Post-transplant lymphoproliferative disorders

PITFALLS

- CD30+ lymphocytes common in many nonneoplastic conditions
- Large cell transformation of MF often CD30+; MF must be excluded
- Large atypical cells may simulate sarcoma, melanoma, carcinoma if CD30 not performed

PEARLS

- By definition, clinical features (i.e. number and behavior of lesions) determine type
- Extracutaneous dissemination of primary cutaneous ALCL is rare (10%), usually limited to regional nodes, and prognosis remains similar to those with skin-limited disease
- Primary cutaneous ALCL is almost always ALK- (i.e., it lacks the t2;5 translocation)
- Post-transplant lymphoproliferative disorders are often EBV+

B-Cell Pseudolymphomas

Diagnostic Criteria

- A cutaneous infiltrate that contains numerousB-lymphocytes that simulates lymphoma clinically and histopathologically but proves to be reactive rather than neoplastic

Differential Diagnosis

- Genuine B-cell lymphomas
- Tumid lupus
- Borrelioisis / Lyme disease
- Post-transplant lymphoproliferative disorders and other immuno compromise related lymphoproliferative disorders
- Nodular scabies
- Drug eruptions (B-cell type), vaccine injection site reactions, secondary syphilis, persistent insect bite reactions, viral infections, tattoo reactions, angiolymphoid hyperplasia with eosinophilia (ALHE)

Pitfalls

- Some B-cell pseudolymphomas may contain B-cell and T-cell clones or 'pseudoclones'
- Some B-cell pseudolymphomas probably do evolve into genuine low-grade B-cell lymphomas (particularly marginal zone and follicle center cell type) due to persistent antigenic stimulation
- Cause is not always identifiable

Pearls

- Features favoring pseudolymphoma over genuine lymphoma include a mixed infiltrate, and recapitulation of 'normal' lymph node architecture
- Dense B-cell infiltrates on the ear, around the nipple and on the scrotum are far more likely to be Borreliaburgdorferi reactions than genuine lymphomas

Primary Cutaneous Marginal Zone Lymphoma (PCMZL)

DIAGNOSTIC CRITERIA

- Indolent behavior
- Solitary or grouped red or violet papules or plaques on trunk or extremities (especially back and upper arms)
- Dermis and upper subcutis containing:
    1. B-cells including lymphoplasmacytoid cells, plasma cells, and marginal zone cells (cells with abundant pale cytoplasm and small indented nuclei, sometimes referred to as centrocyte-like or monocytoid-like B-cells)
    2. Evidence of clonality (see below)
    3. Scattered centroblast and immunoblast like B-cells but no confluent growth of large cells
    4. Reactive T-cells + / - other inflammatory cell types
- Evidence of clonality:
    A. Monotypic expression of light chains detected by IHC or ISH
    B. Clonal rearrangement of immunoglobulin heavy-chain gene detected by molecular methods
- CD20/CD79a/ BCL2 +
- CD5 / CD10 / BCL6 -

DIFFERENTIAL DIAGNOSIS

- B-cell pseudolymphoma
- Primary cutaneous follicle center cell lymphoma (PCFCCL)
- Plasmacytoma

PITFALLS

- Cases with nodules / follicles may simulate PCFCCL
- Myeloma and other plasma cell neoplasms may simulate PCMZL with extensive plasmacytoid differentiation
- 'Blastic transformation' may occur with multiple recurrences and suggests more aggressive behavior (but is very rare)
- Other types of B-cell lymphoma may exhibit extensive plasmacytoid differentiation and light chain restriction
- Light chain restriction is not evident in all biopsies

PEARLS

- Monotypic light chain expression by plasma cells at periphery of nodules is particularly helpful
- In situ hybridization is usually more sensitive than IHC for demonstrating light chain restriction
- Increased number of Ki-67 (MIB-1)+ cells at periphery of nodules is characteristic
- Immunocytoma and plasmacytoma likely represent variants of PCMZL
- Rare association with Borrelia infection in Europe but not in United States
- Association with autoimmune diseases uncommon (coexisting autoimmune disorder suggests secondary cutaneous involvement by underlying systemic marginal zone lymphoma rather than primary cutaneous variant)

- 5 year survival approximately 100%

Primary Cutaneous Follicle Center Cell Lymphoma (PCFCCL)

Diagnostic Criteria

- Relatively indolent
- Solitary or grouped papules, plaques, tumors
- Centrocytes admixed with variable number of centroblasts
- No confluent sheets of centroblasts
- Nodular, diffuse, or mixed growth patterns*
- CD79a / CD20/PAX5 +
- BCL6 +
- CD10 - / +
- MUM-1 -
- BCL2 - (in neoplastic B-cells)

Differential Diagnosis

- Reactive B-cell pseudolymphomas
- Primary cutaneous marginal zone lymphoma
- Diffuse large B-cell lymphoma
- Secondary involvement of skin by systemic B-cell lymphoma

Pitfalls

- Reactive germinal centers may be present, simulating a benign pseudolymphoma
- T-cell rich and macrophage-rich variants exist and these cells may outnumber and obscure the large neoplastic B-cells

Pearls

- Lesions often have erythematous border
- Predilection for head and trunk, especially scalp and back
- Middle aged adults (rather than elderly adults, as in leg-type diffuse large B-cell lymphoma)
- Clues to differentiating PCFCCL from reactive cutaneous lymphoid hyperplasia (B-cell pseudolymphomas with germinal center formation) include:
    - Ill-defined follicles without 'polarization' ("light and dark" zones)
    - A monomorphic proliferation of BCL6+ follicle center cells
    - Absence of tingible body macrophages
    - Decreased Ki-67 (MIB-1) index in comparison to reactive germinal centers
    - Absent or attenuated mantle zones
- Secondary involvement of skin by systemic follicular lymphoma must be excluded by staging work-up
- CD10 may be expressed in nodular pattern but is rare in diffuse pattern
- Neither grading nor growth pattern has clinical significance (as it does in systemic follicular lymphoma)
- "Reticulohistiocytoma of the dorsum" and "Crosti's lymphoma" are older terms used for what is now called PCFCCL

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Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type (DLBCL-LT)

Diagnostic Criteria

- Rapidly growing red or violaceous tumors
- Confluent sheets of medium to large B-cell with round nuclei, prominent nucleoli, and coarse chromatin (resembling centroblasts and immunoblasts)
- Diffuse growth pattern
- **BCL2 +++**
- BCL6 +/-
- CD10 -
- Mum-1 +

Differential Diagnosis

- PCFCCL with large cells

Pitfalls

- T-cell rich and macrophage-rich variants exist and these cells may outnumber and obscure the large neoplastic B-cells
- As in other B-cell lymphomas, reactive germinal centers may be present, simulating a benign pseudolymphoma / reactive follicular lymphoid hyperplasia

Pearls

- Predilection for legs (less than 10% occur at other sites) of elderly females
- Tend to extend into subcutis
- Fewer small reactive lymphocytes than other cutaneous B-cell lymphomas
- Relatively aggressive, with approximately 40% developing extracutaneous disease
- 5 yr survival 55%
- Multiple lesions at presentation confers worse prognosis

LymphomatoidGranulomatosis (LyG)

DIAGNOSTIC CRITERIA

- An angiocentric and angiodestructive infiltrate of **EBV+ B-cells** admixed with reactive T-cells

DIFFERENTIAL DIAGNOSIS

- 'Granulomatous vasculitis' (e.g. Wegener's granulomatosis)
- T-cell lymphomas (since T-cells may predominate numerically)
- EBV+ lymphomas and lymphoproliferative disorders

PITFALLS

- Early lesions may contain only a few of the neoplastic B-cells
- Wegener's and other granulomatous

PEARLS

- Most cases exhibit at least a few histopathologic findings that the process is reactive rather than neoplastic (infiltrate is mixed, viral cytopathic effect is evident, etc)
- Progresses to higher grade with time and ultimately may be indistinguishable from diffuse large B-cell lymphoma

Extranodal NK / T-Cell Lymphoma, Nasal Type

DIAGNOSTIC CRITERIA

- Aggressive course
- NK immunophenotype> T-cell phenotype
- CD3- / CD3 epsilon+ / CD2+ / CD56+ / TIA1+ / Granzyme +/ EBV+
- Rare CD56- cases must be EBV+ and express cytotoxic markers
- Plaques and tumors on mid-face, trunk, and extremities
- Dermis, subcutaneous, occasionally epidermotropic

DIFFERENTIAL DIAGNOSIS

- Lymphomatoidgranulomatosis
- Angioimmunoblastic T-cell Lymphoma
- Wegener's granulomatosis (and other 'granulomatous' vasculitides)
- NK-cell leukemia involving skin
- Rarely ALCL may express CD56

PITFALLS

- Angiocentricity and mixed inflammatory infiltrate common, causing confusion with LyG, Wegener's, Angioimmunoblastic T-cell lymphoma, etc
- May be confused with NK-cell leukemia (which involves skins and is also EBV-associated)
- LMP-1 inconsistently expressed; use EBER for EBV
- TCR gene usually in germ-line configuration (no T-cell clonality)
- CD56 occasionally expressed in ALCL, so always do CD30 and r/o ALCL
- Hydrovacciniforme-like CTCL is a rare EBV-associated cytotoxic T-cell lymphoma that affects children in Latin America and Asia and must not be confused with NK/T-Cell lymphoma, nasal type

PEARLS

- Skin is second most common site of involvement after nasal cavity / nasopharynx, and treatment is same, so differentiating a "primary cutaneous" form is not necessary
- Median survival 5 months if not limited to skin; 27 months if skin only
- Usually adult men
- Asia, Central American, South America have highest incidence

BlasticPlasmacytoid Dendritic Cell Neoplasm (BPDCN)

DIAGNOSTIC CRITERIA

- Aggressive course
- Dermal and subcutaneous infiltrate of monomorphic but blastic cells (large and undifferentiated cells)
- CD4+ / CD56+ / CD8- / CD7 + / CD45RA+ / sCD3-/ cCD3 epsilon+ (IHC) / TIA-1 - / Granzyme B - / Perforin - / CD123+ / TCL1+ / EBV-
- T-cell receptor genes in germline configuration

PITFALLS

- Difficult / impossible to distinguish from AML in some cases
- CD68 may be positive (as in myelomonocytic leukemia)
- TdT may be positive (as in lymphoblastic lymphomas)

DIFFERENTIAL DIAGNOSIS

- Leukemia cutis (esp. especially myelomonocytic, lymphoblastic, and myeloblastic)
- NK/T-cell lymphoma, nasal type
- γ/δ T-cell lymphoma

PEARLS

- BPCDN considered a variant of acute myeloid leukemia by most
- Myeloperoxidase and lysozyme negative (differentiates from other types of AML)
- Skin is frequently the site of initial presentation
- 50% have involvement of marrow, nodes, peripheral blood at time of presentation
- Frequent mitoses, but…
- Inflammatory cells, necrosis, and aniocentricity / angio invasion usually ABSENT (differentiates it from NK/T-cell lymphoma)
- CD3 epsilon (detected by IHC) often positive, BUT *surface* CD3 (detected by flow cytometry) is absent, differentiating it from T lymphoblastic lymphoma
- Median survival 14 months

γ/δ T-Cell Lymphoma

DIAGNOSTIC CRITERIA

- Aggressive course
- Disseminated plaques / nodules / tumors, especially on extremities
- Involvement of mucosa and other extracutaneous sites
- Apoptosis, necrosis, angioinvasion common
- TCRγ+/ βF1-/CD3+/CD5-/CD7CD56+/TIA1+ / Granzyme B+ / Perforin+
- Usually $CD4^-$ / CD8+

DIFFERENTIAL DIAGNOSIS

- SPTL
- Lupus, especially lupus panniculitis and tumid lupus
- BPDCN (CD56+/CD4+)

PITFALLS

- Epidermotropic, dermal, and subcutaneous involvement may be present simultaneously and may vary among sites biopsied
- 'Rimming" common (but NOT specific)
- βF1 expression may be lost by neoplastic cells, causing an α/β lymphoma to be confused for a γ/δ T-cell lymphoma

PEARLS

- Current classifications separate γ/δ T-cell lymphoma from SPTL (which is α/β)
- Median survival 15 months (compared to 82% disease specific survival in SPTL)
- Unknown whether a true 'cutaneous variant' exists; may be part of a spectrum of 'mucocutaneousγ/δ T-cell lymphoma'
- Unlike SPTL, γ/δ T-cell lymphoma tends to involve dermis in addition to subcutis
- Spleen, node, and marrow involvement rare (unlike most other peripheral T-cell lymphomas)
- TCRγ+ immunohistochemical staining now available for paraffin embedded sections

Myelogenous Leukemia

DIAGNOSTIC CRITERIA

- Papules, plaques, or tumors, localized or generalized, composed of dense infiltrates of atypical cells that express one or more of the following markers:
  - Myeloperoxidase
  - NASDCL (Leder stain)
  - CD4
  - CD13
  - CD14
  - CD15
  - CD33
  - CD68
  - CD117

PITFALLS

- LCA often negative
- Expression of CD56, and CD123 may occur in some cases of AML, making distinction from BPDCN difficult
- S100 may be expressed by some forms of AML, causing potential confusion with Langerhans cell histiocytosis and other dendritic cell neoplasms
- Phenotype of cutaneous lesions may differ from that in peripheral blood and bone marrow

PEARLS

- Since classification of AML is now largely based on specific translocations/molecular markers and flow cytometricimmunophenotyping, and the phenotype of skin lesions may differ from that of bone and peripheral blood, specific immunophenotyping by IHC on skin biopsies is generally not recommended
- More 'mature' forms of AML are those most likely to involve the skin (e.g. "myelomonocytic" AML)
- Mucosa is commonly involved in addition to skin
- "Aleukemic leukemia cutis" describes skin lesions of AML in patients without other evidence of leukemia; all of these patients eventually develop leukemia, usually soon after skin lesions appear
- No significant difference in prognosis has been shown between patients with cutaneous involvement and those without it
- Skin involvement by chronic myelongenous leukemia (CML) and myelodysplastic syndromes occurs but is rare

Langerhans Cell Histiocytoses(& Other Histiocytic / Dendritic Cell Tumors)

Langerhans Cell Histiocytoses

Diagnostic Criteria

- Clonal infiltrate of Langerhans cells that are ovoid and devoid of dendritic cell processes
- CD1a +
- S100 +
- CD4 +
- Langerin +
- Birbeck granules +
- Vimentin +
- CD68 +
- HLA-DR +

Differential Diagnosis

- Rosai-Dorfman Disease (Benign Sinus Histiocytosis with Massive Lymphadenopathy)
- Juvenile xanthogranuloma, reticulohistiocytoma, and other forms of xanthogranuloma
- Dendritic cell tumors

Pitfalls

- CD4 positivity may lead to confusion with a T-lymphocyte neoplasm if other markers are not used
- Osteoclast-like giant cells, eosinophils, neutrophils and lymphocytes may accompany LCH cells and sometimes the inflammatory milieu predominates, obscuring the underlying Langerhans neoplasm
- Later lesions may be dominate by
- Differentiation of congenital self-healing Langerhans cell histiocytosis (Hashimoto-Pritzker) from other forms of LCH requires clinical correlation and follow-up to exclude progression / systemic disease
- Association between LCH and T-lymphoblastic lymphoma

Pearls

- Clinical course is related to staging at presentation
- Survival 99% or greater with unifocal disease BUT only 33% for infants or young children with multisystemic disease who do not rapidly respond to therapy
- Involvement of bone marrow, liver, and lung are high risk factors
- Progression from solitary lesion to multisystem involvement occurs, usually in infants
- Extent of disease is a more important prognostic factor than age
- Hemophagocytic syndrome is a rare complication
- Unifocal disease more common in older children and young adults

Cutaneous Mastocytosis

Urticaria Pigmentosa (Maculopapular Cutaneous Mastocytosis)

DIAGNOSTIC CRITERIA

- Papules and macules composed of mast cell aggregates that fill the papillary dermis and usually extend into the dermis as diffuse sheets
- No evidence of systemic involvement*

Diffuse Cutaneous Mastocytosis

DIAGNOSTIC CRITERIA

- Diffuse thickening of skin, without discrete lesions
- Mast cells arranged in a band like distribution in the papillary dermis or in diffuse sheets that occupy the entire dermis
- No evidence of systemic involvement*

Solitary Mastocytoma

DIAGNOSTIC CRITERIA

- A solitary lesion composed of aggregates of mast cells within the dermis, with or without extension into the subcutis
- No evidence of systemic involvement*

For All Forms of Cutaneous Mastocytosis

Mast cell immunophenotype:

- Tryptase + (most specific marker)
- CD117 +
- CD68 +
- CD33 +
- CD45 +
- CD14/15/16 - (absence helps exclude myelomonocytic leukemia)
- CD25/CD2 + in neoplastic mast cells (but difficult to use in sparse infiltrates)

DIFFERENTIAL DIAGNOSIS

- Systemic mastocytosis (see Criteria, below)
- Inflammatory infiltrates rich in mast cells (e.g. urticaria)

PITFALLS

- In adults, urticariapigmentosa / maculopapular cutaneous mastocytosis may contain mast cells in numbers that do not exceed those of urticarial and other inflammatory processes
- Mast cell aggregates occasionally resemble melanocytic nevi and other neoplasms at first glance
- Systemic mastocytosis must be excluded for definitive diagnosis to be made, yet many adults who have UP / MPCM are eventually found to have systemic disease (see below)

PEARLS

- Urticariapigmentosa / maculopapular cutaneous mastocytosis may affect children and adults
- In children, lesions tend to be larger and papules usually predominate
- In adults, lesions are usually more widely disseminated, have a macular appearance, and contain fewer mast cells
- In children, cutaneous mastocytosis has a favorable outcome and lesions may regress spontaneously, especially at puberty; systemic involvement seems to be uncommon
- In adults, lesions usually persist and systemic disease is often detected eventually; **however**, it is usually the **indolent** form of systemic mastocytosis
- Indolent systemic mastocytosis has a good prognosis (usually a normal life expectancy)
- Adverse prognostic factors include late onset of symptoms, absence of cutaneous lesions, thrombocytopenia, elevated LDH, elevated alkaline phosphatase, hepatosplenomegaly, anemia, bone marrow hypercellularity, peripheral blood smear abnormalities.

CRITERIA FOR SYSTEMIC MASTOCYTOSIS

MAJOR:

- Involvement of bone marrow and / or other extracutaneous sites by aggregates of mast cells (aggregate > 15 mast cells)

MINOR:

- More than 25% of mast cells in marrow or other extracutaneous sites have spindled morphology or are atypical
- Detection of activating point mutation at codon 816 in KIT in extracutaneous mast cell aggregates
- Mast cells in extracutaneous sites express CD2 and / or CD25
- Serum total tryptase persistently exceeds 20 ng/mL (in absence of a clonal myeloid disorder)

Part III. The Subcutaneous Pattern

SPTL

DIAGNOSTIC CRITERIA

- Indolent course
- Pleomorphic infiltrate of small and medium sized α/β cytotoxic CD8+ T-cells confined predominantly to subcutis
- βF1 +/ CD4-/ CD8+ / CD56- / TCRγ-

DIFFERENTIAL DIAGNOSIS

- Lupus panniculitis / profunda
- γ/δ T-cell lymphoma
- Infectious panniculitis
- Erythema nodosum
- "Atypical lobular panniculitis" (Magro et al)

PITFALLS

- ANA may be positive (complicating differentiation from lupus profunda)
- 'Rimming' common but not specific to SPTL

PEARLS

- Lupus panniculitis is a rare expression of cutaneous lupus, especially if isolated to legs (i.e, lupus panniculitis localized to legs is SPTL until proven otherwise)
- Some reports suggest co-existence of lupus panniculitis and SPTL
- Necrosis, small reactive lymphocytes, macrophages, and granuloma formation may occur (rare features in B-cell lymphomas involving subcutis)

TABLE 1. COMMON BENIGN MIMICS OF HEMATOLYMPHOID NEOPLASMS

PATTERN	NEOPLASM	BENIGN MIMICS
EPIDERMOTROPIC / ADNEXOTROPIC	MYCOSIS FUNGOIDES	LYMPHOMATOID DRUG ERUPTION LYMPHOMATOID CONTACT DERMATITIS ACTINIC RETICULOID LICHEN SCLEROSUS PIGMENTED PURPURICDERMATOSES PITYRIASISLICHENOIDES SECONDARY SYPHILIS LICHENOID KERATOSIS
	CD8+ AGGRESSIVE EPIDERMOTROPIC LYMPHOMA	ACTINIC RETICULOID PITYRIASISLICHENOIDES
	ATLL	ACTINIC RETICULOID
	LYP TYPE B	PITYRIASISLICHENOIDES / PLEVA
DERMAL +/ - SUBCUTIS	MYCOSIS FUNGOIDES, PLAQUE / TUMOR STAGE	LYMPHOMATOID DRUG ERUPTION INSECT BITE REACTION SECONDARY SYPHILIS BORRELIOSIS / LYME DISEASE TUMID LUPUS LUPUS PANNICULITIS
	CD30+ LPDS	LYMPHOMATOID DRUG ERUPTION INSECT BITE REACTION SCABIES INFESTATION VIRAL INFECTIONS - ORF - MILKER'S NODULE - HERPES VIRUSES - MOLLUSCUMCONTAGIOSUM)
	LANGERHANS CELL HISTIOCYTOSIS	SCABIES INFESTATION INSECT BITE REACTION XANTHOGRANULOMAS
	B-CELL LYMPHOMAS	LYMPHOMATOID TATTOO REACTION LUPUS PANNICULITIS LYMOMATOID DRUG ERUPTION, B-CELL PREDOMINANT SECONDARY SYPHILIS ACRALPSEUDOLYMPHOMATOUSANGIOKERATOMA OTHER B-CELL PSEUDOLYMPHOMAS
	GAMMA-DELTA T-CELL LYMPHOMA	LUPUS PANNICULITIS
	NK / T-CELL LYMPHOMA	WEGENER'S GRANULOMATOSIS OTHER 'GRANULOMATOUS VASCULITIDES'
	LEUKEMIA CUTIS & BLASTICPLASMACYTOID DENDRITIC CELL NEOPLASM	EXTRAMEDULLARY HEMATOPOIESIS LEUKEMIA-LIKE DRUG ERUPTION LEUKEMIA-LIKE REACTION TO TOPICAL IRRITANTS
	SMALL-MEDIUM T-CELL LYMPHOMA	ANGIOLYMPHOID HYPERPLASIA WITH EOSINOPHILIA (ALHE)
	MASTOCYTOSIS	URTICARIA URTICARIA-LIKE INFLAMMATORY PROCESSES
SUBCUTIS	SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA	LUPUS PANNICULITIS

TABLE 2. CRITERIA USEFUL FOR THE DISTINCTION OF EARLY PATCH STAGE MF FROM INFLAMMATORY DERMATOSES

MORE SPECIFIC	LESS SPECIFIC
Microabscess Formation (Pautrier / Darier)	Pagetoid distribution of intraepidermallymphs
Lymphocytes in Epidermis Larger than those in Dermis	Exocytosis of Lymphocytes with Paucity of Spongiosis
Halo Lymphocytes	Basilar Lymphocytes
Four or more Contiguous Lymphocytes in Basal Layer	Small or 'normal sized' convoluted Lymphocytes
Convoluted Lymphocytes Equal in Size to Basilar Keratinocytes	Papillary Dermal Fibrosis ('Wiry Collagen")

TABLE 3. FEATURES OF SPTL VERSUS γ/δT-CELL LYMPHOMA

SPTL	γ/δT-CELL LYMPHOMA
5 year survival > 80%	5 year survival < 1%
More common	Very rare
Usually limited to subcutis	Usually involves dermis in addition to subcutis
CD8+ / CD_4- neoplastic cells	CD8- / CD_4- neoplastic cells
CD56-	CD56+
Hemophagocytic syndrome rare	Hemophagocytic syndrome more common

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NOTES

NOTES

Tropical and Extraordinary Diseases

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Geisinger Medical Center

Tropical and Extraordinary Disease

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Myiasis

- Infestation of tissue by larvae of Diptera (flies)
- *Dermatobia hominis* (human botfly) in warm humid, low land forests of Central and South America
- Female botfly glues her eggs to the abdomen of a captured insect. This vector then bites the host. The larvae sense the change in temperature, detach, and burrow into the subcutaneous tissue through the bite or a follicle. The larva grows and matures over 6-8 weeks before emerging.
- Subcutaneous mass with pore, usually on exposed sites: scalp, face, forearms, legs
- Undulating thick chitinous wall with 2 to 6 rows of dark pigmented setae prevent dislodgement
- Empty cystic space outlined by fibrin and eosinophilic infiltrate suggests myiasis or worm
- Occasionally only the pigmented setae will be present
- Can see a granulomatous response if the larva dies or parts are retained

DDX: Tick

- Do not burrow
- Often engorged with blood
- Thick chitinous wall and pigmented mouth parts
- Wedge shaped necrosis with neutrophilic infiltrate early and polymorphous infiltrate including eosinophils late

DDX: Tungiasis

- Acral lesion due to the sand flea
- Embedded near the surface with blood filled gut

Onchocercoma

- Nematode (round worm)
- *Onchocerca volvulus* in Africa
- Vector – *Simulium* (Black fly)
- Clinically skin can have 1) onchocercoma nodules due to adult worms or 2) pruritic papular rash 3) hanging groin (loose, atrophic skin that contains enlarged painless inguinal nodes) 4) sowda's reaction (pruritic, asymmetrical, darkly pigmented, chronic lichenified dermatitis of one body region), or blindness due to release of microfilariae that easily traverse the skin and connective tissue with extension to the lymphatics and anterior chamber of the eye
- Onchocercoma: Dermal mating ball of coiled worms with weak band of muscle surrounded by dense fibrosis. Adult female worm is gravid with paired uteri containing microfilariae

- Onchocerciasis: microfilaria (thin speckled thread) in skin with sparse perivascular and lymphohistiocytic infiltrate

DDX: Dirofilaria (nematode/round worm)

- Solitary with thick peripheral outer muscular wall
- Usually not gravid – uterine tubes without microfilaria

DDX: Sparganosis (cestode/flat worm/tapeworm)

- Has secretory tegument and no gut
- Loose stroma with wisps of smooth muscle (not striated) and internally calcified excrement

Mycetoma

- Tumefaction, draining sinuses, and grains (filamentous colonies)
- Grains surrounded by suppuration and granuloma forming sinus tracts
- Splendore–Hoeppli (pink amorphous immunoglobulin binding to periphery of grain)

Eumycetoma- usually hands or feet in tropical areas (Madura foot)

- Five micron thick, hollow fungal filaments form grains
- Dark grains: *Madurella mycetomatis, M. grisea, Exophiala jeanselmei*
- Light grains: *Pseudoallescheria boydii, Fusarium, Acremonium*, rarely dermatophytes

Actinomycetoma

- Light grains only: *Nocardia, Actinomyces, Streptomyces*
- Filamentous bacteria less than 1 micron in thickness

DDX: Botryomycosis

- Deep dermal colonies or grains of non-filamentous bacteria (usually *Staphylococci*)

Coccidioidomycosis

- Dimorphic fungus, *Coccidioides immitis*
- Spores inhaled from soil in southwestern US and Mexico (San Joaquin Valley Fever)
- Often verrucous with PEH and pus
- Large (10-80 micron) spherules with refractile wall and gray lacy and granular cytoplasm
    - Cells in various stages of endosporulation
    - Endospores (smaller than inflammatory cells)
    - No central nucleus

DDX: Rhinosporidiosis

- *Rhinosporidium seeberi* – found in stagnant water
- Now thought to be an aquatic protist
- Clinically red, friable papillomatous/polypoid lesions around nose or on conjunctival, rectal, or urethral mucosa that may resemble condylomata
- May have grayish flecks from transepidermal elimination of sporangia

- Large, thick walled, cystic sporangia (up to 300 microns) containing endospores that are larger than those in Coccidiomycosis (approximately the same size as inflammatory cells, 7-10 microns)
- Non-sporulating form, resembles Coccidioides spherules, but rhinosporidiosis has a central nucleus within each organism

Leishmaniasis

- Protozoa
- Old world: L*. tropica, L. major, L. aethiopica, and L. infantum*
- New world: *L. mexicana and L. braziliensis*
- Phlebotomus mosquito (old world) or Lutzomyia sand fly (new world) carries promastigotes
- Mixed infiltrate: lymphocytes, histiocytes, plasma cells, neutrophils
- Amastigotes (2-3 microns) are in histiocytes, best seen on Giemsa, with 1-micron nucleus and smaller rod-shaped paranuclear kinetoplast
- Vacuoles with organisms clustered at edge or lined up around the periphery of the vacuole like light bulbs on a movie theater sign = marquee sign

DDx: Parasitized histiocytes – "Ph Girl"

P – *Penicillium marneffei*
H – Histoplasmosis
G – Granuloma
I – Inguinale
R – Rhinoscleroma
L - Leishmaniasis

DDX: Histoplasmosis

- *Histoplasma capsulatum*
- Soil of Mississippi and Ohio river valleys
- Bird and bat feces, caves, chicken coops
- Yeasts (2-3 microns) are evenly dispersed within the giant cell or histiocyte
- Yeast appear surrounded by capsule (clear space) but really a pseudocapsule

Aspergillosis/Fusarium

- Histologically indistinguishable and both occur in neutropenic patients
- Vasculotropic resulting in cutaneous necrosis
- Congested vessels with slender, septate hyphae with delicate thin walls and 45 degree dichotomous branching
- Blue bubbly cytoplasm

DDX: Mucormycosis (Zygomycetes)

- Acute, rapidly developing, often fatal infection in ketoacidotic diabetics, burn, or immunosuppressed patients
- Similar vascular trophism with resultant cutaneous necrosis
- Eosinophilic, nonseptate, large (up to 30 micron diameter), thick-walled hyphae, hollow in cross-section with right-angle branching
- May have very little inflammation

Phaeohyphomycosis

- Defined as infection of dermis or soft tissue by pigmented (dematiaceous) hyphae
- Numerous different black molds implicated (*Alternaria, Bipolaris, Curvularia, Exophiala,* and *Phialophora*).
- Commonly see cystic granuloma (pseudocyst-no epithelial lining) in immunocompetent patients with or without a splinter
- Pigmented hyphae with bubbly cytoplasm can be seen in the wall

DDX: Chromoblastomycosis

- Pink scaly papule that slowly spreads and grows to large plaque with verrucous or nodular border and central atrophy
- Pseudoepitheliomatous hyperplasia with neutrophilic microabscesses and copper pennies /medlar bodies/sclerotic bodies
    - PEH and pus (DDX: "Here come big green leafy veggies**"**- **H**alogenoderma, **C**hromoblastomycosis, **B**lastomycosis, **G**ranuloma inguinale, **L**eishmaniasis, Pemphigus **V**egetans)

NOTES

NOTES

Selected Molecular Genetic Studies in Dermatopathology

Diya F. Mutasim, MD
University of Cincinnati

Molecular Techniques in Dermatopathology

Diya F. Mutasim, M.D.
Professor and Chair
Department of Dermatology
University of Cincinnati

I. Molecular Techniques

a. Comparative genomic hybridization (CGH).

b. Fluorescence in situ hybridization (FISH).

c. Polymerase chain reaction (PCR).

II. Comparative Genomic Hybridization (CGH)

a. Clinical application = differentiating malignant melanoma (MM) from benign melanocytic neoplasms (and identifying genetic markers of disease).

b. Technique

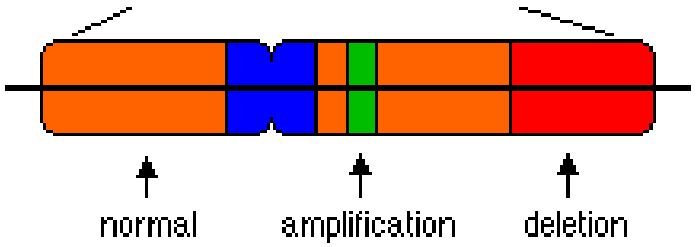
i. Whole-genome screening for chromosomal aberrations, specifically gains or losses (vs. use of specific probes in FISH).

ii. Can be performed on fresh/frozen or FFPE tissue.

iii. Tumoral DNA and (normal) reference DNA are labeled by different fluorochromes, e.g., green fluorescein for tumor DNA and red rhodamine for reference/normal DNA.

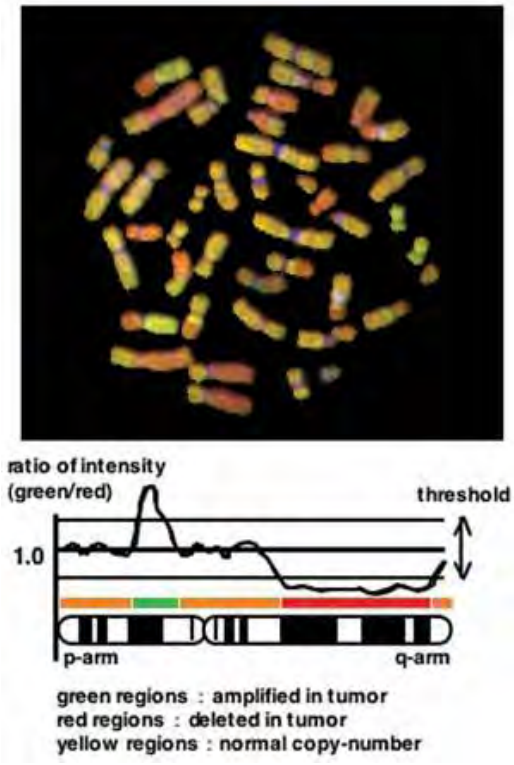
iv. The tumoral and reference DNA are hybridized simultaneously to normal metaphase chromosome spreads.

v. The relative amounts of tumor and reference DNA that are bound at the given chromosomal locus are dependent on the relative amount of those sequences in the two DNA samples.



vi. This can be quantitated by measurements of the ratio of green to red fluorescence. For example, gene amplification or chromosomal duplication in the tumor DNA produces an elevated green to red ratio while deletion or chromosomal loss cause the inverse.

vii. The fluorescence signals are then quantitatively analyzed by a digital image analysis system.



viii. A software program calculates intensity profiles for both colors and hence the green to red ratio along each chromosome.

c. Use of CGH in melanocytic neoplasms.

i. A significant difference in frequency and type of chromosome copy number aberrations was detected between melanoma (132) and nevi (54).

ii. Most frequent gains in melanoma were 6p, 1q, 7p, 7q, 8q, 17q, 20q.

iii. Most frequent losses in melanoma were 9p, 9qm, 10q, 10p, 6q, 11q.

iv. Spitz nevi showed characteristic copy number increase in chromosome 11p that was not present in any melanoma.

III. FISH

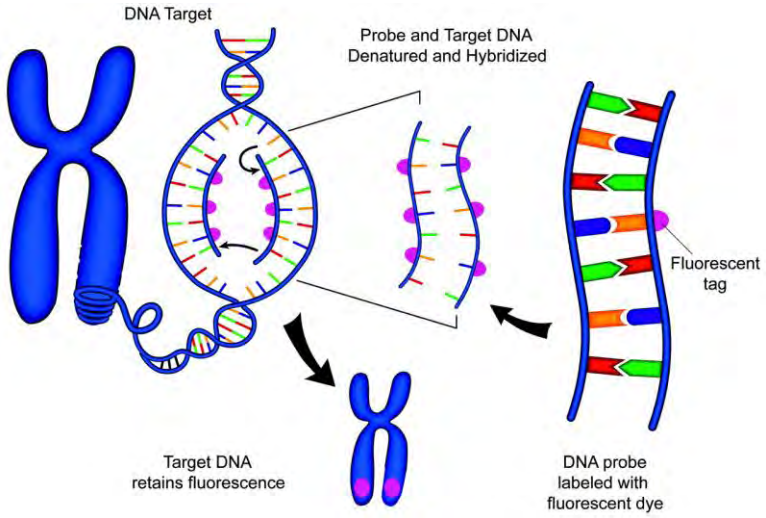
a. Much easier than CGH.

b. Uses information originally derived from CGH.

c. Detects aberrations of chromosome copy numbers in lesional cells by visualization under a fluorescent (or light) microscope.

d. Can be performed on FFPE tissue.

e. Uses hybridization of labeled complementary DNA probes that recognize sequences in specific chromosomal regions or genes that may be present in neoplastic cells.



f. Uses of FISH.

   i. Differentiation among melanocytic neoplasms.

ii. Evaluation of lymphoproliferative disorders.

1. Marginal Zone Lymphoma, ISH

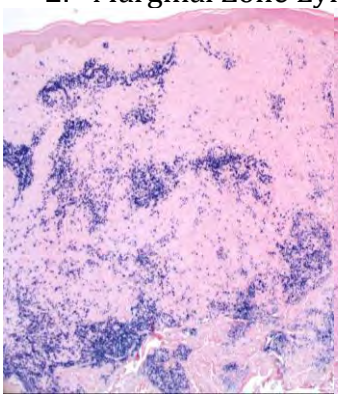


Figure 1: Kappa Chain

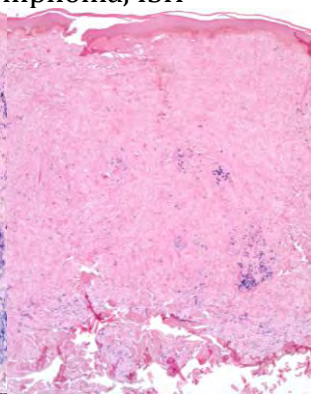


Figure 2: Lambda Chain

iii. Detection of infectious agents, e.g., HPV in digital SCC, Bowenoid papulosis and EDV.

g. Use of FISH in Melanocytic Neoplasms.

i. Chromosomal copy number abnormalities have been detected in melanoma cells by probes targeting 6p25 (RREB1), 6q23 (MYB), 11q13 (CCND1), and centromere 6 (Cep6).

ii. About four abnormalities are able to distinguish melanoma from nevi with 86.7% sensitivity and 95.4% specificity.

iii. Above gene abnormalities were present in 6 of 6 cases with ambiguous pathology. All were later confirmed to be MM because they metastasized.

iv. FISH is helpful in distinguishing between nevus tissue and melanoma tissue in the same specimen.

IV. PCR

a. Aim: Amplification of genetic material for further study.

b. Technique

i. Can be performed on fresh/frozen or FFPE tissue.

ii. Double-stranded DNA is heated to separate the strands.

iii. Cooling of the DNA in the presence of a set of two DNA primers allows the primers to hybridize to the DNA strands.

iv. Incubation with DNA polymerase initiates synthesis of DNA starting from the two primers.

v. The entire cycle is repeated many times.

vi. Newly synthesized DNA fragments serve as templates.

vii. The generated DNA fragments (amplicon) can be detected by a variety of techniques including gene scanning, heteroduplex or single-stranded conformational polymorphism analysis.

c. Practical uses of PCR

i. Detection of T cell clonality.

ii. Detection of B cell clonality.

iii. Detection of some pathogens.

1. HPV.
2. HSV and VZV (in persistent lesions).
3. *m. tuberculosis* (in erythema induratum).

V. References

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c. Gerami P et al. Fluorescence in situ hybridization (FISH) as an ancillary diagnostic tool in the diagnosis of melanoma. Am J Surg Pathol. 2009 Aug;33(8):1146-56.
d. Molecular Biology of the Cell. 4th edition. Alberts B, Johnson A, Lewis J, et al. New York: Garland Science; 2002.
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Tips and Comments from a Recent Diplomate

Garron Solomon, MD
CBLPath, Inc.

How to Prepare for the Dermatopathology Board Examination: Tips and Comments from a Recent Diplomate and Sample Questions

Garron J. Solomon ,M.D.
Staff Dermatopathologist
CBLPath, Inc.
Rye Brook, NY

Important Dates 2012

- Application/Registration:
  - Opens: February 2012
  - Final filing date: May 15, 2012 at 11:59 pm ET
  - Exam fee = $1800
- Late Application/registration:
  - Opens: May 16, 2012
  - Final filing date: June 15, 2012 at 11:59 pm ET
  - Requires a non-refundable late fee of an additional 50% of exam fee ($1800 + $900 = $2700)
- Program Director evaluations due: July 1, 2012
- Date assigments are posted: July, 2012
- Exam: September 11 or 12, 2012
- Results are posted: 4 to 6 weeks after exam

Exam Location/Hotel

- The American Board of Pathology (ABP) Exam Center:
  - 4830 West Kennedy Boulevard, Suite 689, Tampa, Florida, 33609
  - Website: http://abpath.org
  - Phone: 813-286-2444
- InterContinental Hotel
  - 4860 West Kennedy Boulevard, Tampa, Florida, 33609
  - Website: http://intercontampa.com
  - Phone: 813-286-4053 / 866-915-1557

Exam Day Schedule

- Registration (bring photo ID): 7:40 am
- Instructions and practice examination: 7:45-8:00 am
- Microscopic examination: 8:00 am-12:00 pm
  - 95 microscopic slides
  - 5 virtual slides
- Lunch break
- Written examination: 1:00-2:30 pm
  - 100 questions
- Practical examination: 2:45-4:45 pm
  - 100 questions

Comfort in Numbers

	Total Candidates		**First-Time Takers**			**Repeaters**		
	#	% Pass	#	# Pass	% Pass	#	# Pass	% Pass
2010	62	94	50	47	94	12	11	92
2009	65	78	59	47	80	6	4	67
2008	59	92	49	48	98	10	5	50
2007	59	85	36	34	94	23	17	74

Helpful Suggestions

- Start preparing as early as possible (during fellowship)
  - Keep in mind that you probably won't have much time to study after you have begun your new job
- Look at as many study sets as possible
- Get recuts of instructive cases
- See as many patients as possible (for pathology-trained fellows)
- Devise a study plan / calendar
  - Decide which sources you will use to prepare
- Make flashcards
- Take one or two weeks off before exam
  - Request time off as soon as you get hired
- Arrive in Tampa two days before scheduled exam
- Don't take too much with you to exam
  - Bring just flashcards and one small reference text

Exam Format / Content

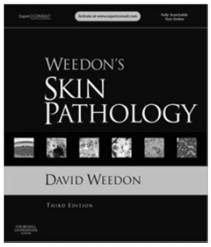
- Candidate must pass both written and practical portions of the exam in order to pass
- All questions are multiple-choice and in the one-best-answer format
- Questions designed to measure body of knowledge and problem-solving ability
- Practical exam includes images of gross lesions and special technical subjects including immunofluorescent, histochemical, microbiologic, and cytologic preparations

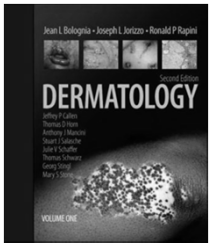
Exam Format / Content

- Subject areas covered include, but are not limited to:
  - Diagnostic dermatopathology and relative clinical and laboratory knowledge
  - Gross and microscopic diagnosis of skin disorders by direct visual inspection and light, fluorescent, and electron microscopy, and histochemical, bacteriologic, mycologic, virologic, and entomologic preparations
  - Laboratory management, quality assessment and assurance, patient care decision making, and consultation

Which books to use?

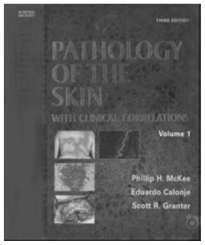
- Choose two reference texts

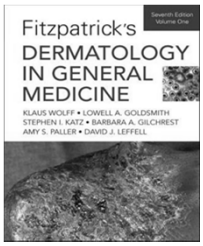




Which books to use?

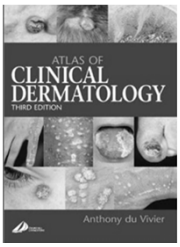
- Choose two reference texts

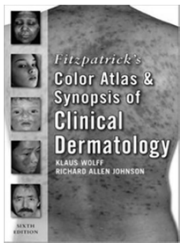




Which books to use?

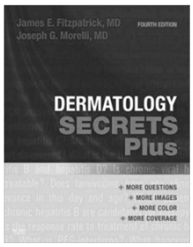
- Choose two clinical atlases





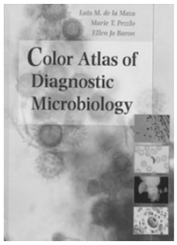
Which books to use?

- Read this book at the gym, on the subway, etc.



Which books to use?

- Best book for microbiology



Which books to use?

- Best book for immunofluorescence

Useful Websites

- Derm101 (http://derm101.com)
  - 900 Interactive Quizzes
- Johns Hopkins Dermatology Atlas and Quizzes (http://dermatlas.com/derm)
- Johns Hopkins Surgical Pathology Unknown Conference (http://pathology2.jhu.edu/sp)
- Dermatology In-Review Study Guide (http://dermatologyinreview.com/Galderma)

Board Review Course

- 26th Annual Combined Skin Pathology Course (Medical Education Resources; University of Pennsylvania)

Sample Questions

Written

1) Which of the following is/are mutated in epidermolysis bullosa simplex (EBS)

- A) α6-β4 integrin
- B) Keratins 5 and 14
- C) Laminin 5 and BP180
- D) Collagen VII
- E) Keratins 1 and 10

2) What of the following is paired incorrectly?

- A) Ichthyosis vulgaris: fillagrin gene
- B) X-linked ichthyosis: steroid sulfatase
- C) Lamellar ichthyosis: calcium ATPase 2C1
- D) Sjogren-Larsson syndrome: fatty aldehyde dehydrogenase
- E) Darier's disease: calcium ATPase 2A2

3) Which of the following is paired incorrectly?

- A) Mal de Meleda: SLURP-1
- B) Papillon-Lefevre syndrome: cathepsin C
- C) Erythrokeratodermia variabilis: connexin 26
- D) Howel-Evans syndrome: TOC gene
- E) Naxos syndrome: plakoglobin

4) A patient with "coast of maine" CALM and polyostotic fibrous dysplasia is likely to also show?

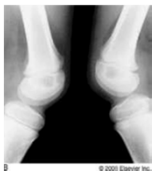
- A) psammomatous melanotic schwannoma
- B) pseudohypoparathyroidism
- C) bilateral vestibular schwannomas
- D) precocious puberty
- E) Lisch nodules

5) Which of the following is paired incorrectly?

- A) Pseudoxanthoma elasticum: angioid streaks
- B) Buschke-Ollendorf syndrome: dermatofibrosis lenticularis disseminata
- C) Lipoid proteinosis: eyelid string of pearls
- D) Marfan syndrome: ectopia lentis
- E) Focal dermal hypoplasia: osteopoikilosis

6) A patient with the following radiographic finding is likely to exhibit all of the following except?

- A) Triangular lunulae
- B) Pili torti
- C) Lester iris
- D) Mutation in LMX1B gene
- E) Glomerulonephritis



http://imaging.consult.com

7) Which of the following distinguishes multiple endocrine neoplasia (MEN) type 2b from 2a?

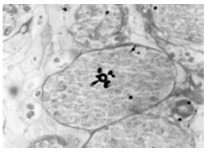
- A) Mucosal neuromas
- B) Pheochromocytoma
- C) Medullary thyroid carcinoma
- D) Marfanoid habitus
- E) A and D

8) Which of the following cyst(s) is not located in the midline?

- A) Bronchogenic cyst
- B) Cutaneous ciliated cyst
- C) Median raphe cyst
- D) Thyroglossal duct cyst
- E) Branchial cleft cyst
- F) B and E

9) The pictured GMS stain shows:

- A) Blastomycosis
- B) Histoplasmosis
- C) Sporotrichosis
- D) Paracoccidiomycosis
- E) Coccidiomycosis



http://www.humenhealth.com/

10) The correct immunophenotype of the neoplastic cell in lymphomatoid granulomatosis is:

- A) CD20 (-) EBV (+) CD3 (+)
- B) CD20 (+) EBV (+) CD3 (-)
- C) CD20 (+) EBV (-) CD3 (-)
- D) CD20(-) EBV (+) CD3 (-)
- E) CD20 (-) EBV (-) CD3 (-)

11) The causative agent of Oroya fever and verruga peruana is:

- A) *Bartonella quintana*
- B) *Bartonella henselae*
- C) *Bartonella bacilliformis*
- D) A and B
- E) None of above

12) The characteristic translocation seen in clear cell sarcoma of soft parts is:

- A) t(12;22)(q13;q12) (ATF1-EWS)
- B) t(17;22)(q22;q13) (PDGFβ-COL1A1)
- C) t(11;22)(q24;q12)(FLI1-EWS)
- D) t(9;22)(q34;q11)(BCR-ABL)
- E) t(11;22)(p13;q12)(WT1-EWS)

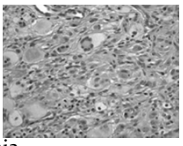
13) Type VII collagen is associated with all of the following except:

- A) Dystrophic epidermolysis bullosa
- B) Epidermolysis bullosa acquisita
- C) Bullous lupus erythematosus
- D) Bullous pemphigoid
- E) Anchoring fibrils

14) Which of the following is/are classically associated with d-penicillamine?

- A) Drug-induced pemphigus
- B) Linear IgA
- C) Lichenoid drug eruptions
- D) Elastosis perforans serpinginosa
- E) Pseudoporphyria
- G) A, C, and D

15) A patient with multiple of the lesion depicted in the image below is at increased risk of all <u>except</u>:



- A) Neurofibromatosis type 1
- B) Hyphema
- C) Chronic myelomonocytic leukemia
- D) Diabetes insipidus
- E) Glaucoma

http://pathology2.jhu.edu/sp

16) Of the following, erythema gyratum repens is most commonly associated with:

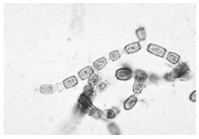
- A) Hodgkin lymphoma
- B) Colorectal cancer
- C) Esophageal cancer
- D) Glucagonoma
- E) Lung cancer

17) A patient with immediate burning of skin on sun exposure and thickening of skin is likely to have a deficiency of which of the following enzymes:

- A) Ferrochelatase
- B) Porphobilinogen deaminase
- C) Uroporphyrinogen decarboxylase
- D) Protoporphyrinogen oxidase
- E) Coproporphyrinogen oxidase

18) Identify the following:

- A) *Histoplasmosis capsulatum*
- B) *Coccidioides immitis*
- C) *Blastomyces dermatitidis*
- D) *Sporothrix schenckii*
- E) *Paracoccidioides brasiliensis*



http://en.wikipedia.org/

19)All of the following are associated with paraproteinemia <u>except</u>?

- A) Glomeruloid hemangioma
- B) Eruptive xanthoma
- C) Necrobiotic xanthogranuloma
- D) Papular mucinosis
- E) Scleredema

20) Which is the target antigen in herpes gestationis?

- A) BPAg1 (230 kD)
- B) BPAg2 (180 kD)
- C) beta-4 integrin
- D) desmoglein 3
- E) desmocollin-1

21) The causative agent of Rhinoscleroma belongs to which of the following genera?

- A) *Escherichia*
- B) *Rhinosporidium*
- C) *Klebsiella*
- D) *Haemophilus*
- E) *Calymmatobacterium*

200 MOST LIKELY ENTITIES TO APPEAR ON MICROSCOPIC EXAM

ACCESSORY NIPPLE
ACCESSORY TRAGUS
ACNE KELOIDALIS
ACQUIRED DIGITIAL FIBROKERATOMA
ACRODERMATITIS ENTEROPATHICA
ALOPECIA AREATA
ALUMINUM CHLORIDE
AMALGAM TATTOO
AMYLOIDOSIS
ANAPLASTIC LARGE CELL LYMPHOMA
ANGIOFIBROMA
ANGIOKERATOMA
ANGIOLEIOMYOMA
ANGIOLIPOMA
ANGIOLYMPHOID HYPERPLASIA WITH EOSINOPHILIA
ANGIOSARCOMA
ARGYRIA
ASPERGILLOSIS
ATYPICAL FIBROXANTHOMA
BACILLARY ANGIOMATOSIS
BLASTOMYCOSIS
BLUE NEVUS
BULLOUS PEMPHIGOID
CALCINOSIS CUTIS
CALCIPHYLAXIS
CANDIDIASIS
CHOLESTEROL EMBOLUS
CHONDRODERMATITIS NODULARIS
CHONDROID SYRINGOMA
CHROMOMYCOSIS
CLEAR CELL ACANTHOMA
COCCIDIOMYCOSIS
CRYOGLOBULINEMIA
CRYPTOCOCCOSIS
CUTANEOUS CILIATED CYST
CUTANEOUS ENDOMETRIOSIS
CYLINDROMA
DERMATITIS HERPETIFORMIS
DERMATOFIBROSARCOMA PROTUBERANS
DERMATOMYOSITIS
DERMATOPHYTOSIS
DESMOPLASTIC MELANOMA
DESMOPLASTIC TRICHOEPITHELIOMA
DIFFUSE NEUROFIBROMA
DIGITIAL MUCOUS CYST
ECCRINE SPIRADENOMA
ECTHYMA GANGRENOSUM
ELASTOSIS PERFORANS SERPIGINOSA
EPIDERMODYSPLASIA VERRUCIFORMIS
EPIDERMOLYTIC HYPERKERATOSIS
EPITHELIOID SARCOMA
ERUPTIVE XANTHOMA
ERYTHEMA ELEVATUM DIUTINUM
ERYTHEMA INDURATUM
ERYTHEMA MULTIFORME
ERYTHEMA NODOSUM
ERYTHRASMA
FIBROMATOSIS
FIBROUS HAMARTOMA OF INFANCY
FIXED DRUG ERUPTION
FLORID PAPILLOMATOSIS OF NIPPLE
FOCAL MUCINOSIS
FOLLICULAR MUCINOSIS
GANGLION CYST
GELFOAM
GIANT CELL TUMOR OF TENDON SHEATH
GLOMANGIOMA
GLOMERULOID HEMANGIOMA
GLOMUS TUMOR
GLUCAGONOMA SYNDROME
GOUT
GRANULAR CELL TUMOR
GRANULOMA ANNULARE
GRANULOMA FACIALE
GROVER'S DISEASE
GYNECOMASTIA
HAILEY---HAILEY DISEASE
HEMOSIDEROTIC DERMATOFIBROMA
HERPESVIRUS
HIBERNOMA
HIDRADENOMA PAPILLIFERUM
HISTOPLASMOSIS
HOBNAIL HEMANGIOMA
ICHTHYOSIS VULGARIS
INFANTILE DIGITAL FIBROMATOSIS
INVERTED FOLLICULAR KERATOSIS
JUVENILE XANTHOGRANULOMA
KAPOSI'S SARCOMA
KELOID
LANGERHANS CELL HISTIOCYTOSIS
LEIOMYOSARCOMA
LEISHMANIASIS
LEPROMATOUS LEPROSY
LEUKEMIA CUTIS
LEUKOCYTOCLASTIC VASCULITIS
LICHEN NITIDUS
LICHEN PLANUS

LICHEN SCLEROSUS ET ATROPHICUS
LOBOMYCOSIS
LUPUS ERYTHEMATOSUS
LYMPHADENOMA
LYMPHANGIOMA
LYMPHOMATOID PAPULOSIS
MALAKOPLAKIA
MASTOCYTOSIS
MEDIAN RAPHE CYST
MENINGIOMA
MERKEL CELL CARCINOMA
METASTATIC BREAST CARCINOMA
METASTATIC RENAL CELL CARCINOMA
MICROCYSTIC ADNEXAL CARCINOMA
MICROVENULAR HEMANGIOMA
MOLLUSCUM CONTAGIOSUM
MONSEL'S SOLUTION
MORPHEA
MUCOCELE
MYCOSIS FUNGOIDES
MYIASIS
MYRMECIAL WART
NECROBIOSIS LIPOIDICA
NEUROTHEKEOMA
NEVUS SEBACEUS
NODULAR FASCIITIS
NODULAR HIDRADENOMA
OCHRONOSIS
OMPHALOMESENTERIC DUCT POLYP
ORAL FIBROMA
ORF
ORNAMENTAL TATTOO
OSTEOMA CUTIS
PAGET'S DISEASE
PALISADED AND ENCAPSULATED NEUROMA
PANCREATIC PANNICULITIS
PAPILLARY ENDOTHELIAL HYPERPLASIA
PAPULAR MUCINOSIS
PARACOCCIDIOMYCOSIS
PARAFFINOMA
PEARLY PENILE PAPULE
PEMPHIGUS FOLIACEUS
PEMPHIGUS VULGARIS
PENICILLIOSIS
PERNIOSIS
PHEOHYPHOMYCOSIS
PIGMENTED SPINDLE CELL NEVUS
PILAR CYST
PILOLEIOMYOMA
PILOMATRICOMA
PITTED KERATOLYSIS
PITYRIASIS LICHENOIDES
PITYRIASIS RUBRA PILARIS
PLEXIFORM FIBROHISTIOCYTIC TUMOR
PLEXIFORM NEUROFIBROMA
POLYARTERITIS NODOSUM
POLYMORPHOUS LIGHT ERUPTION
POROKERATOSIS
POROMA
PORPHYRIA CUTANEA TARDA
PRETIBIAL MYXEDEMA
PROTOTHECOSIS
PSEUDOXANTHOMA ELASTICUM
PSORIASIS
PYODERMA GANGRENOSUM
PYOGENIC GRANULOMA
RADIATION DERMATITIS
RETICULOHISTIOCYTOMA
RHEUMATOID NODULE
RHINOSPORIDIOSIS
ROSAI---DORFMAN DISEASE
SARCOIDOSIS
SCABIES
SCAR
SCHISTOSOMIASIS
SCHWANNOMA
SCLEREDEMA
SCLEROTIC FIBROMA
SEBACEOUS CARCINOMA
SILICONE GRANULOMA
SPINDLE CELL LIPOMA
SPITZ NEVUS
STEATOCYSTOMA
SUTURE GRANULOMA
SWEET'S SYNDROME
SYPHILIS
SYRINGOCYSTADENOMA PAPILLIFERUM
SYRINGOMA
TICK BITE WITH MOUTHPARTS
TINEA NIGRA
TINEA VERSICOLOR
TRIAMCINOLONE
TRICHOEPITHELIOMA
TRICHOFOLLICULOMA
TUFTED HEMANGIOMA
TUNGIASIS
VERRUCIFORM XANTHOMA
VERRUCOUS CARCINOMA
WARTY DYSKERATOMA
WOOD SPLINTER
XANTHELASMA
ZOON'S BALANITIS
ZYGOMYCOSIS