Objectives

- Understand common clinical and histopathologic findings in common cutaneous histiocytoses
- Introduce prospective changes to the WHO classification of skin histiocytic neoplasms
- Understand common clinical and histopathologic findings in rare types of histiocytoses
- Use of molecular and ancillary techniques that can help in the differential between reactive histiocytic infiltrates and neoplastic ones
Cutaneous Histiocytoses

- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Indeterminate dendritic cell tumor
- Erdheim-Chester disease
- Histiocytic sarcoma
- Juvenile and Adult Xanthogranuloma
- Necrobiotic xanthogranuloma
- Rosai-Dorfman disease
- Hemophagocytic lymphohistiocytoses

Histology and somatic mutations of histiocytoses of group L, C, R, M, and H (A) L group: Histology of LCH (skin [i-ii] and bone [iii]) and of ECD (perirenal [iv-v]).

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True Histiocytic malignancy: a vanishing diagnosis

<table>
<thead>
<tr>
<th>Original Diagnosis</th>
<th>Current Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histiocytic lymphoma, nodule and diffuse</td>
<td>DLBCL, FL grade 3, PTL, Histiocytic rich variants of DLBCL, PTC, and CHL, ALC, ALCL</td>
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<tr>
<td>Histiocytic nodular reticulosis</td>
<td>Hemophagocytic syndromes</td>
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<td>Malignant histiocytosis</td>
<td>Hemophagocytic syndromes ALCL</td>
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<td>Regressing atypical histiocytosis</td>
<td>CD30+ LPD</td>
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<td>Intestinal malignant histiocytosis</td>
<td>EAL</td>
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<td>Histiocytic cytophagic panniculitis</td>
<td>SPRCL</td>
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</tbody>
</table>
Langerhans cell histiocytosis

- Clonal neoplastic proliferation of Langerhans cells that express CD1a, langerin, S100 and show Birbeck granules on EM
- Incidence 5/1,000,000
- Male to female 3.7:1
- Primary LCH of the lung is a disease of smokers
- Clinical features: unilesional, multifocal within a system, or disseminated and multisystemic
  - Bone and soft tissue (+++)
  - LN
  - Skin
  - Lungs
- Aggressive clinical course if <2 years-old

Langerhans cell histiocytosis – Clinical Findings

- Cutaneous involvement is most common in multisystem disease in infants and children
  - Erythematous or maculopapular or nodular eruptions
  - Lesions often involve the scalp, intertriginous areas, including the perineum and genitalia of the infant
  - Erosive intertrigo of the axilla, perianal region, and other flexural folds is well-described in infants
- Isolated skin involvement by LCH is infrequent and occurs in ~5% of all cases
  - Skin-limited LCH occurs in the form of one or multiple, often neoplastic but occasionally acute, papules, plaques, nodules and/or ulcerated plaques and nodules, often with scarring
  - Oral and genital involvement in 20% of cases
Langerhans cell histiocytosis – Clinical Findings

• Demonstration of LCs in aggregates in a background of eosinophils, mast cells, lymphocytes, neutrophils and non-neoplastic multinucleated giant cells – medium to large in size, exhibit abundant eosinophilic cytoplasm and have a “coffee bean” shaped grooved nuclei

• Small collections of cells at the dermo-epidermal interface with variable basal vacuolar degeneration or as dense infiltrates throughout the dermis with or without the formation of eosinophilic abscesses

• Epidermotropism of Langerhans cells into the epidermis is common

• Positive staining of Langerhans cells for S-100 protein and CD1a (more specific, commonly used). CD207 (langerin) stains Langerhans cell specifically but is a newer stain not yet as commonly used. PD-L1+, CD68+, Vimentin+, CD30-

• Molecular: BRAFV600E (50%), MAP2K1 (25%) – 30% with IGH, IGK or TCR clonality

Langerhans cell histiocytosis – Histopathologic Findings

Molecular:
- BRAFV600E
- MAP2K1
- IGH, IGK, or TCR clonality

* A positive or negative result indicates the presence of clonal DNA rearrangement.
Langerhans cell histiocytosis – Histopathologic Findings

Langerhans cell histiocytosis – Histopathologic Findings

Langerhans cell histiocytosis – Histopathologic Findings
Langerhans cell histiocytosis – Histopathologic Findings

CD1a
Langerin

Langerhans cell histiocytosis – Histopathologic Findings

Langerhans cell histiocytosis – Histopathologic Findings
Congenital self-healing LCH

• A.k.a. Hashimoto-Pritzker disease
• Lesions typically involve the deep dermis in a nodular fashion, unlike conventional LCH lesions where lesions are mainly in upper dermis, extending to epidermis
• Similar staining with CD1a, S100 and langerin. Langerhans cells of CSH-LCH may show Birbeck granules similar to conventional LCH cells by electron microscopy
• They can be separated ultrastructurally by the presence of unique cytoplasmic dense bodies containing concentrically arranged laminar structures
Langerhans cell histiocytosis – Differential Diagnosis

- LCH
  - ECD
  - ICH
  - LCS
- Non-LCH
  - JXG
  - Reticulohistiocytosis
  - RDD
  - Histiocytic sarcoma
- Reactive langerhans cell proliferations
Fibrous Papule with reactive langerhans cell hyperplasia

LCH?

LCH?
LCH?

CD3

CD1a – Reactive langerhans cell proliferation in a T-cell lymphoma
**Indeterminate dendritic cell tumor**

- Also known as indeterminate cell histiocytosis is a neoplastic proliferation with phenotypic features similar to those of normal indeterminate cells, the alleged precursor of Langerhans cells.
- One or multiple generalized papules, nodules, or plaques on the skin
  - No systemic symptoms
- Dermal based histiocytic proliferation with +/- extension to the adipose tissue
  - Diffuse infiltration similar to LCH, irregular nuclear grooves and clefts, abundant eosinophilic cytoplasm
  - Multinucleated giant cells
  - Spindle cells
- IHC: S100+, CD1a+, Langerin-, CD30-, CD21-,CD23-,CD35-
- Variable clinical presentation: spontaneous regression or rapid progression

**Indeterminate cell histiocytosis**
BRAFV600E

FISH targeting the ETV3-NCOA2 gene fusion in ICH. Red probe for ETV3 in chromosome 1 and green probe for NCOA2 in chromosome 8.

Ryanne A. Brown et al. Blood 2015;126:2344-2345

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Typical age of onset
Isolated skin involvement
Most common sites of involvement

<table>
<thead>
<tr>
<th>Molecular Findings</th>
<th>Immunophenotype</th>
<th>Association with other malignancies</th>
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<tbody>
<tr>
<td></td>
<td>CD1a Langerin S-100 CD68</td>
<td>Indeterminate cell histiocytosis</td>
</tr>
<tr>
<td>BRAF mutations</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
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</tbody>
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78% 87% 13% of patients had one or more histiocytoses identified in 1 of 6 positive cases (O'Malley); 32% focal, 13% focal, including:

- FL (4 cases)
- AML (3 cases)
- CLL (2 cases)
- AITCL (2 cases)
- BALL (1 case)
- Acute mast cell translocation leukemia (1 case)

Langerhans cell histiocytosis

3.5 - 5 years

<5% Bone (77%), skin (39%), and lymph nodes (19%)

Approximately 50% of cases harbor BRAF mutations

Positive Positive

Positive Positive

Associated with lymphomas, leukemias, and other solid tumors. 3.5% of patients had an associated malignancy in one study of 116 patients (Egeler)

Juvenile

5 months

74% (Dehner)

Skin (approximately 2/3)

Associated with Negative Negative

Rarely Positive

Associated with JMML xanthogranuloma (Janssen) 2003) cases present as solitary neurofibromatosis positive cutaneous lesions) > type I subcutaneous soft tissue > deep soft tissue; <5% have visceral-systemic involvement

Multicentric

43 - 53 typically

Skin and joints

No well- Negative Negative

Rare Positive

Associated with malignancy in reticulohistiocytosis

Dendritic cell sarcomas

Predominantly adults in 4th and 5th decades

Rare Lymph nodes; skin involvement has been reported but is uncommon

No well-documented molecular findings

FDCS: negative

IDCS: negative

INDCS: positive

Typically positive

Typically positive

N/A

FDCS: negative

IDCS: negative

INDCS: positive

Indeterminate cell histiocytosis
Erdheim-Chester Disease

- Now part of the ‘L’ group of histiocytosis
- 75% of cases have BRAFV600E mutations
- Symmetric diaphyseal and metaphyseal osteosclerosis of long bones as well as cardiac, retroperitoneal, vascular, and cerebral involvement
- Clinical presentations are diverse and range from bone pain to diabetes insipidus, and neurological and constitutional symptoms
- 30% cutaneous manifestations are the first sign of the disease
  - XLL 83%
  - Other patches, papulonodular lesions, rare erythema
- Histologically diffuse dermal infiltrate of xanthomatized histiocytes and Touton-type giant cells
- IHC: CD68+, CD163+, Factor XIII+, BRAFV600E+, CD1a-, Langerin-, S100-
- Mixed LCH/ECD show histopathologic and IHC of LCH

Erdheim-Chester Disease

Histopathological and Clinical Findings in Cutaneous Manifestation of Erdheim-Chester Disease and Langerhans Cell Histiocytosis Overlap Syndrome Associated With the BRAFV600E Mutation.
Liersch, Julia; Carlson, J; Andrew MD, FRCPC; Schaller, Jorg
DOI: 10.1097/DAD.0000000000000793

FIGURE 3. Xanthelasma-like tumors as cutaneous EC D manifestations in case 2. A, Large xanthelasma-like tumor around the eyes.  B, Diffuse accumulation of foamy cells, fibrosis of the connective tissue (hematoxylin and eosin x40).  C, Multiple Touton giant cell and hemosiderin deposits in the dermis (hematoxylin and eosin x400).

Langerhans cell sarcoma

• Malignant neoplasm with Langerhans cell phenotype
• Very rare
  – All cases reported in adults
  – Median age: 41
  – Some cases in association with Merkell cell polyomavirus
  – Rare association with FL
• Clinical
  – Skin and soft tissue most cases; hepatosplenomegaly; pancytopenia
• Histopathology
  – Malignant neoplasm with marked pleomorphism
  – Nuclear grooves variable
  – High mitotic rare: >50 mitoses / 10 HPF
  – + Birbeck granules
  – IHC: CD1a+, S100+, Langerin+
  – One case with BRAF V600E mutation; possible TCR and IGH rearrangements
Langerhans cell sarcoma

Langerhans cell sarcoma

Langerhans cell sarcoma
Langerhans cell sarcoma

Juvenile Xanthogranuloma and Adult Xanthogranuloma

- Group 'C' for cutaneous limited forms and group 'L' for the systemic variants
- 0.5% of pediatric tumors
- +++ infants and young children, but adolescents and adults also
- Solitary, well demarcated, firm nodule
  - Head and neck, trunk and upper limbs
  - Keratotic, pedunculated, linear, flat, or plaque-like
  - Usually 5 to 10 mm in diameter but can measure up to a few centimeters
  - Initially, the lesion is raised and pink to erythematous in color but over time they become yellow-brown and may flatten
  - Regression may occur over a period of months to years with residual hyperpigmentation, atrophy or anetoderma
  - Lesions are multiple in 10% of cases

Juvenile Xanthogranuloma and Adult Xanthogranuloma

- Extracutaneous sites with or WITHOUT skin involvement (15%)
  - Soft tissue
  - Multifocal visceral and osseous sites are involved in about 5% of cases and may include the oropharynx, nasopharynx, gastrointestinal tract, liver, lung, testis, spleen, lymph nodes, central nervous system and kidney
  - Systemic cases occur in young children under the age of two years
- Association with NF-1 and JMML
  - Mutations in the GTPase neurofibromin, which is present in NF1, leads to RAS dysfunction
- Systemic presentations of JXG with CNS involvement have shown BRAF V600E mutations
  - Should those cases be qualified as ECD/L group lesions that haven't presented themselves with systemic findings (i.e. brain only), or there is a truly separate group of JXG/BRAF V600E positive tumors?
JXG - Histopathology

- Dense mononuclear histiocytic infiltrate in the dermis extending to the interface with the epidermis
- Limited to the dermis, but in large lesions extends to the subcutis
- Flattening of the epidermis, and sometimes collarette
  - Epidermis and adnexae are spared
- Epithelioid histiocytes, xanthomatized cells and multinucleated Touton-type giant cells
  - Giant cells might be absent, particularly in extracutaneous lesions
- Lymphocytes, eosinophils, plasma cells, neutrophils, and mast cells may be scattered throughout the infiltrate or altogether absent
- The morphology of the histiocytes can vary depending on the “age” of the lesion
  - Early: epithelioid histiocytes without vacuolization
  - Mature: histiocytes with lipidized or xanthomatized cytoplasm
- Scalloped histiocytes with an angulated or jagged border and spindled histiocytes may also be seen
- Mitotic figures are common, but NOT atypical mitoses
- CD68+, CD163+, CD4+, CD14+, factor XIIIa+, HLA-DR+, fascin+, vimentin+, and lysozyme+ and are negative for CD1a, and langerin
- S100 stains rich background in dendritic cells (JXG cells NEGATIVE)
JXG – spindle cell variant

Benign cephalic histiocytosis
- Early form of JXG affecting young children
- Multiple tan-pink papules on the cheek, neck, and upper trunk are the clinical manifestations with sparing of the palms and soles, mucous membranes, and viscera
- Self-limiting disorder
- Histologically: diffuse dermal infiltrate of mononuclear histiocytes with ill-defined pale cytoplasm

JXG family variants

Benign cephalic histiocytosis
- Early form of JXG affecting young children
- Multiple tan-pink papules on the cheek, neck, and upper trunk are the clinical manifestations with sparing of the palms and soles, mucous membranes, and viscera
- Self-limiting disorder
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Generalized eruptive histiocytosis
- Both children and adults
- Numerous round or oval, reddish papules symmetrically distributed on the trunk and extremities surfaces of the extremities without visceral involvement
- Lesions develop rapidly and tend to resolve spontaneously with no residual findings or at most slight hyperpigmentation
- In adults frequently associated with underlying leukemia / lymphoma
- Numerous mononuclear histiocytes, including spindled forms, are present within the upper to mid dermis and a perivascular distribution may be present.
- Scattered lymphocytes may be seen but foamy cells or giant cells are generally absent

Progressive nodular histiocytosis
- Adults 40 to 60 years of age and is characterized by the presence of two types of skin lesions: multiple small, superficial yellow-brown papules and larger, deeper subcutaneous nodules with a predilection for the trunk
- A dermal infiltrate of histiocytes, predominantly spindle-shaped forms, and foamy cells (including Touton cells) are the histologic feature
Benign cephalic histiocytosis

JXG – Differential diagnosis
- 'L' Group: LCH, ICH, ECD
- Non 'L'
  - NXG
  - Reticulohistiocytoma
  - RDD
  - BCH
  - Histiocytic sarcoma
- Spitz nevi
- Dermatofibroma
- Lymphomatoid papulosis
- Xanthoma/Xanthelasma
- Xanthomatized Sweet’s syndrome

There is a circumscribed dermal nodule, often with overlying epidermal thinning. As with multicentric reticulohistiocytosis, there is an irregular admixture of oncocytic mononuclear histiocytes, multinucleate giant cells with a ground-glass appearance, and inflammatory cells. Phagocytosis of leukocytes is sometimes seen. A few Toton giant cells may be present and these may contain lipid. Reticulin fibers are increased and surround individual cells. There is usually more of a neutrophilic infiltrate than in multicentric reticulohistiocytosis, and a further point of distinction is the greater propensity for the stroma in reticulohistiocytoma to have many spindle-shaped cells and for there to be xanthomatized cells. Nowadays, reticulohistiocytoma are considered VARIANTS of JXG. More typically in adults than children: hands.
Lymphomatoid papulosis

Spitz Nevus
Xanthoma / Xanthelasma

- Foam cells in dermis (positive for lipid with special stains such as oil-red-O)
- Touton giant cells sometimes
- Small numbers of lymphocytes or neutrophils in younger lesions, especially in eruptive xanthomas
- Fibrosis or cholesterol clefts in older lesions
- Xanthelasma: eyelids, associated with hypercholesterolemia in 50% of cases.

Xanthelasma
Lipophagic polyp

- Usually solitary or few polypoid lesions that mimic papillomas
- Variable age
- Retention mastitis?
- Sheets of benign lipidized histiocytes in the absence of multinucleated giant cells.
- IHC: CD68+, CD163+, CD1a

Am J Dermatopathol 2015

Lipophagic polyp

Lipophagic polyp
Histiocytoid Sweet’s Syndrome

- Tender erythematous plaques and nodules on the extremities and trunk accompanied by systemic symptoms such as fever and arthralgia
- Hematologic malignancies were present in 8 patients (24%)
  - MDS, AML, CMML, CML
  - Solid tumors
- Histopathology
  - spared epidermis
  - papillary edema
  - no evidence of vasculitis
  - dense, bandlike, inflammatory infiltrate involving the superficial and mid-dermis predominantly composed of mononuclear cells
- IHC: MPO+, CD163+

JAMA Dermatol 2017
Necrobiotic xanthogranuloma (NXG)

- Palisading granulomas with areas of necrosis (more severe degeneration than the "necrobiosis" seen with GA or NLD)
  - Rare cases (5-10%) without necrobiosis
- Cholesterol clefts common
- Foamy histiocytes, Touton giant cells and foreign body giant cells, lymphocytes, plasma cells, neutrophils
- Characteristic association with plasma cell neoplasms (IgG-lambda, 60-70%)
- Other hematologic malignancies too!

**NXG without necrobiosis**

**Cutaneous RDD**

- Uncommon histiocytosis with less than 600 cases reported
- 80% present in first 2 decades
- Cutaneous dissemination in SRDD occurs in 1/3 of cases while pure CRDD is extraordinary rare
  - SRDD young adult men and children
  - CRDD adult white women
- Etiologic factors:
  - HHV-6
  - Parvovirus B19
  - ALPS (autoimmune lymphoproliferative syndrome)
  - IgG4 – autoimmune disorders

**Cutaneous RDD**

- Clinical presentation
  - Benign and self-limited
  - Exacerbations and remissions
  - Fever, massive, non-tender, bilateral lymph node enlargement
  - LAD can be focal
  - 40% extranodal involvement
  - Skin, soft tissues, bone
  - Intrathoracic manifestations: airway, pleural effusion, ILD (GOOD prognosis)
  - Lower respiratory tract, liver and kidney (POOR prognosis)
- Cutaneous manifestations:
  - Eyelids, malar region
  - Multiple, focal, erythematous-brown, xanthomatous papules, pustules, nodules and plaques
- Histopathologic findings
  - LNs: dilated sinuses containing PMNs, lymphocytes, plasma cells, and histiocytes
  - Skin: histiocytes, PMNs, plasma cells, lymphocytes in the dermis
  - Histiocytes are polygonal, with abundant foamy, eosinophilic cytoplasm, feathery borders, and large vesicular nuclei
  - Emperipolesis
  - Multinucleated histiocytes (boutron-type giant cells); plasma cells with Russell bodies, xanthoma cells
  - IHC: CD68+, CD163+, S100+, CD1A-, IgG4+/PCs
Cutaneous RDD - Molecular

- RDD pattern has been associated with autoimmune hemolytic anemia, systemic lupus erythematosus, and juvenile idiopathic arthritis.
- Always evaluate serum levels of IgG4 - overlap with IgG4 syndrome.
- H syndrome is an autosomal genetic condition characterized by hyperpigmentation, hypertrichosis, hepatosplenomegaly, hearing loss, heart anomalies, hypogonadism, low height (short stature), hyperglycemia/diabetes mellitus, and hallux valgus/flexion contractures – mutation within the SLC29A3 gene.
- RDD lesions in 25% of cases.
- Patients with ALPS type Ia have RDD lesions in 41% of cases.
  - TNFRSF6 heterozygous germ line mutations affecting the gene encoding Fas.

RDD

- RDD

- RDD

- RDD
RDD

Cutaneous Plasmacytosis

- Rare entity (<100 cases reported)
- Middle age
  - Slight male predominance
- Affects individual of Asian descent
  - +++ Japanese
- Closely related to plasma cell variant of Castleman disease
- IgG4-related disorders
- Clinical: red to brown macules, plaques and papules
  - Face, trunk and extremities
  - Superficial LAD 58%
  - Hypergammaglobulinemia – POLYCLONAL
  - Interstitial nephritis, ILD
Cutaneous plasmacytosis

- Histopathology
  - Dermal infiltrate of plasma cells, with admixed lymphocytes and histiocytes
  - PC infiltrate is perineural and perivascular, but also diffuse
  - Heavier in superficial to mid dermis, +/- deep involvement
  - Follicles and GC can be present
  - Lack cytologic atypia
  - POLYCLONAL INFILTRATE
  - IgG4+
Cutaneous IgG4-related disease

- LN, skin, lung and pancreatic involvement
  - Autoimmune pancreatitis
  - Sclerosing cholangitis
  - Sclerosing sialadenitis
- LN often show Castleman-like changes
- >15 PC/hpf
- IgG4/IgG ratio >40%
- Fibrosis, phlebitis
- Other diseases linked to IgG4: pemphigus vulgaris

Cutaneous IgG4-related disease

Cutaneous Castleman Disease

- Most cases of CD present in HIV+ patients
  - 5-10% are HIV+ and typically associated with HHV-8 infection
- Cutaneous involvement in CD is very rare (<15 cases reported)
- LAD, hyperproteinemia, hypergammaglobulinemia, systemic symptoms, POEMS
- Skin: multiple erythematous to brownish nodules
- Histopathology: hyaline vascular type (90%), plasma cell (10%), mixed
Cutaneous Castleman Disease

• Originally described by Crotty and Winkelmann (JAAD 1981) as multiple subcutaneous nodules experiencing a terminal hemorrhagic diathesis with variable clinical course (6 months – 10 years).
• Clinical course is variable:
  – Systemic symptoms include fever, weight loss, hepatosplenomegaly, cytopenias, serosal effusions, coagulation abnormalities; etc
  – Some cases are associated with subcutaneous panniculitis-like T-cell lymphoma or cutaneous γδ T-cell lymphoma
  – HLH can also occur in association with infectious processes, or specific gene mutations

Cytophagic histiocytic panniculitis (CHP) – 'H' group

• Originally described by Crotty and Winkelmann (JAAD 1981) as multiple subcutaneous nodules experiencing a terminal hemorrhagic diathesis with variable clinical course (6 months – 10 years).
• Clinical course is variable:
  – Systemic symptoms include fever, weight loss, hepatosplenomegaly, cytopenias, serosal effusions, coagulation abnormalities; etc
  – Some cases are associated with subcutaneous panniculitis-like T-cell lymphoma or cutaneous γδ T-cell lymphoma
  – HLH can also occur in association with infectious processes, or specific gene mutations
Histopathology

- Mixed septal and lobular panniculitis with a variable infiltrate of histiocytes and lymphocytes
  - Erythrophagocytosis ('bean bag cells') and cytophagocytosis
  - IHC can help: CD163, CD68
- Always look for coexistence of LPD: SPTCL or PGDTCL
  - Clonality studies are always recommended
  - If cytopenias present: systemic work-up (bone marrow bx, visceral organ bx)
- Other diagnostic considerations: Weber-Christian, connective tissue disorders, etc

Clinical Presentation
Melkerson-Rosenthal Syndrome

- Marked dermal edema and perivascular inflammation with lymphs, plasma cells, eos, histiocytes
- Loose granulomas, tuberculoid, small naked collection of epithelioid cells
- Sometimes Schaumann bodies are present
- Lymphatics are widely dilated and contain collections of inflammatory cells
- Older lesions show dermal fibrosis
- Cutaneous histiocytic lymphangitis and angioendotheliomatosis in the spectrum (also RA related), intravascular histiocytosis
Melkerson-Rosenthal Syndrome
Histiocytic sarcoma

- Malignant neoplasm with morphologic and immunophenotypic features of mature histiocytes
  - Extramedullary myeloid sarcoma / leukemia cutis are EXCLUDED
- Clinical features
  - Most cases in adults (median 52)
  - Some cases with pre-existent or metachronous NHL (CLL; FL); AML and MDS
  - Some cases in association with germ cell tumors (teratomas)
  - Extranodal tumors+++
    - G2, skin and soft tissue
    - Hepatosplenomegaly; pancytopenia
- Histopathologic features
  - Dense dermal infiltrate with marked pleomorphism; spindle cell variant
  - Large tumor cells with vesicular nuclei and prominent nucleoli; malignant multinucleated giant cells
  - Frequent mitoses
  - Sometimes hemophagocytosis and tumor cell ‘cannibalism’
- IHC: CD68+, CD163+, Lysozyme+, CD4+, CD45+, CD1a-, S100-, Langerin-, variable EMA (focal), CK-, CD21-, CD35-
- Molecular: variable IGH and TCR rearrangements, >50% BRAF V600E+
Histiocytic sarcoma

Histiocytic sarcoma – CD163

Histiocytic sarcoma – CD43
Histiocytic sarcoma - EMA

Histiocytic sarcoma

Histiocytic sarcoma
Histiocytic sarcoma

[Images of histological sections]

Histiocytic sarcoma

[Images of histological sections]

Histiocytic sarcoma

[Images of histological sections]
Histiocytic sarcoma

Histiocytic sarcoma – CD45

Histiocytic sarcoma – CD163
Histiocytic sarcoma – CD68

Differential Diagnosis

- Anaplastic large cell lymphoma
- Soft tissue sarcomas
  - Epithelioid Sarcoma
- Melanoma
- Carcinomas
- Follicular dendritic cell sarcoma
- Interdigitating dendritic cell sarcoma

| Table 72-1. Salient Features: Histiocytic and Dendritic Cell Sarcoma |
|-----------------------------|---------------|---------------------|---------------------|
| HS                          | FDCS          | IDCS                | INDCS               |
| Clinical findings           |               |                     |                     |
| Solitary or multiple         | Asymptomatic  | Solitary            | Papules, nodules,    |
| cutaneous lesions            | lymph node    | or multiple         | and plaques,       |
|                             | lesions       |                     | on skin             |
| Morphology                   |               |                     |                     |
| Discoid epithelioid          | Spindle       | Epithelioid         |                     |
| spindle cells                | to          | cells with          |                     |
|                             | epithelioid   | nuclear grooves     |                     |
|                             | cells, with   | and clefs           |                     |
|                             | whorls        |                     |                     |
| Immunophenotype              |               |                     |                     |
| CD68 +                      | CD68 +        | CD68 +              | CD68 +              |
| CD163 +                      | N/A           | N/A                 | N/A                 |
| Lysozyme +                  | N/A           | N/A                 | N/A                 |
| CD1a -/++                   | N/A           | N/A                 | N/A                 |
| S100 -/++                    | ++            | ++                  | ++                  |
| CD21 +                      | Absent        | Absent              | Absent              |
| CD23 +                      | Absent        | Absent              | Absent              |
| CD35 +                      | Absent        | Absent              | Absent              |
| CD4 +                       | Numerous      | Mature               | Mature              |
| Ultrastructural characteristics |             |                     |                     |
| Cytoplasmic processes       | Absent        | Desmosomes          | Desmosomes          |
| Desmosomes                   | Absent        | Birbeck granules    | Birbeck granules    |
| Birbeck granules             | Absent        | Lysosomes           | Lysosomes           |
| Lysosomes                    | Abundant      | Sparse              | Sparse              |
| | | Unknown             | | |

Follicular dendritic cell sarcoma

- Malignant tumor of FDC
- Association with HV-CD
- 31% of cases LN; extranodal 58%
  - GI, soft tissue, mediastinum, RT etc
- Large tumors
- Fascicular, whorls, storiform spindle cell
  - + mitoses
  - + necrosis
  - Tumor infiltration by small lymphocytes
- CD21+, CD23+, CD35+, D2-40+, fascin+, EMA variable, S100 variable
- Sometimes BRAF mutated

Thank you for your attention!