Histiocytic Lesions of the Skin

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Histocytic Lesions of the Skin: Disclosure

• I am not an expert on this!
• Sophie and Jonathan: “We’re sure you’ll do a great job!”
  - My translation: “The experts turned us down. We’re sure you’ll read up on it, find some cool cases, and share with us what you’ve learned.”
• Focus: Cases that Dermatopathologists might show to a Hematopathologist (what we need to know!)
  - Not the zillion things they sign out themselves (from xanthelasma to sarcoidosis)
  - Emphasize things we don’t typically think about and won’t find in Hematopathology WHO book or texts
Histiocytic Lesions of the Skin that Might be Shown to a Hematopathologist

- **Benign/reactive lesions**
  - Rosai-Dorfman disease
  - Intravascular histiocytosis

- **Uncertain (non-Langerhans’ cell histiocytoses)**
  - Xanthogranuloma group
  - Reticulohistiocytoma group

- **Neoplastic/malignant lesions**
  - Langerhans cell histiocytosis
  - Langerhans cell sarcoma
  - IDC sarcoma
  - FDC sarcoma
  - Histiocytic sarcoma
  - Blastic plasmacytoid dendritic cell neoplasm
Benign/reactive histiocytic lesions

- Rosai-Dorfman disease
- Intravascular histiocytosis
Rosai-Dorfman disease: Cutaneous Manifestations

- **Extranodal involvement: 25-40%**
  - Skin (9%) > upper respiratory tract > soft tissue > orbit > bone > salivary gland > CNS > breast > pancreas*

- **Primary presentation in skin = rare**
  - Median age 45yr (older than nodal cases)
  - Female predominance (unlike nodal cases)
  - Whites and Asians predominate (ditto)

- **Clinical features**
  - Solitary or multiple dermal or subcutaneous nodules or plaques on face, trunk or extremities
  - May resolve spontaneously or become chronic

*Rezk et al, Diagnostic Hematopathology, Ch. 51, 2010*
64-Year-Old African American Woman: 8 cm painful nodule on abdomen
39 Year-Old African-American Woman: 4 cm subcutaneous plaque on flank
CD20  CD3
Diagnostic Area
Enperipolesis
Rosai-Dorfman Disease: Features

- Involvement of dermis, subcutis, either or both
- Large S100+ histiocytes with prominent nucleoli and emperipolesis
  - May be present only very focally extranodal sites
  - May form aggregates that resemble sinuses
- Numerous plasma cells, neutrophils, histiocytes may be present, especially at edges of lesion
- Characteristic edematous plasma-cell-rich background
  - A clue to look for the large histiocytes
Intralymphatic histiocytosis

- Dilated lymphatics containing histiocytes
  - Frequent association with rheumatoid arthritis
  - Erythematous plaques near affected joints

- 16 cases reported by Requena et al
  - 12 on arms or legs
    - 5 rheumatoid arthritis
    - 2 in scar of THR
    - 2 in scar of mastectomy
  - 1 presented as unilateral swelling of the eyelid
    - Clinical diagnosis: Melkerson-Rosenthal syndrome

Requena et al. Am J Dermatopathol 2009;31:140-51
Intralymphatic Histiocytosis

- 56-year-old man
  - History of mild facial rosacea
  - MGUS
  - 2-year history of unilateral periorbital edema
    - Difficulty opening his eye
Diagnosis

• Changes consistent with granulomatous rosacea (dilated blood vessels, superficial edema, perifollicular and perivascular granulomatous inflammation)

• Demodex follicularum
  - Often associated with rosacea

• Intralymphatic histiocytosis with marked superficial and deep dermal edema
Intralymphatic histiocytosis

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Requena et al. Am J Dermatopathol 2009;31:140-51
Solid Facial Edema of Rosacea

- **Unilateral periorbital/facial swelling in a patient with rosacea**
  - Rare complication, may be presenting symptom
  - Unresponsive to treatment for rosacea (antibiotics)
- **Related entities:**
  - Solid facial edema of acne
  - Morbihan’s syndrome (idiopathic)
  - Melkerson-Rosenthal syndrome/granulomatous cheilitis
    - Facial/lip swelling
    - Furrowed tongue
    - Facial nerve palsy
    - May be familial
- **Characteristic features**
  - Edema in all layers of the dermis
  - Perivascular and periadnexal inflammatory infiltrates
  - No mention of intravascular histiocytes
Solid Facial Edema and Intralymphatic Histiocytosis

• Two cases:
  - Case 15 of Requena (rosacea history not known)
  - Current case (mild rosacea)

• Both characterized by granuloma-like lymphohistiocytic clusters in dermal lymphatics
  - Distinct from bland, purely histiocytic collections in RA/scar-associated cases
  - Blockage of lymphatics by histiocytes may produce edema

• Our case
  - Methotrexate and prednisone (given because of diagnosis of “histiocytosis” [a neoplasm]): no response
  - Clinicians were contemplating radiation
  - Case re-reviewed and edema of rosacea suggested
    ▪ Currently on isotretinoin therapy
    ▪ Rx of demodex with metronidazole
Histiocytoses

- Xanthogranuloma group
- Reticulohistiocytoma group
- Langerhans cell histiocytosis
Xanthogranuloma Group

• Normal counterpart
  - Histiocyte or interstitial dendritic cell

• Histopathology/Immunophenotype
  - Histiocytic infiltrate with foam cells and Touton giant cells
  - CD68+ CD163+ F13a+ S100- CD1a- Langerin-

• Clinical syndromes
  - Localized cutaneous
    ▪ (Juvenile/adult xanthogranuloma)
  - Disseminated cutaneous
    ▪ (JXG, progressive nodular and generalized eruptive histocytosis)
  - Disseminated: skin, mucosae, CNS (diabetes insipidus), bones, soft tissue, lung, heart
    ▪ (Xanthoma disseminatum, disseminated JXG, Erdheim Chester Disease)

• Genetic features
  - Not known for cutaneous cases
  - ECD clonal in some (most?) cases
Juvenile Xanthogranuloma

- (Not likely to be shown to a hematopathologist!)
- **Clinical**
  - Child (80%), young adult (20%)
  - Cutaneous: solitary orange-red-brown lesions: head-neck > trunk, limbs, oral cavity, eye
  - Disseminated: viscera, soft tissues, heart, CNS, bones
- **Histology**
  - Histiocytes with eosinophilic or vacuolated cytoplasm, bland nuclei
  - Spindle cells
  - Multinucleated Touton giant cells
    - Peripheral rim of vacuolated cytoplasm
    - Central ring of nuclei
    - Inner zone of eosinophilic cytoplasm
    - (May not be identifiable in extracutaneous sites)
34-Year-Old Man
Pink Papule, Lower Abdomen
Xanthoma Disseminatum

- A 63-year-old man with
  - Diabetes insipidus
  - Skin lesions on face (eyelids, nasolabial folds) and flexor surfaces of limbs (axillae, groin)
  - Submucosal lesions of larynx with stenosis and stridor

Erdheim-Chester Disease

Case Records of the Massachusetts General Hospital
Case 25-2008 — A 43-Year-Old Man with Fatigue and Lesions in the Pituitary and Cerebellum
John A. Mills, D., R. Gilberto Gonzalez, M.D., Ph.D., and Ronald Jaffe, M.D.
N Engl J Med
Volume 359(7):736-747
August 14, 2008
• Renal, perinephric tissue biopsy
  - Mild, non-diagnostic kidney changes
  - Histiocytic infiltrate in peri-renal fat, nonspecific

• Clinical diagnosis
  - Neurosarcoidosis with involvement of soft tissues; possible aortitis
  - Rheumatology consultant (Dr. Mills) made the diagnosis of ECD based on the imaging studies

• Pathology re-examined by Ron Jaffe
Pathological Features of the Perirenal Infiltrate

CD68

CD168

F13A
Peri-renal Tissues

- Bland histiocytes, lacking malignant features
- Xanthomatous, foamy component
- Few giant cells, no Touton giant cells
  - No granulomas or epithelioid cells
  - No evidence of vasculitis
- Immunophenotype (CD68+ CD163+ F13A+ CD1a-) consistent with ECD
Characteristic Clinical Picture of ECD

- In this patient
  - Hypothalamic-pituitary axis, CNS
  - Retroperitoneum, kidney
  - Heart and peri-aortic tissue
  - Bone

- Other sites that may be involved
  - Lung
  - Orbit

- Tissue diagnosis
  - Histiocytes, foam cells, +/- Touton giant cells
  - Foci of Langerhans cells may occur
  - May appear nonspecific; need clinical correlation
  - Important to exclude granulomatous diseases, vasculitis

- Mortality >50% due to lung, cardiac involvement
Xanthogranuloma Group

• A group of probably related diseases with similar histological and immunophenotypic features but variable clinical manifestations

• Unisystem: Cutaneous (single/multiple)
  - Juvenile xanthogranuloma (single or multiple)
  - Adult xanthogranuloma (single)
  - Generalized eruptive histiocytosis (multiple, relapsing)
  - Progressive nodular histiocytosis (multiple)

• Multisystem
  - Xanthoma disseminatum
    ▪ Skin, CNS (diabetes insipidus, mucosae)
  - Disseminated JXG [child]/Erdheim-Chester disease [adult]
    ▪ Bones, CNS (diabetes insipidus), soft tissue, lung, skin (in children; rarely in adults)
Reticulohistiocytoma Group

• Clinical
  - Nodular yellow papules, single or multiple (face, hands, ears)
    - (Reticulohistiocytoma)
  - Systemic condition with skin lesions, destructive arthritis, fever; occasionally with occult malignancy (25%), rheumatic disease
    - (Multicentric reticulohistiocytosis)
  - Both: mucous membranes (nose, oral cavity)
  - F>M, child or adult

• Morphology:
  - Bland nuclei, eosinophilic ground glass cytoplasm, giant cells (non-Touton)
  - Similar infiltrate in affected joints

• Immunophenotype
  - CD68+ S100- CD1a- lysozyme+/− F13a-
Adult F with generalized papular eruption, fever, uveitis. Courtesy of Jonathan Said and Larry Weiss
Multicentric Reticulohistiocytosis

- **Immunophenotype**
  - CD68+ CD163+ S100+
  - Lysozyme, CD15, CD30, EMA, CD4: negative

- **Morphologic features most c/w multicentric reticulohistiocytosis**
  - Atypical immunophenotype
  - No mention of arthritis
Langerhans Cell Neoplasms

• A clonal tumor of Langerhans cells
• Two subtypes
  - **Langerhans cell histiocytosis**
    ▪ Morphologically typical Langerhans cells
  - **Langerhans cell sarcoma**
    ▪ High-grade sarcomatous lesion with the immunophenotype of LC
• **Morphology (LCH)**
  - Grooved nuclei, eosinophils
• **Immunophenotype**
  - S100+ CD1a+ Langerin+ Birbeck granules (EM)
  - CD68 variable, lysozyme-
Langerhans Cell Histiocytosis

- **Unisystem** (bone/soft tissue, skin, lymph node, lung [some cases])
  - **Unicentric** (single site)
    - Eosinophilic granuloma
  - **Multicentric** (multiple cutaneous or bony sites)
    - Hand-Schuller-Christian disease (bone and adjacent soft tissue, pituitary stalk; skin may be involved [multisystem])

- **Multisystem**
  - **Acute** (Letterer Siwe disease)
    - Skin, bone, liver, spleen, lung, lymph nodes, bone marrow
  - **Chronic** (Hand-Schuller-Christian disease)

- **Prognosis**
  - Good for unisystem disease
  - May be poor for multisystem disease ~50% mortality in LS
84-Year-Old Woman
Lesions on Chest and Arm
Histiocytoses: Common Features

- Within each group, tumors of identical cells have a spectrum of clinical presentation and behavior
  - Child vs adult
  - Localized vs disseminated
  - Unisystem vs multisystem
- Nomenclature traditionally based on clinical presentation
  - Leads to a confusing array of names/eponyms
- Problem largely solved for LCH group
  - Known to be clonal, neoplastic
  - Classify by systems involved (stage)
  - Unclear what genetic abnormalities underly behavior
- Need unifying nomenclature for the other 2
  - Evidence that ECD is clonal; lacking for others
  - Rarity of lesions hampers further study
Histiocytoses Revisited

• Xanthogranuloma group
  - Unisystem (skin)
    ▪ Unicentric
    ▪ Multicentric
  - Multisystem
    ▪ Skin, CNS, bone, soft tissue, mucosae, heart, lungs

• Reticulohistiocytoma group
  - Unisystem (skin)
    ▪ Unicentric
    ▪ Multicentric
  - Multisystem
    ▪ Skin, joints

• Langerhans cell histiocytosis (clonal)
  - Unisystem (skin, bone, lymph node, lung)
    ▪ Unicentric
    ▪ Multicentric
  - Multisystem
    ▪ Skin, bone, liver, spleen, lung, lymph nodes, bone marrow
Neoplastic Diseases

- Langerhans cell histiocytosis
- FDC sarcoma
- IDC sarcoma
- Histiocytic sarcoma
- Blastic plasmacytoid dendritic cell tumor
Interdigitating Dendritic Cell Sarcoma

- A tumor of cells resembling IDC of lymph nodes
- Lymph nodes > skin, soft tissues
- Oval to spindled cells, variable nuclear atypia, lymphocyte-rich background
- S100+ CD1a- FDC markers– CD68+/- lysozyme+/- ; lymphocytes T>>B
- Clinically aggressive, often fatal
Follicular Dendritic Cell sarcoma

- A neoplasm of oval to spindled cells with morphology and immunophenotype of FDC
- Lymph nodes (2/3), skin, soft tissue, GI, liver, spleen
- Spindled cells with bland nuclei, often binucleate, forming whorls; lymphocyte-rich background with follicles
- Immunophenotype
  - CD21+ CD23+ CD35+ CD68/-/+ S100/-/+ CD1a-
  - Lymphocytes B>T
- Usually indolent, may recur after excision; late metastases, death in up to 20%
Follicular Dendritic Cell Sarcoma of Skin
67F lesion of lower leg; ipsilateral inguinal lymphadenopathy
Histiocytic Sarcoma

- Malignant tumor with morphologic and immunophenotypic features of a mature tissue histiocyte
- Sites
  - GI tract, skin, soft tissues, lymph nodes
  - Solitary or multiple cutaneous nodules
- Large eosinophilic cells, giant cells, vacuoles
- Immunophenotype
  - Lysozyme, CD68, CD168 positive
  - Myeloperoxidase, CD1a, FDC markers negative
  - CD45+/− CD4+/− CD43+ S100 variable
Histiocytic Sarcoma
50F: bilateral tonsillar enlargement
Histiocytic Sarcoma: Immunophenotype

- CD1A
- S100
- CD68
- LYSOZYME
- CD1A
Histiocytic Sarcoma: DDX

- Non-hematopoietic tumors
  - Melanoma
  - Other sarcomas

- Other hematopoietic tumors (more common!)
  - Myeloid or monocytic leukemia
  - Blastic plasmacytoid dendritic cell tumor
  - Dendritic cell sarcomas
  - T-cell or B-cell lymphomas
Blastic Plasmacytoid Dendritic Cell Neoplasm

• A tumour of a precursor of the plasmacytoid dendritic cell (professional type 1 interferon producing cell or plasmacytoid monocyte), involving skin and bone marrow

• Sites:
  - Skin, bone marrow, lymph nodes

• Morphology:
  - Monomorphous medium-sized blastic cells; mitoses

• Immunophenotype:
  - CD4+ CD56+ CD123+ BCDA1+ Tcl1+ CD68+ (50%) TdT + (30%)
  - CD2, CD7, CD33 variably+
  - CD3- CD5- CD20- MPO- lysozyme- CD34- GCP-
BPDC Cutaneous Lesions
BPDC Immunophenotype

CD123
CD4
CD56
CD3
BPDC: Differential Diagnosis

• Leukemic infiltrate of AML or T-ALL
  - May be CD33+ CD2+ CD7+
  - AML or ALL may be CD56+
  - Monocytes may be CD123+
  - Absence of MPO, CD3 helpful; need a broad panel
  - Treatment like AML, so distinction may not affect management

• Expansion of mature PDC in MDS/AMML
  - Expression of CD56, TdT
  - Increased proliferation fraction
Histiocytic Lesions of the Skin: Summary

- A heterogeneous group that range from idiopathic/reactive to aggressive malignancies
- True neoplasms are relatively straightforward
  - Rare, and thus always challenging
  - Some cases cannot be classified precisely by normal counterpart
  - Extensive immunophenotyping often required
- Idiopathic/non-LCH histiocytoses more difficult
  - Histologic and immunophenotypic features may not distinguish nonspecific histiocytic infiltrates from specific lesions and histiocytoses
  - Small biopsies yield non-diagnostic areas (RDD)
  - Characteristic cells may be lacking in non-lymph node or non-cutaneous sites
    - Emperipolesis less common in skin (RDD)
    - Touton giant cells less common in soft tissue (ECD)
Histiocytic Lesions of the Skin: Summary

- Need clues to look for diagnostic cells
  - Plasma cells, edema, histiocytes, neutrophils: think of RDD
  - Foamy cells in soft tissue with no apparent cause: think of ECD

- Don’t “blow off” a histiocytic infiltrate (cutaneous or non-cutaneous) as non-specific inflammation without a search for the cause
  - Discuss with clinicians whether there is reason to suspect a histiocytosis

- Avoid the term “histiocytosis” for obviously reactive lesions
  - E.g. “Intralymphatic histiocytosis”
  - Clinicians may interpret this as indicating a neoplastic process

- I hope this was helpful!
Acknowledgments

• Judith Ferry
• Russell Ryan
• Valentina Nardi
• Rosalyn Nazarian
• Lyn Duncan
• Jonathan Said
• Ronald Jaffe
• Others….
I’ll be happy to answer any questions....

Dan Harris, ABC news, Kandahar (Oct 2001)