Non-Malignant Histiocytic Disorders of the Thorax: Typical and Variant Presentations

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Disclosures

- No relevant financial relationships to disclose.
Learning Objectives / Outcomes

- Review the genesis and classification of non-malignant histiocytic disorders affecting the thorax
- Illustrate histopathological, immunohistochemical, and typical / atypical imaging findings of these disorders
- Enumerate imaging features that allow diagnosis of these disorders
- Target audience: general radiologists, imaging trainees
Histiocytoses

- Rare disorders characterized by accumulation of macrophage, dendritic, or monocyte-derived cells
- >100 subtypes described
- Histiocytes:
  - Immune cell group including macrophages & dendritic cells
  - Histiocyte is a tissue-resident macrophage
- Mononuclear phagocyte system: dendritic cells (DC), monocytes, macrophages
  - DCs: non-phagocytic; present antigens, activate T cells; classified / sub-classified by immunohistochemical expression; Langerhans cell (LC) is DC subtype
Histiocytoses

- Previously classified into 3 categories:\(^1,^2\)
  - Langerhans cell histiocytosis (LCH)
  - Non-Langerhans cell related histiocytosis
  - Malignant histiocytoses

- Also previously classified as 1\(^\circ\) or 2\(^\circ\) depending on whether causative insult known;\(^2\) further categorized based on whether histiocytic proliferation is a major or minor component of histopathologic findings

- Recent insights regarding histology, phenotype, molecular alterations, clinical manifestations, & imaging presentations has prompted revised classification\(^1\)
Histiocytoses: Revised Classification

L Group
- Langerhans cell histiocytosis (LCH)
- Indeterminate cell histiocytosis
- Erdheim-Chester Disease (ECD)

C Group
- Rosai-Dorfman Disease (RDD)

R Group
- Juvenile or adult xanthogranuloma
- Solitary reticulohistiocytoma
- Benign cephalic histiocytosis
- Generalized eruptive histiocytosis
- Progressive nodular histiocytosis

M Group
- 1° or 2° malignant histiocytosis

H Group
- Others
- Monogenic inherited conditions leading to hemophagocytic lymphohistiocytosis
Langerhans Cell Histiocytosis

- **Proliferation/infiltration of LCs in ≥ 1 organ**
  - Older terms: *eosinophilic granuloma, histiocytosis X*
  - LC multisystemic syndromes (typically affect children): *Letterer-Siwe, Hand-Schüller-Christian, Hashimoto-Pritzker*

- **Pulmonary LCH:**
  - As part of systemic disease: typically children, not smoking-related; clonal neoplasm
  - Isolated:
    - Most commonly affects lung
    - Non-neoplastic; adults, 20-40 years old, smokers
    - Abnormal immune response to cigarette smoke
PLCH: Histopathology

- Pathology depends on disease phase; all show background smoking changes (RB, SRIF)
- Proliferative phase
  - Cellular airway centered nodules & cysts
  - Mixed inflammation, eosinophils, giant cells, smoker’s macrophages & numerous hallmark LCs
PLCH: Histopathology, cont.

- **Fibrotic phase**
  - centrilobular stellate scars
  - less frequent to absent LC

- **Hallmark cell**
  - histiocytes with crumpled tissue paper or coffee bean-shaped nuclei

- **EM: Birbeck granule**
  (not used in practice)
  - LC immunostaining:
    - CD1a\(^+\), CD207\(^+\), CD68\(^+\)
    - S-100\(^+\), Factor XIII\(^-\)
PLCH Imaging: Typical Manifestations

**Limited Disease**
- "Bizarre"-shaped cysts

**Extensive Disease**
- Upper lobe predominant **centrilobular nodules, cysts, cavities**
- **Pneumothorax**
- **Larger Nodules**

**End – stage disease resembling severe emphysema**
PLCH Imaging: Atypical Manifestations

- Nodules only (20%)
- Basal predominant disease
- Multifocal groundglass opacity; no cysts
- Pulmonary hypertension: enlarged pulmonary arteries
Erdheim-Chester Disease (ECD)

- Histopathology overlaps with LCH: up to 20% with ECD have LC lesions, and both disorders have clonal mutations of MAPK pathway in > 80%.
- Mean age: 55 – 60 years; ♂:♀ = 3:1.
- Classification:
  - Classical
  - ECD without bone involvement
  - Associated with myeloproliferative disorder
  - Extra-cutaneous / disseminated JXG with MAPK-activating mutation or ALK translocation
ECD: Histopathology

- Unique pattern of pleural and septal fibrosis
- Sharp transition to alveolar parenchyma
- Dense fibrosis with nodules of inflammation
Embedded xanthomatous or “foamy” mononucleated histiocytes with small nuclei

- Rare Touton cells
- ECD histiocytes: CD68⁺, CD163⁺, Factor XIII⁺
- CD1a⁻
ECD – PLCH Overlap

- Fibrohistiocytic pleural thickening
- Factor XIII$^+$ in ECD cells
- CD1a$^+$ in PLCH cells
ECD: Typical Imaging Manifestations

- >95% osseous involvement (metaphyseal, diaphyseal cortical sclerosis)
- 50% cardiopulmonary:
  - Smooth interlobular septal thickening
  - Pericardial, pleural infiltration
ECD: Typical Imaging Manifestations

- Cardiopulmonary
  ECD:
  - Perivascular, pericardial infiltration; tissue enhances
  - may be FDG-avid
ECD: Typical Imaging Manifestations

- Renal, perirenal involvement: 33%
- CNS: diabetes insipidus, exopthalamos, orbital masses

Perirenal infiltration: “hairy” kidney

Bilateral orbital enhancing masses
ECD: Pre- & Post-Treatment

• Current Rx: corticosteroids, interferon-alpha, chemotherapy, radiation

• V600EBRAF mutation in 50%: implies BRAF kinase inhibitor therapy may be effective

Interval reduction in pleural and pericardial effusions, with clinical improvement, after cladribine therapy.
ECD: Atypical Imaging Manifestations

- Absence 1 or more “typical” features (perirenal, aortic infiltration, osteosclerosis)

- LCH – like lesions

Biopsy-proven ECD: cysts, some clustered, more suggestive of LCH, peribronchial & subpleural masses? IgG-4 disease. Typical osseous, periaorti & perirenal lesions were absent.
ECD: Atypical Imaging Manifestations

Biopsy-proven ECD: **centrilobular nodules, nodular perivascular thickening, faintly nodular septal thickening, & ground-glass opacity.** Typical osseous, periaortic & perirenal lesions are absent.
Cutaneous Non-LC Histiocytosis

- “C” group lesions: cutaneous & mucocutaneous histiocytosis
- May be associated with systemic involvement
- Juvenile xanthogranuloma most common of this group
- Non-juvenile xanthogranulomatous lesions in this group include cutaneous Rosai-Dorfman disease, necrobiotic xanthogranuloma (may be associated with myeloma) & multicentric reticulohistiocytosis
Cutaneous Non-LCH: Histopathology, Clinical, & Imaging

- S100⁻, CD1a⁻
- Imaging expressions rare: micronodules & larger nodules, up to 25 mm, reported
- A sarcoid-like appearance may occur⁵

Clustered nodules along the bronchovascular bundles & fissures resembling sarcoid, successfully treated with methotrexate
Rosai-Dorfman Disease (RDD)\textsuperscript{1}

- aka Sinus histiocytosis with massive lymphadenopathy
- Primarily disorder of children, young adults, affecting lymph nodes
- Most commonly presents as bilateral, painless, cervical lymphadenopathy
- Extranodal involvement (43\%):  
  - Skin, nasal cavity, bone, soft tissue, retro-orbital tissue  
  - CNS: pachymeningitis
RDD: Histopathology

- Fibrohistiocytic expansion of the pleura, septum, & bronchovascular bundles
- Background of moderate mixed inflammatory cell infiltrate
- Lymphoid follicles
RDD: Histopathology

• Nodules & aggregates of histiocytes, mixed background inflammation
  - $\text{S100}^+$, $\text{CD68}^+$, $\text{CD14}^+$, $\text{CD163}^+$
  - $\text{CD1a}^-$, $\text{CD207}^-$
  - histiocytes engulf erythrocytes, plasma cells, lymphocytes = emperipolesis

Histiocytes with emperipolesis

Histiocytes with inflammation

S100$^+$ histiocytes
RDD: Histopathology

- Background moderate mixed inflammatory cell infiltrate
  - numerous plasma cells, may be IgG⁺; ddx= IgG4 dz⁶

- Dense bronchovascular inflammation
- S-100⁺ histiocytes (light brown)
- IgG4⁺ plasma cells in background
RDD: Imaging Manifestations

- Thoracic involvement may be more common than previously recognized:\n  - Mediastinal, peribronchial lymph node enlargement
  - “Interstitial” disease (NSIP-like)
  - Pleural effusion
  - FDG-avid

Pt. with headache; MR shows pachymeningitis. Pre-brain biopsy testing prompted thoracic CT & FDG-PET. Brain and bronchoscoptic biopsy confirmed RDD
## Thoracic Histiocytoses

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<td>CD1a⁺ CD68⁺ CD207⁺ S100⁺ Factor XIII⁺⁻</td>
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<td><strong>Imaging</strong></td>
<td>upper lobe nodules, cysts emphysma</td>
<td>periaortie, perinrenal infiltration septal thickening osteosclerosis pleural, pericardial effusion</td>
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References


Histiocytoses: Revised Classification

- **L (Langerhans) Group**: LCH, Indeterminate cell histiocytosis (ICH), Erdheim-Chester disease (ECD)
- **C Group**: cutaneous non-LCH, juvenile xanthogranuoma, adult xanthogranuloma, solitary reticulohistiocytoma, benign cephalic histiocytosis, generalized eruptive histiocytosis, & progressive nodular histiocytosis
- **R Group**: Rosai-Dorfman disease (RDD)
- **M Group**: 1° malignant histiocytosis, 2° to or following other hematologic malignancy
- **H Group**: Monogenic inherited conditions leading to hemophagocytic lymphohistiocytosis (HLH)