Differential Diagnosis of Lymphoid Infiltrates of the Lung

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Objective
• Common benign lymphoproliferative disorders of the lung
• Common malignant lymphoproliferative neoplasms of the lung
• Including few rare entities

Lung and Lymphatics
Rich in lymphatics
Bronchial associated lymphoid tissue (BALT)
Intraparenchymal lymph node
**Bronchus-associated Lymphoid Tissue (BALT)**

- BALT is a specific type of MALT that is present in the lungs and involved in the immune response to inhaled antigens
- BALT is composed primarily of B cells at the center with peripheral clusters of T cells
- BALT can develop follicles with distinct germinal centers when antigenically stimulated
- BALT is not present at birth, develops in infants and young children
- Chronic antigenic stimulation of BALT in adulthood can result in a variety of benign and malignant lymphoid diseases

**Lung Diseases with lymphatic distribution**

- Lymphangitic carcinoma
- Sarcoidosis
- Lymphoma

**Differential Diagnosis of Lymphoid Lesions Presenting as Micronodules and Ground Glass Opacities**

**Follicular Bronchiolitis**

- Polyclonal hyperplasia and expansion of the BALT from chronic antigen stimulation, resulting in hyperplastic lymphoid follicles primarily composed of polytypic B cells
- More common in males
- Congenital or acquired immunodeficiency, collagen vascular disease

Follicular bronchiolitis in a 53-year-old woman with a history of Sjögren’s syndrome

**Lymphoid Interstitial Pneumonia**

- First described by Leibow and Carrington in 1969 as a diffuse and dense lymphocytic interstitial infiltrate
- Often associated with underlying systemic disease
- Most frequent in females in fifth decade but can present at any age
- Ill-defined granulomas and giant cells have been found in 20%–50% cases
- Always exclude underlying lymphoproliferative disorder

Multiple well-defined thin-walled cysts (arrow) on a background of ground-glass attenuation

**Idiopathic Lymphoid Interstitial Pneumonia**

- Very Rare
- Clinical course varies from resolution without treatment to progression to end stage disease
- Median survival reported around 11.5 years
- Progression to lymphoma in limited cases (~5% cases)
Differential Diagnosis of Lymphoid Lesions Presenting as Macronodules

**BENIGN**

**Nodular Lymphoid Hyperplasia**
- Adults with altered immune status
- Mixture of B and T cells
- Lymphoepithelial lesions are common

**Inflammatory Myofibroblastic Tumor**
- Lung: most frequent site
- Majority seen in children and young adults with no gender predilection
- Prevalence of up to 1% of all lung tumors
- Spindle cells admixed with inflammatory elements
- ALK-1 positive in ~40% cases

**IgG4 related sclerosing disease**
- Multi organ system disease
- Tissue infiltration with lymphocytes, and plasma cells which are IgG4 positive
- Variable amount of fibrosis
- Usually associated with serum IgG4 elevation
- Nearly any organ system can be involved
- Pancreatic/hepatobiliary and salivary/lacrimal gland involvement common
- Lungs involved in <1/5th of cases overall
**Proposed Diagnostic Criteria for IgG4RD**

1. Clinical or radiologic exam showing characteristic diffuse/localized swelling or masses in single or multiple organs
2. Hematological exam shows elevated IgG4 levels (>135mg/dl)
3. Histopathologic exam shows findings consistent with IgG4 related disease (>40% IgG4/IgG cells and > 50/HPF IgG4 cells on SLB, or >20 IgG4 cells on TBBx)
4. Absence of clinical, laboratory or histopathologic features to suggest an alternate diagnosis such as malignancy, granulomatosis with polyangiitis etc.

**Definite IgG4 related disease:** 1+2+3+4  
**Probable IgG4 related disease:** 1+3+4  
**Possible IgG4 related disease:** 1+2+4

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**Differential Diagnosis of Lymphoid Lesions Presenting as Macronodules**

**MALIGNANT**

**Marginal Zone Lymphoma**
Pulmonary Marginal Zone Lymphoma (PMZL)

- Most common primary and secondary lymphoma of the lung (~ 70% of cases)
- First described in 1973
- Median age 50-60 years; M>F
- 80-90% survival at 5 years
- Acquired as secondary response to various antigens
  - Smoking
  - Immunological disease such as Sjögren’s syndrome, rheumatoid arthritis, Hashimoto’s thyroiditis, systemic lupus erythematosus
  - Infections such as hepatitis C and HIV

- Pulmonary MZL can be associated with prominent stromal deposition of amyloid in 1% to 6% of cases
- Pulmonary MZL with light chain deposition disease has also been reported, one of them present in an HIV-positive male
- Light chain deposition disease shows deposits similar to amyloid, but these are Congo red negative, whereas amyloid has characteristic Congo red positivity
**Lymphoepithelial Lesions**

- Bronchial or bronchiolar epithelium
- Significant luminal narrowing
- Both reactive and neoplastic lesions

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**Diffuse Large B Cell Lymphoma**

- Primary pulmonary diffuse large B-cell lymphoma is the second most common type of primary pulmonary lymphoma, accounting for 12% to 20% of cases
- Adults in the sixth and seventh decades of life, seen in both immunocompromised and immunocompetent patients
- Subset of these lymphomas arise by transformation of preexisting or concurrent MZL, small lymphocytic lymphoma, and follicular lymphoma.
- Immunophenotype of the neoplastic cells: Positive for CD19, CD20, and CD79a, and those of germinal center origin also express CD10 and bcl-6

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**Intravascular Large B Cell Lymphoma (IVLBCL)**

- Intravascular large B-cell lymphoma (IVLBCL) is characterized by the selective growth of large lymphoma cells within smaller vessel lumina.
- Uncommon primary presentation in the lungs, most common skin and CNS involvement.
- Diagnosis could be very difficult due to the lack of detectable tumor masses and it is usually made by surgical lung biopsy or autopsy examination.
Other rare B and T cell Lymphomas

- Follicular lymphoma
- Mantle cell lymphoma
- Small lymphocytic lymphoma
- Burkitt lymphoma
- Anaplastic large cell lymphoma
- Peripheral T cell lymphoma, NOS

Differential Diagnosis of Macronodules with Polymorphous Background and Areas of Necrosis

AFTER EXCLUDING INFECTIONS

Polymorphous background with atypical cells

Hodgkin Lymphoma

Flow cytometry, molecular studies not very helpful

Morphology: Reed Sternberg cells and variants
Mixed inflammatory cell population
Primary Pulmonary Hodgkin Lymphoma

- Primary Pulmonary Hodgkin lymphoma: rare entity
- Affects young adults: mean age of 42 years and slight female predisposition
- Single or multiple parenchymal masses
- Endobronchial lesions
- Pneumonia-like consolidation
- No mediastinal lymph node involvement or disease elsewhere

Secondary Involvement of the lung by Hodgkin Lymphoma

- Pulmonary involvement in Hodgkin's disease can occur in 15% to 40% of cases
- Most patients present with concomitant cervical, mediastinal, or supraclavicular lymph nodes enlargement
- Granulomatous response
- Prognosis is favorable (slightly less than nodal)

Factors associated with a poor prognosis

- Age greater than 60 years
- B symptoms
- Multiplicity and bilaterality of lung lesions
- Pleural effusion
- Cavitation

Polymorphous background with atypical cells and areas of necrosis

- Cellular infiltrate is composed of large atypical cells, small lymphocytes, histiocytes, and plasma cells
- Variable areas of necrosis

Lymphomatoid Granulomatosis

- Angiocentric, angiodestructive
- Direct invasion of blood vessels by T cells
- Chemokines and cytokines from the EBV positive cells
**EBV positive B cells:**
- CD20, PAX5, CD79a positive
- Variably CD30 positive
- CD15 negative

**Background of CD3 positive T cells:**
- Mixture of CD4 and CD8
- CD8 cells are often granzyme B positive

**Immunophenotype**

**Grading of Lymphomatoid Granulomatosis**

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<tr>
<th>Grade</th>
<th>Description</th>
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<tr>
<td>1</td>
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<td>3</td>
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Based on number of large atypical B cells, number of EBV-infected large B cells, and amount of necrosis

**Lymphomatoid Granulomatosis**

- Risk: Underlying immune defect
- Sites of involvement:
  - Lung: 90%
  - Brain: 25%
  - Other: Liver, kidney, skin
  - Lymph nodes and spleen are rare
- Aggressive disease – median survival <2 years

**NK/T Cell Lymphoma**

- Also an angiocentric, angiodestructive lesion
- Is EBV positive
- Rarely involves the lung (<10%)
- Classic phenotype of neoplastic cells: CD2, cytoplasmic CD3, CD56, EBER

**Post transplant Lymphoproliferative Disorder**

PTLD of the lung as a complication of liver transplant for autoimmune hepatitis in a 35-year-old woman.
Post transplant Lymphoproliferative Disorder

- Post stem cell and organ transplant setting that range from benign polyclonal proliferation to malignant monoclonal disease
- 80% of PTLD cases consist of EBV-infected B-cell proliferations occurring within the first 2 years after transplant
- The World Health Organization has organized PTLD into four categories
  - Hyperplastic/early lesions
  - Polymorphic lesions
  - Monomorphic lesions
  - Classic Hodgkin-like PTLD

Conclusion

- Pulmonary lymphoid lesions are diagnostically difficult
- Broad differential exists
- Integrated approach
  - Pathology and radiology
  - Pulmonary pathologist and hematopathologist
  - Routine sections and ancillary studies
    - Immunophenotyping
    - Molecular genetic analysis
    - Cytogenetics
- Correct diagnosis and treatment even in difficult cases

THANK YOU