An Integrated Approach to the Diagnosis of Lymphoproliferative Neoplasms of the Lung

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Objectives

- Common lymphoproliferative lesions of lung
- Rare lymphoproliferative lesions of the lung
- Problems/pitfalls in diagnosis
- Case based study

Case 1

NO FINANCIAL DISCLOSURES
History

- 65 year old male, former smoker (25 pack year); quit 20 years ago.
- On routine chest imaging, two lung nodules were identified
- No history cough, dyspnea, chest pain
- Patient also had symptoms of gastritis

Pertinent Labs

- CBC normal
- Fungal serological markers - Negative
- Fungal urine antigens – Negative
- Helicobacter pylori IgG antibody serology - Negative

CT Chest / PET CT

Transbronchial Biopsy

- Chronic inflammation
- Immunohistochemistry work up non-contributory
Wedge Resection (Dec 2011)

Considerations

- Nodular Lymphoid Hyperplasia
- Lymphoid Interstitial Pneumonia
- Follicular Bronchiolitis
- IgG4-Related Sclerosing Disease
- Low grade lymphoma
  - Marginal zone lymphoma and small lymphocytic lymphoma

Lung and lymphatics

- Rich Supply of lymphatics
- Sparse sub mucosal aggregates of lymphocytes (BALT)
  - Interlobar septa
- Intraparenchymal bronchovascular lymph nodes

Lung diseases with lymphatic distribution

- Lymphangitic carcinoma
- Lymphoma
Nodular Lymphoid Hyperplasia
- Adults with altered immune status
- Mixture of B and T cells
- Lymphoepithelial lesions are common
- Intraepithelial lymphocytes can be B or T cells

Lymphoid Interstitial Pneumonia
- Adults and children with altered immune status
- Dominant interstitial pattern of distribution
- Primarily T cells
- Polytypic B cells and plasma cells

Follicular bronchiolitis
- More common in males
- Congenital or acquired immunodeficiency, collagen vascular disease
- Eccentric peribronchiolar accumulation of lymphoid tissue
- Polytypic B cells

IgG4 related sclerosing diseases
- Polytypic plasma cells
- Dense fibrosis
- Vascular involvement
- >40% ratio of IgG4+ to IgG+ plasma cells
Flow Cytometry

Immunophenotype: Monotypic lambda positive B cells; CD5 and CD10 negative

Immunohistochemistry

Immunostaining for H. pylori - negative

Stomach Biopsy

NOTE: PCR analysis - gastric and lung lesions clonal with same IgH rearrangement
Diagnosis

Secondary Involvement of Lung by Extra-nodal Marginal Zone Lymphoma of the Mucosa-associated Lymphoid Tissue

Extranodal Marginal Zone Lymphoma of Mucosa-associated Lymphoid Tissue (MALT Lymphoma)

- Comprise <10% of all B cell lymphomas
- Morphology
- Immunophenotype and immunoarchitecture
**Molecular / FISH / Cytogenetics**

IgH rearranged

Other genetic abnormalities

- t(11;18)
- t(14;18)
- t(3;14)
- Trisomy 3, 12, 18
- p53 LOH/mutation

MALT1 Break Apart FISH Probe (Chromosome 18)

**Courtesty: Cytogenetics Laboratory; Dr. Yanming Zhang, Director**

**Our patient**

**Molecular / FISH / Cytogenetics**

IgH rearranged

Other genetic abnormalities

- t(11;18)
- t(1;14)
- t(14;18)
- t(3;14)
- Trisomy 3, 12, 18
- p53 LOH/mutation

MALT1 Break Apart FISH Probe (Chromosome 18)

**Courtesty: Cytogenetics Laboratory; Dr. Yanming Zhang, Director**

**Our patient**

t(11:18) most common in lung and gastric lesions

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**Importance of Genetic Findings**

Gastric MALT lymphoma – correlates with antibiotic response

- Antibiotics – Successful in ~75% of cases
- Usually see no response to antibiotic eradication of H. pylori
  - IF
  - Stage II or greater
  - Ia2 (beyond submucosa) > Ia1, failure rate
  - t(11:18)
  - t(1:14)

Pulmonary MALT lymphoma – unknown

- Has been rarely treated with antibiotics – clarithromycin
  - Regression, but not complete response

- Most treated with chemotherapy, immunotherapy and/or radiation

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**MALT - Imprinting / Circulation Relationship to MALT Lymphoma Sites**

- Enter via HEV
- Mesenteric Lymph Node
- General Circulation
- Other MALT Organs (i.e. lung, thyroid, etc.)

- Lymphocyte Homing Receptors

- sL-selectin

- MAb CAM 5.2

- sL-selectin

- General Circulation

- Other MALT Organs (i.e. lung, thyroid, etc.)

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*Addressins/chemokines: MAdCAM-1, CCL25/Ecad, CCL28
Antibody receptors: CD103, CD62L (L-selectin)
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 Sjogren’s syndrome, rheumatoid arthritis, Hashimoto’s thyroiditis, systemic lupus erythematosus
  - Infections such as hepatitis C and HIV

Lymphoepithelial Lesions

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

PMZL with stromal amyloid deposition

- 1 to 6% of the PMZL
- Sjogren’s syndrome, RA and ITP
- Prominent plasma cell component
- Congo red positive
- Amyloid light chain similar to the lymphoma
PMZL with Light Chain Deposition Disease (LCCD)

- Resembles amyloid but without Congo red positivity
- Light chain deposits: kappa
- Amyloid: lambda light chain
- EM: fibrils in amyloid granular deposits in LCCD

PMZL with massive crystal storing histiocytosis

- Few case reports
- Numerous histiocytes with crystalline cytoplasmic inclusions
- Crystals may be derived from abnormal Ig which promotes crystallization and inhibits lysosomal degradation

Primary Pulmonary Lymphoma

- Presence of single or multiple pulmonary lesions with no clinical, pathologic, or radiographic evidence of lymphoma elsewhere in the past, at present, or for 3 months after presentation (stage IE).
- Primary pulmonary lymphoma
  - 0.3% of primary lung neoplasms
  - 3.6% of extranodal lymphomas
  - Less than 0.5% of all lymphomas

Table 1—Marginal Zone Lymphoma With Primary Pleural Presentation: Reported Cases

<table>
<thead>
<tr>
<th>Case No/Source</th>
<th>Age</th>
<th>Sex</th>
<th>Presentation</th>
<th>Associated Pulmonary Lesions</th>
<th>Associated Dysphonia</th>
<th>Associated Gastrointestinal</th>
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<tr>
<td>1/Roberts et al. (2005)</td>
<td>78</td>
<td>Male</td>
<td>Dyspnea, chest pain</td>
<td>Yes</td>
<td>Yes</td>
<td>Light</td>
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<td>2/Boon et al. (2005)</td>
<td>56</td>
<td>Male</td>
<td>Dyspnea, chest pain</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>3/Boon et al. (2005)</td>
<td>54</td>
<td>Male</td>
<td>Dyspnea, cough, weight loss</td>
<td>Yes</td>
<td>Yes</td>
<td>Not specified</td>
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<tr>
<td>4/Boon et al. (2005)</td>
<td>72</td>
<td>Male</td>
<td>Pleural effusion</td>
<td>Yes</td>
<td>No</td>
<td>Not specified</td>
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<tr>
<td>5/Boon et al. (2005)</td>
<td>47</td>
<td>Male</td>
<td>Dyspnea, cough, weight loss</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

CHEST 2006; 129:791–794
**Patient Course**

- Triple antibiotic therapy (amoxicillin, clathrimocyin and Omeprazole) for stomach MZL
- Rituximab X 4 doses
- Residual disease in stomach (March 2012)
- Radiation therapy completed in May 2012

**Follow Up**

- Patient has no evidence of disease (May 2013)
- Surveillance: Esophagogastroduodenoscopy (EGD) and CT Chest in 6 months.

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**History**

- 29 year old female presented with chronic cough for 6 months
- Had been treated with oral antibiotics, but cough did not improve
- Infectious disease workup had been done, but was negative
- CBC and chemistry labs all normal
CT Chest and PET CT (Feb 2006)

No Mediastinal lymphadenopathy

Transbronchial Biopsy

- BAL, brushings: negative
- Work up for infectious process: negative
- Biopsy: Mixed inflammatory cell infiltrate with atypical large cells

Lung Findings: Wedge Resection

Considerations

- Inflammatory myofibroblastic tumor
- Infectious Process
- Lymphoma
Inflammatory myofibroblastic tumor

• Lung: most frequent site
• Majority seen in children and young adults with no gender predilection
• Spindle cells admixed with inflammatory elements
• ALK-1 positive in ~40% cases

Infectious Process

• Viral Pneumonia
• Intranuclear and Intracytoplasmic inclusions
• Necrotizing Granulomas

Lymphoma

Morphology and Location
• Immunodeficiency-related polymorphic lesion
• Peripheral T-cell Lymphoma (PTCL)
• Classical Hodgkin Lymphoma

Mediastinal Mass into Lung
• Primary Mediastinal B-cell Lymphoma (PMBCL)
• Classical Hodgkin Lymphoma
• T-Lymphoblastic Lymphoma

Lung Findings: Wedge Resection
**Diagnosis**

Primary Pulmonary Classical Hodgkin Lymphoma

**Diagnostic Tools**

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
• 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
Management/Course

- ABVD 4 cycles completed on 10/19/2006
- External Beam Therapy

Follow Up

August 2013: Remission
Follow Up with CT/PET

Case 3

History

- Initially treated with prednisone for about 8 months then switched to azathioprine
- Disease under control
History (2010)

- 6 years later presented with shortness of breath and clear sputum production
- Clinical suspicion: pneumonia - treated with antibiotics
- Fungal serology negative
- No significant improvement

Radiology

Needle Core Biopsy

Wedge Resection (Nov 2010)
Considerations

- Wegener's granulomatosis
- Granulomatous Inflammation
- Hodgkin lymphoma
- Iatrogenic immunodeficiency-associated lymphoproliferative disorder

Wegener's Granulomatosis

- Geographic necrosis with surrounding palisade of epithelioid histiocytes
- Necrotizing vasculitis
- Inflammatory background of lymphocytes, plasma cells, scattered giant cells
- ANCA (usually cANCA) positive

Granulomatous Inflammation

Histoplasmosis  Coccidiodymycosis

Granulomatous Inflammation

Dirofilaria  Mycobacteria
Hodgkin Lymphoma

- Reed Sternberg cells and variants
- Mixed inflammatory cell population

Diagnosis
Lymphomatoid Granulomatosis, Grade 2
**Diagnostic Tools**

**Morphology**
- Angiocentric, angiodestructive
- Direct invasion of blood vessels by T cells
- Chemokines and cytokines from the EBV positive cells

**Immunophenotype**
- 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

**Grading**

Based on the Number of EBV Positive Cells
- Grade 1: <5 per high power field
- Grade 2: 5–20 per high power field
- Grade 3: >20 per high power field
Other EBV Positive LPDs in the Lung

Immunodeficiency LPDs:
- PID, PTLD, HIV, iatrogenic

EBV positive age related LPDs

EBV positive classical Hodgkin lymphoma (some)

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

Clinical 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

Inflammatory bowel disease: RARE
- Risk for LPDs due to disease probably not increased
- Specific types of drugs increase risk: Thiopurines 3-5x risk

Follow-up

On initial staging found to have brain lesions
Received combination chemotherapy and MTX to CNS
Progressive CNS disease – died 10 months after diagnosis
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

Acknowledgements

• Amy Chadburn, MD - Hematopathology
• Juehua Goa, MD PhD – Molecular Diagnostics Laboratory
• Yanming Zhang, MD – Cytogenetics Laboratory
• Anjana Yeldandi, MD – Surgical Pathology
• Northwestern Memorial Hospital
  Immunohistochemistry Laboratory

Questions?