RADIOLOGIC FEATURES OF LUNG INVOLVEMENT BY LYMPHOMA

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Learning objectives

- To make a review of lung involvement in the different types of lymphoma.
- To demonstrate the broad spectrum of radiologic manifestations and recognize most common radiological patterns.
- To make a differential diagnosis.

Background

The diagnosis of lymphoma can be difficult to make when a biopsy specimen is small. Besides the imaging characteristics are frequently non-specific. That is why a multidisciplinary approach with imaging correlation may be necessary to make a diagnosis.

It is valuable to understand the breadth of imaging patterns in pulmonary lymphoproliferative diseases and the radiologist can have a pivotal role differentiating these entities.

For these reasons we have found interesting to carry out this studio.

We have reviewed the radiological findings in simple x-ray and CT scan of multiple patients with pulmonary involvement by lymphoma. All of them come from our hospital (Hospital Clínico Universitario de Valladolid. SPAIN), and they all have histologic confirmation of lung involvement. We present images of the most representative cases.

Imaging findings OR Procedure details

Pulmonary lymphoproliferative diseases are characterized for lymphoid cells proliferation and lung parenchymal infiltration by cells of the lymphoid series. This cell proliferation can be benign or malignant.

Classification:

Benign or reactive:

- Pulmonary nodular lymphoid hyperplasia, initially described as pseudolymphoma
- Follicular bronchiolitis
Lymphocytic interstitial pneumonia

Malignant:

- Primary lung lymphoma
- Secondary involvement of the lung:
  - Hodgkin disease (HL)
  - Non-Hodgkin lymphoma (NHL)
    - Immunocompromised patient’s lymphomas. (AIDS related lymphoma and lymphoma in transplanted patients)

Our study is only focused on malign lymphomas.

Primary pulmonary lymphoma (PPL):

PPL is defined as lung involvement by monoclonal lymphoid proliferation, without extrathoracic disease for at least three months after diagnosis, no mediastinic mass evidence or bone marrow infiltration. It is very rare (less than 1% of lymphoproliferative diseases).

Classification:

- Low grade B cell lymphoma: BALToma. (otherwise known as a MALToma) Their development depends on mucosa associated lymphoid tissue (MALT) of the bronchus. It represents 80% of primary lymphomas. Usually these lesions are asymptomatic and their prognosis is good. The histological differentiation between benign parenchymal lymphoproliferative disease and BALToma can be difficult.
- High grade lymphomas: Difusse B cell lymphoma (15-20%). It is characteristically seen in patients with underlying immunodeficiency and it has a poor prognosis.
- Lymphomatoid granulomatosis: It is a rare Epstein- Barr virus associated lymphoproliferative disorder, with a propensity for blood vessel destruction.

Radiological findings:

Low grade or BALToma:

Fig. 1 on page 8, Fig. 2 on page 9, Fig. 3 on page 10, Fig. 4 on page 10.

- Single nodule or focal consolidation.
• Multiple nodules or areas of consolidation. These are the main patterns that occur in the majority of the cases (70%).
• Air bronchogram is common (more than 50%)
• Interlobular septal thickening, centrilobular micronodules and bronchial wall thickening (25%)
• BALTomas have relatively indolent course, with slow growing pattern (months or years).
• Pleural effusion (10%) and lymphadenopathy (5-30%) are uncommon.

High grade:

Fig. 5 on page 11 Fig. 6 on page 12 Fig. 7 on page 13

• Single or multiple nodules/masses.
• Cavitation is a usual feature.
• Consolidation or diffuse reticulonodular pattern are less common.

Lymphomatoid granulomatosis:

• Multiple ill defined nodules with lower lobes predominance, rapid progress and sometimes with cavitation.
• It looks like Wegener disease.

Secondary lung lymphoma:

Secondary spread occurs from nodal or extrathoracic lymphoma. It is the most common form of presentation of pulmonary lymphoma, both Hodgkin and non-Hodgkin, with variable incidence depending on authors. Although a greater proportion of patients with HL rather than NHL have lung involvement, more NHL with pulmonary involvement is seen in clinical practice because NHL is the most prevalent condition. It is not usually present at diagnosis but during the course of disease and recurrences. Clinically there are not specific symptoms. Ann Arbor staging system is used to determine the stage (important in HL) and also histology (important in NHL).

Hodgkin lymphoma (HL)

• The frequency of lung involvement at diagnosis is 10%, most common in recurrent disease. The presence of lung involvement has a worse prognosis and it determines stage IV.
• HL is almost always associated with mediastinal or hilar lymphadenopathy (although they may not be present in previously radiotherapy treated patients).
Radiologic findings:

- **Direct lung extension from hilial or mediastinal nodal disease:** linear perihiliar opacities, in CT seemed as bronchovascular interstitial thickening and sometimes interlobular septal thickening (similar to lymphangitis)

- **Single or multiple pulmonary nodules or pulmonary consolidations:**
  The size is variable (0,5-5 cm). They have upper lobes predominance and frequently there are air bronchograms or cavitation.

- **Other findings:** - Atelectasis: Usually caused by bronchial extrinsic compression or less common because of endobronchial masses. - Lipoid pneumonitis caused by bronchial obstruction. - Pleural effusion (15%): Due to lymphatic or venous obstruction. - Uncommon: pleural masses.

**Non Hodgkin Lymphoma (NHL):**

NHL is the commonest lymphoma (3% of the malignant tumors of the adult).

Although the commonest intra-thoracic manifestation is mediastinal lymphadenopathy, isolated lung disease without mediastinal involvement can occur.

The frequency of pulmonary involvement is 30% (up to 60% in autopsy series).

The classification is based on the histologic type: Low grade, Intermediate grade, High grade and other: up to 10 subtypes depending on the cellular type.

Overall, prognosis depends on the histological type.

**NHL Radiologic findings:**

- Single or multiple nodules sharply or ill defined, with variable size.
• Masses or "mass-like" consolidation: sometimes they simulate pneumonia with air bronchogram and segmental atelectasis.

• Peribronchial and perivascular interstitial disease, mimicking lymphangitis: With bronchovascular thickening, interlobular septal thickening, centrilobular nodules and ground glass opacities.

• Mediastinal lymphadenopathy is only present in 20-40%.

**Inmunocompromised patient´s lymphomas:**

*Fig. 23 on page 28 Fig. 24 on page 29*

Lymphoproliferative disease occurring in the immunocompromised patient warrants special consideration, as their disease is generally more aggressive and has more varied radiological appearances. These lesions can cause both primary and secondary lymphoma within the lung parenchyma and include two groups: AIDS related lymphoma and transplanted patient lymphoma

**AIDS related lymphoma (ARL):**

Lymphoma is the second most common tumor occurring in AIDS patients, after Kaposi´s sarcoma. It is thought to occur as a consequence of B-lymphocyte proliferation due to long term stimulation by HIV. It occurs in patients with advanced disease. The prevalence is 40-100 times more than general population although it had diminished with antiretroviral therapy. It tends to be associated with very low CD4 cell counts.

ARL is characterised by high histologic grades. It is clinically aggressive and it is the cause of death in up to 20% of HIV infected patients.

**Radiological findings:**

• Multiple pulmonary nodules (generally peripheral, sharply defined and may cavitate)
• Pleural effusions are the commonest thoracic manifestation (sometimes pericardial effusion)
• Lymphadenopathy is not so frequent (10-50%)
• **The triad: pleural effusions, pulmonary nodules and lymphadenopathy in VIH+ patient is highly suggestive of ARL.**
• Less common: focus of consolidation or ground glass opacity
Transplanted patient lymphoma (TPL):

TPL is uncommon (< 2% of the total). It occurs following solid organ transplantation or hematopoietic stem cell transplantation, most common in children and lung transplant.

The etiology is associated with Epstein Barr virus and it is related to immunosuppressive therapy. Most are B cell NHL (only 14% are T cell). The majority of cases occur within two years of transplantation. The clinical presentation is variable (fever, lymphadenopathy, abdominal pain… Mortality rates are high (60%) although there is a broad spectrum: from relatively indolent forms to high grade disease.

Radiological findings:

-Multiple nodules, ill defined, sometimes "halo sign"

-Mediastinal and hilar adenopathy (30- 60%)

-Patchy airspace consolidation or ground glass opacity

-Septal thickening

Differential Diagnosis:

Two different situations may occur:

A_ Patients previously diagnosed of lymphoma (HL or NHL) with a new pulmonary lesion:

Fig. 25 on page 30 Fig. 26 on page 31

- Infection: It is the most common cause of lung involvement in lymphoma patients
- Chemotherapy-associated reaction: pneumonitis
- Radiation-induced changes
- Organizing pneumonia
- Others: Granulomatous disease, primary lung cancer, metastasis.

B_ Patients without a previous lymphoproliferative disease diagnosis:
There is a broad spectrum of differential diagnosis (DD) depending on radiological presentation:

- Single nodule or mass: differential diagnosis with **Lung cancer**

- Multiple nodules: DD with **Lung metastasis, Sarcoidosis**

- Alveolar Consolidation: DD with **Pneumonia, Organized pneumonia (COP), Hypersensitivity pneumonia, Bronchioloalveolar carcinoma.**

- Interstitial pattern: DD with **Carcinomatous lymphangitis, Sarcoidosis, Drugs toxicity**

- Hilar mass + lung spread: DD with **Lung cancer + lymphangitis, Tuberculosis,** ...

That is why almost always a clinical, microbiological and histological confirmation will be needed.

Images for this section:
Figure 1. Primary lung lymphoma in a female patient with history of Sjogren disease.

a): Focal consolidation with air bronchogram.  
b): small nodules and ground glass opacities.

Fig. 1

Fig 2. Primary pulmonary lymphoma. Focal consolidation with air bronchogram.  
Biopsy: MALT lymphoma

Fig. 2
Figure 3. Same patient of fig 2. Coronal and sagital MPR

Fig. 3
Fig. 4: Biopsy of the patient of fig 2 and 3 provided by the Department of Pathology. Hospital Clínico Universitario de Valladolid. (Dra H.Borrego)
Fig. 5. 72 year-old woman with constitutional syndrome. Bilateral consolidation, air bronchogram and multiple nodules.
Fig 6. Same patient. Consolidation areas with air bronchogram and multiple nodules. (The subpleural lesions-arrow- are better visualized because of lung-biopsy secondary pneumothorax). Histology: low grade non-Hodgkin lymphoma
Fig 7. Same patient. One year later control: radiologic improvement.
Fig. 8. Hodgkin disease. Mediastinal and hilar adenopathy and multiple pulmonary nodules.
Fig. 9. Hodgkin lymphoma: lung direct extension from mediastinal nodal disease. Atelectasis due to bronchial compression. Pleural effusion.
Fig. 10. Hodgkin disease. Recurrent mediastinic disease with lung secondary spread.
Fig. 11. Same patient of fig 10. Progression in three months

Fig. 11
Fig. 12. Hodgkin disease. CT images of the same patient: Recurrence of mediastinic disease with direct lung spread, cavitating masses and nodules. Pleural and chest wall invasion. Lipoid pneumonitis was demonstrated in lung biopsy.
Fig 13. Hodgkin lymphoma. Coexistence of different forms of presentation: direct extension from mediastinum, multiple pulmonary nodules, cavitating masses and septal thickening.
Fig. 14. 46 year-old male in study for cardiac arrhythmias. Incidental finding in a chest x-ray: multiple nodules. Lung biopsy: large B cell non-Hodgkin lymphoma

Fig. 15. Multiple nodules simulating metastasis. This is the most common finding
Fig 16. Air bronchogram in four different patients. It represents peribronchial tumoral infiltration without destruction of bronchial wall.
Fig. 17. Patient with history of renal pelvis urothelial cell tumor. Pulmonary mass. Surgical biopsy: diffuse large-B cell NHL
Fig. 18

a) low-magnification photomicrograph (hematoxylin-eosin, x40) demonstrate a proliferation of lymphoid cells involving lung parenchyma

b) low-magnification photomicrograph (immunohistochemical staining for CD 20) reveals positive staining for CD 20, confirming B-cell lineage of neoplastic cells.
Fig 19. 70 year-old woman in treatment for rheumatoid arthritis for years. She presented splenomegaly, adenopathies and lung mass. Biopsy: large B-cell NHL
Fig 20. 55 year-old male who was diagnosed years ago of Lymphoid interstitial pneumonia. Clinical worsening: Multiple consolidations and mass-like lesions. Biopsy: large B-cell non-Hodgkin lymphoma
Fig 21. 70 year-old woman. Constitutional syndrome, cervical adenopathies. Interstitial disease, septal thickening, reticular pattern and nodules.
Histology: Non-Hodgkin lymphoma (angioinmunoblastic type)
Fig. 22. Mediastinal adenopathy. Only in 30% of cases.
Fig. 23. Immunosuppressed patient: pulmonary nodules, pleural effusion and pleural involvement with paravertebral pleural thickening.
Fig 24. Immunossupresed patient. a) pulmonary window CT: Interstitial disease with septal thickening and small nodules. b) Mediastinal-window CT: Axillary and mediastinal adenopathy. Histology: NHL (high grade diffuse large B-cell type)
Differential diagnosis in patient previously diagnosed of lymphoma:

The most common

- Infection
- Organizing pneumonia
- Chemotherapy pneumonitis
- Others: granulomatous disease, lung cancer,....
- Radiation-induced changes

Fig. 25
Fig. 26. Patient on treatment of HL recurrence. She presented with fever: Ground glass opacities and air space consolidation: Microbiology: Bilateral mycoplasma pneumonia.
### Differential diagnosis depending on radiological presentation

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single nodule or mass</td>
<td>- Lung cancer</td>
</tr>
<tr>
<td>Multiple nodules</td>
<td>- Lung metastasis&lt;br&gt;- Sarcoïdosis&lt;br&gt;- Abscess</td>
</tr>
<tr>
<td>Alveolar consolidation</td>
<td>- Pneumonia&lt;br&gt;- Organizing pneumonia, hypersensitivity pneumonia&lt;br&gt;- Bronchioloalveolar carcinoma</td>
</tr>
<tr>
<td>Interstitial pattern</td>
<td>- Carcinomatous lymphangitis&lt;br&gt;- Sarcoïdosis&lt;br&gt;- Drus toxicity</td>
</tr>
<tr>
<td>Hilar mass + lung spread</td>
<td>- Lung cancer + lymphangitis&lt;br&gt;- Tuberculosis</td>
</tr>
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Fig. 27
Conclusion

- Nodules
- Masses or consolidation
- Direct spread from mediastinum
- Interstitial pattern

- Pulmonary involvement is more commonly seen in secondary lymphoma (both Hodgkin and non-Hodgkin). Primary pulmonary lymphoma and benign forms are rare.
- Lung involvement worsens the prognosis, principally in HL; in NHL the cell type and the histologic grade have more influence than pulmonary disease.
- In immunosuppressed patients, recognizing pulmonary lymphoproliferative disease may expedite treatment, as this group has frequently a more aggressive disease.
- There are some characteristic radiological findings, although the broad spectrum of radiological presentations should make think in lymphoma in almost all thoracic patterns.
- We have to remember that the main cause of pulmonary lesion in a patient with lymphoma is infection.
- The majority of those with clinically or radiologically suspected lymphoproliferative disease still usually require a histological sample to confirm the diagnosis and define the treatment options.
Conclusions

We have to remember four radiological characteristic patterns:

<table>
<thead>
<tr>
<th>Nodules</th>
<th>Masses or consolidation</th>
<th>Direct spread from mediastinum</th>
<th>Interstitial pattern</th>
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Fig. 28
Personal Information

María Rosa López Pedreira
Medical doctor. Radiologist.
Department of radiology.
Hospital Clínico Universitario de Valladolid. Spain. Fig. 29
e-mail: marosalopezpedreira@hotmail.com

Images for this section:

a) Situation of the city of Valladolid in Europe  b) and Spain. c) Hospital Clínico Universitario

The authors: María Rosa López Pedreira, Pilar Cartón Sánchez, Nuria Andrés García, Laura Casadiego Matarranz, Raquel Esteban Sáiz, Israel Sánchez Lite, Reyes Petruzzella Lacave, Margarita Rodríguez Velasco and Eduardo Cortejoso Gonzalo

Fig. 29
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