It's that lung lymphoma? Lets keep it simple! The practical pictorial atlas

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Learning objectives

The learning objectives of this Educational exhibit are:

- To recognise and classify lymphoproliferative pulmonary disorders according to primary (reactive or malignant) or secondary lung involvement
- To provide an easily accessible atlas to illustrate and correlate the main radiological and histological features of lymphoproliferative disease

Background

Pulmonary lymphoproliferative disorders are an heterogeneous group characterised by primary or secondary evolvement of the organ, which represents only 0.3% of all primary pulmonary malignancies (1,2,3).

Primary disorders may be reactive resulting primarily from antigenic stimulation of bronchial mucosa-associated lymphoid tissue (MALT) and comprises three main entities: follicular bronchiolitis, lymphoid interstitial pneumonia and nodular lymphoid hyperplasia.

Secondary lymphomatous neoplasms are the most common and include Hodgkin's disease and non-Hodgkin lymphomas (2,3).

Computed Tomography (CT) has been the imaging modality of choice in the evaluation of these disorders reveals a wide spectrum of imaging findings which are frequently non-specific and require correlation with clinical findings. Consequently, histological confirmation is required for a definite diagnosis (3).

Imaging findings OR Procedure details

We have reviewed patients followed in our Cancer Institute between 2006 and 2013, with histological proven diagnosis and correlated imaging patterns to histological types. The result aspires to be an easily accessible pocket atlas with typical imaging patterns for a given histological diagnosis and brief resume of the main CT and pathological features (Fig.1).
This pocket atlas, organised in a straightforward pictorial assessment, will provide an illustrated pragmatic view of the anatomy, classification, radiological findings and histological type of lung lymphoproliferative disorders (Fig.2).

I. BASIC ANATOMIC CONCEPTS

In order to understand the lymphoproliferative disorders it is vital to recognize the basic lymphoid tissue anatomy. This tissue just like bronchi, vessels, alveolus and interstitial supportive tissue, is a normal component of the lung (Fig. 3). According to lymphoid tissue location and function it may be schematized in:

- Hilar or intrapulmonary lymph nodes
- Bronchus associated lymphoid tissue (BALT)
- Peripheral lymphocytic aggregates, solitary lymphocytes and phagocytic cells

In CT lymph nodes are easily recognized in hilar anatomic position with axial projection, meanwhile intrapulmonary lymph nodes may be mistaken with lung nodules. Therefore they require CT reconstructions in at least 2 projections, axial, coronal and sagittal to meet lentiform or triangular shape, an homogeneous solid appearance, and sharp margin criteria (4).

BALT consists of organized aggregates of lymphoid tissue within the bronchial walls and is a component of the much larger and extensive mucosa- associated lymphoid tissue (MALT) or common mucosal immune system, which is probably a distinct form but not necessarily exclusive of the lymph node and spleen-based somatic lymphoid systems (5). However, the well-developed lymphoid aggregates typical of BALT are absent in normal individuals (5).

Sparse numbers of bronchial and bronchiolar lymphocytes are normally present in the lung. They tend to distribute along the axial interstitium and are somewhat more abundant at bronchial bifurcations and near distal respiratory bronchioles (5).

II. CLASSIFICATION
According to the review of the literature, there are several forms to systematise the lymphoproliferative disorders; nevertheless all of them are based on pathology and immunohistochemical characterization.

From our perspective and keeping in mind the World Health Organization (WHO) classification of lymphoid neoplasm, we find more comprehensive to classify these disorders as primary or secondary according to location where they first arise: as abnormal proliferation of indigenous cell lines or infiltration of lung parenchyma by lymphoid cells (Fig. 4) (1,2,6).

Furthermore within the primary disorders we might also divide in reactive or neoplastic disorders. Reactive lesions are rare and the polyclonal nature of within the lymphoid cells must be demonstrated to differentiate from pulmonary lymphoid neoplasms ,which are typically mono-clonal in nature (Fig. 5).

Secondary pulmonary lymphomas can affect the lung via hematogenous dissemination or by secondary involvement from tumor in adjacent or contiguous sites (1,2,6). We also include leukemia and plasma cell neoplasms in secondary involvement of the lung. Posttransplantation lymphoproliferative disorders constitute a special type of lymphoid proliferation occurring in the setting of the chronic immunosuppression required for solid organ and bone marrow transplantation (Fig 6.) (2,6).

III. PRIMARY LYMPHOPROLIFERATIVE DISORDERS (Fig. 7-13)

Primary lymphoproliferative lung disorders has a wide spectrum of focal or diffuse abnormalities, which may be classified as reactive or neoplastic on the basis of cellular morphology and clonality (1,2,5,6).

Primary reactive disorders are thought to arise from the stimulation of lymphoid tissue by antigens or other factors, and as an initial event leads to the development of lymphoproliferation. These reactive entities are usually associated with immunological disturbances and are commonly seen in patients with immunodeficiency or autoimmune disorders (2,5).

Primary neoplastic lymphoid disorders of the lung are defined as monoclonal lymphoid proliferations affecting one or both lungs (parenchyma, bronchi or both) in a patient with no detectable extrapulmonary involvement at the time of diagnosis or during the subsequent 3 months (1,6).
1. NEOPLASTIC DISORDERS (Fig. 7-12)

These neoplasms represent 3%-4% of extranodal lymphomas, and only 0.5%-1% of primary lung malignancies (1,2,5,6).

Many of these primary lymphoproliferative disorders are of low histologic grade and can be difficult to differentiate from reactive processes (6).

The primary lymphoid neoplasms range from a relatively indolent MALT lymphoma to more aggressive forms of diffuse large B-cell lymphoma. These two entities gather the majority of cases of neoplastic primary lymphoid disorders, which is overall a rare disorder (1).

Non-Hodgkin B-cell lymphoma (NHL-B) is the most frequent type and accounts for roughly 80% of all primary lymphoid neoplasms. The majority of these are MALT lymphomas, which are frequently associated with autoimmune diseases. Diffuse large B-cell lymphoma accounts for the majority of the other and it is characteristically seen in patients with underlying immunodeficiency, such as transplant patients with ciclosporin treatment. The incidence of diffuse large B-cell lymphoma may well be underestimated, as it could potentially spread rapidly from the lung into mediastinal and extrathoracic locations (1).

According to surface antigens, most of these disorders are B-cell non-Hodgkin’s. The T-cell and pulmonary Hodgkin lymphoma rare (6).

T-cell lymphomas are a subtype of large cell lymphomas and represent 3% of all pulmonary lymphomas (6).

In this pocket atlas we decided to approach each type in a schematic method and for each type of lymphoma we gathered a brief resume of the main CT and pathological features that are easily found in the corresponding figures.

1.1 - B-CELL NON-HODGKIN’S LYMPHOMA

- Low-grade marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALToma)
- High-grade primary pulmonary lymphoma-B (large B-cell and Burkitt-type lymphoma)
• Follicular or mantle lymphocytic non-Hodgkin's lymphoma or chronic lymphocytic leukemia
• Pulmonary intravascular large B-cell lymphoma

1.2 - T-CELL LYMPHOMA

• Hodgkin's lymphoma with primary pulmonary involvement
• Lymphomatoid granulomatosis
• Angioimmunoblastic lymphoma

2. REACTIVE DISORDERS (Fig. 13-19)

Patients affected with reactive pulmonary lymphoid lesions are often asymptomatic and are typically discovered incidentally because of abnormal chest radiographs. Imaging findings include focal nodules, diffuse bilateral centrilobular nodules and hilar or mediastinal masses (5).

The three main forms of reactive disorders are follicular bronchiolitis, pulmonary nodular lymphoid hyperplasia and lymphocytic interstitial pneumonia. These disorders are regarded as part of the spectrum of lymphoid hyperplasia of the bronchus-associated lymphoid tissue (2).

Follicular bronchiolitis is characterised by lymphoid follicular hyperplasia, often with reactive germinal centres, in the walls of bronchioles with narrowing of the lumen (1,2).

Pulmonary nodular lymphoid hyperplasia (pulmonary pseudo-lymphoma) is a distinct form of reactive lymphoid proliferation with links to the family of IgG4- related sclerosing diseases, characterised by a dense nodular infiltration of mature, polyclonal lymphocytes and plasma cells, which are well-circumscribed and mainly sub-pleural, with some dense fibrosis between the follicles. The dominant feature of lymphocytic interstitial pneumonia is a diffuse lymphoid infiltrate within the alveolar interstitium consisting of T-cells and variable numbers of polyclonal plasma cells; follicular hyperplasia is evident along the bronchiolo-vascular bundles and at the periphery of the secondary lobules (interlobular septa and sub-pleural interstitium), and loosely formed epithelioid granulomas are commonly seen (1,2,5).

• Nodular lymphoid hyperplasia
• Lymphocytic interstitial pneumonia
• Follicular bronchiolitis
• Angiofollicular hyperplasia
• Intrapulmonary lymph nodes
• Angioimmunoblastic lymphadenopathy

IV. SECONDARY LYMPHOPROLIFERATIVE DISORDERS (Fig. 20-25)

The incidence of lung involvement at initial presentation is 12% for patients with HL and 4% for those with NHL (6). Although a greater proportion of patients with HL rather than NHL have lung involvement, more NHL SPL is seen in clinical practice because NHL is more prevalent (1).

Secondary involvement of the lung is commonly found at autopsy in approximately 20.5% of cases. Approximately 30%-40% of patients with HL have pulmonary involvement at some stage of their disease, frequently occurring as secondary or recurrent disease (6).

The pathogenesis of secondary pulmonary lymphoma depends on the type of primary lymphoma and all the different forms of lymphoma may secondarily involve the lungs, but the mature B-cell neoplasms are the most frequent (1).

B-cell lymphomas and leukemias frequently show a lymphangitic pattern of spread, whereas nodular and central interstitial growth patterns are mainly observed in Hodgkin’s and T-cell lymphomas (2,6,7).

Since any form of lymphoma can secondarily involve the lungs, the imaging features are varied and non-specific, ranging from a solitary nodule to lymphangitic parenchymal involvement. Although non-specific, the radiological features described below should raise the possibility of secondary lung involvement in any patient with a known history of lymphoma. The commonest intrathoracic manifestation is mediastinal lymph node enlargement (1,2,14).

Lymphoproliferative disorders occurring in the immunocompromised patient are generally more aggressive and present with more varied radiological appearance. AIDS related lymphoma are usually lymphomas primarily involving the lung, as diffuse large B-cell lymphoma and Burkitt while post-transplantation lymphoproliferative disorder includes reactive processes, neoplasms and lymphoid proliferations of uncertain nature (1).

• Non-Hodgkin's lymphoma (NHL)
• Hodgkin's lymphoma (HL)
• Lymphoplasmacytic lymphoma or Waldenstrom macroglobulinemia
• Leukemia-associated lung disease
• Plasma cell neoplasm (Multiple myeloma ; Plasmacytoma)
• AIDS and Post-transplantation lymphoproliferative disorders

Images for this section:

**Fig. 1:** It's that lung lymphoma? Let's keep it simple! The practical pictorial atlas
Fig. 2: Poster Contents
Fig. 3: Basic anatomic concepts
Fig. 4: Classification
Fig. 5: Classification

- B-cell non-Hodgkin's lymphoma
  - Low-grade marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALToma)
  - High-grade primary pulmonary lymphoma-B (large B-cell and Burkitt-type lymphoma)
  - Follicular or mantle lymphocytic NHL or chronic lymphocytic leukemia
  - Pulmonary intravascular large B-cell lymphoma

- T-cell lymphoma
  - Hodgkin's lymphoma with primary pulmonary affection
  - Lymphomatoid granulomatosis
  - Angioimmunoblastic lymphoma

- Reactive
  - Nodular lymphoid hyperplasia
  - Lymphocytic interstitial pneumonia
  - Follicular bronchiolitis
  - Angiofollicular hyperplasia (Castleman disease)
  - Intrapulmonary lymph nodes
Fig. 6: Classification

- Non-Hodgkin's lymphoma
- Hodgkin's lymphoma
- Lymphoplasmacytic lymphoma or Waldenstrom macroglobulinemia
- Leukemia-associated lung disease
- Plasma cell neoplasm
  - Multiple myeloma
  - Plasmacytoma
- AIDS and Post-transplantation lymphoproliferative disorder
**Fig. 7:** Low-grade marginal zone B-cell: MALToma a) Maltomas' radiological findings might are commonly segmentar consolidation with air-bronchogram (black arrow) or b) nodular consolidation with air-bronchogram (black arrow) and ground glass (white arrow) c) Pathology specimen shows massive infiltration of lymphocytes, forming a mass-like lesion. d) Note the small lymphocytes.
Fig. 8: Diffuse large B-cell lymphoma a) Contrast enhanced CT shows a large mass (black arrow) in right upper lobe with the angiogram sign. Para-traqueal adenophaties are also depicted (white arrow). b) Another patient with diffuse large B-cell lymphoma multiple bilateral nodules ranging 1-3 cm are noted (white arrow) c) Diffuse sheets of large atypical lymphoid cells replacing lung architecture
Fig. 9: Pulmonary intravascular large B-cell lymphoma a) CT axial image shows opacities throughout the bilateral lungs with no obvious mediastinal involvement. b) Hematoxylin-eosin staining of pulmonary interstitium intravascular lymphoma (400X), the alveolar septae was widen and filled with tumour cells showed in high power field
Fig. 10: Hodgkin’s with primary pulmonary involvement a) Axial CT image shows bilateral lung masses. Angiogram sign is depicted on the right lower lobe mass. b) Typical Reed-Sternberg cells, mononuclear cells, lacunar variants in background of mixed inflammatory infiltrate
**Fig. 11**: Lymphomatoid Granulomatosis a) CT demonstrates multiple bilateral lower lobes nodules coalescing to form larger masses with bronchogram (arrows) b) Pathological specimen shows the angiocentric nature of the lesion, where infiltration of the intima by lymphoid cells is seen. The muscular wall of the artery.
Fig. 12: Angioimmunoblastic lymphoma a,b) On HRCT a ground glass pattern with peri-bronchial distribution and bronchial wall thickening is depicted. b) The same patients presents with bilateral basal consolidation with air-bronchogram c) High-power photomicrograph shows lymphoid cells admixed with immunoblasts and plasma cells (black arrows). Vascular proliferation is also noted. The term angioimmunoblastic in the name of this condition is due to the vascular proliferation and admixed immunoblasts.
Fig. 13: Nodular lymphoid hyperplasia a) Axial CT image reveals an incidental finding of a round solitary nodule in left upper lobe. b) Microphotograph shows a dense lymphoid and plasma cell infiltrate that in conjunction with policlonality proven to be nodular lymphoid hyperplasia.
Fig. 14: Follicular bronchiolitis a) HRCT axial image demonstrates tiny parenchymal nodules (arrows) and subtle mosaic attenuation. There is a mosaic pattern due to small airways disease. b) The image shows chronic inflammation of membranous bronchioles (arrows) with reactive lymphoid follicles (arrowheads). Note the normal appearing pulmonary artery (curved arrow) adjacent to an abnormal bronchiole. The intervening lung parenchyma is preserved.
Fig. 15: Lymphocytic Interstitial Pneumonia a) CT axial image demonstrates multifocal thin-walled air-filled cysts of various sizes and small multifocal scattered centrilobular nodules. b) Microphotograph demonstrates alveolar septal thickening by a lymphoid aggregate containing reactive germinal centers
Fig. 16: Angiofollicular hyperplasia - Castleman Disease a) Contrast-enhanced Ct demonstrates an ovoid retrocardiac mediastinal mass with intense contrast enhancement and central foci of coarse calcification (arrow). b) Low-power microphotograph demonstrates a lymph node that consists of lymphoid tissue with penetration by hyalinized vessels in keeping with angiofollicular hyperplasia , localized hyaline vascular type.
**Fig. 17:** Angiofollicular hyperplasia - Castleman Disease

a) CT demonstrates multiple bilateral small nodules. These are closely associated with pulmonary vessels, have variable sizes, and exhibit rounded and irregular morphologies, some with surrounding ground-glass opacity.  

b) Intermediate-power microphotograph demonstrates aggregates of plasma cells and small lymphoid cells in the pulmonary interstitium in keeping with angio follicular hyperplasia, multifocal plasma cell type.
Enlarged intrapulmonary lymph nodes

- Intra-pulmonary and perifissural lymph nodes are frequently found at CT scans and might be confused with lung nodule.
- Recognition of lymph nodes can reduce the number of follow-up examinations required for the workup of suspicious nodules (7).
- It’s mandatory to study a probable lymph node with sagittal and coronal reconstructions and applying morphological criteria (7,8)

Fig. 18: Enlarged intrapulmonary lymph nodes
Fig. 19: Enlarged intrapulmonary lymph nodes
Fig. 21: Hodgkin's lymphoma & Non-Hodgkin's lymphoma CT Features

- Commonly present with evident mediastinal lymph node enlargement
- May have solitary or multiple lung nodules (≈1 cm in diameter)
- Mass/mass-like consolidation
- Nodules/masses with/without air bronchogram are commonest features
- Cavitation may occur
- Air bronchogram (61% NHL and 47% HL).
- Pleural effusion
- Bronchovascular thickening mimicking lymphangitis carcinomatosa
- Nodal enlargement:
  - HL > NHL.
- HRCT appearances of HL and NHL are similar
- Lymphangitic spread is frequently seen
Fig. 20: Hodgkin's lymphoma & Non-Hodgkin's lymphoma Pathological features

- Secondary lymphoma cannot be reliably distinguished from primary just with pathological tissue analysis as they show identical morphological features.
- An integration of clinical and radiological features is needed.
Fig. 22: Hodgkin’s lymphoma & Non-Hodgkin’s lymphoma - Large B-cell 

a,b) Patient with symptoms of cough and dyspnea shows on CT several parenchymal nodules (white arrow) and masses (black arrow) some revealing discrete air-bronchogram. c,d) The microphotos show lymphoma cells filling the alveolar spaces, and conferring a pneumonic aspect to the tissue. b) Note the lymphocytes filling the alveolar spaces.
**Fig. 23:** Hodgkin’s lymphoma & Non-Hodgkin’s lymphoma - T-Cell lymphoma Axial CT image shows a) right lower lobe an area of consolidation with surrounding ground-glass. b) In the same lobe a large solid node is also depicted. On the contralateral several nodules are seen in peri-bronchovascular distribution, with peri-bronchial thickening. c) the same patient has also some areas of consolidation with "Atol-sign". c,d) Pathological specimen shows interstitial pattern of lung infiltration. a) Lymphoma cells infiltrate along the alveolar septa b) These alveolar septa become clearly thickened
Fig. 24: Hodgkin’s lymphoma & Non-Hodgkin’s lymphoma - Esclero-nodular a,b) In a patient with classical hodgkin lymphoma, sclerosis type, an extensive area of consolidation with air-bronchogram is seen along the median lobe. c) In pathology specimen, broad collagen bands separating the lymphoid tissue into nodules are seen.
Fig. 25: Hodgkin’s lymphoma & Non-Hodgkin’s lymphoma - Lymphoplasmacytic lymphoma a) Chest CT shows basal consolidation with air-bronchogram and adjacent ground glass opacity. b) HRCT depicts in the same patient, in the upper lob another zone of consolidation, with adjacent ground-glass and septal thickening, resembling crazy-paving. c) Image shows monotonous proliferation of small lymphocytes, variably plasmacytic small cells, and occasional transformed cells associated with prominent hemosiderin.
Conclusion

Despite the great anatomopathological variability of lung diseases, the imaging semiology that translates pathological processes is poor. This means that the imaging appearances of lung disease is often more correlated to the site or structures affected than to the specific cell types involved.

In other words, the imaging findings reflect more accurately the 'where' (e.g. whether it causes alveolar filling or interstitial thickening) than the 'what' (e.g. what cellular types are involved and how that relates to prognosis or treatment options).

However, the growing recognition of the lung's complex lymphatic network provides the theoretical foundation to understand subtle differences between different disease processes, either reactive or neoplastic. This opens interesting possibilities for narrowing the differential diagnosis, define a smarter strategy for histological sampling and better infer about prognostic factors.

References


Personal Information