Pulmonary Lymphoproliferative Disease

Pulmonary Lymphoproliferative Disease (LPD)

S.S. Hare MA (Cantab) MBBS FRCR

Bronchial MALT

The hyperplastic or neoplastic proliferation of bronchial MALT underlies the pathogenesis of all LPD

1973 - Bienstock et al described submucosal lymphoid tissue sited along bronchial tree, interlobular septae, subpleural nodes

“Healthy humans” – Bronchial MALT only found in children/adolescents

Bronchial MALT hyperplasia seen in: smokers, autoimmune diseases, infection

• Chronic antigenic stimulation

• Bronchial MALT hyperplasia

Classification

Reactive spectrum

• FOCAL: Nodular Lymphoid Hyperplasia

• PERIBRONCHIAL: Follicular Bronchiolitis

• DIFFUSE: Lymphoid Interstitial Pneumonia

• Varying degrees of polyclonal lymphoid hyperplasia

Malignant Spectrum

PRIMARY

• Marginal Zone Lymphoma of MALT origin (former MALToma)

• Diffuse Large B-cell Lymphoma

• Lymphomatoid Granulomatosis

SECONDARY

• NHL (70-75% cases) – 50% have intrathoracic disease at presentation

• HD (25-30%) – 85% have intrathoracic disease at presentation

0.5% primary lung neoplasms

Secondary spread from nodal or extrathoracic lymphoma
Other Malignant

- AIDS-related Lymphoma (ARL)
- Post Transplant LD (PTLD)

- More aggressive disease
- Varied radiological appearances
- Cause both primary and secondary pulmonary lymphoma

Radiology-Pathology Correlation

- Diagnosis of lymphoma on a small biopsy specimen is difficult
- LIP versus Lymphoma is particularly problematic
- Radiologist pivotal
- Need to appreciate the breadth of HRCT patterns in pulmonary LD

Nodular Lymphoid Hyperplasia

‘pseudo lymphoma’

Nodular Lymphoid Hyperplasia

- Rare
- No HRCT series in literature
- Benign, localised lesion
- Incidental finding (70%)
- Surgical resection curative
- *Abbondanzo et al validated the existence of NLH using immuno-histochemistry and molecular genetic analysis in small series of 14 documented cases
- Can be difficult to distinguish radiologically and pathologically from MALT lymphoma


HRCT – Key Features

- Well circumscribed nodular lesion: solitary pulmonary nodule or focal consolidation
- Average size 2cm (range 0.6-6cm)*
- Occasionally 2-3 nodules coalesce to form a discrete mass
- Very mild, focal lymphangitic spread may be seen
- Differs from LIP/FB as it forms a discrete nodular mass rather than affecting the lung diffusely

**Follicular Bronchiolitis**

**FB**

- Benign peribronchial MALT hyperplasia
- PRIMARY – associated with CTDs (RA, Sjögren’s) and immunodeficiency syndromes
- SECONDARY – frequent incidental finding on lung biopsy

- Chronic bronchial inflammation
- Peribronchiolar lymphoid follicles
- Lacks extensive alveolar septal infiltration of LIP
- Predominantly peribronchiolar pattern of FB and the more diffuse pattern of LIP are considered to be a continuum of the same entity

**HRCT demonstrating**

- Small centrilobular and peribronchovascular nodules (arrows) in a patient with rheumatoid arthritis

***Follicular Bronchiolitis***

**HRCT – Key Features**

- Bilateral small (1-3mm, range 1-12mm) nodules
- Centrilobular (100%)/Peribronchial (42%)
- Bilateral patchy ground glass opacity (75%)
- Tree-in-bud pattern i.e. small airways involvement
- Bronchial dilatation (peribronchial location)
- Limited to the airways (i.e. no diffuse interstitial involvement as in LIP)


**Lymphoid Interstitial Pneumonitis**

**LIP**
**LIP**

- Diffuse lymphoid hyperplasia which primarily expands the alveolar interstitium
- Most commonly seen in context of HIV – children
- Rare in HIV-infected adults
- 40-60 yrs, females with CTDs
- First described in *Liebow and Carrington’s initial classification of idiopathic interstitial pneumonias*
- Steroid treatment – response unpredictable
- *Lymphoma supervenes in some patients – controversial - malignant lymphoma from the very outset?*


**HRCT findings of LIP depend on underlying disease present:**

- **Sjogren’s syndrome**: LIP is typically associated with lung cysts – thin-walled, round, limited in number
- **Congenital immunodeficiency**: LIP most often appears as patchy GGO
- **AIDS**: LIP most often seen as nodules

> Cysts not always present

**LIP in Sjogren’s Disease**

HRCT demonstrates bilateral diffuse ground glass opacity, cystic airspaces and small nodules

**LIP with Amyloid in Sjogren’s**

HRCT in a different patient ground glass opacity and lung cysts.

Biopsy of one of the nodules showed amyloid

**LIP in common variable immune deficiency**

Patchy ground glass
LIPLIP in AIDS: innumerable small bilateral centrilobular nodules and patchy ground-glass opacities with no lung cysts seen. The diagnosis was confirmed with transbronchial lung biopsy. There is also a right hilar nodal mass.

*HRCT – Key Features*

- Ground glass opacity – bilateral (100%)
- Nodules – poorly defined, centrilobular (100%) and subpleural (86%)
- Nodules – bilateral (90%)/unilateral (10%)
- Cystic airspaces (1-30mm) (68%)
- Bronchovascular bundle interstitial thickening (86%)
- Interlobular septal thickening (82%)
- Mediastinal lymph node enlargement (68%) – more common than traditionally recognised


LIP versus MALT Lymphoma

- MALT lymphoma is the most commonly considered differential diagnosis for LIP
- Can be similar clinically, pathologically and radiologically
- LIP thought NOT to progress to marginal zone lymphoma of MALT origin

LIP vs MALT Lymphoma - HRCT

*Honda et al: Compared HRCT findings of LIP (n=17) vs malignant lymphoma (n=44)

- Cysts: LIP (82%) vs lymphoma (2%)
- Consolidation: LIP (38%) vs lymphoma (66%)
- Large nodules (11-30mm): LIP (6%) vs lymphoma (41%)
- Pleural effusions: LIP (0%) vs lymphoma (25%)
- Distribution of parenchymal lesions: No difference found


Primary Pulmonary Lymphoma

PPL

Lymphoma involving the lung can be considered primary pulmonary lymphoma if:

- No history of lymphoma
- No mediastinal lymph node enlargement is seen on CXR
- No associated extrathoracic disease
- No evidence of extrathoracic dissemination for at least 3 months after initial diagnosis

Uncommon monoclonal lymphoid proliferation <1% lymphomas

Primary Pulmonary Lymphoma

PPL

- Range: Indolent marginal zone lymphoma of MALT origin to aggressive forms of diffuse large B-cell lymphoma
- 80% PPL is NHL – MALT lymphoma are the majority (80-90%)
- Diffuse large B-cell lymphoma (11-19%) - usually seen in immunodeficiency - but overall incidence may be underestimated as can rapidly spread into mediastinum
- 5 year survival:
  - 0-60% DLBCL
  - 84-94% MALT lymphoma

Marginal Zone Lymphoma of MALT origin

MALT Lymphoma

HRCT – Key Features

- Marginal zone lymphomas of MALT origin exhibit diverse patterns of lung abnormality on CT scans
- Single OR multiple nodules OR areas of consolidation are the main patterns that occur in the majority (>70%)
- Multiple, bilateral lesions (>70%)
- Lesions tend to be peribronchovascular
- Bronchiolectasis also recognised due to peribronchial location
- Hilar/mediastinal lymphadenopathy in approximately 30% cases
**MALT Lymphoma**

Consolidating mass RML

Sheets of small lymphocytes

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**Diffuse Large B cell Lymphoma**

**HRCT – Key Features**

- Single or multiple solid pulmonary masses/nodules
- Cavitation – common (regardless of immune status)
- Mediastinal LN enlargement may be present
LYG

• 1st described 1972 by *Liebow et al as an entity distinct from Wegener’s granulomatosis
• Rare
• EBV-associated LPD
• Propensity for blood-vessel destruction - Intra- and perivascular infiltration by atypical lymphoid cells
• Comprises EBV +ve B-cells and reactive T-cells
• Granulomas not a feature
• Multi-system disease ie extrapulmonary manifestations common
• Males 30-50 years
• Poor prognosis median survival < 2 years – but spontaneous remission has been reported**


HRCT – Key Features

• Bilateral, round, poorly marginated nodules 0.5-8cm diameter
• Nodules usually <1cm
• Basal predominance
• Peribronchovascular distribution
• Can coalesce and cavitate
• ‘Reverse halo sign’
• ‘Migratory’ nodules due to ‘waxing and waning’
Secondary Pulmonary Lymphoma

**SPL**

- Commonest intrathoracic finding is mediastinal lymphadenopathy
- HD — disease spreads continuously from adenopathy
- Greater proportion of patients with HD > NHL have lung involvement BUT more NHL-SPL is seen in clinical practice because NHL is the more prevalent condition
- Frequency of parenchymal involvement difficult to quantify due to lack of recent HRCT series
* Lewis ER, Caskey CI and Fishman EK. Lymphoma of the lung: CT findings in 31 patients. AJR 1991;156:711-714

**SPL**

- Lung involvement usually asymptomatic
- SPL cannot be reliably distinguished from PPL solely on the basis of pathological tissue analysis as similar appearances can be seen in both entities
- In contrast to secondary involvement of the lung with HD, primary pulmonary Hodgkin lymphoma of the lung is exceptionally rare

**SPL**

- *Lewis et al*: n=31 (15 HD, 16 NHL), cases with parenchymal CT chest abnormalities
- Commonest CT abnormality in HD - mass or mass-like consolidation (80%)
- Commonest CT abnormality in NHL - peribronchial and/or perivascular interstitial thickening, mimicking lymphangitis, (69%)
- Nodules less than 1 cm, infiltrates (alveolar or interstitial), pleural-based masses and pleural effusions were seen with fairly equal frequency in both HD and NHL
- Lymphadenopathy in the chest was seen in 53% HD patients and in 19% NHL
* Lewis ER, Caskey CI and Fishman EK. Lymphoma of the lung: CT findings in 31 patients. AJR 1991;156:711-714
Mass-like right upper lobe consolidative opacity + further bilateral areas of parenchymal involvement.

Large anterior mediastinal soft tissue mass with pleural extension and a left pleural effusion.

PET-CT: Parenchymal areas of increased PET activity (arrow) due to lymphomatous involvement.

PET-CT: Also confirms pleural involvement with lymphoma.

Widespread thickening of interlobular septae in the RLL in keeping with lymphangitic spread.

Recurrence of NHL in the lung parenchyma. CT scan demonstrates multiple peripheral pulmonary masses.

CT scan at a different level in the same patient shows cavitation of a nodule in the medial basal segment of the right lower lobe (arrow).
**HRCT – Key Features**

- Nodules <1cm – solitary or multiple
- Mass/mass-like consolidation greater than 1cm
- Bronchovascular thickening mimicking lymphangitis carcinomatosa
- Cavitation may occur
- Air bronchograms
- Pleural effusion
- Nodal enlargement: HD > NHL

**AIDS related Lymphoma**

**ARL**

- Younger patients
- Usually symptomatic: cough, SOB
- More aggressive disease, often with bone marrow involvement
- Diffuse disease
- Pulmonary nodules > 1cm commonest parenchymal finding
- Extent of mediastinal adenopathy is typically less than lymphoma in general population - depends on the CT series quoted and it ranges from 3%-54%
- Poorer prognosis

**ARL**

- Lymphoma is the 2nd most common tumour in AIDS < Kaposi’s sarcoma
- Prevalence: 40-100x general population
- Almost exclusively NHL, usually aggressive B-cell type
- Primary pulmonary involvement accounts for 10% cases
- Cause of death in 20% HIV infected patients
- Associated with advanced AIDS, CD4 count <55/Dl
- *Autopsy series of AIDS patients with systemic NHL: 71% (n=20/28) had lung involvement in the form of nodules, infiltrates or masses vs a recorded incidence of 5.8% in the corresponding clinical database = parenchymal disease often undetected*


**ARL**

- HIV positive patient with a CD4 count of 66/66 demonstrates a single, well-defined, peripheral large pulmonary non-Hodgkin’s lymphomatous mass (arrow)
NHL in AIDS CT shows ill defined nodules which are perihilar and peribronchovascular. Appearance mimics Kaposi's sarcoma.

NHL in AIDS. CT shows ill defined nodules which are perihilar and peribronchovascular. Biopsy of the consolidation revealed NHL lymphoma.

HRCT – Key Features

• Well-defined pulmonary nodules (0.5–5cm) +/- cavitation OR a large solitary pulmonary nodule/mass (2-5cm)
• Pleural effusions = commonest thoracic manifestation
• Pericardial effusions can be present
• Focus of consolidation and/or ground glass opacity

Nodules + Effusions + Adenopathy = highly suggestive of ARL (if HIV +ve)

Post Transplantation Lymphoproliferative Disorder

PTLD

• Lymphoid proliferation following solid organ transplantation or hematopoietic stem cell transplantation
• Spectrum: Polyclonal lymphoid hyperplasia <-> monoclonal, aggressive lymphomas
• Closely associated with EBV; EBV-induced B-cell proliferation continues unopposed due to the host’s pharmacologically suppressed T-cells
• Seen in < 2% of all transplant cases
• Clear association with the specific organ transplanted: highest incidence in lung transplantation (6-9%) VS cardiac (2-5%), liver (2-5%), pancreas (2.1%), renal (1%), and BMT (0.5-1%)
• Risk of children developing PTLD is 2-3x > adults

PTLD

• Majority of cases occur < 2 years of transplantation
• *Late-onset PTLD can be seen as much as 20 years after transplantation, is usually monoclonal and heralds a worse prognosis
• PTLD, irrespective of histology, is a significant cause of morbidity/mortality in transplant patients and can be fatal if left untreated – mortality rates 60-100%
• Unexplained infectious syndrome in a transplant recipient should always raise the suspicion of a PTLD
• Fever, lymphadenopathy, abdominal pain with diarrhoea, a mononucleosis-like syndrome, upper respiratory tract infection, CNS symptoms, and weight loss

PTLD

- The majority of polyclonal PTLD lesions either resolve completely or improve significantly with reductions in immunosuppression alone (60-70%)
- Early diagnosis is key and the radiologist should consider this diagnosis in those post-transplantation
- Commonest intra-thoracic manifestations of PTLD are randomly distributed, well-circumscribed pulmonary nodules (0.3 -5cm) – peripheral, basal
- Can take form of a solitary pulmonary mass

PTLD after double lung transplant. HRCT shows LLC nodule with a ground glass halo

HRCT – Key Features

- Nodules – single > multiple, size range: 0.3 – 5cm
- Well-defined > ill-defined nodules
- ‘Halo sign’ around nodules
- Patchy/focal consolidation or ground glass opacity
- Peribronchial/subpleural > diffuse distribution of nodules
- Lymphadenopathy (30 – 60%)

Conclusions

- Complex spectrum of focal/diffuse abnormalities - usually classified as reactive or neoplastic
- Benign LPDs and PPL are relatively rare whereas SPL is far more common
- Radiological appearances are not pathognomonic
- Commonest finding is multiple nodules but the breadth of potential HRCT findings is wide
- Recognising LPD in the immunosuppressed may expedite treatment as this group frequently have more “aggressive” disease
- Most patients with clinically/radiologically suspected LPD still usually require a histological sample to confirm

Questions are guaranteed in life; Answers aren’t.