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Imaging Spectrum of Pulmonary Lymphoma

Pictorial Essay

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Abstract

Lung involvement in lymphoma may be primary or secondary. Primary lung involvement is rare and more usually seen in Non-Hodgkin Lymphoma. The main radiological findings of pulmonary lymphomas include- Pulmonary lesions appearing as a mass or mass like consolidation with or without cavitation or bronchogram, masses of pleural origin- single or multiple nodules of sub-centimetre size, alveolar or interstitial infiltration and peribronchial, perivascular thickening with or without atelectasis. The pulmonary lymphoma can be confused with carcinoma lung, metastases, pneumonia, organising pneumonia, fungal infection and interstitial lung disease. Imaging manifestations of primary and secondary pulmonary lymphomas may be similar. Since the treatment options of these two are different, it is necessary to differentiate primary pulmonary lymphoma (PPL) from the secondary disease (SPL). Certain characteristic features like peripheral mass, cavitation, consolidations are more common in PPL. Mediastinal and hilar-adenopathy, central, peripheral lung lesions, nodules are more observed in SPL.

Keywords: Pulmonary lymphoma; Lung; Non-Hodgkin's lymphoma

Introduction

Pulmonary involvement is common especially in secondary and recurrent disease than in primary lymphoma. The clinical and imaging diagnosis is critical and is to be differentiated from other conditions. Lymphomatous proliferation in chest can occur in three ways. It may be haematogenous dissemination by either Hodgkin's Lymphoma (HL), Non-Hodgkin's Lymphoma (NHL) or by direct extension from hilar or mediastinal adenopathy. The first two situations occur by either progression of disease or relapse of a pre-existing lymphoma. Here treatment focuses on control of haematological spread. The third pattern is primary pulmonary lymphoma which needs proper differentiation from other diseases and starting the appropriate treatment in time.

Lung involvement in lymphoma may be primary or secondary. Imaging manifestations of these two may be similar. Primary lung involvement is rare and more usually seen in NHL. When clonal proliferation occurs in lung parenchyma or bronchi without any detectable extra-pulmonary lymphoma at the time of diagnosis or in subsequent 3 months of diagnosis, it is called primary pulmonary lymphoma (PPL) [1]. It may be associated with or without mediastinal lymphadenopathy. PPL accounts for <1% of all lymphoma and 0.5-1% of all lung primaries [2]. Most common type of PPL is MALT (Mucosa associated lymphoid tissue lymphoma). Other frequent form is Diffuse Large B Cell lymphoma (DLBCL). Primary NHL of lung is rare subtype of extra-nodal lymphoma and is low grade Bcell type accounting for <1%of all lymphoma [3]. Secondary pulmonary lymphoma (SPL) is more common, and it may be HL or NHL.12% of HL and 4% of NHL involve lung parenchyma on basis of chest radiographic findings at initial presentation [4]. An autopsy series demonstrated higher frequency of lung involvement up to 62% [5]. In HL, the pulmonary involvement is common in recurrent disease and determines stage 4. It is almost always associated with mediastinal and hilar nodes (Figure 1). In immune-compromised patients the lymphoma can be aggressive. Lymphoma is the second most common malignancy after Kaposi's sarcoma in HIV/AIDS patients. It is thought to be due to consequence of long stimulation by HIV to B lymphocyte proliferation. Prevalence of lymphoma is 40-100 times

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more common in AIDS patients as compared to general population. Transplant related lymphoma (TRL) is uncommon and is related to Epstein virus and immune suppressant therapy. Most of them are B Cell NHL.

A wide variety of radiologic findings are described in pulmonary lymphoma. These findings are explained on basis of anatomy of lymphatic system in lung. Either retrograde flow spread of tumour directly from involved hilar or mediastinal node or ante grade spread from multiple foci can occur. Haematogenous spread is rare [5]. The main radiological findings include i) Pulmonary lesions appearing as a mass or mass like consolidation with or without cavitation or bronchogram, ii) Masses of pleural origin- Single or multiple nodules of Subcentimeteric size or <3cms,iii) Alveolar or interstitial infiltration, iv) Peri bronchial, perivascular thickening with or without atelectasis. The pulmonary lymphoma can be confused with carcinoma lung, metastases, pneumonia, organising pneumonia, fungal infection and ILD. For local MALT lymphoma treatment is surgery and for high grade pulmonary lymphoma the treatment is chemotherapy. With recent advancements of treatment with bone marrow transplantation the survival of these patientsis longer. Hence early diagnosis is important, and CT is extremely useful diagnostic modality for this clinical challenge. In this review we tried to focus on important diagnostic clues for pulmonary lymphoma.

Nodules

Single or multiple pulmonary nodules with smooth or poorly outlined borders may be noted (Figure2, 3). Multiple nodules are more common. Peribronchovascular bundle thickening forms the nodules and masses in pulmonary interstitium near the bronchus or sub pleural areas. Hence location of nodules is typical. Most of these nodules have shaggy borders in NHL than HL. Halo sign indicates ground glass opacity surrounding a pulmonary nodule in CT. It is of clinical significance in early diagnosis of *Aspergillus* infection and it represents pulmonary infarction surrounded by haemorrhage. In case of lymphoma the lesion represents infiltration of surrounding interstitium by less densely arranged tumour cells relating to invasiveness of PPL. Another proposed theory for halo-sign in lymphoma is invasion of tumour cells into blood vessels with resultant bleeding into surrounding tissue [6]. Halo sign more frequently seen in non-MALT than MALToma (Figure 4A) [1]. The close differentials of these nodules are infections, vasculitis, and bronchogenic carcinoma (Figure 4B).

Consolidation

Consolidation is another common feature of pulmonary lymphoma seen frequently in MALT and non-MALT form. Air bronchogram sign is more frequent in MALTOMA than in non-MALTOMA. Primary pulmonary MALTOMA is monoclonal B cell proliferation in sub mucosal collection of B and T cells present beneath areas of specialised bronchial epithelium throughout the airway and especially at bronchial bifurcation. Tumour infiltrate along sub mucosal epithelium and lumen appear smooth. These consolidations may be sub pleural (Figure 5) which appear polygonal along pleura/fissure, lobular when a segment/lobe is involved (Figure 6), peribronchial when consolidation is distributed along the broncho-vascular bundle with a tapered shape with tip towards hilum (Figure 7). Halo of ground-glass opacity (GGO) may be observed surrounding the consolidation. CT- angiogram sign is normal pulmonary vessels within consolidation or mass after enhancement (Figures 1,2). This is a specific sign in bronchiole-alveolar carcinoma and is more commonly seen in MALTOMA. It is seen when lymphoma infiltrates along Peribronchovascular interstitium without invading the vascular wall. However high-grade malignant lymphoma can develop rapidly and invade pulmonary vessels. An important differential at this stage is lung cancer. Here the cancer cells infiltrate the vessel wall to cause vascular distortion and destructions. Even in aggressive lymphoma pulmonary vessels show distortion and destruction as in consolidation (Figures 8,9A). Hence in non-MALTOMA, CT angiogram sign is less observed. Lesions cross lobes, fissures and infiltrate the adjacent lobes on CT. Distribution from hilum to periphery across lobe fissure is defined as butterfly sign. This sign is due to Lymphangitic spread along pleura, Interlobular septa and bronchovascular bundle [7]. Similar phenomenon is seen in Carcinoma lung as well. Bulging fissure due to massive consolidation is also observed in lymphoma. Kliebsilla pneumonia is also a differential at this stage. Clinical scenario differentiates the two. Lung cancer with distal collapse also can present with bulging fissure (Figure 9B).

Mass

There may be mass or mass like consolidation in lungs. It may be single or multiple. Size may vary from 0.5 to 8cms.Pleural based mass predominantly seen in PPL (Figure 10). Pleural based masses seen in 32% cases in HL and 31% in NHL [8]. Size is more than 3cms and lesions may be associated with air bronchogram and CT angiogram sign (Figures 9,11). On contrast administration there may be intense homogenous or heterogeneous enhancement. Jung et al studied 24 cases of PPL, 29.2 % patients had single or multiple nodules, 16.7% had masses,41.7 % had infiltrates and 20.8% showed consolidation. Hilar adenopathy was found in 5 of 24 cases and one had chest wall invasion [9]. Mass invades the chest wall and erodes the bone as seen in figure- 10.Cavitation may be observed in the mass (Figure 11) and usually seen in DLBCL. HL is usually associated with mediastinal adenopathy. DLBCL are associated with mediastinal adenopathy and pleural effusion than the low-grade form of PPL.

Interstitial Disease Pattern

Diffuse ground glass opacities are often seen imaging finding in lymphoma. They may be seen as patchy areas of GGO randomly distributed in both lungs (Figure 5,10). CT findings of MALT lymphoma have varied pattern. Interstitial disease pattern presenting as GGO is not uncommon with an incidence of 6 to 10% in pulmonary MALT lymphoma [10]. On histology masses, consolidation, nodules represent alveolar infiltration and GGO is lymphomatous infiltration of interlobular septae and alveolar wall [10].The spread is via vascular rather lymphatic pathway. Pathologically tumour cells in DLBCL, form sheets that distort or destroy lung architecture. Differentials are infection, diffuse alveolar hemorrhage and interstitial diseases. A few reports described diffuse GGO in DLBCL without lung nodules, masses, or consolidations [11]. Intravascular large B-cell lymphoma (IVLBCL) is characterised by tumour cells located almost entirely in

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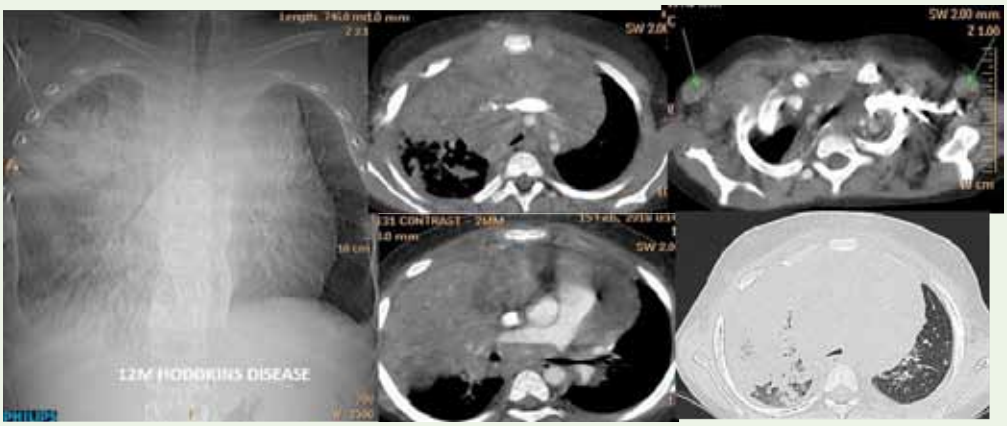

Figure 1: Hodgkin's' lymphoma in12-yearmale; shows extensive mediastinal adenopathy and extension to lung. Large lobar consolidation with positive CT angiogram in right upper lobe. Smaller nodules with irregular margin along bronchovascular bundle in same lobe posteriorly.

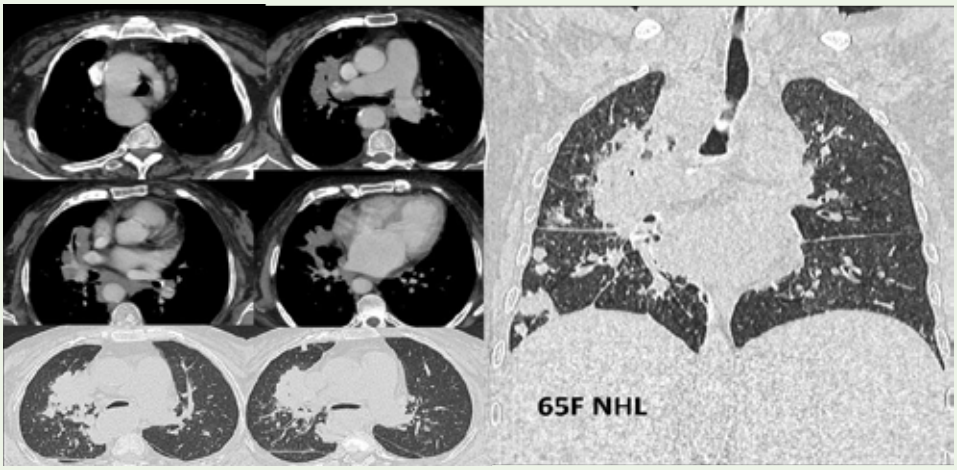

Figure 2: Multiple pulmonary nodules of varying sizes and ill-defined irregular margins. Few of nodules also show peripheral halo. Extension of lesions from large hilar adenopathy as evidenced by perihilar linear opacities with thickening of bronchovascular bundle. A patch of consolidation is noted in right perihilar region showing air-bronchogram and angiogram. Note: There is right aortic arch.

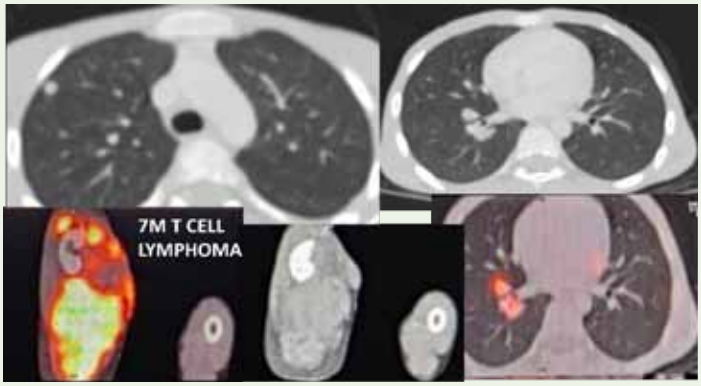

Figure 3: Single discrete smoothly out-lined pulmonary nodule in a case of secondary lymphoma. Primary is in right femur. There is also right hilar adenopathy

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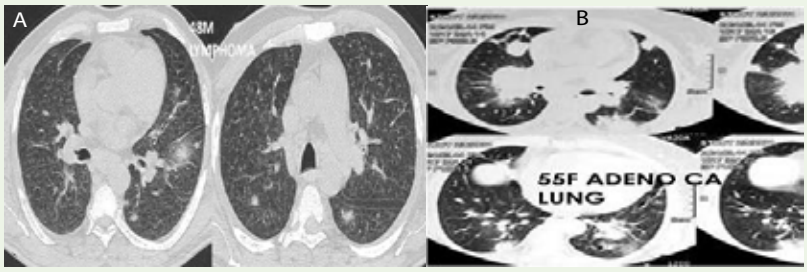

Figure 4: A: Ground glass appearance surrounding pulmonary nodules scattered in both lungs. B: Irregularly outlined pulmonary nodules in both lungs in a case of right hilar mass[Adenocarcinoma]. Note the nodules are random in carcinoma lung whereas the nodulesin lymphoma are along the bronchovascular bundle.

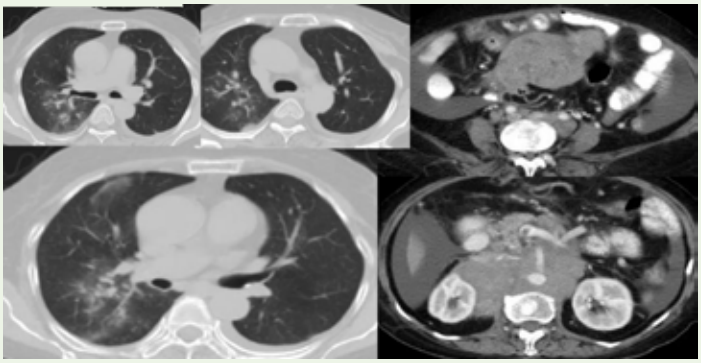

Figure 5: 48-year female: Extensive lymph node mass in mesentery, retroperitoneum, ascites, and pleural effusion. There is sub pleural consolidation in superior segment of right lower lobe, extensive ground glass appearance in right upper lobe, right middle lobe, right lower lobe and left lingula.

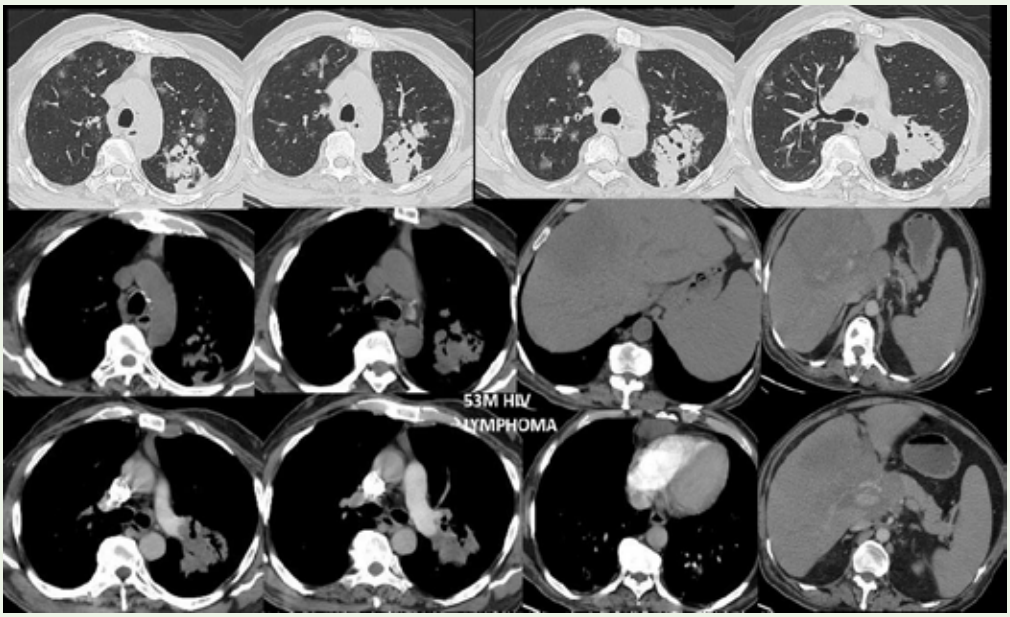

Figure 6: Segmental consolidation with air bronchogram in superior segment of left lower lobe and multiple ground glass opaque nodules in both lungs. There are prevascular and right internal mammary enlarged nodes, hepatosplenomegaly with minimally enhancing mass in liver in segment 4 in a HIV positive male.

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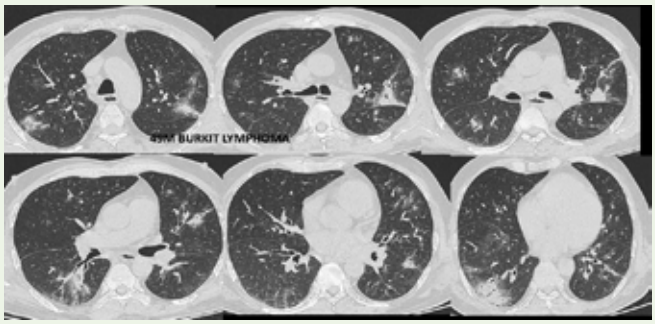

Figure 7: 49-year male with Burkett's lymphoma. Multiple patchy consolidations along the bronchovascular bundle in bilateral lungs. Air-bronchogram is visualised and they have pointed tip towards hilum. A few of consolidations show ground glass opacities surrounding it. Ill-defined areas of ground glass opacities and nodules surrounded by ground glass opacities are also scattered bilaterally.

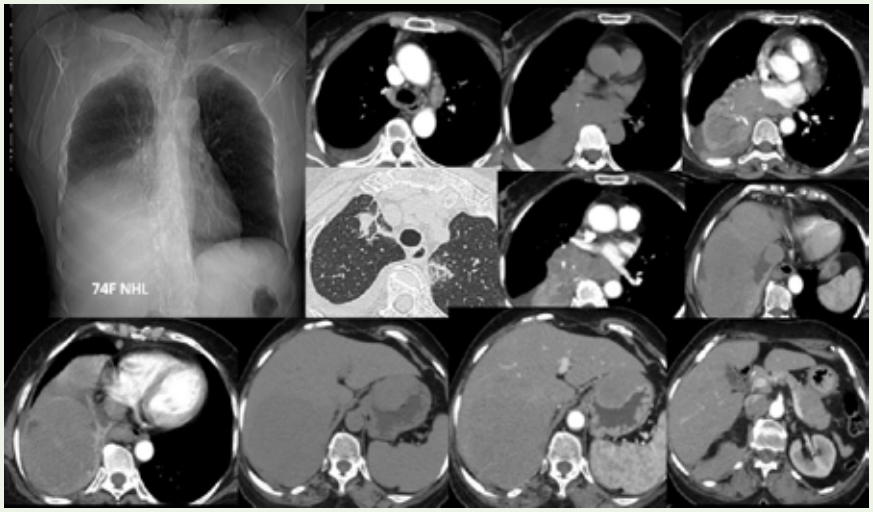

Figure 8: 74-year female: Histopathologically proven primary pulmonary lymphoma (NHL). Large pleural based mass in right lower lobe, with intense inhomogeneous enhancement with areas of necrosis/cavitation and minimal adjacent pleural effusion. Subcentimeteric irregularly outlined pulmonary nodules in bilateral upper lobes. There are enlarged prevascular, internal mammary lymphnodes and gastric, hepatic, pancreatic deposits.

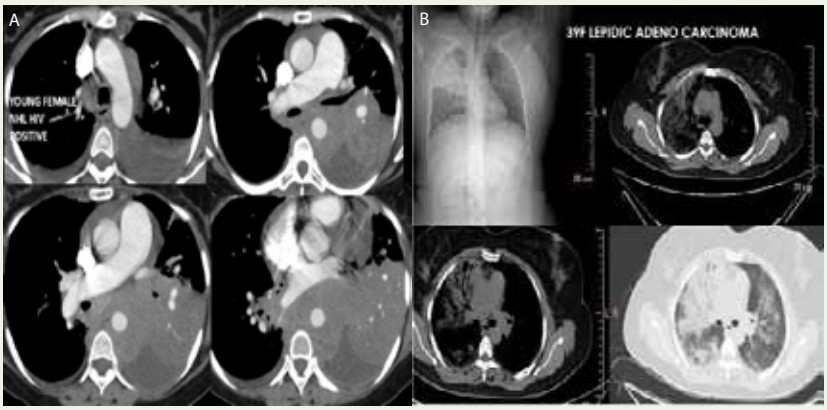

Figure 9: A: HIV positive young female proven to be NHL in lung. A large consolidation with distorted CT angiogram in left lower lobe and an area of necrosis in left lower lobe. Associated pleural effusion andmediastinal adenopathy. B: A Case of Adenocarcinoma lung showing large lobar consolidation bulging the adjacent fissure and air bronchogram, a differential for lymphoma.

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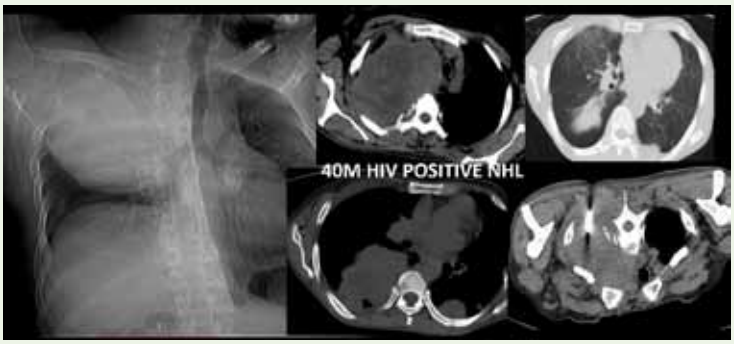

Figure 10: NHL in HIV positive 40- year-old male. Large pleural based right upper lobe mass and smaller one in left upper lobe. Adjacent rib is eroded in right upper thorax. Small pulmonary nodules and ground glass opacities are noted right middle lobe.

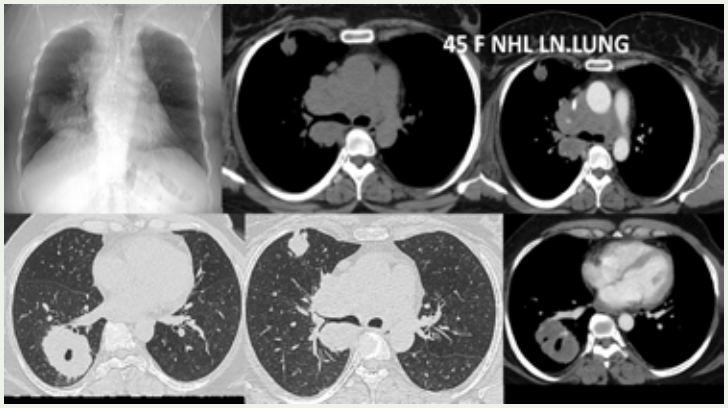

Figure 11a: 45-yearfemale:NHL Extensive, mediastinal, and hilar adenopathy. Large enhancing mass with necrosis, CTangiogram and pulmonary nodule in right middle lobe.

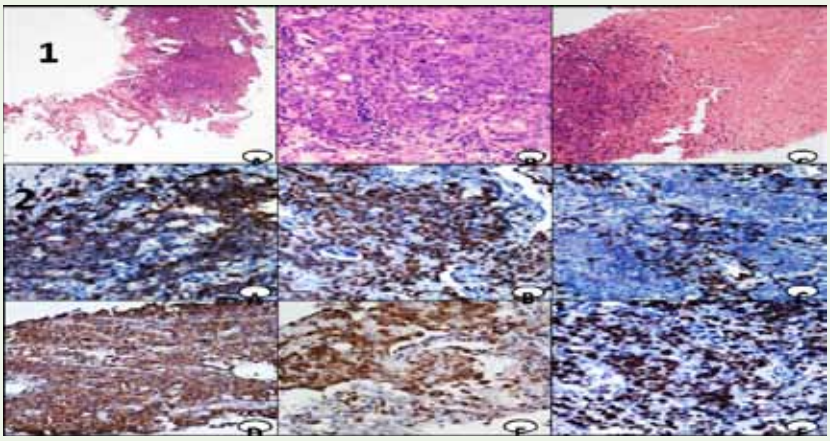

Figure 11b: (1) Histological sections of core needle biopsy of lung. (a) Shows normal lung parenchyma (lower left) with rest of the core involved by lymphoma. (b) Higher magnification of involved area showing alveoli filled with atypical lymphoid cells having round vesicular nuclei with scant to moderate cytoplasm. Admixed some normal small mature lymphocytes can be seen in between the atypical lymphoid cells. (c) Shows area of necrosis with adjacent viable lymphoma. (Haematoxylin& eosin; a x40, b x400, c x200)
(2) Immunohistochemistry findings. The atypical lymphoid cells show (a) diffuse membranous positivity for CD20, (b) diffuse nuclear positivity for pax5 whereas (c) negative staining with CD3. CD3 positive cells seen are admixed normal mature T lymphocytes. The atypical lymphoid cells also showed diffuse positivity for (d) CD10 and (e) BCL2 with (f) high ki67 labelling index. (HRP-polymer; x400).

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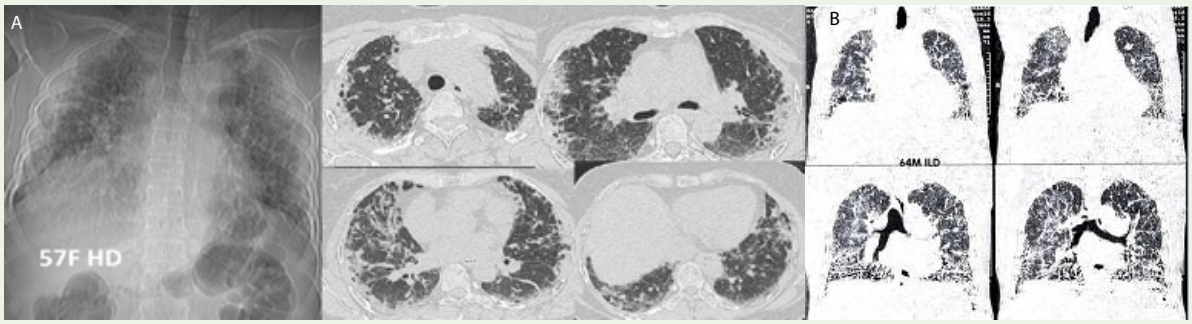

Figure 12: A:Hodgkin's lymphoma in 57-year female: Reticulonodular opacities along with peribronchovascular thickening mimicking diffuse interstitial lung disease. B: a 64 year-old male with ILD with typical subpleural septal thickening. Peri-bronchovascular thickening differentiates it from lymphoma.

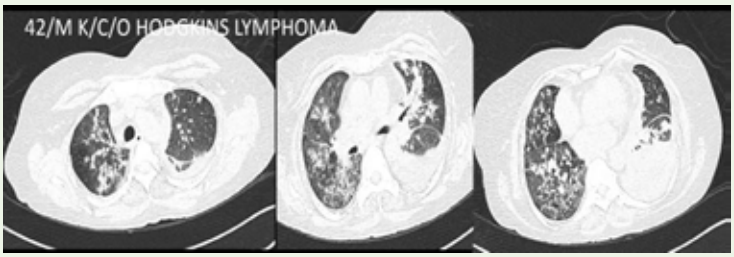

Figure 13: Hodgkin's lymphoma in 42-year male: Multiple centrilobular nodules in both lungs. Note -per bronchialnodular thickening is more prominent in left lingula.

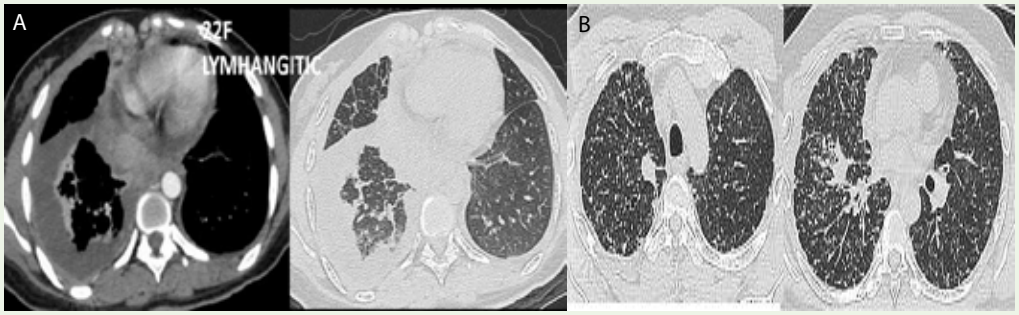

Figure 14: A: Interlobular septal thickening with pleural effusion in a case of lymphoma in 22-year-oldfemale. B: A case of bronchogenic carcinoma in right upper lobe and lymphatic spread to both lungs.

the intravascular, peripheral blood and bone marrow which makes it difficult to differentiate from other tumours. It is classified as special type of lymphoma. In 2008, WHO identified it as a rare type of NHL. There is diffuse occlusive proliferation especially in capillaries, small arteries, and veins [12]. CNS, skin, lung, and kidney are usually involved, and liver, spleen and lymph nodes are rarely involved. Lung involvement can present as GGO, centrilobular nodules, interlobular septal thickening, interstitial shadow and thickening of bronchovascular bundle suggesting lymphatic and or haematological spread. The differentials of GGO are infections, alveolar hemorrhage, and interstitial lung disease (Figure 12A,B). The differentiation is made on clinical grounds and other associated imaging features. Less than 10% of patients have bilateral diffuse reticulo-nodular opacities, atelectasis, or pleural effusion [13]. Miliary densities <3mm nodules in linear fashion distributed diffusely throughout the lungs along the bronchi may be observed. A well described imaging findings of lung involvement in lymphoma are lymphangitic spread characterised by nodular thickening along pleura, interlobular septal thickening and thickening along bronchovascular bundle (Figure 13,14A). SPL is known to present as thickening of bronchovascular bundle and interlobular septal thickening in 41% of cases [14]. This represents the retrograde spread of lymphoma from involved hilar/mediastinal lymphadenopathy. Sarcoidosis and lymphangitis carcinomatosis are differentials (Figure 14B).

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HIV Lymphoma and Transplant Related Lymphoma

25-40%HIV patients develop malignancy and 10% will develop NHL [3] (Figure 9, 10). The NHL is aggressive diffuse large B cell lymphoma (DLBCL). Imaging findings are primarily mass and lymphadenopathy [15]. Usually, the nodes show central necrosis, and the mass is large and may have bone destruction (Figure 10). Lung involvement is usually secondary. Transplant related lymphoma (TRL) is uncommon and is related to Epstein virus and immunosuppressant therapy. Most of them are B Cell NHL. It is relatively uncommon, but when occurs, it is fatal. Imaging findings of TRL are similar to that of lymphoma without transplantation. Lymphadenopathy, pulmonary nodules, and mass may be observed.

Conclusion

Pulmonary manifestations of lymphoma are varied. Distribution of lesions is typical. When there are multiple findings with typical distribution one has to think of pulmonary lymphoma. Since the treatment option of PPL and SPL are different, it is necessary to differentiate PPL from SPL. Certain characteristic features like peripheral mass, cavitation, consolidations are more common in PPL. Mediastinal and hilar adenopathy, central, peripheral lung lesions, nodules are more observed in SPL.

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