

Pulmonary Nodular Lymphoid Hyperplasia: A Rare Case Mimicking Malignancy

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ABSTRACT

Pulmonary nodular lymphoid hyperplasia (PNLH) is a reactive lymphoid proliferation manifesting as multiple solitary nodules or localized infiltrates in the lungs. It is a type of benign lymphoproliferative disease that can affect the lungs. We present the case of a 41-year-old female patient with respiratory symptoms such as productive cough, left chest pain, and dyspnea. Imaging findings revealed two lesions with lobulated contour in the left upper lobe apicoposterior segment and left lower lobe superior segment. After examining the minimally invasive diagnostic methods, this rare PNLH case mimicking malignancy was both diagnosed and treated by surgery. Further studies including more patients and longer follow-ups are needed for this rare disease.

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Introduction

Pulmonary nodular lymphoid hyperplasia (PNLH) or initial pulmonary pseudo-lymphoma is a reactive lymphoid proliferation manifesting as multiple solitary nodules or localized infiltrates in the lungs. It is a type of benign lymphoproliferative disease that can affect the lungs. The clinical and histopathologic differentiation between PNLH and other diseases is difficult. The diagnosis of PNLH has been controversial (1, 2). Primary lymphoid lesions of the lung encompass:

- 1) Non-neoplastic lymphocytic proliferations, including reactive lymphoid hyperplasia, follicular bronchiolitis, lymphoid interstitial pneumonia (LIP), and nodular lymphoid hyperplasia (PNLH).
- 2) Neoplastic lymphocytic proliferations, including low-grade B-cell lymphoma of mucosa-associated lymphoid tissue, other non-Hodgkin lymphomas, and Hodgkin lymphoma, and a miscellaneous group of lesions, consisting of lymphomatoid granulomatosis, posttransplant lymphoproliferative disorder,

acquired immunodeficiency syndrome-related lymphoma, and intravascular lymphoma/lymphomatosis.

PNLH is in the array of non-neoplastic lymphocytic proliferations with reactive lymphoid hyperplasia, follicular bronchiolitis, and lymphoid interstitial pneumonia (LIP; Table 1) (3). These three rare forms are regarded as a part of the spectrum of lymphoid hyperplasia of the bronchus-associated lymphoid tissue. PNLH is an Immunoglobulin G4 (IgG4)-related sclerosing disease, characterized by dense nodular infiltration of mature, polyclonal lymphocytes and plasma cells, which are well-circumscribed and mainly subpleural, with some dense fibrosis between the follicles (4). In this study, we present a rare PNLH case mimicking malignancy, which was both diagnosed and treated only by surgery.

Case Presentation

A 41-year-old female patient presented with

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Table 1. Primary lymphoid lesions of the lung (3)

Primary lymphoid lesions of the lung
Non-neoplastic
Reactive hyperplasia
Follicular bronchiolitis
Lymphoid interstitial pneumonia (LIP)
Pulmonary nodular lymphoid hyperplasia (PNLH)
Neoplastic
Primary pulmonary lymphoma
MALT lymphoma
Others- non-Hodgkin lymphoma and Hodgkin lymphoma
Miscellaneous
Lymphomatoid granulomatosis
Post-transplant lymphoproliferative disorder (PTLD)
AIDS-related lymphoma
Intravascular lymphoma

MALT: Mucosa-Associated Lymphoid Tissue, AIDS: Acquired Immunodeficiency Syndrome

respiratory symptoms such as productive cough, left chest pain, and dyspnea. Physical examination was unremarkable, except for the coarse crackles on auscultation. The haemogram and the tumor markers were normal. A left paracardial opacity was detected in chest X-ray. Thorax computed tomography revealed two lesions with irregular contour in the left upper lobe apico-posterior segment and left lower lobe superior segment. Positron emission computed tomography (PET/CT) showed increased ^{18}F -fluorodeoxyglucose (FDG) uptake in both lesions (Figure 1). Maximum standardized uptake values (SUV max) were 5,1 and 7,1, in the left upper and left lower lesions respectively. The diameter of both tumors was measured to be 2 x 2 cm. Endobronchial lesion was not observed in fiberoptic bronchoscopy.

Selective lavage and brush biopsy were performed from the left upper lobe apicoposterior segment and left lower lobe superior segment. However, they were non-diagnostic. Transthoracic biopsy was not

considered because of the localization of lesions. The case was discussed in our multidisciplinary council, which was attended by pulmonologists, thoracic surgeons, medical oncologists, and radiation oncologists. It was decided to perform exploratory thoracotomy due to the high malignant potential. Therefore, left lateral thoracotomy was carried out using muscle sparing, and wedge resection was performed on both lesions. Pre- and postoperative course was uneventful. Thus, the patient was discharged on the fourth postoperative day. Histopathologic examination revealed PNLH for both lesions. The tumors had similar histopathologic features.

Well-demarcated masses consisting of the amount of lymphoid follicles with reactive germinal centers were noted on histological sections. Germinal centers were separated by interfollicular fibrosis and polyclonal plasma cells. Granuloma, necrosis, amyloid depositions Dutcher's bodies, lymphoepithelial lesions, and lymphocyte permeation in cartilage/bronchial structures were not observed. Immunohistochemical staining with CD20, CD79a, and PAX5 was detected in B lymphocytes localized in germinal centers of follicles and staining with CD3 and CD5 was seen in perifollicular T lymphocytes. Heterogeneous reaction was observed in the increased number of perinodular plasma cells with CD138, lambda, and kappa antigens. Staining with IgG4 was seen at low levels in plasma cells. For many other antigens, negative reactions occurred (Figure 2). It was a kind of pulmonary lymphoproliferative disorder considered as a non-neoplastic pulmonary disease. There was no evidence of recurrence on CT follow-up six months postoperation.

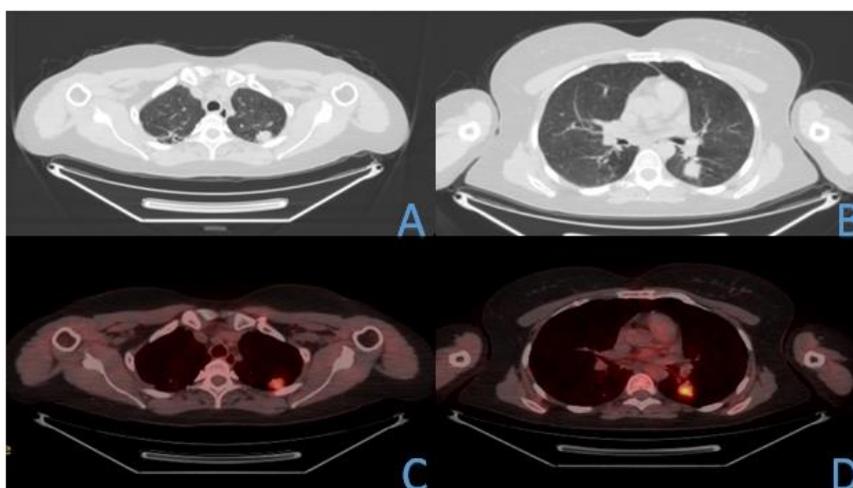


Figure 1. A, B: Thorax-CT scans reveal two lobulated lesions in the left upper lobe apicoposterior segment and left lower lobe superior segment. C, D: PET/CT scans reveal malignant uptake, the standardized uptake values were 5,1 and 7,1, in the left upper and left lower lesions respectively

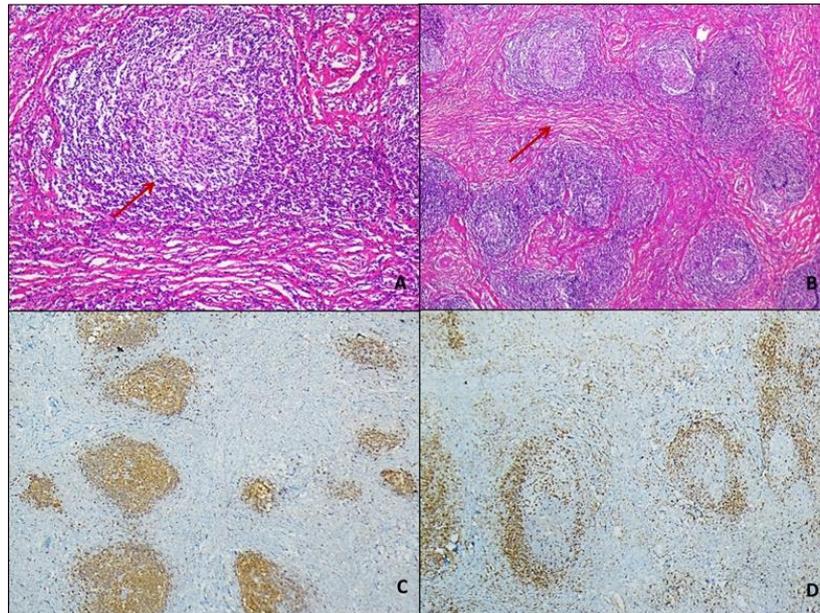


Figure 2. Histopathological features of lung parenchyma. A, B: Lymphoid follicles with reactive germinal centers (red arrow) and, B, C: Interfollicular fibrosis with polyclonal plasma cells

Discussion

Pulmonary nodular lymphoid hyperplasia is a rare benign disease, the exact clinicopathologic characteristics of which remain unknown. PNLH was first defined by Kradin (5) as a reactive lymphoid proliferation in 1983. PNLH was placed into the subgroup of pulmonary lymphoproliferative disorders by the World Health Organization. This disorder is considered to develop as a consequence of abnormal stimulation and response of the bronchial lymphoid tissue and manifests as a spectrum of lymphoproliferative disorders (6). Primary lymphoid lesions encompass a wide range of benign and malignant lesions. PNLH can transformate low-grade lymphoid proliferations or low-grade B-cell lymphomas as mucosa-associated lymphoid tissue (MALT) or bronchus-associated lymphoid tissue (BALT). Of all the lymphomas, MALT or BALT has the best prognosis. The PNLH may rarely progress to diffuse large-cell lymphomas (7).

The radiologic findings of PNLH are often nonspecific and are best interpreted in conjunction with clinical and pathologic findings. Differentiation of pulmonary lymphoproliferative disorders by biopsy is highly challenging. Firstly, the differential diagnosis of PNLH includes primary lung carcinoma, metastasis, and primary pulmonary lymphoma. The absence of mediastinal and hilar pathologic lymphadenopathy, pleural effusion, or invasion of the surrounding structures do not suggest malignancy. However, in radiological images, it is difficult to distinguish among PNLH, lung carcinoma,

metastasis, and primary pulmonary lymphoma; thus, surgical confirmation is necessary (3). For our case, we could not reach a definitive diagnosis with minimally invasive techniques, hence performing surgery.

Although most cases of PNLH are asymptomatic, in some cases, it may cause cough, dyspnea, and pleuritic chest pain. Radiological examination is often nonspecific, except for solitary non-cavitary pulmonary nodule. Some cases can present with cavitation (8). Abbondanzo et al. (9) reported 14 cases with PNLH in their study. In that study, most lesions (71%) were found incidentally and most of the cases (64%) had a single lesion. They performed surgical excision for all the cases and there were no cases of recurrence and mortality during the median follow-up period of 30 months. Histopathologic examination revealed abundant reactive germinal centers, intense interfollicular polyclonal plasmacytosis, and a variable degree of interfollicular fibrosis in all cases, and no case showed a molecular re-arrangement of the immunoglobulin heavy chain gene or the minor or major breakpoint region of the t(14;18) in the same study.

Dense nodular infiltration of mature, polyclonal lymphocytes and plasma cells with multiple reactive germinal centers are considered for the diagnosis of PNLH. These are sharply demarcated from the surrounding parenchyma with central areas of scarring. Organizing pneumonia may be commonly seen at the periphery. There can also be mild, local lymphangitic spread of lymphocytes

Table 2. Clinico-pathologic, main imaging, and differential diagnosis features of PNLH (3)

Clinical data: Usually found in asymptomatic patients. May be associated with collagen vascular disease or dysgammaglobulinemia.
Histopathologic findings: Localized infiltration of polyclonal lymphocytes (predominantly T cells); "focal LIP" Polymorphous population of B and T cells with multiple germinal centers.
Main imaging findings: Radiography: Nodule, mass, or mass-like opacity; single or multiple CT: Nodule, mass, or masslike area of consolidation; single or multiple; air bronchograms PET/CT: No significant data available given rarity of this disease
Differential diagnosis: Lung cancer, metastasis, primary pulmonary lymphoma
LIP: Lymphoid Interstitial Pneumonia

permeating into the perivascular interstitium. Immunohistochemical staining for kappa and lambda light-chain restriction shows a polyclonal pattern in PNHL, but a monoclonal pattern in most cases of BALT lymphoma (10). Our case was symptomatic and had two nodular lesions. Clinical recurrence was not observed in the six-month follow-up after surgery. Nodular structure forming lesions in the lung parenchyma with germinal centers are separated with sclerotic bands from each other. There was an increased number of CD138, lambda, and kappa antigens in the perinodular plasma cells.

Pulmonary nodular lymphoid hyperplasia may show heavy lymphoplasmacytic infiltrates with increased IgG4-positive plasma cells. However, it is unclear whether PNLH could be a manifestation of IgG4-related diseases (11). In our case, immunohistochemical examination showed low IgG4 level in plasma cells.

Lymphoproliferative disorders are assumed to be associated with autoimmune diseases like systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, scleroderma, systemic sclerosis, dermatomyositis, polymyositis, Behcet disease, and ankylosing spondylitis. Several similarities have been recognized between autoimmune diseases and lymphoproliferative disorders. Chronic inflammatory process, immune dysregulation, anti inflammatory response have been suggested to have a role in the association between autoimmune diseases and lymphoproliferative disorders. In addition, lymphoproliferative disorders can be found in patients receiving immunosuppressive treatment for autoimmune diseases (12). We did not detect any autoimmune diseases in our case for explain possible PNLH formation.

It has been reported that PET/CT may be shown to be positive in PNHL with unifocal and multifocal lesions and may be confused with malignancy (13, 14). In our case, PET/CT showed high FDG uptake at the SUVmax value that would suggest malignancy in both two lesions. Clinicopathologic features of PNHL was summarized in Table 2 (3).

Conclusion

Pulmonary nodular lymphoid hyperplasia is

an uncommon non-neoplastic disease with polyclonal lymphoid proliferation, which is difficult to distinguish from low-grade lung lymphomas. PNHL should be reminded for PET/CT positive unifocal or multifocal lesions. A little biopsy with needle or true-cut may not always be sufficient to diagnose PNLH. Surgery plays an important role in its diagnosis and treatment. Further studies are needed involving larger series of cases of this rare disease.

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None.

Conflict of Interest

The authors declare no conflict of interest.

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