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Case Report

Pulmonary Nodular Lymphoid Hyperplasia presenting cavitating pulmonary nodules

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ABSTRACT

Pulmonary Nodular Lymphoid Hyperplasia (PNLH) is a rare benign pulmonary disorder characterized by a localized, reactive polyclonal lymphoproliferation. Although the radiological features of this disease have not been clearly defined, they usually consist of a solitary non-cavitatory pulmonary nodule. In this report, we describe two cases of histologically confirmed PNLH presenting as multiple bilateral cavitatory lesions on CT Thorax.

1. Teaching cases

We report two cases of Pulmonary Nodular Lymphoid Hyperplasia (PNLH) presenting as multiple, bilateral cavitating nodules.

PNLH is a rare benign disorder thought to represent a localized reactive hyperplasia of the bronchus-associated lymphoid tissue (BALT) [1,2]. Diagnosis is usually made following the incidental finding of a solitary nodule on radiological imaging with subsequent histological analysis confirming the presence of reactive germinal centres with sheets of interfollicular plasma cells [1]. Cavitating lesions are rare [3]. A recent study suggested that IgG4-positive plasma cells may be increased in PNLH as compared with other lymphoid proliferations [4]. PNLH might thus be a distinct form of reactive lymphoid proliferation, distinct from low-grade lymphoma of the BALT.

2. Introduction

Pulmonary Nodular Lymphoid Hyperplasia (PNLH) is a rare benign disorder of the lungs. Our current understanding of PNLH is based on immunohistological and genetic analyses performed in a small number of case reports, which postulate that PNLH represents a localized reactive hyperplasia of the bronchus-associated lymphoid tissue (BALT) [1,2]. Diagnosis is usually made following the incidental finding of a solitary nodule on radiological imaging with subsequent histological analysis confirming the presence of reactive germinal centres with sheets of interfollicular plasma cells [1]. Cavitating lesions are rare [3]. A recent study suggested that IgG4-positive plasma cells may be increased in PNLH as compared with other lymphoid proliferations [4]. This finding potentially supports the classification of PNLH as a distinct form of reactive lymphoid proliferation, and may aid its distinction from low-grade lymphoma of the BALT.

In this report we describe two cases of atypical PNLH with increased levels of IgG4-positive plasma cells presenting as multiple, bilateral, cavitating lesions on CT Thorax.

Abbreviations: ACE, angiotension-converting enzyme; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; BALT, bronchial-associated lymphoid tissue; CRP, c-reactive protein; CT, computed tomography; dsDNA, double-stranded DNA; ENA, extractable nuclear antigens; ESR, erythrocyte sedimentation rate; MALT, mucosa-associated lymphoid tissue; MPO, myeloperoxidase; PNLH, Pulmonary Nodular Lymphoid Hyperplasia; PR3, proteinase-3; VATS, Video-Assisted Thoracoscopic Surgery.

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Table 1
Antibodies used for automated immunohistochemistry and in situ hybridization (ISH).

Antibody	Clone	Supplier	Dilution
CD3	565	Novocastra	1.300
CD20	L26	Dako	1.300
bcl-2	NCL-L-BLC2	Novocastra	1.20
Cytokeratin Cam5.2	345779	BD Biosciences	1.50
IgG4	HP6025	The Binding Site MC011	1.2400
IgG	NCL-L-IgG	Novocastra	1:300
Kappa light chain (ISH)	PB0645	Vision Biosystems	RTU
Lambda light chain (ISH)	PB0669	Vision Biosystems	RTU

RTU, ready to use.

3. Teaching cases

3.1. Case 1

A 58-year-old male was referred to the lung clinic with an incidental 3 cm left upper zone opacity on a routine chest X-ray performed following a mechanical fall. His respiratory risk factors included a 40 pack year smoking history and occupational exposure to asbestos 40 years previously while working as a welder. He had no history of allergy or TB exposure. Full blood count, renal and liver profile, ESR and CRP were within normal range. Blood results also showed an elevated ANA (homogenous, titre 200), ANCA (atypical perinuclear) and anti-smooth muscle antibody positivity. Anti-MPO and PR3 antibodies were negative. Rheumatoid factor and serum ACE were within normal range. Serum protein electrophoresis showed a faint monoclonal IgM lambda band. Pulmonary function tests were normal. CT Thorax showed multiple nodules in various states of cavitation (Fig. 1a). The largest nodule was located in the apical segment of the right lower lobe and measured 1.8 cm.

3.2. Case 2

A 26-year-old female was referred to the lung clinic with an abnormal chest X-ray following outpatient investigation of dyspnoea on exertion, productive cough of clear sputum, night sweats and pleuritic chest pain. She was a non-smoker with no history of TB exposure or allergy. Physical examination revealed crepitations in the left mid-zone. Full blood count showed a microcytic anaemia, and raised CRP (>200). Viral serology and throat swab cultures were negative. Serum ANA was positive (speckled and centromere, titre 400). Anti-dsDNA, ENA, rheumatoid factor, anti-MPO and anti-PR3 antibodies were negative. No monoclonal band was seen on serum protein electrophoresis. Pulmonary function tests showed restriction with a FVC of 61% and FEV1 of 63% predicted. High resolution CT Thorax showed multiple ill-defined subpleural nodular opacities bilaterally, measuring between 3 and 6 cm on average. She was followed up in respiratory clinic, and as she continued to complain of dyspnoea on exertion and pleuritic pain, a repeat CT was ordered 1 year later. Multiple bilateral nodules (some with cavitation, Fig. 1b) were noted on this repeat CT Thorax.

For both patients, Video-Assisted Thoracoscopic Surgery (VATS) wedge resection was performed for a definitive diagnosis on a right upper lobe nodule for Case 1 and left upper and lower lung nodule for case 2.

For reasons related to surgical approach and ease of biopsy, peripheral subpleural solid nodules (yellow arrows on Fig. 1a and b) were sampled, as cavities (green arrows) were more deeply seated and more risky to access by VATS.

Immunohistochemical stains and in situ hybridization for light chains were performed on the Ventana Benchmark XT and Bond automated immunostainers. See Table 1 for antibodies and dilutions. Special stains for organisms to exclude an infectious process were also performed.

As shown in Fig. 1, histological analysis of this tissue confirmed PNLH with immunostaining for bcl-2 showing a reactive pattern. Immunohistochemical staining analyses for IgG4 showed increased numbers of IgG4-positive plasma cells (absolute count = 64, ratio of IgG4/IgG of 61% for case 1 and a similar reactive lymphoid infiltrate with increased numbers of IgG4-positive plasma cells (absolute count = 51, ratio of IgG4/IgG = 64%) in case 2.

In both cases, polyclonality was observed on kappa and lambda light chain in situ hybridization. FISH analysis for the MALT lymphoma-specific 18q21 rearrangement was negative (Vysis LSI-MALT1 probe, Abbott).

Special stains (Ziehl-Neelsen, PAS and Grocott) for organisms were negative.

Case 1 was not commenced on treatment and was followed up at the lung clinic. At 2-year follow-up, he had noticed an improvement in his dyspnoea on exertion and had not developed any new clinical symptoms or signs. Routine blood tests remained normal. ANA remained positive (homogenous and speckled, titre 80) while ANCA, ENA, anti-MPO, anti-PR3 and anti-dsDNA antibodies were negative. CT Thorax showed stable cavitatory lesions in all lobes of both lungs 4.5 years later, with no septic or symptomatic events, further supporting that the cavities and solid nodules are part of the same PNLH process.

Case 2 was treated with 40 mg of oral prednisolone once daily tapered over a 6 month period. She experienced good symptomatic relief from this treatment, and the pulmonary nodules have remained stable or have decreased in size on CT Thorax, with an uneventful asymptomatic follow-up over 4 years to date.

Understanding of the aetiology and significance of PNLH has evolved in recent years. Initially thought of as a pulmonary 'pseudolymphoma' [5], then as a variant of low-grade BALT lymphoma, current understanding of PNLH is that it is a localized, reactive polyclonal lymphoproliferative disorder, characterized by numerous germinal centres with interfollicular reactive lymphocytes, a reactive bcl-2 pattern, abundant plasma cells and mild to moderate fibrosis [1]. FISH for MALT translocation and clonality studies are negative. It is therefore considered to be part of the spectrum of reactive pulmonary lesions ranging from follicular bronchitis to lymphoid interstitial pneumonitis. In both cases, the absence of a MALT-1 rearrangement excludes the t(11:18) translocation, as well as polyclonality by light chain studies, supporting a diagnosis of a benign process.

A recent study (based on a small cohort of PNLH cases) suggested that increased numbers of IgG4-positive plasma cells are found in PNLH compared to other pulmonary lymphoproliferative disorders [4]. This finding may have diagnostic implications, as the identification of reactive lymphoid follicles with increased numbers of IgG4-positive plasma cells (without other features of lymphoma) from a pulmonary nodule needle biopsy could more strongly support the diagnosis of PNLH.

Increased numbers of IgG4-positive plasma cells in PNLH may also suggest that this disorder is a manifestation of IgG4-related sclerosing disease [4], which is characterized by tumour-like masses and/or fibrosis with infiltration by numerous IgG4-positive plasma cells and lymphocytes at different organ sites (e.g. pancreas, salivary gland, and kidney) as well as obliterative phlebitis [6,7]. Serum IgG4 levels are often elevated and lesions respond well to steroid therapy [6,7]. However, the significant fibrosis typically present in IgG4-related sclerosing disease was not seen in either case, and both patients did not have other phenotypic features of this disease, despite increased absolute Ig4 counts and IgG4/IgG ratios by immunohistochemistry; serum IgG4 was not measured. In addition, pulmonary cavities have not been described in thoracic involvement of IgG4 disease [7,8]. Further studies are therefore