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## Case report

## Pulmonary nodular lymphoid hyperplasia presenting as multifocal subsolid nodules: A case report and literature review

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## ABSTRACT

Pulmonary nodular lymphoid hyperplasia (PNLH) is a rare, benign lymphoproliferative disease, which is characterized by nonclonal lymphoproliferation. PNLH is usually asymptomatic and usually detected incidentally on imaging studies. Common imaging findings include a solitary nodule, multiple nodules, or focal consolidation. Atypically, PNLH may present with persistent subsolid nodules, mimicking adenocarcinoma. Here, we report a rare case of PNLH presenting as multifocal subsolid nodules in both lower lobes. During follow-up, persistency and growth of the subsolid nodules suggested the possibility of malignancy. Wedge resection was performed bilaterally, and PNLH was confirmed on pathological examination.

## 1. Introduction

Pulmonary nodular lymphoid hyperplasia (PNLH) is rare benign spectrum of lymphoproliferative disorders, in which an abnormal proliferation of lymphoid cell lines infiltrates the lung parenchyma [1,2]. In 1983, Kradin et al. [3], first suggested the term nodular lymphoid hyperplasia, although the etiology and pathophysiology of PNLH remain unclear [1,4]. The most common findings of PNLH include either a solitary pulmonary nodule, multiple nodules, focal consolidation, or one or more masses. Atypically, PNLH may mimic adenocarcinoma, presenting as persistent subsolid nodules. Here, we report a rare case of PNLH presenting as multifocal subsolid nodules in both lower lobes. This study was approved by the Institutional Review Board of our hospital. The requirement for patient informed consent was waived because of the retrospective nature of the study.

## 2. Case report

A 53-year-old woman presented with an abnormal chest computed tomography (CT) taken during a routine health examination. She was a healthy non-smoker without any respiratory complaints. There was no medical history such as connective tissue disease or lymphoproliferative disease. Basic serologic test results were negative. Chest radiography showed no abnormality (Fig. 1). The initial chest CT revealed multiple irregularly shaped part-solid nodules or pure ground glass nodules (GGN) in the subpleural areas in both

; CT, Computed tomography; GGN, Ground glass nodule; LIP, Lymphoid interstitial pneumonia; NSIP, Non-specific interstitial pneumonia; PNLH, Pulmonary nodular lymphoid hyperplasia.

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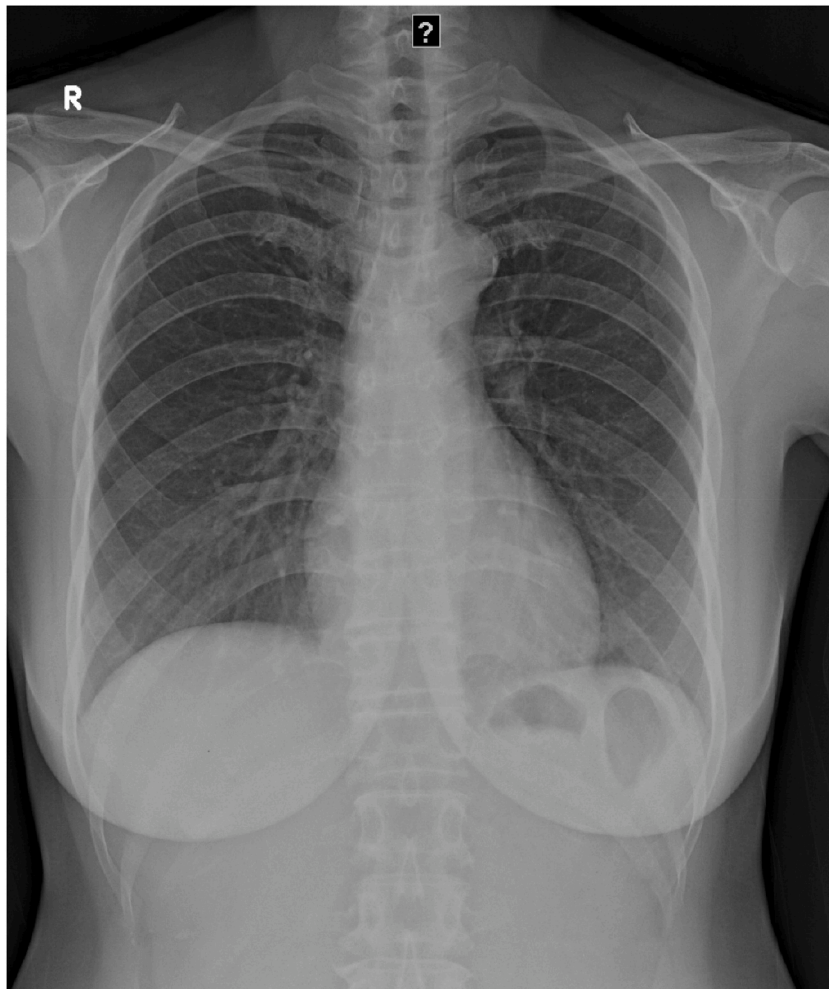
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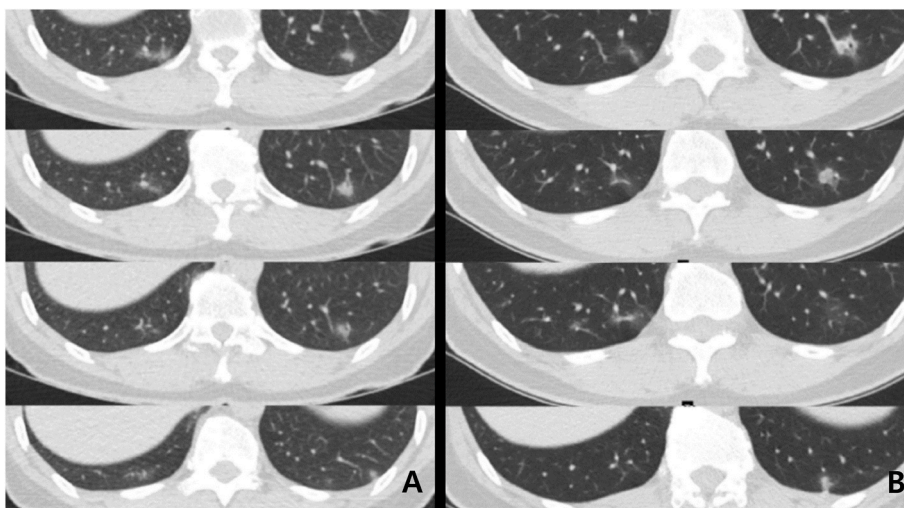
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lower lobes. The part-solid nodules in the left lower lobe measured approximately 10.1 mm and 7.6 mm, while the pure GGN, which was also visualized within the left lower lobe, measured approximately 6.2 mm. In the right lower lobe, the part-solid nodules measured approximately 12.7 mm and 10.2 mm. The pure GGN measured 6.1 mm and 3.5 mm. These features are shown in Fig. 2A. A follow-up chest CT 6 months later showed persistency of the multifocal subsolid nodules, and the largest part-solid nodule in the left lower lobe enlarged to 15 mm in size from approximately 10 mm. The differential diagnosis included early lung cancer, organizing pneumonia, and lymphoproliferative disease including MALT lymphoma (Fig. 2B). On the  $^{18}\text{F}$ -FDG PET/CT images, the largest lesion in the left lower lobe showed mildly increased FDG uptake (max SUV = 1.8) (Fig. 3). For diagnostic and therapeutic purposes, a wedge resection of the left lower lobe was performed. On gross examination, three ill-defined semitransparent nodules were found in the subpleural area, measuring 15 mm, 10 mm and 7 mm, respectively (Fig. 4). On microscopic examination, all three lesions visible on gross examination were relatively well-defined subsolid lesions under low power magnification (Fig. 5A). The lesions were composed of lymphocytes and fibrosis containing many reactive lymphoid follicles with some germinal centers (Fig. 5B). The alveolar spaces were relatively preserved, although fibrosis and lymphocytic infiltration were predominant towards the center. The lesions showed gradual transition to normal parenchyma, and at the periphery of the lesion, only a few lymphocytes infiltrated into the alveolar walls. However, there were no features of adenocarcinoma, such as nuclear atypia of alveolar cells, stromal invasion, or desmoplastic reaction. As the infiltrating lymphocytes were small to medium in size, formed follicles and germinal centers, follicular lymphoma, extranodal marginal zone B-cell lymphoma (MALToma), and a mass forming lymphoproliferative lesion such as IgG4-related disease were also included in the differential diagnosis. However, on immunohistochemistry, CD20 and CD3 showed reactive patterns in the lymphoid follicles and bcl-2 was negative in the germinal center; therefore, lymphoma was excluded from the diagnosis (Fig. 5C–E). Although plasma cells were present, IgG4 immunohistochemistry revealed only a few IgG4-labeled plasma cells (Fig. 6). Fibrosis within the lesion accounted for a lesser proportion when compared to the lymphocytic component, and was mostly loose fibrosis, which was different from the short storiform fibrosis typically associated with IgG4-related disease. Therefore, IgG4-related disease

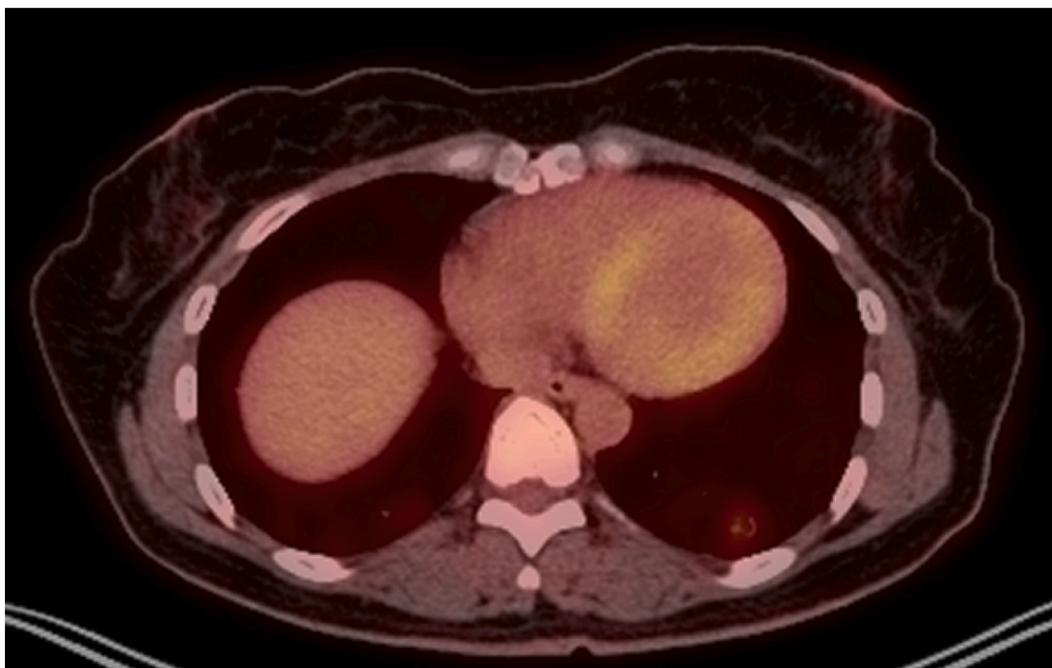


**Fig. 1.** Initial chest radiography  
The initial chest radiography shows no abnormality.



**Fig. 2.** Chest CT findings

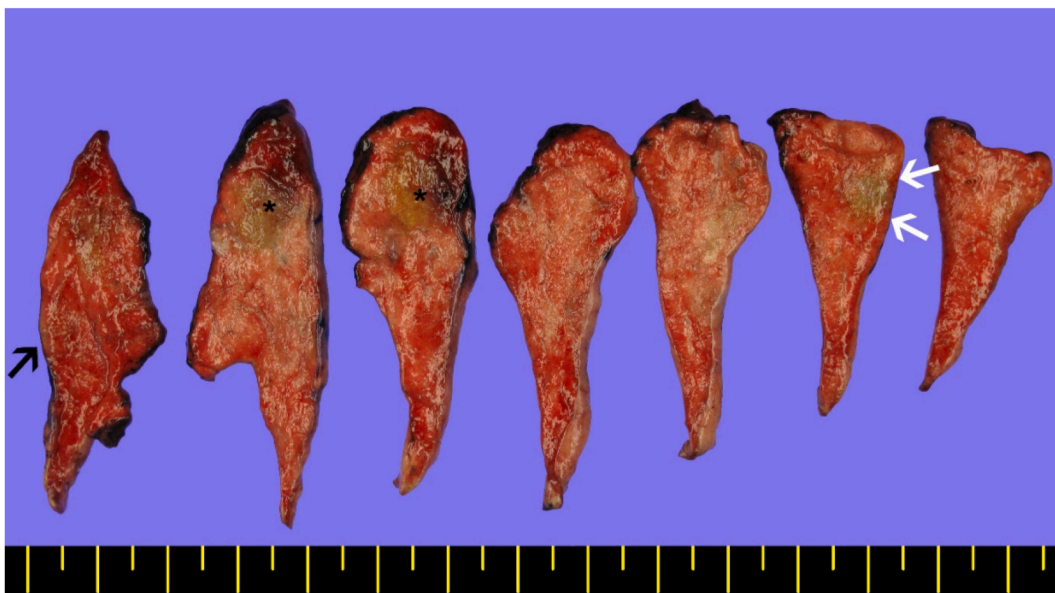
Initial chest CT (A) reveals multiple irregularly shaped part-solid nodules or pure ground glass nodules (GGN) in both lower lobe subpleural areas. A follow-up chest CT after 6 months (B) shows persistency of the multifocal subsolid nodules, and the largest part-solid nodule in the left lower lobe enlarged to 15 mm in size from about 10 mm.



**Fig. 3.**  $^{18}\text{F}$ -FDG PET/CT findings

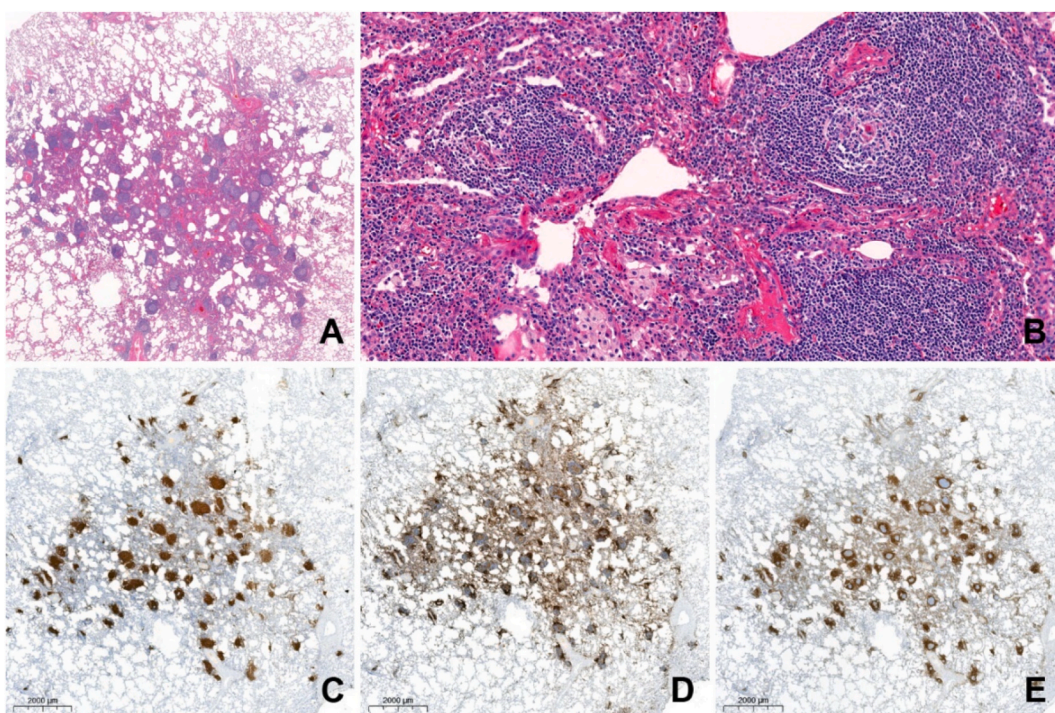
On the  $^{18}\text{F}$ -FDG PET/CT scan, the largest lesion in the left lower lobe shows mildly increased FDG uptake (max SUV = 1.8).

was excluded. In conclusion, a final diagnosis of PNLH was rendered. Among the multiple lesions, smaller lesions that were matched with pure GGNs on chest CT showed a very low number of lymphoid follicles within the lesion (Fig. 7A), whereas larger lesions, which appeared to be part-solid nodules, showed more densely packed lymphoid follicles and central fibrosis (Fig. 7B). The background lung tissue showed unremarkable findings. After 3 weeks from the initial wedge resection of the left lower lobe, lesions seen in the right lower lobe were also removed by wedge resection. Three ill-defined yellow to whitish lesions were found on gross examination in the subpleural area measuring 17 mm, 12 mm, and 6 mm, respectively. Microscopic findings were compatible with PNLH.



**Fig. 4.** Gross examination of the wedge resection specimen

Serially cut wedge resection specimen of left lower lobe. Three ill-defined white to yellowish, semitransparent nodules are seen in the subpleural area. The black arrow, \*, and white arrow indicate pulmonary nodular hyperplasias of 7 mm, 15 mm, and 10 mm, respectively.

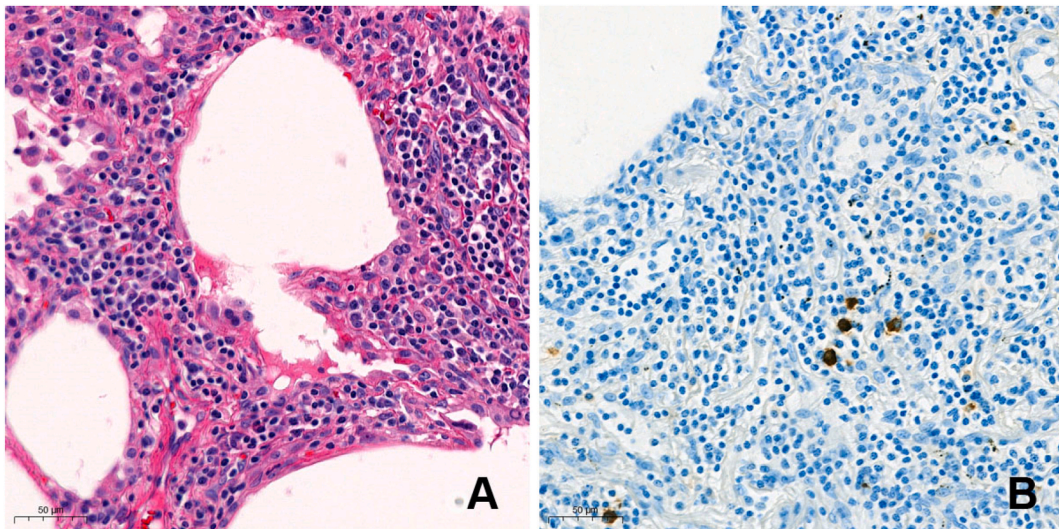


**Fig. 5.** Histology and immunohistochemistry of pulmonary nodular lymphoid hyperplasia

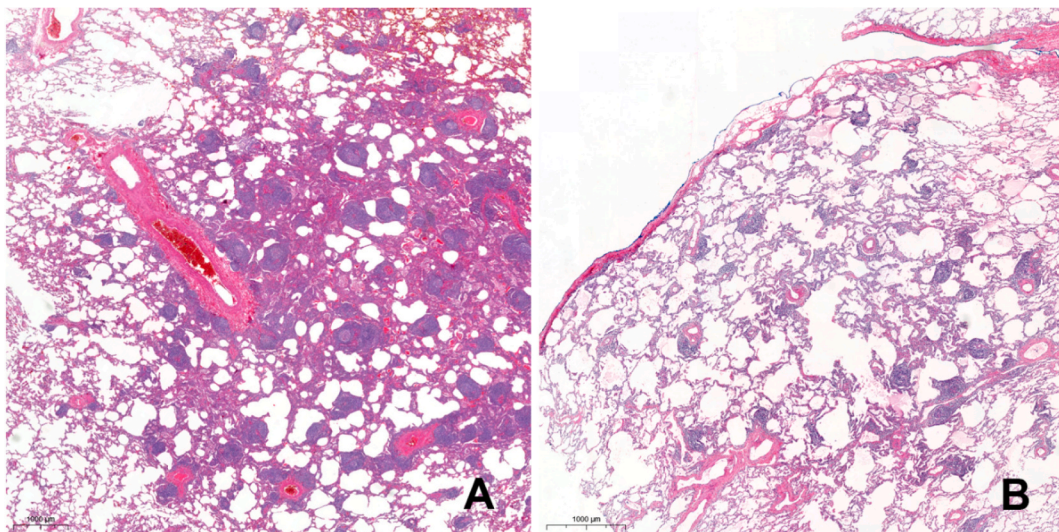
(A) Under low magnification, pulmonary nodular lymphoid hyperplasia (PNLH) presents as a partly solid nodular lesion that can be discriminated from the adjacent normal parenchyma.

(B) On high power view, PNLH consists of lymphoid follicles with germinal centers, fibrosis, and lymphoplasmic cells.

CD20 (C), CD3 (D), and bcl-2 (E) immunohistochemical staining reveal a reactive pattern in the lymphoid tissue.



**Fig. 6.** Higher magnification view of infiltrating plasma cells and IgG4 immunohistochemistry. Plasma cells are frequently seen within the pulmonary nodular lymphoid hyperplasia (A), IgG4 immunohistochemical staining labels only rare plasma cells (B).



**Fig. 7.** Scan power view of pulmonary nodular lymphoid hyperplasias: Comparison of part-solid nodules with pure ground glass nodules. (A) Pulmonary nodular lymphoid hyperplasia (PNLH) recognized as a part-solid nodule on chest computed tomography (CT). (B) PNLH seen as a pure ground glass nodule on chest CT. Note the dense proliferation of lymphoid follicles and central fibrosis of the left-sided PNLH (A) compared with the sparsely scattered lymphoid follicles and lack of fibrosis of the right-sided PNLH (B).

### 3. Discussion

PNLH is a rare benign lymphoproliferative lesion of the lung and has been thought to be a reactive hyperplasia of bronchus-associated lymphoid tissue [5]. Nodular lymphoid hyperplasia is rare, and its pathogenesis has not yet been well established. Usually, PNLH is asymptomatic but occasionally cough, shortness of breath, and chest pain can occur [1]. The mean age at diagnosis is approximately 60 years old with similar prevalence in both genders [5]. Major imaging findings of PNLH include a well-circumscribed single nodule, multiple nodules, and a mass or consolidation 0.6–6 cm in size [1,6]. Atypically, PNLH may present as either one or more ground glass opacities, one or more subsolid nodules, or a combination of both [7]. Most radiological findings are persistent, slowly growing, or both, and commonly mimic adenocarcinoma, metastasis, or lymphoma. As a result, surgical resection is often indicated and performed [8]. Pathologically, PNLH is characterized by florid germinal centers with interfollicular fibrosis and plasma cells [5,7]. Associations with IgG4-related disease are suggested but are still controversial [9,10]. Among the neoplastic lymphoproliferative pulmonary lesions, differential diagnosis of PNLH includes extranodal MALToma, which has overlapping histomorphologic features: a mixed population of lymphoid cells with abundant plasma cells [11]. However, PNLH shows polyclonality,

whereas extranodal MALToma presents with monoclonal tumor cells [5,10]. Other non-tumor lesions, including follicular bronchiolitis, lymphoid interstitial pneumonia (LIP), and non-specific interstitial pneumonia (NSIP) may also be differential diagnoses. LIP is characterized by diffuse alveolar widening caused by dense infiltration of lymphocytes, plasma cells, and histiocytes [12]. NSIP shows diffuse lymphocytic infiltration and lymphoid follicles; germinal centers can also be present in the presence of a connective tissue disease [13]. The growth patterns in both LIP and NSIP are different that of PNLH, given that they are diffuse and involve the whole lung, rather than “nodular” in appearance. Follicular bronchiolitis is a lymphoid follicular hyperplasia with a germinal center distributed along the bronchiolar walls [12]. It has a similar cellular element and growth pattern but the location differs; PNLH is usually located in the subpleural area [4,7]. While PNLH manifests as a benign proliferative disease, surgical resection is still the treatment of choice [8]. The prognosis after surgical resection is excellent without recurrence [2].

In conclusion, we reported a rare case of PNLH that involved bilateral lung and showed unusual radiologic presentation.

### Declaration of competing interest

None.

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