CASE REPORT

Suspected *Aspergillus* nodule histologically consistent with pulmonary nodular lymphoid hyperplasia : a case report

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Abstract : *Aspergillus* nodules (AN) are an unusual form of chronic pulmonary aspergillosis. On the other hand, pulmonary nodular lymphoid hyperplasia (PNLH) is classified as a reactive pulmonary lymphoproliferative disorder. A 65-year-old male was referred to our hospital due to a nodule in the left upper lobe. Histologically, a mixture of prominent lymphoid follicular formation, and hyaline necrosis were observed. Grocott staining revealed morphological forms of *Aspergillus* spp. in the necrosis. The final clinical diagnosis was suspected AN histologically consistent with PNLH. This case suggests that there may be PNLH cases in which local infection with *Aspergillus* contributes to its pathophysiology. J. Med. Invest. 70 : 499-502, August, 2023

Keywords **:** *Aspergillus nodule, pulmonary nodular lymphoid hyperplasia, bronchus-associated lymphoid tissue*

INTRODUCTION

Aspergillus spp. resides in natural environments and can form various lung lesions depending on the immune function of the host and the presence or absence of underlying lung disease. Chronic pulmonary aspergillosis (CPA) in immunocompetent patients is usually triggered by infection in pre-existing cavitary lesions, but, in rare cases, isolated or multiple nodule(s) without cavitation occur in the patients without underlying lung disease. This type of CPA is classified as an *Aspergillus* nodule (AN) and is often resected on suspicion of lung cancer (1). We report the first case of an isolated, provable AN that was histologically consistent with pulmonary nodular lymphoid hyperplasia (PNLH).

CASE REPORT

A 65-year-old asymptomatic male smoker (45 pack-years) was referred to our hospital due to a solitary nodule with calcification in the left upper lobe detected during a medical check-up. Computed tomography (CT) showed the nodule was an irregular shape, with spotty internal calcification and an indistinct surrounding ground-glass opacity (Fig. 1A-C). He had no history of allergic diseases. Initial laboratory data were as follows : white blood cell count 6030/μL (neutrophils, 63.4% ; eosinophils, 0.3%) ; C-reactive protein 0.06 mg/dL ; sialyl Lewis X-1 38 (< 39) U/mL ; CYFRA 21-1 1.0 (< 3.5) ng/mL ; pro-gastrin-releasing peptide 54.4 (< 81) pg/mL ; *Aspergillus* galactomannan antigen value 0.1 (> 0.5 cut-off index). An interferon-gamma release assay (IGRA), IgA antibody test against *Mycobacterium avium* complex glycopeptidolipid and *Aspergillus*-specific precipitating antibody were negative. The other laboratory tests results are shown in Table1. The nodule had slightly increased in size compared to CT images taken at another facility three years earlier, which was thought to be a post-inflammatory change (Fig. 1D). No other lesions were observed on whole-body contrast-enhanced CT. The maximum standardized uptake value of the nodule measured by ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) was 1.1 (Fig. 1E), but two diagnostic radiologists at separate institutions considered the nodule to be a primary lung cancer because of its slow growth and surrounding ground-glass opacity. Although calcification within pulmonary nodules is generally considered a positive finding for chronic inflammation, the negative IGRA result virtually ruled out pulmonary tuberculoma. Moreover, it was reported that calcification was detected on CT in 5.4% of primary lung cancers and 9.1% when limited to adenocarcinomas (2). Therefore, we determined that the nodule was most likely lung cancer. However, bronchoscopic examination did not lead to a definitive diagnosis. The patient agreed to a surgical biopsy to obtain an early and accurate diagnosis and underwent video-assisted thoracoscopic partial lung resection for suspected lung cancer. Histologically, a mixture of prominent lymphoid follicular formation, and hyaline necrosis in and around the airways with calcification were observed continuous with the bronchiole (Fig. 2A-C). Atrophic germinal centers surrounded by an expanded mantle zone, polytypic plasmacytosis in the interfollicular space, and vascular proliferation in the follicles and interfollicular region were not observed, suggesting that the lesion was not due to Castleman's disease (Fig. 2D-E). A few neutrophils were observed in the necrosis, but there was no eosinophilic infiltration. No fibrous capsule formation was observed. An immunocytochemical study demonstrated tightly packed CD20-positive B-cells predominantly within follicles (Fig. 2F), and Bcl-2-positive lymphocytes outlining the follicles (Fig. 2G), showing a reactive pattern with a mixed population of lymphocytes. These findings were compatible with PNLH. Interestingly, Grocott staining revealed septate hyphae with acute-angle branching compatible with morpholog-

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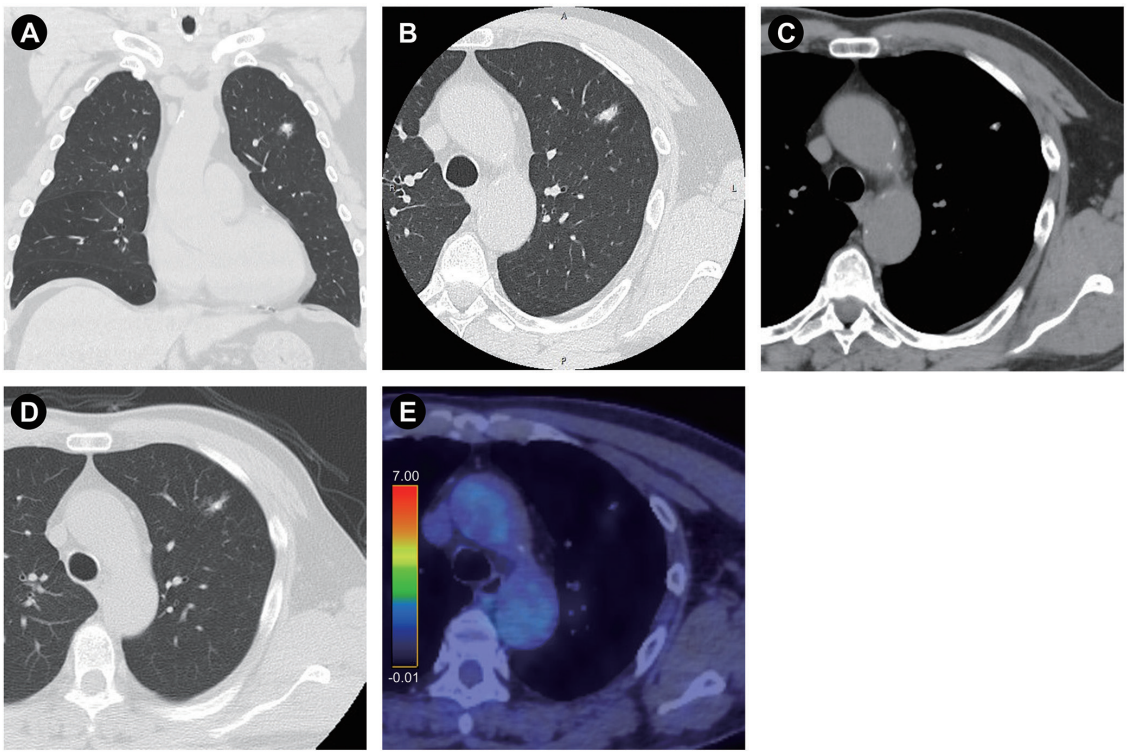

Fig 1. Chest CT images. (A-C) A solitary nodule with calcification in the left upper lobe. (D) An image of the nodule taken at another facility three years earlier. (E) ^{18}F-FDG-PET/CT.

Table 1. Laboratory data

Hematology		Alb	4.5 g/dL	Urinaly test	
RBC	507×10^4/μL	CRP	0.06 mg/dL	gravity	1.022
Hb	17.0/dL	HbA1c	5.4%	pH	6.0
WBC	6030/μL	BG	103 mg/dL	protein	(1+)
Neutrophils	63.4%	sialyl Lewis X-1	38 U/mL	glucose	(−)
Lymphocytes	29.5%	CYFRA 21-1	1.0 ng/mL	urobilinogen	(+/−)
Eosinophils	0.3%	pro-gastrin-releasing peptide	54.4 pg/mL	bilirubin	(−)
Monocytes	6.1%	Rheumatoid factor	11 U/mL	ketones	(−)
Basophils	0.7%	*Aspergillus* galactomannan antigen value	0.1		
Plt	21.0×10^4/μL				
Biochemistry		Immunology			
AST	24 IU/L	IgG	727 mg/dL		
ALT	37 IU/L	IgA	117 mg/gL		
ALP	203 IU/L	IgM	52 mg/dL		
LDH	193 IU/L	IgG4	36.7 mg/dL		
γGTP	72 IU/L	*Aspergillus*-specific precipitating antibody	negative		
T-Bil	0.78 mg/dL				
BUN	14.3 mg/dL	Interferon-gamma release assay (T-SPOT.TB)	negative		
Creatinine	0.78 mg/dL				
Na	139.0 mEq/L	IgA antibody test against *Mycobacterium avium* complex glycopeptidolipid	negative		
K	3.6 mEq/L				
TP	6.8 g/dL				

RBC : red blood cell, Hb : hemoglobin, WBC : white blood cell, Plt : platelet, AST : aspartate amino transferase, ALT : alanine amino transferase, LDH : lactate dehydrogenase, γGTP : gamma-glutamyl transpeptidase, T-Bil : total bilirubin, BUN : blood urea nitrogen, Na : sodium, K : potassium, TP : total protein, Alb : albumin, CRP : C-reactive protein, BG : blood glucose.

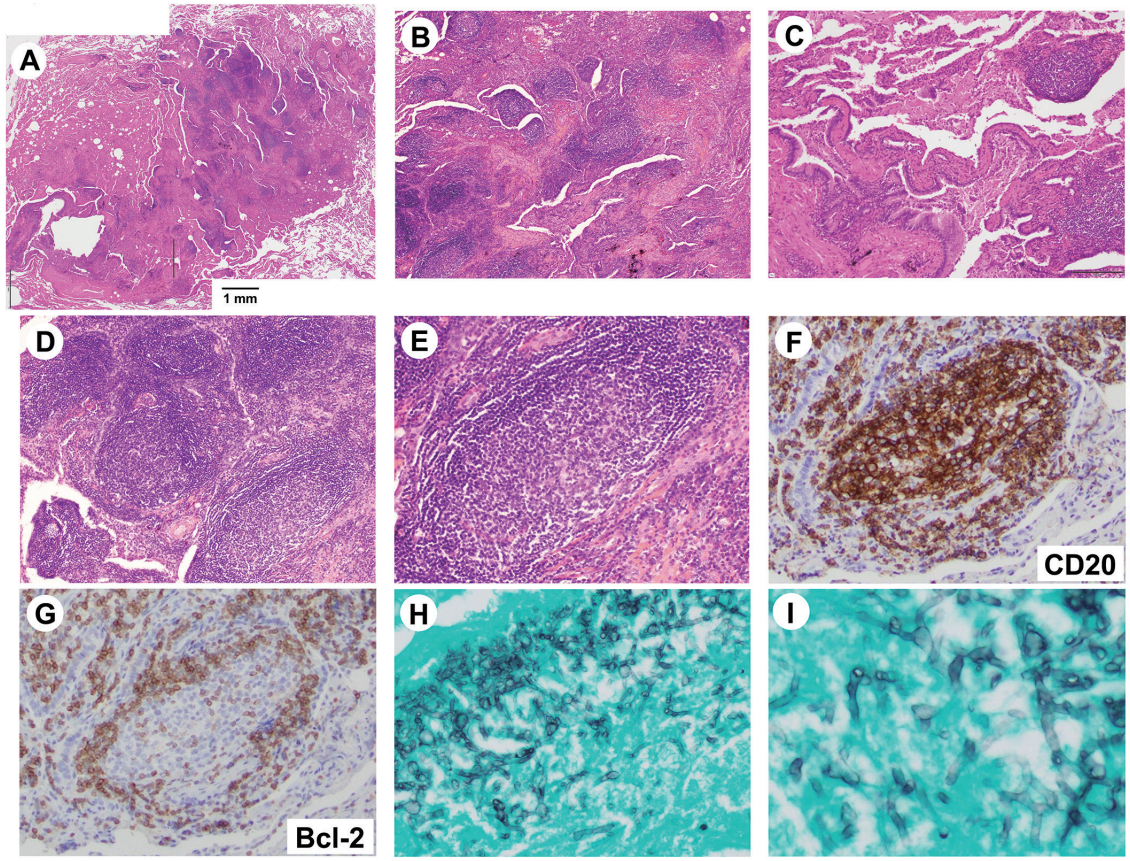

Fig 2. Histology of a biopsy specimen (A-E : hematoxylin and eosin staining, F-G : immunohistochemical staining, H-I : Grocott staining, A-B : low-power field, C-D : medium-power field, E-I : high-power field). (A-C) A mixture of prominent lymphoid follicular formation, and hyaline necrosis in and around the airways. (D-E) Lymphoid follicles and interfollicular region (F) Tightly packed CD20-positive B-cells predominantly within reactive follicles. (G) Bcl-2-positive lymphocytes outlining the follicles. (H-I) Septate hyphae with acute-angle branching compatible with morphological forms of *Aspergillus* spp.

ical forms of *Aspergillus* spp. in the necrosis (Fig. 2H-I) without invasion into surrounding tissues. No neoplastic cells were present in the resected specimen. A real-time polymerase chain reaction test for *Aspergillus* spp. (BML, Inc., Tokyo, Japan) of the paraffin embedded tissue failed to detect the microorganism due to insufficient DNA extraction. No antifungal medications were administered, and there has been no recurrence one and a half years after resection.

DISCUSSION AND CONCLUSIONS

Since identification of fungi detected in the nodule was not successful, the possibility of infection with fungi with branching septate hyphae other than *Aspergillus*, such as *Trichosporon* or *Mucor*, could not be ruled out. However, pulmonary mucormycosis and trichosporonosis generally occur in immunocompromised patients and progress rapidly with tissue invasion if left untreated (3, 4). Trichosporonosis usually presents with diffuse consolidation or multiple patchy shadows (3). Mucormycosis shows a variety of multiple shadows, and the reverse halo sign is observed at initial imaging in the majority of patients (4). Our patient, without underlying disease, had a solitary slowly-growing nodule and filamentous fungi were detected in the nodule, suggesting CPA in an immunocompetent patient.

One or more nodules (< 3 cm), which do not usually cavitate, are an unusual form of CPA and are defined as AN. Although histological studies are inadequate, AN is not necessarily an independent category and is thought to overlap with other types of CPA. Central necrosis is frequent, but tissue invasion is not demonstrated in AN (1). One-third of patients with AN have a single lesion, but most patients with AN, including these patients, complain of cough and/or dyspnea (5). The natural history of AN has not been clarified, but non-resected cases with clinical symptoms, high *Aspergillus*-specific IgG antibody titers or with *Aspergillus* detected in respiratory specimens are treated with antifungal agents. On the other hand, antifungal agents are not usually administered in resected cases (5). Therefore, postoperative treatment with antifungal agents was not given to our patient.

PNLH is a rare benign localized lesion classified as a reactive pulmonary lymphoproliferative disorder. PNLH is generally found incidentally in asymptomatic adult patients by routine chest radiograph or CT. Two-thirds of patients have solitary lesions, and most lesions are solid or subsolid and less than 3 cm in diameter (6). The differential diagnosis of PNLH includes lung cancer, metastatic tumor, and primary lymphoma, which can present with similar radiological findings and ultimately require surgical biopsy. Histologically, it consists of a prominent proliferation of lymphoid tissue, including abundant follicles with a germinal center without infiltration by interfollicular cells. The interfollicular cells are composed of small lymphocytes and plas-

ma cells without cytologic atypia. As in this case, CD20-positive B cells are abundant in lymphoid follicles, whereas germinal center B cells do not co-express Bcl-2. PNLH is regarded as a nodular hyperplastic lesion of bronchus-associated lymphoid tissue (BALT) (7). Resection of the nodule(s) is the only treatment for patients with PNLH, and recurrence has not been reported in resected cases (6). In fact, no recurrence has been observed in our case. Recently, a case of PNLH presenting as multiple subsolid nodules in both lungs was reported in which all six foci were surgically resected (8). Even so, to the best of our knowledge, there are no reports on the prognosis of non-resected PNLH cases.

Although several cases of PNLH with autoimmune disease, histologically suspected as actinomyces infection, and history of tuberculosis treatment have been reported, the details of its etiology have not been fully elucidated (9-11). Chronic inflammatory conditions and various infectious diseases, including pneumocystis infection, are known to induce BALT ectopically (12, 13). In addition, lymphoid follicles were observed in a resected specimen from a patient with allergic bronchopulmonary aspergillosis (14). However, there are no reports of PNLH related to *Aspergillus* spp. infection.

The detailed mechanism is unknown, but this case suggests that there may be PNLH cases in which local infection with *Aspergillus* contributes to its pathophysiology. While the pathological presentations of chronic pulmonary aspergillosis are diverse, it can be sometimes difficult to detect *Aspergillus* spp. by hematoxylin and eosin staining alone. Further research into the involvement of pathogenic microorganisms in PNLH is needed.

CONFLICT OF INTEREST

The authors declare no competing interests.

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