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Case Series

Five cases of pulmonary *Aspergillus* nodules diagnosed at surgery and by pathology in immunocompetent patients, with a literature review

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***Abstract*:** A pulmonary *Aspergillus* nodule is a rare subtype of chronic pulmonary aspergillosis. The diagnosis is difficult and is histological. There are only a few reports on such cases. Here, we report five cases of pulmonary *Aspergillus* nodules confirmed by surgery and pathology in immunocompetent patient and review the literature. Among the five patients in this group, three were females and two were males, aged 44–73 years old. Two cases had hemoptysis onset, and three cases were found to have a slow disease course on chest CT during imaging, ranging from months to years. The white blood cell count, carcinoembryonic antigen, and blood Galactomannan (GM) tests in five cases were all within normal range. Four cases had normal blood C-reactive protein, and one case had an increase. On imaging, there were two cases in the upper lobe of the right lung, two cases in the lower lobe of the left lung, one case in the upper lobe of the left lung, three cases were solitary nodular shadows, and two cases were nodular shadows with cavity formation, including one case with calcification, four cases with bronchial dilation shadows, and one case with gas containing cavity shadows. Five cases were treated with surgical resection and confirmed by histopathological examination. All five patients did not receive antifungal treatment after surgery, and there was no recurrence of Aspergillus nodules during regular follow-up.

Plain language summary

Report 5 cases of pulmonary aspergillosis nodules confirmed by histopathology after surgical resection.

Pulmonary aspergillosis nodules are a relatively rare manifestation in the spectrum of chronic pulmonary aspergillosis. This article reports five cases of pulmonary aspergillosis nodules confirmed by surgical resection and histopathological examination, all of which were patients with normal immune function, atypical clinical symptoms, varying severity, and normal Galactomannan (GM) tests. All five cases did not receive antifungal treatment after surgery, and the nodules did not recur during regular follow-up. The diagnosis of pulmonary aspergillosis nodules is difficult, and lung biopsy and bronchoalveolar lavage fluid (BALF) metagenomics next generation sequencing (mNGS) may be considered. There are various treatment methods, including surgical treatment, antifungal drug therapy, and sometimes local bronchial perfusion therapy can also be considered.

Keywords: *Aspergillus*, *Aspergillus* nodule, chronic pulmonary aspergillosis

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Introduction

Chronic pulmonary aspergillosis (CPA) is a serious slowly progressing lung disease in the pulmonary aspergillosis spectrum. It often occurs in patients with underlying lung diseases or mild immunodeficiency, and even in patients with normal immune function. Among the five recognized subtypes of CPA, pulmonary *Aspergillus* nodules are rare. On imaging, there are one or more nodules with or without cavities. Most are <3 cm in diameter, although lesions are occasionally larger with necrotic centers.[1] They are nonspecific and difficult to distinguish from lung cancer, metastasis, cryptococcal nodules, and tuberculosis. Recently, Denning *et al.* reported that fewer than 10% of the cases reported to the national aspergillosis center were *Aspergillus* nodules.[2] They can only be diagnosed histologically based on the presence of fungal hyphae without tissue invasion.[3,4] We provide five cases of pulmonary *Aspergillus* nodules and review the literature in the hope of improving clinicians' understanding of the disease.

Case data

Case 1: A 73-year-old man with diabetes complained of recurrent hemoptysis once or twice a year for more than 50 years. There was at most 50 ml of hemoptysis. Two months before presentation, he was misdiagnosed with pulmonary tuberculosis and treated with antituberculosis drugs. When the hemoptysis recurred, he presented to our hospital for treatment. Chest computed tomography (CT) showed a mass-like lobulated high-density shadow in the right upper lung segment measuring 33 × 27 mm, with a peripheral bronchiectasis shadow and thin, patchy peripheral exudation shadows [Figure 1(a)]. The C-reactive protein (CRP) was 22.2 mg/L and the immunoglobulin E 739.7 (normal 0–87) kU/L. The serum galactomannan antigen (GM) and blood carcinoembryonic antigen were normal.

Despite antibiotic treatment and hemostatic agents, the hemoptysis recurred. He had the right upper lung lobe resected under general anesthesia on 29 November 2012. At surgery, there was obvious adhesion of the right upper pleura, a 3-cm mass in the right upper lung with a distinct boundary, and no pleural invasion. Pathology showed an inflammatory right upper lung lesion accompanied by necrosis, with many tissue cells and multinucleated giant cell reactions in the stroma, fungi in the bronchial lumens, and reactive hyperplasia of four lymph nodes at the bronchial root accompanied by many dead bacteria-like objects [Figure 1(b)]. Periodic acid Schiff (PAS) staining was positive (+), which indicates fungal hyphae in the tissue sample. The diagnosis was a right upper lung *Aspergillus* nodule. He was not given antifungal treatment postoperatively. There was no recurrence at the 5-year follow-up.

Case 2: An otherwise healthy 50-year-old rural woman complained of repeated hemoptysis 2–3 times annually for 10 years. She was diagnosed with pulmonary tuberculosis in a local hospital

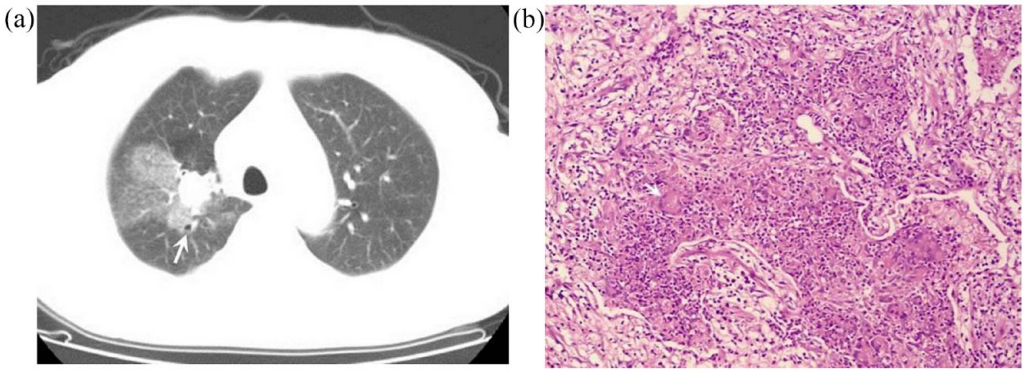

Figure 1. (a) Chest CT shows a mass like high-density shadow in the apical segment of the right upper lung, with a diameter of about 33 mm × 27 mm. Bronchiectasis shadow (see arrow) is seen in the periphery, lobulated change, and thin flake, and patchy exudation shadow is seen around. (b) 'Right upper lung' inflammatory lesion with necrosis, a large number of histiocytes and multinucleated giant cell reaction in the stroma (see arrow), and fungal flora (Hematoxylin-Eosin staining HE ×100) in the lumen of the bronchi.

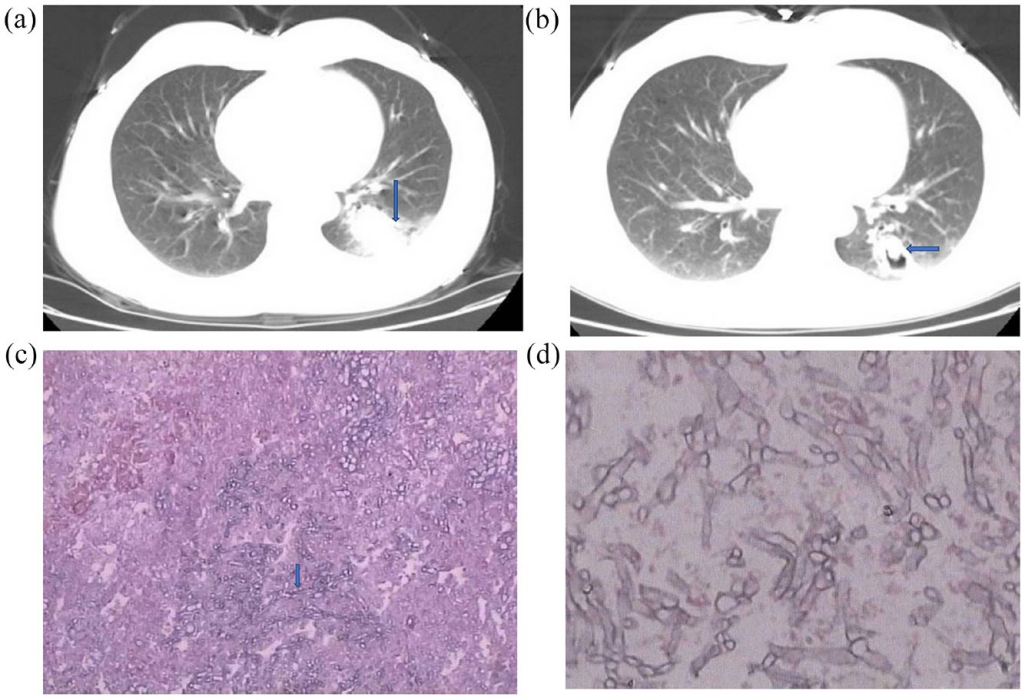

Figure 2. (a) Chest CT: the lower lobe of the left lung is patchy and surrounded by fuzzy flocculent shadow (see arrow). (b) Chest CT: left lower pulmonary nodule with cavity formation with a diameter of about 16 mm × 32 mm (see arrow). (c) 'Left lower lung' mycosis with bronchiectasis, a large number of inflammatory cells and multinucleated giant cell reaction in the lung stroma, and a large number of fungal flora can be seen in the bronchial lumen (see arrow) (HE ×100). (d) **Hyaline** fungal hyphae and acute branching (HE ×400).

and treated with antituberculosis agents for 6 months. The hemoptysis recurred 5 days before coming to our hospital, with a volume of 30–50 mL/day. Chest CT showed a mass shadow in the left lower lung surrounded by a fuzzy flocculent shadow [Figure 2(a)]. Bronchoscopy examination showed congestion, edema, and bronchial mucosa stenosis in the left lower and outer basal segments; the lavage fluid was normal. Blood CRP and GM and carcinoembryonic antigen were normal.

After 10 days of antibiotic treatment, repeat chest CT showed a left lower lobe nodule with cavity formation [Figure 2(b)]. She underwent a left lower lobectomy under general anesthesia on 20 May 2013. During the operation, a 1.5-cm mass with an indistinct boundary was found in the left lower lobe. Pathology showed left lower lung mycosis with bronchiectasis, many inflammatory cells and a multinuclear giant cell reaction in the lung stroma, and many fungi in the bronchial lumen [Figure 2(c)]. After magnification, hyaline hyphae with acute branching can be seen [Figure 2(d)]. The diagnosis was a left lower lung *Aspergillus* nodule. There was no postoperative antifungal treatment and no recurrence at the 5-year follow-up.

Case 3: An otherwise healthy 68-year-old housewife had repeated hemoptysis for more than 1 year, with blood filaments in her sputum. Fifteen days before admission, the hemoptysis recurred and she came to our hospital for treatment. Chest contrast-enhanced CT showed a high-density 11 mm × 13 mm nodule at the right pulmonary apex; its surface was irregular, with a surrounding bronchodilation shadow [Figure 3(a)]. No abnormality was seen at bronchoscopy. Blood CRP, carcinoembryonic antigen, and serum GM were normal.

After treatment with antibiotics and hemostatic agents, the hemoptysis recurred. A wedge resection of the right upper lung was performed under general anesthesia on 26 October 2011. At surgery, dense adhesions were seen at the top of the right lung, and the right upper lobe contained a

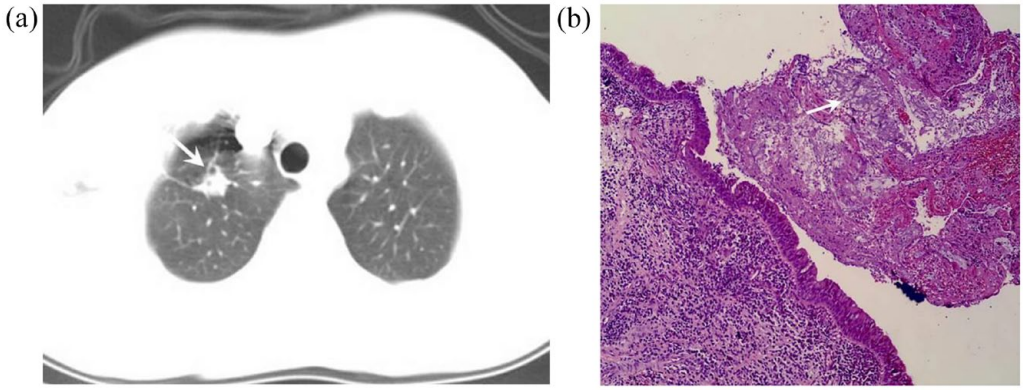

Figure 3. (a) Chest CT: a high-density nodular shadow with a diameter of about 11 mm × 13 mm can be seen in the right upper lung apex, the surface is not smooth, and bronchiectasis shadow can be seen around it (see arrow). (b) The bronchiectasis of the right upper lung is accompanied by fibrosis of surrounding lung tissue, a large number of lymphocytes and plasma cells infiltrate, a large number of foam like tissue cells in the alveolar cavity, and a fungus group (see arrow) in the expanded bronchoalveolar cavity (HE ×100).

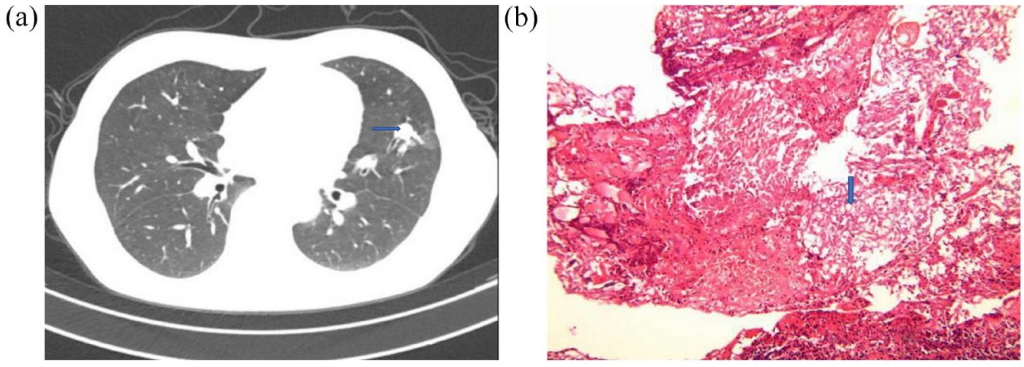

Figure 4. (a) Chest CT lung window: a high-density nodule with a diameter of about 11 mm × 13 mm with calcification can be seen in the left upper lung lingula segment, the surface is not bright, and bronchiectasis shadow can be seen around (see arrow). (b) Fungal mass resembling Aspergillus (see arrow) in the lumen of the 'left upper lung tongue' branch, accompanied by inflammatory changes in the surrounding lung tissue and local regional lymphoid tissue hyperplasia (HE ×100).

medium-hard 1.5 cm × 1.5 cm nodule, with a distinct boundary. Pathology showed right upper lung bronchiectasis with peripheral lung tissue fibrosis, many infiltrating lymphocytes and plasma cells, many foam-like tissue cells in the alveolar cavity, and fungi in the expanded bronchi cavity [Figure 3(b)]. The tissue was PAS (+), which indicates fungal hyphae in the tissue sample. The diagnosis was a right upper pulmonary aspergillosis nodule. There was no postoperative antifungal treatment and no recurrence at the 5-year follow-up.

Case 4: An otherwise healthy 64-year-old man underwent chest CT, which showed a left upper lung nodule. He was followed regularly for more than 2 years. Four days before admission, the chest CT showed that the calcified left upper lung lingual nodule had grown. Enhanced chest CT showed an 11 mm × 13 mm high-density nodule with calcification in the lingual segment of the right upper lung, with peripheral bronchiectasis [Figure 4(a)]. The blood CRP, carcinoembryonic antigen, and serum GM were normal.

On 8 November 2017, the patient underwent thoracoscopic resection of the left upper lung lingual segment under general anesthesia. At surgery, there were no chest adhesions, and no obvious mass was detected in the left upper lung.

Pathology showed fungal hyphae in the bronchi of the left upper lung lingual segment accompanied by inflammatory changes in the surrounding lung tissue and local regional lymphoid tissue hyperplasia [Figure 4(b)]. The diagnosis was an *Aspergillus* nodule in the left upper lung. There was no postoperative antifungal treatment and no recurrence at the 4-year follow-up.

Case 5: An otherwise healthy 44-year-old woman underwent chest CT 3 years before admission that showed an 8-mm-diameter cavity shadow in the left lower lung [Figure 5(a)]. The lesion was followed by regular chest CT. One month before admission, chest CT showed a cystic cavity in the lower lobe of the left lung with the formation of medial wall nodules, and the focus was enlarged compared with the previous CT [Figure 5(b)]. Whole-body positron emission tomography (PET)-CT showed an air-containing cavity in the anterior basal segment of the left lower lobe with mural nodules, increased glucose metabolism, and a standardized uptake value of 3.3. Tracheoscopy examination and the bronchoalveolar lavage GM, and blood GM tests were normal. *Aspergillus* Immunoglobulin G (IgG) antibody was 81 (normal 0–80) AU/mL. Blood CRP and carcinoembryonic antigen were normal.

On 24 August 2021, she underwent thoracoscopic wedge resection of the left lower lung under general anesthesia. During the operation, some adhesions were seen in the chest. After cutting the specimen, a spherical 5-mm-diameter lesion was found in the cavity. The postoperative pathology showed cystic bronchiectasis, pus in the cystic cavity, including fungal hyphae, peripheral fibrosis, and many lymphocytes, plasma cells, and neutrophils, accompanied by multinucleated giant cell reaction and lymphoid tissue hyperplasia [Figure 5(c)]. The staining was PAS (+), silver hexamine (+), and mycobacterium acid fast staining (–). The diagnosis was a left lower lobe *Aspergillus* nodule. There was no postoperative antifungal treatment and no recurrence at the 1-year follow-up.

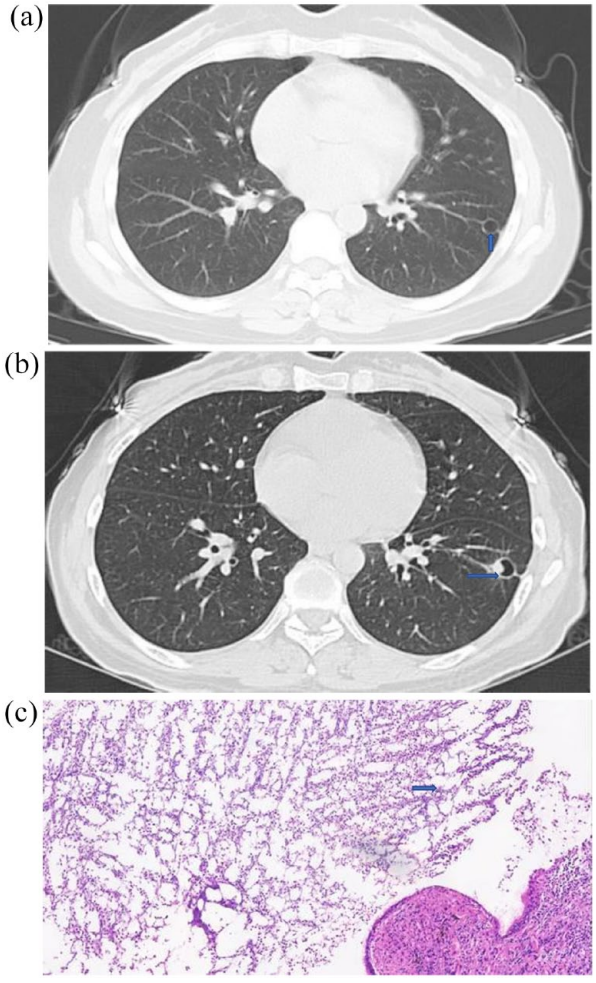

Figure 5. (a) Chest CT in 2018 shows 8-mm circular translucent shadow with surrounding fibrous strip shadow in the left lower lung (see arrow). (b) 2021-7-30 chest CT: the lower lobe of the left lung is like a circular high transparency shadow, with a size of about 12 mm × 13 mm. There is a nodular shadow protruding into the cavity on the inner wall (see arrow). (c) 'Wedge-shaped specimen of left lower lung' (HE × 100): cystic bronchiectasis, pus in the cystic cavity, containing fungal mass resembling Aspergillus (see arrow), peripheral fibrosis, infiltration of a large number of lymphocytes, plasma cells, and neutrophils, with multinuclear giant cell reaction and lymphoid tissue hyperplasia.

Discussion

The majority of patients with *Aspergillus* nodules have underlying diseases.[2,5] In our series, one patient had diabetes, while the remaining four had no underlying disease. They had no history of immune deficiency such as tumor, hormone use and other immunosuppressant diseases (Table 1). The incidence rate of the disease in men and women is not clear. In a retrospective study of pulmonary aspergillosis, Denning *et al.* reported the incidence was slightly higher (54.5%) in males, with an average age of 58 years.[2] By contrast, Kang *et al.* found 46 (58%) of 80 aspergillosis nodules in women.[5] The natural course of the disease is not clear, but it is chronic, which may be related to the immune state, ranging from months to years.[2] Our patients' age range is

Table 1. General clinical characteristics of five cases.

General situation	Case 1	Case 2	Case 3	Case 4	Case 5
Gender	Male	Female	Female	Male	Female
Age (years)	73	50	68	64	44
Underlying diseases	Diabetes	None	None	None	None
Symptom	Hemoptysis	Hemoptysis	Hemoptysis	None	None
Previous treatment	Antituberculosis treatment	Antituberculosis treatment	Anti-inflammatory therapy	Follow-up	Follow-up

Table 2. Laboratory examination of five cases.

Auxiliary inspection	Case 1	Case 2	Case 3	Case 4	Case 5
Leukocyte ($\times 10^9$/L)	8.0	5.5	5.5	5.4	4.4
Blood CRP (0–8 mg/L)	22.2	4.2	1.7	6.4	0.4
Serum GM 0–0.5)	0.254	0.330	0.432	0.210	0.140
Purified protein derivative test	Negative	Negative	Negative	Negative	Negative

between 44 and 73 years old. The clinical symptoms and signs are nonspecific, such as cough, dyspnea, hemoptysis, and weight loss.[2,5] Many cases are found incidentally on thoracic CT. Three patients had recurrent hemoptysis, while two were asymptomatic. Pulmonary nodules were present in all cases. With the popularization of low-dose chest CT in physical examinations, the diagnostic rate of asymptomatic pulmonary *Aspergillus* nodules may increase.

The laboratory examinations of our five cases included normal routine liver and kidney function, blood parameters, coagulation function, and tumor markers carcinoembryonic antigen. Three patients underwent tracheoscopy: two had no abnormalities and one showed congestion, edema, and bronchial mucosa stenosis. Five cases that had blood GM tests were all normal (Table 2). Although the serum GM test is widely used to diagnose invasive pulmonary aspergillosis, its positive rate in CPA is low.[6] The bronchoalveolar lavage fluid (BALF) GM test is more sensitive than the serum test and can be used in the diagnosis of CPA.[7] However, there are limitations of the test accuracy depending on the GM cutoff value used and should not be used as a single test to determine CPA.[8] But in this group of cases, one case was sent for BALF and the GM test was normal . For CPA, *Aspergillus* IgG antibody is usually a confirmatory test, which can help monitor the treatment response and CPA recurrence. Its sensitivity is 80–96% and specificity 85%.[9] *Aspergillus* IgG antibody is not CPA-specific, and it can be positive in allergic bronchopulmonary aspergillosis and *Aspergillus* bronchitis and sinusitis. According to the latest guidelines, *Aspergillus* PCR is a very useful for diagnosing CPA and is used to confirm the presence of *Aspergillus* in sputum. With negative cultures, the positive rate of samples can reach 50%.[10] The positive rates of these two laboratory tests are lower in pulmonary *Aspergillus* nodules. In Denning *et al.*, 32 patients underwent *Aspergillus* IgG antibody testing, with a positive rate of 69% and sputum samples from 22 patients were subject to *Aspergillus* PCR analysis, with a positive rate of 45%.[2] Since Wilson *et al.*[11] reported a case of leptospira diagnosed through cerebrospinal fluid metagenomic sequencing in 2014, mNGS has attracted attention and research. mNGS has higher sensitivity than traditional culture methods and is more accurate in diagnosing

Table 3. Chest imaging of five cases.

Computed tomography	Case 1	Case 2	Case 3	Case 4	Case 5
Infection site	Right upper lung segment	Left lower lobe of lung	Right upper lung segment	Left upper lung lingual segment	Left lower lobe of lung
Imaging features	Nodular shadow, with a diameter of 33 mm × 27 mm, with peripheral bronchodilation sign visible and blurry boundary	Nodular shadow with cavity formation, inner wall nodular shadow, 16 mm × 32 mm, peripheral bronchial dilation sign visible	Nodular shadow, 11 mm × 13 mm, with bronchodilation sign visible around and blurry boundary	Nodular shadow with calcification, with a diameter of approximately 11 mm × 13 mm, and bronchiectasis seen around it	Cystic cavity, inner wall nodule, diameter approximately 12 mm × 13 mm

tuberculosis, fungi, viruses and anaerobes.[12,13] The diagnostic accuracy of BALF mNGS positive for Aspergillus in immunocompromised IPA patients reached 82.3%,[14] but its diagnostic value in CPA lacks relevant research data. Due to limitations in conditions and high costs, our group of cases were unable to undergo preoperative BALF mNGS testing.

The imaging features of pulmonary *Aspergillus* nodules are one or more nodules, often in the upper lungs, which may or may not be accompanied by cavity formation.[2–3] Of our five cases, three had solitary upper lung lobe nodules without cavity formation (two in the right upper lobe and one in the left); the other two cases were in the lower left lobe, including one in the dorsal segment of the lower left lung (Table 3). While calcification is rare in pulmonary *Aspergillus* nodules, one of our patients had calcified *Aspergillus* nodules on chest CT.[2,5] Bronchiectasis was seen in cases 1–4 on chest CT, and case 5 had air-containing cavities. Based on the pathology, it is thought that this was a secondary change caused by *Aspergillus* blocking the bronchial lumen. Studies need to examine whether imaging combined with bronchiectasis has diagnostic significance in pulmonary *Aspergillus* nodules. PET-CT of most pulmonary *Aspergillus* nodules shows low to medium fluorodeoxyglucose (FDG) uptake.[2,15] Case 5 underwent PET-CT, which showed increased FDG uptake. *Aspergillus* nodules are easily misdiagnosed as lung malignancies.

The clinical, laboratory, and imaging features of pulmonary *Aspergillus* nodules are nonspecific. The diagnosis depends on a histopathological examination. When there is only a small amount of mycelium, hexamine silver and PAS staining can be used for pathogen detection. But this method has no specificity. Hyaline hyphae with regular intervals visible under the microscope, accompanied by acute angle as well as dichotomous branching, without vascular invasion, can distinguish the genus Aspergillus.[16] All five resected specimens in our group showed bronchiectasis with fungal hyphae, inflammatory cell infiltration, exudation, and tissue cells or giant cell reaction in the lung stroma, without vascular invasion, consistent with the pathological characteristics of *Aspergillus* nodules (Table 4). Unfortunately, the identification of specific Aspergillus subspecies was not carried out. PAS staining was positive in three cases, and dead bacteria-like matter was seen in the peribronchial lymph nodes of case 1. It is difficult to obtain pathological specimens on bronchoscopic biopsy and the positive rate is low, while patients often refuse highly invasive thoracoscopic or thoracotomy lung biopsies, delaying the diagnosis.[2,3]

At present, the treatment options for pulmonary aspergillosis nodules include drug therapy such as voriconazole, itraconazole systemic antifungal therapy, and surgical resection, and local bronchial perfusion therapy.[1,3] Scholars have studied the use of local infusion of amphotericin B under bronchoscopy to treat pulmonary mycosis. The effective rate of treatment for pulmonary aspergillosis is 73.81% (imaging safety or partial absorption), with some cases showing nodular shadows on imaging. The disadvantage of endoscopic injection is that it has poor therapeutic effect on multiple lesions and is invasive. Some patients may experience pain and poor compliance after medication injection and may also experience intraoperative and postoperative bleeding.[17] It is not clear whether asymptomatic *Aspergillus* nodules need

Table 4. Pathological results of five cases.

Pathology features	Case 1	Case 2	Case 3	Case 4	Case 5
Specific staining:	PAS (+)	Not done	PAS (+)	Not done	PAS(+), Hexamine silver (+), anti-acid (–)
Fungal hyphae	Within the bronchial lumen	Within the bronchial lumen	Within the bronchial lumen	Within the bronchial lumen	Within the bronchial lumen
Peripheral lung tissue	Inflammatory lesions with necrosis	Inflammatory lesions	Inflammatory lesions with partial fibrosis, a large number of foam like tissue cells in the alveolar cavity	Inflammatory lesions	Inflammatory lesions with partial fibrosis
Interstitial	Tissue cell and multinucleated giant cell reactions,	Inflammatory cells and multinucleated giant cell reactions	Inflammatory cells reactions	Inflammatory cells reactions	Inflammatory cells and multinucleated giant cell reactions
lymphoid tissue/ Lymph nodes	Reactive hyperplasia of lymph nodes with extensive peripheral fungal necrosis	Chronic inflammation of lymph nodes with partial collagenization	Undescribed	Lymphatic tissue hyperplasia	Lymphatic tissue hyperplasia

only CT follow-up, without drug or surgical treatment.[1,18] When deciding on treatment, clinicians must consider the patient's symptoms, serum *Aspergillus* IgG, dynamic imaging changes, and *Aspergillus* culture or PCR-positive airway samples.[2,19] Surgical treatment of pulmonary *Aspergillus* nodules is effective and the recurrence rate is low.[2,15] The role of perioperative antifungal therapy needs further study. None of our patients were given postoperative antifungal treatment. The prognoses were good and there were no recurrences of nodules. If pulmonary aspergillosis can be diagnosed before surgery, local infusion of amphotericin B under bronchoscopy or systemic/oral antifungal therapies can be considered to avoid surgical treatment.

Conclusion

When clinicians see healthy patients with normal immune function, and single or multiple nodule shadows on imaging, in addition to considering pulmonary tuberculosis, lung cancer, and other diseases, they need to consider pulmonary *Aspergillus* nodules. Tracheoscopy examination should be performed, and pathogen examination including BALF mNGS. After definite diagnosis, surgical resection, the first-line treatment of pulmonary Aspergillus nodules, and drugs are sometimes used; also local bronchoscopic lavage with amphotericin B can be attempted.

Declarations

Author's note

English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/EGzhPv

Ethics approval and consent to participate

This case series was approved by the Ethics Committee of the Dingli Clinical Institute of Wenzhou Medical University (Wenzhou Central Hospital). Consent to participate was taken from patients at the time of treatment. The authors have no ethical conflicts to disclose.

Consent for publication

Written informed consent for publication of this case series and the accompanying images was provided by the patients.

Author contributions

Shuangxia Dong: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Fengxiang Wang: Formal analysis; Writing – original draft.

Haizhen Jin: Data curation; Investigation.

Xinjian Dai: Conceptualization; Formal analysis; Writing – review & editing.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and material

All data are available from the corresponding author on reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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