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【 CASE REPORT 】

Chronic Nodular Pulmonary Aspergillosis in a Patient with Rheumatoid Arthritis

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Abstract:
Chronic pulmonary aspergillosis, which features nodular lesions known as *Aspergillus* nodules, is a relatively uncommon disorder. We herein report a case of slowly progressing chronic multiple nodular pulmonary aspergillosis in a 59-year-old man with rheumatoid arthritis, dyspnea, and fatigue. One nodule was surgically resected. The surgical specimen featured central necrosis and was located adjacent to a respiratory bronchiole and pulmonary artery, without parenchymal invasion. Branching septate hyphae, compatible with *Aspergillus,* were seen inside this necrotic nodule. Chronic pulmonary aspergillosis should therefore be considered in the differential diagnosis of patients who present with slowly progressing pulmonary multiple nodules.

Key words: *Aspergillus fumigatus*, *Aspergillus* nodule, chronic pulmonary aspergillosis, voriconazole, antifungal therapy, rheumatoid arthritis

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Introduction

Pulmonary aspergillosis is a broad term used to refer to a number of conditions caused by infection with a fungus of the *Aspergillus* genus. Depending on a host's immune status and the degree of pulmonary infection, three major forms of aspergillosis have been recognized: invasive, non-invasive, and allergic. The invasive form of pulmonary aspergillosis is characterized by tissue invasion by hyphae on histology and is further sub-classified as either invasive pulmonary aspergillosis, which occurs within one month, or subacute invasive aspergillosis, which occurs within one to three months. Non-invasive forms of pulmonary aspergillosis are further subclassified into chronic cavitary pulmonary aspergillosis, chronic fibrosing pulmonary aspergillosis, simple aspergilloma, or *Aspergillus* nodules (1). A single, simple nodule or multiple nodules are typically seen on computed tomography images of invasive pulmonary aspergillosis. In one study of 45 patients with non-HIV immunocompromised invasive pulmonary aspergillosis, 20 patients (43%) presented with multiple small nodules (2). In contrast, nodular lesions, termed *Aspergillus* nodules in the 2016 European Society for Clinical Microbiology and Infectious Disease and European Respiratory Society (ESCMID/ERS) guidelines for chronic pulmonary aspergillosis, are uncommon in cases of chronic pulmonary aspergillosis (1). Cases of *Aspergillus* nodules have not been well described in the literature. We therefore describe a patient with pre-existing rheumatoid arthritis who presented with multiple aspergillus nodules that were diagnosed via surgical lung biopsy.

Case Report

A 59-year-old man was referred to our hospital with a 1-month history of dyspnea upon exertion and fatigue. Two years previously, a chest computed tomography (CT) scan demonstrated emphysema without nodular lesions (Fig. 1a-d). Eight months previously, he was diagnosed with rheumatoid arthritis and treated with prednisolone (10 mg

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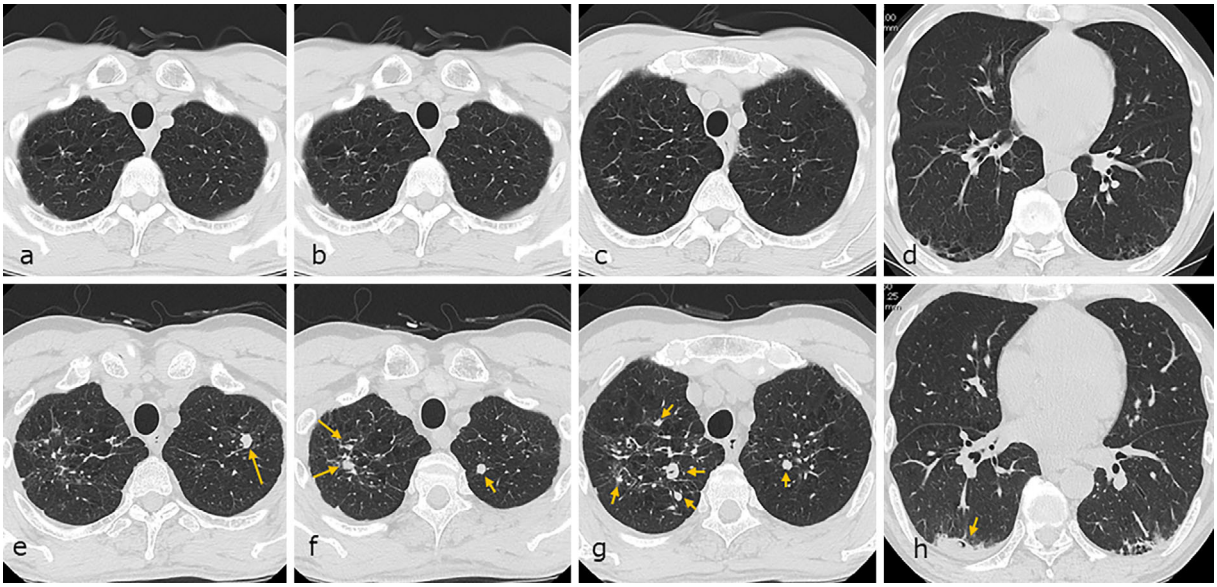

Figure 1. The computed tomography findings at two years before presentation (a-d), and at presentation (e-h). Multiple well-defined nodules of soft tissue attenuation were seen (e-h). A nodule in the left upper lobe (f) was resected thoracoscopically five months after presentation.

daily). However, after the worsening of his joint pain two months prior to presenting to our hospital, methotrexate (4 mg once weekly) treatment was initiated. Ten days before presenting to our hospital, his prednisolone dose was tapered (7.5 mg daily). Additionally, the patient had a history of smoking 20 cigarettes per day for 30 years. He had no inhalation history and no past medical history beyond emphysema and rheumatoid arthritis. A physical examination performed at the time of his initial presentation revealed the following findings: height, 170 cm; weight, 71 kg; body mass index, 24.5; blood pressure, 136/52 mmHg; body temperature, 36.8℃; heart rate, 86 beats per min; respiratory rate, 18 breaths per min; and percutaneous oxygen saturation, 98% on room air. Chest auscultation revealed normal breath sounds. His laboratory findings were as follows: total protein, 7.1 g/dL; albumin, 3.9 g/dL; alanine aminotransferase, 12 IU/L; aspartate aminotransferase, 19 IU/L; lactate dehydrogenase, 151 IU/L; blood urea nitrogen, 18 mg/dL; creatinine, 0.65 mg/dL; C-reactive protein, 0.11 mg/dL; white blood cell count, 7,100/μL with 83.7% neutrophils and 8.4% lymphocytes; red blood cell count, 4.66×10^6/μL; hemoglobin, 5.3 g/dL; hematocrit, 19.1%; and platelet count, 44.3×10^4/μL; beta-D-glucan assay, <6.0 pg/mL; IgG, 1,503 mg/dL; IgA, 226 mg/dL; and IgM, 42 mg /dL. The patient was positive for *Aspergillus* precipitating antibodies and specific IgE antibodies for *Aspergillus*, whereas *Aspergillus* galactomannan antigen testing was negative. An interferon gamma release assay, serum cryptococcal antigen testing, and serum IgA antibody testing against a glycopeptidolipid core antigen specific to the mycobacterium avium complex were also negative. Chest radiography revealed multiple nodules in the bilateral lung fields. Chest CT also revealed multiple nodules in both lungs including fifteen nodules of 0.4 to 1.3 cm in diameter in the right upper lobe, two nodules of 0.4 cm in diameter in the right middle lobe, one subpleural cavitary nodule of 2.3 cm in diameter in the right lower lobe, eight nodules of 0.4 to 0.9 cm in diameter in the left upper lobe, and one subpleural nodule of 1.7 cm in diameter in the left lower lobe (Fig. 1e-h). Since chronic aspergillosis was suspected based on positive *Aspergillus* precipitating antibody testing, bronchoscopy was also performed but revealed no significant findings. Cultures of bronchial washings obtained from the right B^{10} and B^{2} were negative for fungi, bacteria, and acid-fast bacilli, and cytology was negative for malignancy. Due to the patient's severe anemia, a transfusion of two units of packed red blood cells was administered and upper gastrointestinal endoscopy was performed, which revealed gastric ulcers. He was treated with oral iron and a proton pump inhibitor, after which his anemia gradually improved. At one month after his initial presentation, methotrexate was stopped, and three months after his initial presentation, the prednisolone dose was tapered to 2.5 mg daily and the patient was carefully followed. As a CT scan two months after this dose tapering revealed no improvement in his nodular lesions, one of the nodules in the left upper lobe was resected thoracoscopically so that a more definite, histopathological diagnosis could be obtained (Fig. 1f). A histological examination during surgery revealed a nodular lesion of 5 mm in size with central necrosis and a dense fibrous capsule adjacent to a respiratory bronchiole and pulmonary artery (Fig. 2). Grocott staining revealed branching septate hyphae compatible with *Aspergillus* spp. inside the necrotic nodule and no parenchymal invasion. Ziehl Neelsen staining further revealed no acid-fast bacilli. There was no evidence of palisading histiocytes, as are seen in rheumatoid nodules. A culture of the resected specimen was negative for fungi, bacteria, and acid-fast bacilli. No evidence of rheumatoid arthritis-related lung lesions,

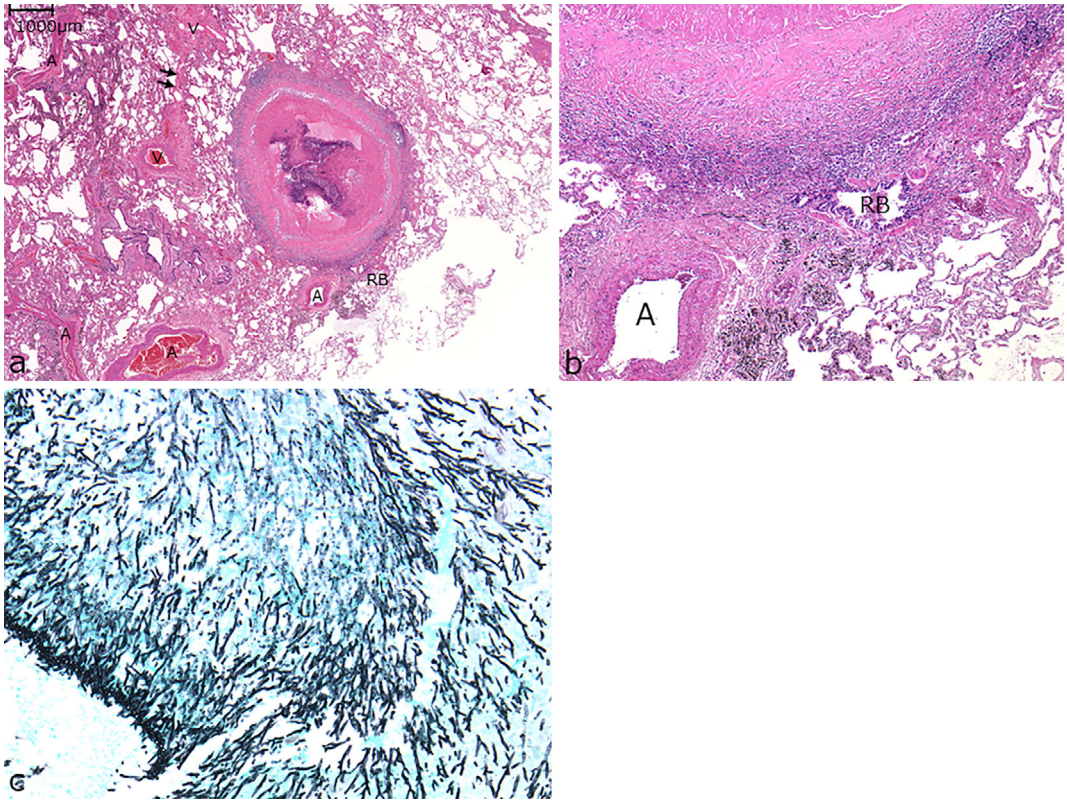

Figure 2. **At low magnification, a necrotic nodule was seen adjacent to the respiratory bronchiole (RB) and pulmonary artery (A) [Hematoxylin and Eosin (H&E) staining]. Interlobular septa (arrows) and a pulmonary vein (V) were identified near the nodular lesion (a). At 40× magnification, no parenchymal invasion was seen around the fibrous capsule (H&E staining) (b). Grocott staining at 200× magnification revealed branching septate hyphae compatible with *Aspergillus* spp. inside the necrotic nodule (c).**

such as interstitial lung disease, or follicular bronchiolitis was found. We detected *Aspergillus fumigatus* in the lung tissue using a PCR-based method (3, 4). Briefly, this involved DNA extraction from formalin-fixed paraffin-embedded (FFPE) samples of the resected lung tissue using a QIAmp DNA FFPE tissue kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. A PCR targeting the internal, transcribed spacer and D1/D2 regions was then performed as described previously (3, 4). The PCR products were electrophoresed in 2% ME agarose gel and stained with ethidium bromide. Specific bands were cut and directly sequenced, revealing a 100% match with *A. fumigatus*. Consequently, the patient was diagnosed with chronic nodular pulmonary aspergillosis without tissue invasion (i.e., *Aspergillus* nodules). Since he denied a history of symptoms consistent with asthma, such as episodic cough, wheezing, or dyspnea provoked by typical triggers, and CT showed no central bronchiectasis or mucous plugging, the possibility of allergic bronchopulmonary aspergillosis was ruled out. CT performed six months after his first visit revealed that all nodules remained the same size and had not improved. He was consequently started on voriconazole antifungal therapy and CT performed an additional six months later revealed that some nodules had decreased in size, and that the cavity wall of his right lower lobe lesion had thinned (Fig. 3, 4).

Discussion

This case of chronic pulmonary aspergillosis revealed three important characteristics of the condition: 1) multiple nodular lesions, 2) slow progression, and 3) the complexity of its presentation and treatment in a comorbid rheumatoid arthritis patient.

Chronic pulmonary aspergillosis presents with one or more nodular lesions (<3 cm), also termed *Aspergillus* nodules per the 2016 ESCMID/ERS guidelines for chronic pulmonary aspergillosis (1). The histologic features of *Aspergillus* nodules include an absence of tissue invasion, which distinguishes it from subacute invasive aspergillosis. The patient in the present case was diagnosed with *Aspergillus* nodules based on the results of a histological analysis. Only two reports of *Aspergillus* nodules have been published in the literature. Hou et al. reported that 3 of 69 patients with chronic pulmonary aspergillosis were diagnosed with *Aspergillus* nodules (5). Similarly, Muldoon et al. reported 33 cases of *Aspergillus* nodules, 13 of which showed no evidence of tissue invasion upon pathological examination (6). Before the 2016 ESCMID/ERS guidelines were proposed, few reports of histologically-confirmed chronic pulmonary aspergillosis with nodule(s) or masses had been reported,

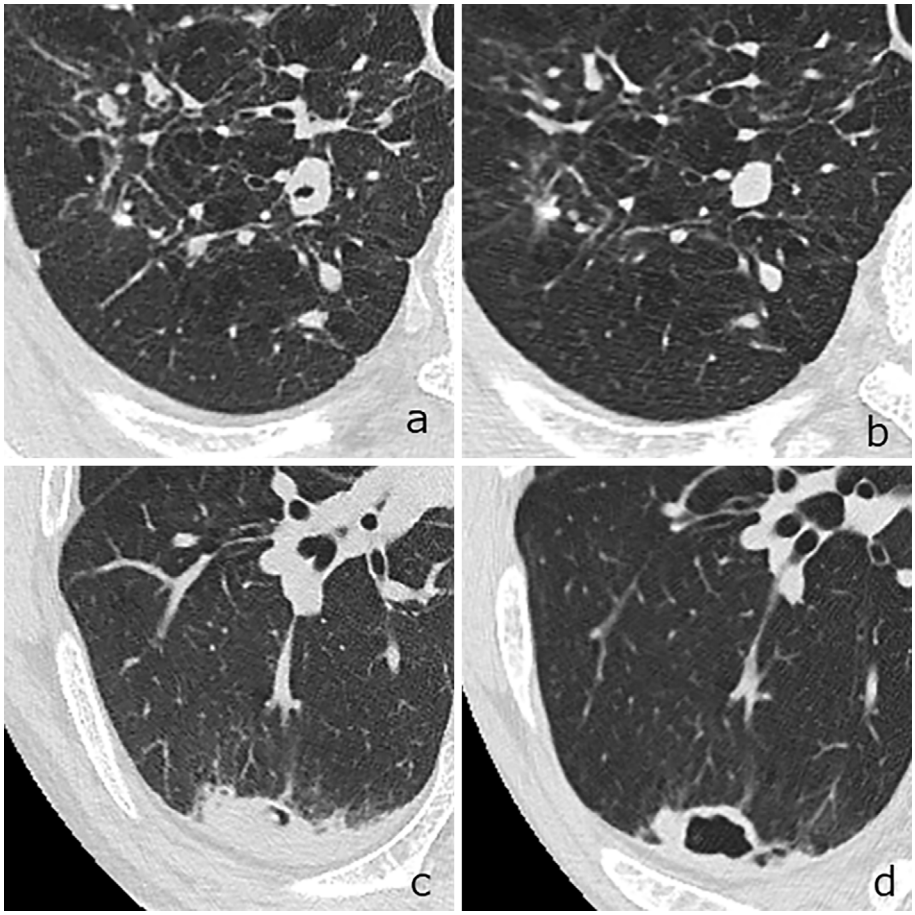

Figure 3. **The computed tomography findings at the patient's first visit (a, c) and six months after the initiation of antifungal therapy (b, d). One of the patient's nodules decreased in size from 13 to 10 mm in diameter (a, b). The cavity wall of the right lower lobe lesion showed thinning (c, d).**

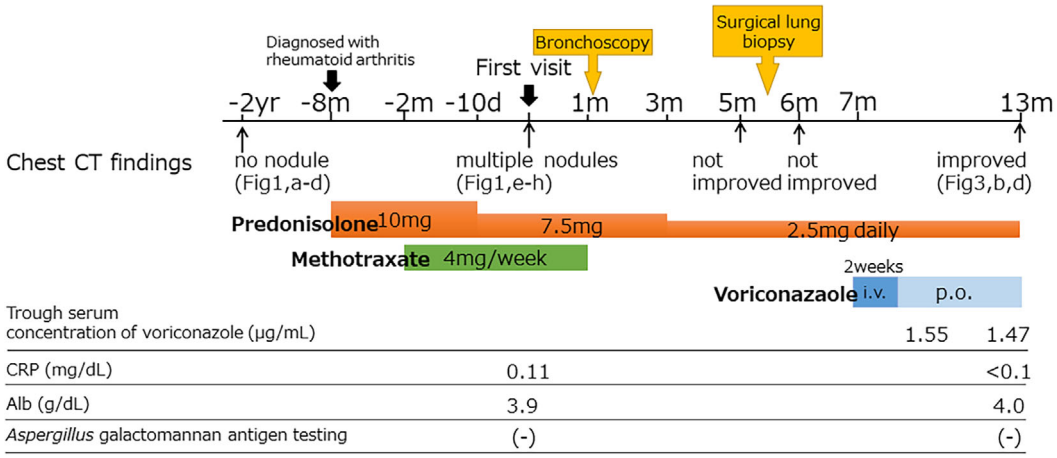

Figure 4. **The clinical course. Voriconazole was administered intravenously for two weeks, then orally. Alb: albumin, CRP: C-reactive protein, CT: computed tomography, i.v.: intravenous, m: months, p.o.: oral, yr: year(s)**

and the number of lesions, lesion background (i.e., underlying lung lesion), and presence of tissue invasion varied in each case (Table) (6-13). It is understandable that patients with chronic pulmonary aspergillosis and histologically-evident tissue invasion sometimes also have nodule(s) and that half have multiple lesions, as both findings suggest a relatively severe disease state. In contrast, chronic pulmonary aspergillosis without histologically-evident tissue invasion rarely features nodular lesions, with most cases having only a single lesion (11-13). The present case is important in that it uniquely featured chronic pulmonary aspergillosis without tissue invasion and with evidence of multiple nod-

Table. Published Cases of Histologically Confirmed Chronic Pulmonary Aspergillosis Presenting with Nodule(s) in English Literature.

Reference	Number	Cases of single nodule/ mass/multiple nodules	Background (underlying lung lesion)	Tissue invasion[¶]	Increased in size
7	3	0/0/3	COPD	(+)	NA
8	1	0/1/0	no underlying disease	(+)	NA
9	1	0/0/1	COPD	(+)	(+)[§]
10	1	0/0/1	acute leukemia	(+)	NA
11	9	NA/NA/0*	no undelying lung lesion	(-)	NA
12	7	5/2/0	no undelying lung lesion	3; (-) 4; (+)	NA
13	1	0/1/0	no undelying lung lesion	(-)	(+)[¥]
6	13[#]	6/0/7	emphysema on CT in some cases[&]	(-)	NA

[¶]Confirmed on pathology, [#]Thirty-three cases of *Aspergillus* nodules were originally reported, 13 of which evidenced no tissue invasion upon assessment of pathological specimens. *Single nodule or mass ranging from 1.5 cm to 4 cm, [&]Eleven cases out of 33 cases showed emphysema on CT. A detailed description on background of 13 cases with pathological specimen was not available. [§]The nodular lesion was first detected 6 years before, slow enlargement was observed over months to years. [¥]Slow enlargement in six months. COPD: chronic obstructive pulmonary disease, CT: computed tomography, NA: not available

ules.

The present case provides evidence to suggest that *Aspergillus* nodules manifest in a slowly progressing course. As multiple nodular lesions are frequently seen in invasive pulmonary aspergillosis cases, we initially suspected that this patient had invasive pulmonary aspergillosis. However, given that serological tests did not reveal findings typical of invasive pulmonary aspergillosis (the patient was negative for aspergillus galactomannan antigen), and its clinical manifestations were not particularly severe, we suspected that this was a case of chronic nodular pulmonary aspergillosis and decided to reduce the dose of immunosuppressive therapy and carefully follow the patient. Careful observation enabled us to identify nodular lesions that manifested and progressed slowly. While the natural history of *Aspergillus* nodules has not been well described, similar findings have been reported in the literature on chronic nodular pulmonary aspergillosis, which is also noted to progress slowly (over months to years). Tashiro et al. reported a case of chronic multiple nodular pulmonary aspergillosis with tissue invasion in which nodular lesions were first detected 6 years previously, which slowly increased in size over years (9). Yasuda et al. also reported a case of chronic pulmonary aspergillosis without tissue invasion, which presented as a single mass that increased in size over the course of six months (13). An interesting clinical course in a patient with multiple *Aspergillus* nodules and an initial cavitary lesion, which became solid on repeated CT imaging, was reported by Muldoon et al. (6). One nodule in the present case followed a similar clinical course (Fig. 3a, b).

The therapeutic effect of antifungal agents on *Aspergillus* nodules is an additional area that we sought to clarify with the present case. Based on the fact that all of the patient's nodules emerged within a two-year span, we decided to start him on voriconazole. Imaging findings revealed that some of his nodular lesions had improved, after six months of therapy. We are planning to maintain voriconazole therapy for at least another year after the nodules stop improving. Kim et al. reported a case of chronic pulmonary aspergillosis that presented as a single mass that decreased in size for one-month with antifungal therapy (8). Little is known about whether nodular *Aspergillus* lesions are reversible, and decrease in size or disappear with treatment. The treatment of *Aspergillus* nodules may be sufficient to suppress the exacerbation of nodular lesions (i.e., nodule enlargement or the emergence of new lesions). However, further studies are needed to clarify the long-term outcomes and treatment strategies most applicable to *Aspergillus* nodules. Critically, once multiple nodules compatible with chronic pulmonary aspergillus have emerged during immunosuppressive therapy, we suggest reducing this therapy and closely observing the patient to assess whether there is any continued disease activity. If nodules do not improve, a thorough investigation including examination of cultures and lung biopsy specimens obtained by bronchoscopy or CT-guided biopsy should be considered. If a definitive diagnosis cannot be obtained by such procedures, surgical lung biopsy may be considered- this can also be used for the pathological evaluation of disease activity (i.e., tissue invasion in the pathological specimen). The surgical specimen assessed in the present case was a necrotic nodule that was located adjacent to a respiratory bronchiole and the pulmonary artery in the centrilobular region of the lung. Based on these pathological findings, we hypothesized that the patient's nodular lesions may have resulted from the endobronchial spread of *Aspergillus* from a cavitary nodular lesion in the right lower lobe. Similar findings were reported by Yoon et al. in six of seven cases of chronic nodular pulmonary aspergillosis in patients with nodular lesions primarily located in the bronchial tree (12). Kang et el. also reported on four surgical specimens of chronic single nodular pulmonary aspergillosis with nodular lesions involving the bronchi or bronchioles (11). In

summary, the mechanisms by which nodular lesions present in chronic pulmonary aspergillosis cases may include: 1) the filling of internal, pre-existing cavitary lesion spaces, such as those resulting from emphysema or cysts after inflammatory exudation; 2) a reduction in cavitary lesion infection by *Aspergillus*, resulting in cavity loss during recovery; and 3) endobronchial spread from another lesion site containing abundant *Aspergillus* spp.

Cases of chronic multiple nodular pulmonary aspergillosis in patients with rheumatoid arthritis are rare. There are some reports of chronic nodular pulmonary aspergillosis in patients with chronic obstructive pulmonary disease, with most showing evidence of tissue invasion upon pathological assessment (7, 9). There are no reports of chronic nodular pulmonary aspergillosis in patients with rheumatoid arthritis, though some previous reports have suggested that *Aspergillus* colonizes pre-existing rheumatoid nodules (14-16). It does not, however, seem likely that the present case followed this pattern for several reasons. First, although rheumatoid nodules are typically located in the interlobular septa or pleura, the nodular lesion identified in the present case was mainly located in the centrilobular region. Second, the present case did not have a typical pathological finding of rheumatoid nodules-nodules surrounded by palisading histiocytes. Third, no pre-existing nodular lesions were identified on CT imaging collected two years prior to the patient's presentation to us. Critically, little is known about whether *Aspergillus* nodules have a peculiar predilection to underlying lung disease, and future work should evaluate this association more carefully.

Conclusion

In conclusion, the present case demonstrated that chronic pulmonary aspergillosis without histological evidence of tissue invasion may present as multiple nodules in a patient with rheumatoid arthritis. This case further suggested that *Aspergillus* nodules may manifest along a slow, progressive course. Additional case reports and studies are required to further clarify the clinical features, pathogenesis, and long-term outcomes of *Aspergillus* nodules in the clinical setting, especially in patients complicated by other inflammatory diseases such as rheumatoid arthritis.

The authors state that they have no Conflict of Interest (COI).

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