Morphological analysis of bronchoalveolar lavage fluid in diagnosing pulmonary aspergilloma in a patient with rheumatoid arthritis: A case report

YULI ZHOU[1], YUYI LAI[2], FUXIAN ZHOU[3], XINXIN WANG[4], XIAO HE[5], JUAN JIN[6] and RUIKAI ZHANG[6]

[1]Department of Laboratory Medicine, Affiliated Hangzhou First People's Hospital, Westlake University School of Medicine, Hangzhou, Zhejiang 310006, P.R. China; [2]Department of Laboratory Medicine, The First People's Hospital of Nanning, Nanning, Guangxi Zhuang Autonomous Region 530016, P.R. China; [3]Department of Laboratory Medicine, Yanbian University Hospital, Yanji, Jiling 133000, P.R. China; [4]Department of Laboratory Medicine, The First People's Hospital of Jinzhong, Jinzhong, Shanxi 030699, P.R. China; [5]Department of Radiology, Affiliated Hangzhou First People's Hospital, Westlake University School of Medicine, Hangzhou, Zhejiang 310006, P.R. China; [6]Department of Nephrology, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Traditional Chinese Medicine), Hangzhou, Zhejiang 310000, P.R. China

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Abstract. Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder that primarily affects the joints and may be associated with systemic complications. Patients with RA have an increased susceptibility to opportunistic infections, attributable to inherent immune dysregulation as well as immunosuppressive therapies, including tocilizumab, particularly among those with comorbidities or high disease activity. Notably, the use of tumor necrosis factor inhibitors, such as adalimumab and etanercept, has been associated with a higher incidence of invasive pulmonary aspergillosis and chronic pulmonary aspergillosis. The present study reports a rare case of pulmonary aspergilloma in a 75-year-old female RA patient with prior tuberculosis and long-term tocilizumab use. The patient was diagnosed via bronchoalveolar lavage fluid morphology, fungal culture, *Aspergillus* galactomannan assay, metagenomic next-generation sequencing and pathology, and the patient achieved symptom resolution and improved imaging after 6 months of treatment with voriconazole. These findings underscore the need for vigilant monitoring and individualized management strategies in this patient population.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that primarily affects the joints but may also present with a wide range of extra-articular manifestations. With a global prevalence of 0.5-1.0%, it predominantly occurs in middle-aged and elderly populations (1) Patients with RA are at increased risk of opportunistic infections due to underlying immune dysregulation and the frequent use of immunosuppressive therapies, particularly among those with comorbidities and high disease activity (2). Biological agents, including tumor necrosis factor inhibitors (for example adalimumab or etanercept) and interleukin-6 receptor antagonists (such as tocilizumab), have been well documented to elevate the risk of *Aspergillus*-related pulmonary infections, such as invasive pulmonary aspergillosis (IPA) and chronic pulmonary aspergillosis (CPA) (3,4). Notably, the diagnosis of pulmonary aspergilloma remains challenging due to its non-specific clinical manifestations, often requiring a multimodal approach combining clinical, radiological, microbiological and pathological evidence (5).

The present study reports a rare case of pulmonary aspergilloma in a patient with RA who developed the infection as a result of disease-related immune dysregulation and long-term immunosuppressive therapy. The patient was a 75-year-old woman with RA and a pre-existing pulmonary cavity secondary to prior tuberculosis. Following prolonged immunosuppressive treatment, the patient was diagnosed with pulmonary aspergilloma. Through detailed morphological analysis of bronchoalveolar lavage fluid and lung tissue specimens, the current report aims to enhance diagnostic awareness of pulmonary aspergilloma, emphasize the infection risk associated with long-term immunosuppressive therapy in patients with autoimmune diseases, and highlight the diagnostic and management challenges posed by *Aspergillus* infections, particularly CPA, for infectious disease specialists.

Case report

Case presentation. In January 2024, a 75-year-old woman presented to Hangzhou First People's Hospital with recurrent

Correspondence to: Mr. Ruikai Zhang, Department of Nephrology, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Traditional Chinese Medicine), 54 Youdian Road, Shangcheng, Hangzhou, Zhejiang 310000, P.R. China
E-mail: 17858187659@163.com

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Table I. Laboratory test results.

Laboratory tests	Results	Reference range
White blood cell count, /l	$11.4x10^9$	$4\text{-}10x10^9$
Neutrophils, %	73.6	50-70
Lymphocytes, %	16.9	17-50
Red blood cell count, /l	$4.11x10^{12}$	$3.5\text{-}5.0x10^{12}$
Hemoglobin, g/l	117	110-150
Platelet count, /l	$241x10^9$	$100\text{-}300x10^9$
Serum amyloid A, mg/l	270.6	≤10
Serum transferrin saturation, %	9.18	33-35
Serum iron, μmol/l	3.9	7.8-32.2
Total iron-binding capacity	42.5 μmol/l	45-81 μmol/l
Urinary red blood cells, /μl	36 (mixed)	<3
Urinary occult blood	(++)	(-)
Rheumatoid factor, IU/ml	23.2	0-20
Leukocyte esterase	(+)	(-)
Anti-nuclear antibody	Positive (1:100)	(-)
Sub-karyotype of anti-nuclear antibody	No karyotype	\
Cyclic citrullinated peptide antibody, U/ml	>500.00	0-20
hypersensitive C-reactive protein, mg/l	36.1	<10
Erythrocyte sedimentation rate, mm/h	53	0-15
BALF nucleated cell count, /μl	260	<100
BALF neutrophils, %	82	<50
GM assay	0.98	<0.5

BALF, bronchoalveolar lavage fluid; GM, galactomannan.

polyarticular swelling and pain for >2 years, accompanied by a 1-week history of productive cough. The patient had been diagnosed with RA 2 years previously. Physical examination revealed swelling, pain and stiffness of the interphalangeal and wrist joints of the index and middle fingers of both hands, without obvious joint deformity. The patient subsequently received immunosuppressive therapy with tocilizumab 400 mg monthly injections in January, February, March and April 2022. Despite treatment, the condition of the patient progressed, and a boutonniere deformity developed in the right middle finger. The patient also had a history of pulmonary tuberculosis and poorly controlled RA; 1 week before admission, the patient developed a cough with yellow sputum and was admitted in Hangzhou First People's Hospital for further evaluation. On admission, the blood pressure of the patient was 174/81 mmHg (reference: 90-139/60-89 mmHg). The patient was conscious and alert, with no cyanosis of the lips. Lung auscultation revealed no obvious dry or wet rales, and the remainder of the physical examination was unremarkable. Peripheral blood analysis showed a white blood cell count of $11.4x10^9$/l (reference: $4.0\text{-}10.0x10^9$/l), neutrophil count of 73.6% (reference: 50-70%), lymphocyte count of 16.9% (reference: 20-40%), red blood cell count of $4.11x10^{12}$/l (reference: $3.68\text{-}5.13x10^{12}$/l), hemoglobin level of 117 g/l, (reference: 110-150 g/l) platelet count of $241x10^{12}$/l (reference: $100\text{-}300x10^9$/l), hypersensitive C-reactive protein level of 36.1 mg/l (reference: 0-3 mg/l) and erythrocyte sedimentation rate of 53 mm/h (reference: 0-20 mm/h). Urinalysis revealed occult blood (dry chemistry) ++, leukocyte esterase (dry chemistry) +, red blood cell count of 36/μl (reference: 0-13 /μl and mixed red blood cell morphology. *Mycobacterium tuberculosis* (MTB) antigen ESAT-6 was 13.00 (reference: <5) and MTB antigen CFP10 was 8.00 (reference: <5) with a positive T-SPOT test (Xiamen Wantai Biological Pharmacy Enterprise Co., Ltd.). Sputum smears for acid-fast bacilli and cryptococcal antigen were negative (data not shown). Molecular testing for MTB and rifampicin resistance showed no detection of MTB DNA by Xpert assay (Cepheid Inc.). Bronchoscopic brush smears for acid-fast bacilli were negative (data not shown). Laboratory test results are summarized in Table I.

Upper abdominal ultrasonography (including liver, bile, pancreas and spleen): revealed gallbladder polyposis, right kidney stones and a small amount of pleural effusion (Figs. S1 and S2). Routine electrocardiography and vectorcardiography demonstrated sinus rhythm with frequent atrial premature beats (with differential intraventricular conduction), presenting as double rhythm, and notched P waves. ST-segment and T-wave abnormalities were noted (ST segments in leads I, II, III, aVL, aVF and V4-V6 showed horizontal depression of 0.03-0.09 mV; T waves in leads I, aVL, V3 and V4 were low and flat; and leads II, III, aVF, V5 and V6 showed biphasic changes). A prolonged Q-T interval was also observed (460 ms; normal maximum: 380 ms).

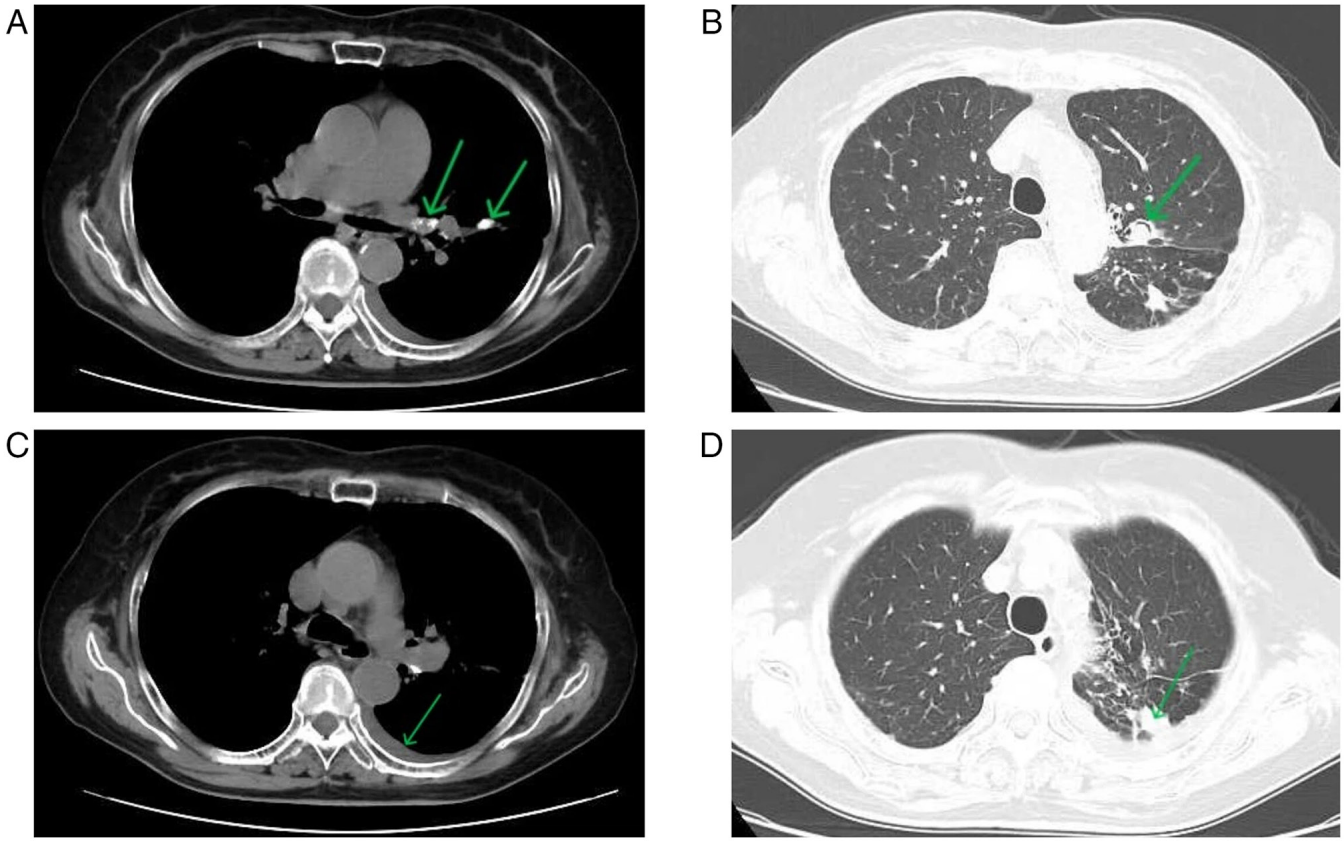

Figure 1. Imaging findings. (A) Calcified lymph nodes (indicated by arrows); (B) air crescent sign (crescent-shaped low-density area within a high-density nodule, indicated by arrow); (C) left pleural effusion (arcuate fluid density shadow, indicated by arrow); (D) left lung inflammatory lesion (patchy high-density shadow with ill-defined border, indicated by arrow). CT parameters: 120 kV, 80 mAs, 1-mm slice thickness, lung window (WL: -600 HU, WW: 1,500 HU), mediastinal window (WL: 40 HU, WW: 400 HU). CT, computed tomography; WL.

Transthoracic echocardiography showed left heart enlargement, left ventricular insufficiency, mild regurgitation of the mitral, tricuspid and aortic valves, and arrhythmia, with a Simpson ejection fraction of 0.42. Chest computed tomography (CT; plain scan plus high-resolution target scan) revealed slightly increased lung markings bilaterally, with multiple nodular, patchy, and strip-like high-density shadows. Some lesions had indistinct margins, and an air crescent sign was observed in certain areas (Fig. 1B). Multiple infectious lesions were present in both lungs, some showing a tendency toward chronic fibrosis (Fig. S3). Additional small nodules measuring 3-6 mm in diameter were noted bilaterally. Multiple calcified lymph nodes were observed in the left hilum and mediastinum. No significant pleural thickening was identified, while an arcuate effusion was present in the left thoracic cavity (Fig. 1C).

Cell morphology analysis of bronchoalveolar lavage fluid (BALF). Cytological examination of the BALF revealed blood-tinged fluid, with a total nucleated cell count of 260 cells/μl (reference: 100-200 cells/μl). Differential cell count analysis identified a predominant neutrophilic inflammatory pattern, with 82% neutrophils (reference: <3%), 6% lymphocytes (reference: 5-15%), 9% alveolar macrophages (reference: 80-95%), and 3% eosinophils (reference: <1%).

Microscopic evaluation revealed numerous dense fungal clusters, with thick, intertwined hyphae aggregated into irregular masses and clumps (Fig. 2A, C and F). Clear septation of the fungal hyphae (a key morphological marker for *Aspergillus*) was visualized under high-magnification staining (Fig. 2B and D), and abundant fungal mycelia were further confirmed by fluorescence staining (Fig. 2E). No fungal spores were detected in the BALF specimens; however, the hyphal morphological features were highly suggestive of Aspergillus infection, which was subsequently verified by fungal culture and phenotypic identification (Fig. 2H and I).

Microbiological examination. Culture and identification of bacteria and fungi from BALF yielded growth of *Aspergillus fumigatus*. Routine bacterial and fungal cultures were otherwise negative, with no additional fungal or bacterial growth detected. The *Aspergillus* galactomannan (GM) assay was positive, with a value of 0.98, supporting the diagnosis of *Aspergillus* infection. Sputum cultures were repeatedly negative for bacterial and fungal pathogens.

Pathological examination. The pathological report of the 'left anterior lobe brush smear' showed scattered hyperplasia of bronchial mucosal epithelial cells without significant atypia. Another pathological report of the 'BALF cell block (left upper lobe proper branch)' revealed no malignant cells; however, clusters of *Aspergillus* hyphae were noted. Pathological examination of the 'biopsy of the anterior left upper lobe' demonstrated fragmented mucosal tissue with extensive infiltration of lymphocytes, plasma cells and neutrophils within the mucosal interstitium, along with

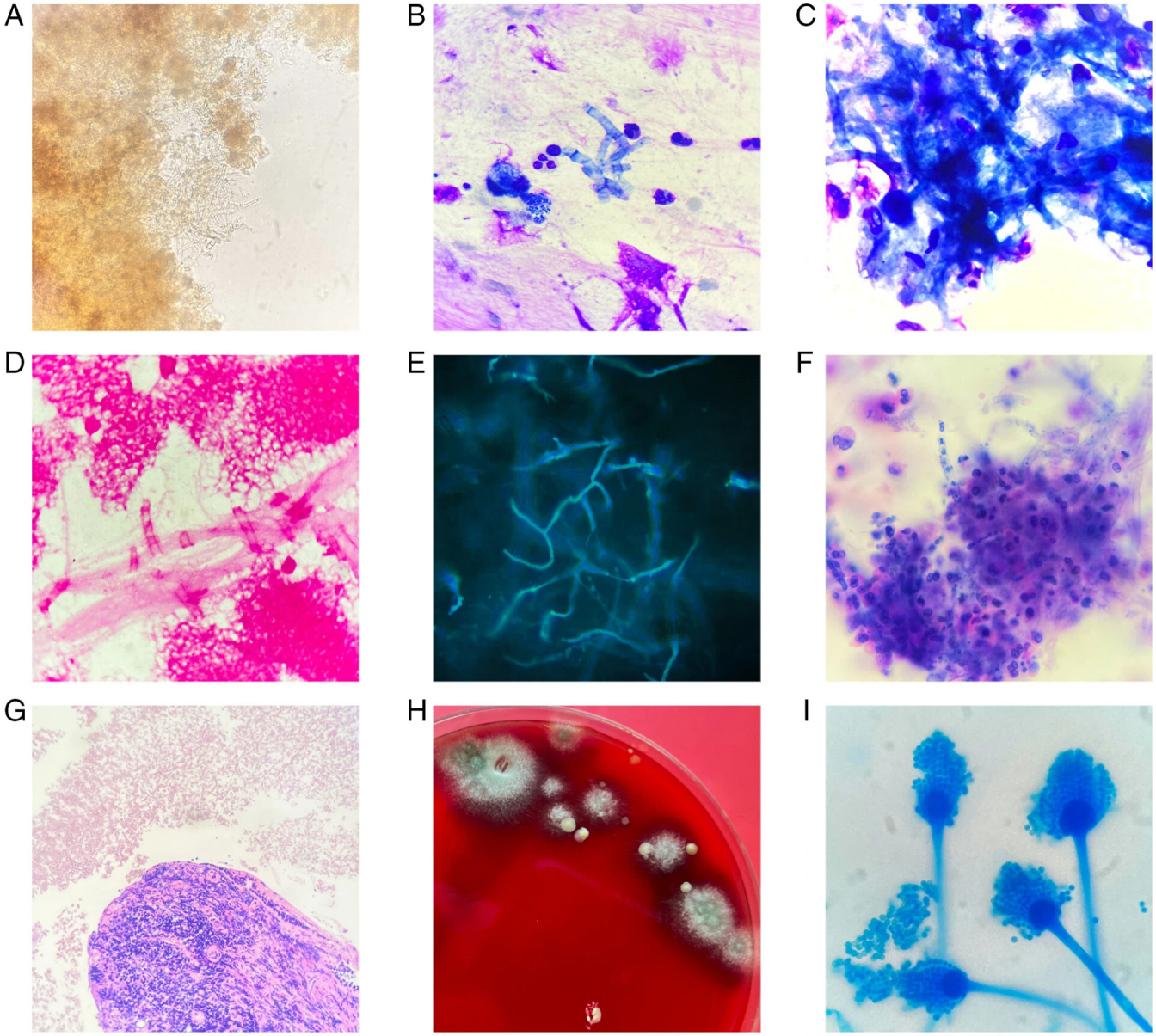

Figure 2. Morphology of pulmonary *Aspergillus fumigatus* aspergilloma. (A) BALF, wet film unstained (magnification, x400), a large number of fungi can be seen in dense clusters, and the mycelium can be seen at the edge of each other and disorderly arrangement. (B) BALF, Wright-Giemsa stain (magnification x1,000), small segments of mycelia-like bamboo, dyed light blue, and mycelia division is clear. (C) BALF, Reichsen-Giemsa staining (magnification x1,000), numerous mycelial interleaved fungal clusters. (D) BALF, Gram staining (magnification, x1,000), mycelium staining is light, and obviously visible. (E) BALF, fungal fluorescence staining (magnification, x400), showing a large number of fungal mycelia. (F) BALF cell block (magnification, x400), clumps of *Aspergillus* hyphae. (G) A biopsy of the anterior segment of the upper lobe of the lung, broken mucosal tissues (magnification, x100), extensive infiltration of lymphocytes, plasma cells and neutrophils in the mucosal interstitium (black arrow): Also see *Aspergillus* cluster (red arrow). It can be seen that *Aspergillus* cluster and lung tissue separation, in line with the formation of aspergilloma structure characteristics. (H) Lavage culture, colony after 3 days of Columbia blood plate culture, arrow point. (I) *A. fumigatus* after 3 days of lavage culture, phenol cotton blue staining (magnification, x1,000). BALF, bronchoalveolar lavage fluid.

visible *Aspergillus* clusters. Metagenomic next-generation sequencing (mNGS) of two BALF samples further supported Aspergillus infection, and these two samples correspond to the two datasets under accession no. PRJNA1397972 in the National Center for Biotechnology Information Sequence Read Archive database.

Treatment and follow-up. The patient received antifungal therapy with oral voriconazole at a dose of 200 mg every 12 h (q12 h). The patient's inflammatory indices decreased significantly and normalized after treatment. The specific paired pre- and post-treatment levels (reference range in parentheses) were: white blood cell count (WBC) 11.4x10^9/l (4-10x10^9/l) → 5.4x10^9/l (3.6-9.6x10^9/l); neutrophil percentage (NEUT%) 73.6% (50-70%) → 60.2% (40-75%); absolute neutrophil count 8.4x10^9/l (1.8-6.3x10^9/l) → 3.3x10^9/l (1.8-6.3x10^9/l); hypersensitive C-reactive protein (hs-CRP) 36.1 mg/l (<10 mg/l) → 9.5 mg/l (0-17.0 mg/l). All elevated markers returned to the normal range after treatment, and the patient was discharged after her condition improved. After discharge, oral voriconazole 200 mg q12h was continued for 6 months. At follow-up in November 2024, the patient's cough and sputum symptoms resolved completely.

Discussion

Pathogenesis. The present patient had poorly controlled RA for 2 years and had received four standard monthly doses of tocilizumab as immunosuppressive therapy. The patient also had multiple comorbidities, including gallbladder polyposis, right kidney stones, pleural effusion, arrhythmias (frequent atrial and ventricular premature beats) and chronic heart failure. Advanced age, RA-associated immune dysregulation, long-term immunosuppressive therapy and pre-existing comorbidities constitute major high-risk factors for *Aspergillus* infection (6). Notably, the patient's history of pulmonary tuberculosis resulted in the formation of tuberculous cavities. These avascular structures provide an ideal niche for *Aspergillus* colonization, as supported by a study from New Delhi reporting that 57% of post-tuberculosis patients develop pulmonary aspergillosis (7), with tuberculous cavities facilitating microbial persistence and survival (8). Such colonization may ultimately lead to aspergilloma formation, the hallmark radiological feature of CPA, along with the characteristic air crescent sign on chest CT (9).

Aspergillus species are saprophytic molds that thrive on decaying organic matter and produce airborne conidia that are readily inhaled by humans (10). Clinical manifestations depend on host immune status and underlying pulmonary structure and are broadly classified as allergic bronchopulmonary aspergillosis, CPA and IPA (11), with aspergilloma considered a pathognomonic manifestation of CPA (12). *Aspergillus* is the most common cause of pulmonary fungal balls, which are termed aspergillomas. Immunocompromised individuals, including those with chronic diseases such as asthma, chronic obstructive pulmonary disease, diabetes and rheumatic diseases (13), as well as those undergoing chemotherapy, organ transplantation or invasive medical procedures, are particularly susceptible to tuberculosis-fungal co-infections, which may result in severe pulmonary dysfunction and increased mortality (14). Over the past 5 decades, the global incidence of invasive fungal infections has markedly increased, driven by the expanding population of susceptible hosts .

The present case underscores the importance of heightened vigilance for *Aspergillus* infections, particularly CPA, in patients receiving long-term immunosuppressive therapy (15). In addition to corticosteroids, biological agents, including tumor necrosis factor inhibitors (infliximab, etanercept and adalimumab), anti-CD20 monoclonal antibodies (rituximab), anti-CD28 fusion proteins (abatacept) and interleukin-6 receptor antagonists (tocilizumab), have been associated with an increased risk of fungal infections in patients with autoimmune diseases (4,16,17). Consistent with these findings, Baliga *et al* (18) reported five cases of pulmonary aspergillosis in immunosuppressed patients with antineutrophil cytoplasmic antibody-associated vasculitis. Deana *et al* (19) described pulmonary aspergillosis following tocilizumab therapy in a patient with coronavirus disease 2019. These reports parallel the current case, in which CPA developed after four standard monthly doses of tocilizumab, suggesting that cumulative immunosuppression, rather than dosing frequency alone, plays a critical role in infection risk (20). For high-risk patients requiring biological therapy, the 2023 Spanish Society of Rheumatology guidelines recommend abatacept as a safer alternative due to its lower associated infection risk (21). In addition, mesenchymal stem cell therapy has emerged as a potential treatment strategy for RA, demonstrating effective inhibition of T-cell proliferation with minimal reported adverse effects (22,23).

Diagnostic challenges. The initial potential misclassification of the current case as IPA highlights the diagnostic complexity of *Aspergillus*-related pulmonary diseases. According to the 2016 European Society of Clinical Microbiology and Infectious Diseases guidelines for CPA, the clinical features observed in the present patient, including the presence of an aspergilloma within a pre-existing tuberculous cavity, an air crescent sign on chest CT, and the absence of neutropenia or high-dose corticosteroid use, support a diagnosis of CPA (aspergilloma subtype) rather than IPA. This distinction is critical for accurate clinical management and appropriate research reporting. The diagnosis of CPA relies on a combination of clinical, radiological, microbiological and pathological evidence, as no single diagnostic gold standard exists (5).

i) BALF-based diagnostics. Direct morphological identification of septate, branching hyphae consistent with *Aspergillus* species enables early diagnosis and is considerably faster than culture-based methods, which may require days to weeks (17). Knox *et al* (16) emphasized the pivotal role of BALF cytomorphology in the diagnosis of pulmonary fungal infections, including aspergillosis. Furthermore, the BALF GM assay, using a cutoff value of >0.5, demonstrates a sensitivity of 89% and specificity of 79% for *Aspergillus* infections (24). In the present patient, a GM value of 0.98 provided strong microbiological support for diagnosis.

ii) Imaging findings. The presence of an air crescent sign and an aspergilloma within a pre-existing tuberculous cavity represents classic CT hallmarks of CPA, both of which were clearly demonstrated in the current case.

iii) Metagenomic NGS (mNGS). This technique offers high sensitivity, rapid pathogen identification, and a broad detection spectrum, including mixed infections (25). It has been shown to outperform conventional etiological methods and serum (1,3)-β-D-glucan testing in patients with pulmonary aspergillosis (26).

iv) Laboratory and histopathological findings. Elevated total white blood cell counts and neutrophil levels (27), consistent with our patient's laboratory results, support an inflammatory response. Furthermore, pathological biopsy revealing isolated *Aspergillus* clusters, separated from the surrounding lung tissue, confirms the structural characteristics of an aspergilloma. Non-specific respiratory symptoms, such as cough and productive sputum, are common in immunocompromised patients (28). This lack of specificity frequently leads to diagnostic delays, which may adversely affect treatment outcomes. Therefore, we recommend early implementation of BALF cytological examination, GM testing and mNGS in immunosuppressed patients presenting with respiratory symptoms, complemented by multidisciplinary evaluation to exclude diseases with overlapping clinical and radiological features (29), thereby facilitating timely and accurate diagnosis of CPA.

Treatment dilemmas. The management of pulmonary aspergilloma, a subtype of CPA, remains controversial, with the choice between surgical and conservative approaches guided by patient-specific factors (30). Surgical resection is presently considered the gold standard for symptomatic patients with recurrent or severe hemoptysis, as it is associated with a 5-year survival rate of 84%, which is significantly higher than that achieved with medical therapy alone (41%) (31). However, postoperative complications, including bleeding, empyema, bronchopleural fistula and *Aspergillus* seeding, occur in ~28% of patients with cavitary disease, a rate that is 5-10 times higher than that observed in the general population (32). By contrast, among asymptomatic patients, survival outcomes are comparable between surgical and medical management (75 vs. 65%, respectively) (31), supporting a conservative treatment strategy in this group.

Conservative management of aspergilloma is often challenging because the avascular nature of pulmonary cavities and aspergillomas limits antifungal drug penetration (29). Nonetheless, antifungal therapy can effectively alleviate clinical symptoms. Voriconazole is preferred over itraconazole for patients with aspergilloma or cavitary disease, as it is associated with fewer adverse effects and more reliable achievement of therapeutic drug concentrations (33-34). Other non-surgical interventions, including endovascular antifungal infusion and bronchoscopic resection under general anesthesia, have been described in a small retrospective study (35).

Learning points. Clinicians should maintain a high index of suspicion for *Aspergillus* infection, particularly CPA, in older adults with autoimmune diseases such as RA who are receiving biological therapy, especially tocilizumab. This is particularly important in patients with pre-existing pulmonary cavities, such as those resulting from prior tuberculosis. Standardized terminology and accurate disease classification, specifically distinguishing CPA from IPA, are essential for effective clinical communication and management. Multimodal diagnostic approaches, including BALF morphology, GM assay, mNGS, imaging and histopathological examination, facilitate early and accurate diagnosis. For asymptomatic patients with CPA who have comorbidities that preclude surgical intervention, voriconazole-based conservative therapy may achieve favorable outcomes. Moreover, selection of biological agents for high-risk patients with RA should adhere to relevant clinical guidelines to minimize the risk of opportunistic fungal infections.

Conclusion. Older adults, immunocompromised populations and patients with autoimmune diseases, particularly those receiving immunosuppressive therapy, should be carefully monitored for the development of *Aspergillus* infections, especially CPA. The disease often presents with an insidious onset and non-specific clinical manifestations. Morphological examination of BALF provides valuable diagnostic specificity and may enable early presumptive diagnosis. GM testing and mNGS of BALF should be performed promptly when *Aspergillus* infection is suspected. When combined with comprehensive assessment of imaging, histopathology, microbiological and molecular findings, early and accurate diagnosis can be achieved, thereby guiding appropriate antifungal therapy. A history of pulmonary tuberculosis and the presence of pulmonary aspergilloma further increase the complexity of antifungal management. Overall, heightened clinical vigilance for rare infections in patients with rheumatic diseases receiving immunosuppressive agents, together with early diagnosis of fungal infections, is essential for effective treatment outcomes.

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Availability of data and materials

The raw mNGS data generated in the present study may be found in the National Center for Biotechnology Information Sequence Read Archive database under accession number PRJNA1397972 or at the following URL: https://www.ncbi.nlm.nih.gov/sra/PRJNA1397972. All other relevant data in the present study may be requested from the corresponding author.

Authors' contributions

YZ contributed to study conception and design, collated clinical cases, acquired and interpreted data, drafted the manuscript, and provided experimental and writing guidance. YL performed morphological examination of bronchoalveolar lavage fluid. FZ prepared laboratory experiments and assisted with sample processing. XW conducted culture, identification and morphological analysis of pathogenic microorganisms. XH collected imaging data and performed diagnostic analysis. JJ contributed to study conception and design and provided critical revision and writing guidance. RZ contributed to data analysis and interpretation, drafted the manuscript and critically revised the intellectual content. YZ and RZ confirm the authenticity of all raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Affiliated Hangzhou First People's Hospital (Westlake University School of Medicine; approval no. 2025ZN488-1) with a waiver of written informed consent, as the patient's data and images were fully de-identified and the publication posed no potential risks to the patient's privacy or rights. The study was conducted in accordance with the Declaration of Helsinki.

Patient consent for publication

Patient consent for publication was waived by the Ethics Committee of Affiliated Hangzhou First People's Hospital

(Westlake University School of Medicine; approval no. 2025ZN488-1). All patient data and images have been fully de-identified, and the publication poses no potential risks to the patient's privacy or rights.

Competing interests

The authors declare that they have no competing interests.

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