Case Report

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Fusarium species causing invasive fungal pneumonia in an immunocompetent patient: a case report

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Abstract

Fusarium is a large genus of filamentous fungi that are rarely associated with disease in humans. In the clinical setting, *Fusarium* species are often difficult to distinguish from other fungal organisms, particularly *Aspergillus* species. Invasive fungal pneumonia caused by *Fusarium* species has rarely been reported, especially in immunocompetent patients. In this study, we reported a case of invasive *Fusarium* pneumonia in a previously healthy 68-year-old woman. The disease was initially misdiagnosed as invasive *Aspergillus* pneumonia because of the similarity in radiologic and histopathologic findings between these conditions. After *Fusarium* was identified via microbiological analysis, the antifungal agent was changed, and the patient recovered fully.

Keywords

Fusarium, *Aspergillus*, fungal pneumonia, immunocompetence, lung, thorax, computed tomography

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Introduction

Fusarium species are ubiquitous fungi that are commonly found in soil and organic debris.[1] They can cause a range of opportunistic infections in humans from localized cutaneous infections to disseminated infections depending on the immune status of the host. In general, localized cutaneous infection by *Fusarium* species is more common in immunocompetent patients,

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whereas disseminated infection is more common in immunocompromised patients.[2] *Fusarium* infection with pulmonary involvement is more frequently observed in immunocompromised patients[3]. Conversely, only two reports of *Fusarium* pneumonia in immunocompetent patients have been published to date.[4,5]

In this study, we presented a case of community-acquired *Fusarium* pneumonia that was difficult to diagnose in an immunocompetent patient. We reviewed the radiologic findings of *Fusarium* pneumonia and discussed its differential diagnosis.

Case presentation

A 68-year-old woman visited our hospital with a 10-day history of hemoptysis. She had mild respiratory symptoms, including a cough, sputum, and rhinorrhea, which had begun 1 month before her visit to our hospital. On initial presentation, her vital signs were normal as follows: blood pressure, 120/80 mmHg; pulse rate, 78 beats/minute; respiratory rate, 18 breaths/minute; and body temperature, 36°C. On physical examination, mild wheezing was detected in areas of both lung fields. No cutaneous rash or peripheral edema was identified. The patient was alert, and the findings on neurological examination were normal. Laboratory tests performed at the time of admission revealed an elevated C-reactive protein level (7 mg/dL; reference range: 0–0.3 mg/dL). Her white blood cell count was within normal limits ($4.81 \times 10^3/\mu L$; reference range: 4.8×10^3–$10.8 \times 10^3/\mu L$), as was her absolute neutrophil count ($3.97 \times 10^3/\mu L$; reference range: 1.5×10^3–$8.0 \times 10^3/\mu L$). The initial microbiologic diagnostic work-up, which included bacterial culture, acid-fast bacillus smear and culture of sputum samples, bacterial and fungal blood cultures, and serological testing for respiratory viruses, yielded negative results. The patient also tested negative for human immunodeficiency virus infection.

A chest radiograph taken at the time of admission (Figure 1a) revealed several nodules and masses of various sizes in both lung fields. Some of these lesions had air cavitation. An axial computed tomography (CT) image viewed using the lung window setting (Figure 1b) also disclosed several cavitary and non-cavitary pulmonary nodules and masses with faint surrounding areas of ground-glass opacity (halo sign). Masses with central air cavitation had thick and irregular walls, and they contained irregular septa-like structures. When viewed in the mediastinal window setting, one of these lesions exhibited a hypoattenuating area (Figure 1c). A coronal maximum intensity projection reformatted image (Figure 1d) did not reveal the occluded-vessel sign, indicating that the vessels within the lesions were patent. A small bilateral pleural effusion was also present.

On further investigation, it was established that the patient had no known history of malignancy or factors leading to immunocompromise, such as long-term steroid therapy or diabetes mellitus. In addition, there was no evidence of underlying vasculitis. The patient's cytoplasmic antineutrophil cytoplasmic antibody titer was within normal limits (1:2.6; normal level: <1:20), as was her perinuclear antineutrophil cytoplasmic antibody titer (1:2.6; normal level: <1:20).

To establish a diagnosis for the pulmonary nodules, bronchoscopy with bronchoalveolar lavage was performed initially. Histopathologic analysis of the transbronchial biopsy specimen revealed diffuse granulomatous inflammation, but it cannot differentiate between infection and types of granulomatous vasculitis such as granulomatosis with polyangiitis because of the insufficient tissue volume. No organism was detected in a bronchoalveolar lavage specimen. To establish whether the pulmonary nodules had a possibility of vasculitis,

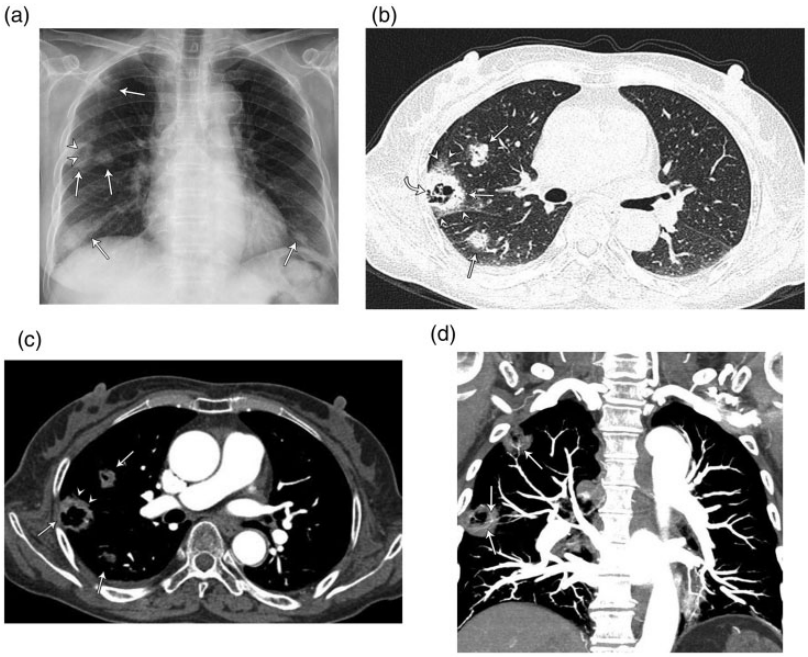

Figure 1. Radiologic findings in a case of *Fusarium* pneumonia in a 68-year-old immunocompetent woman. (a) A chest radiograph taken at initial presentation revealed several nodules and masses in both lung fields (arrows). One of these lesions had an internal area of cavitation (arrowhead). (b) An axial computed tomography image viewed using the lung window setting revealed several cavitary and non-cavitary pulmonary nodules and masses (arrows) in the right lung, with faint surrounding areas of ground-glass opacity consistent with the halo sign (arrowheads). Masses with central air cavitation exhibited a thick and irregular wall and featured irregular septa-like structures (curved arrows). (c) An axial computed tomography image at the same level as (B), viewed with the mediastinal window setting, disclosed an internal hypoattenuating area (arrow) in a mass in the right upper lobe. (d) A coronal maximum intensity projection reformatted image revealed patent vessels within the lesions.

video-assisted thoracoscopic surgery wedge resection rather than CT-guided biopsy was subsequently performed on the largest cavitary mass lesion in the right upper lobe. The results of histopathologic analysis of the surgical specimen revealed diffuse necrotizing granulomatous inflammation and the presence of some fungal spores (Figure 2a). Methenamine silver staining revealed yeast-like structures associated with hyphae (Figure 2b). At that time, the tentative pathologic diagnosis was necrotizing granulomatous inflammation, possibly caused by invasive aspergillosis. Intravenous (IV) voriconazole administration was initiated at 6 mg/kg every 12 hours, which is the usual dosage regimen for the treatment of aspergillosis. However, the patient's symptoms did not improve, and follow-up chest radiographs also revealed no evidence of improvement. After a few days of treatment with voriconazole, *Fusarium* species, but not *Aspergillus* species, were identified on sputum culture. Therefore, the treatment was revised to IV amphotericin B at 50 mg/day (1 mg/kg), which was temporarily switched to IV liposomal amphotericin B at 200 mg/day (4 mg/kg) because an increase in the patient's serum creatinine level.[6] After 5 weeks of treatment with amphotericin B

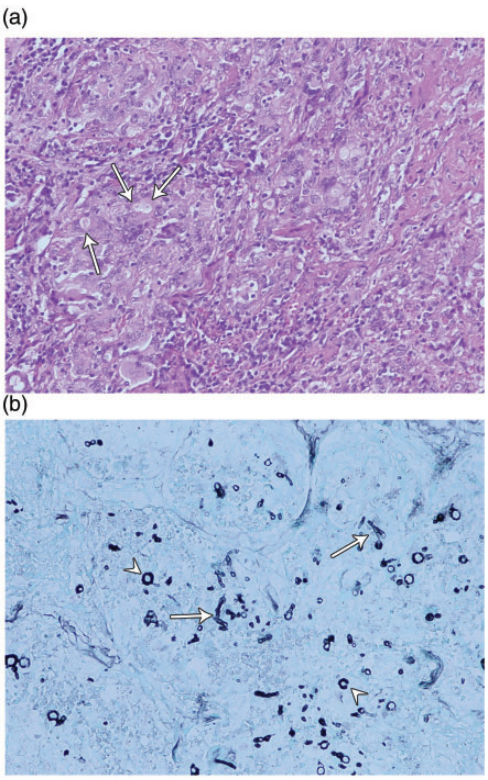

Figure 2. Pathologic findings in a case of *Fusarium* pneumonia in a 68-year-old immunocompetent woman. (a) A photomicrograph of a biopsy specimen revealed necrotizing granulomatous inflammation with visible fungal spores (arrowheads). (b) A photomicrograph of a biopsy specimen stained with methenamine silver revealed both yeast-like structures (arrowheads) and septate hyphae with acute-angle branching (arrows).

and liposomal amphotericin B, the patient's symptoms had improved, and subsequent follow-up chest radiographs illustrated that the extent of the lesions had decreased and the cavitary lesions had disappeared. Finally, the patient was discharged from the hospital.

Discussion

Fusarium species usually cause localized cutaneous infections in immunocompetent patients, whereas pulmonary involvement is rare in such patients. The exact mechanisms by which *Fusarium* species causes invasive infection in immunocompetent patients are not fully understood, but possible hypotheses have been described in the murine infection model.[7] In a previous study of a murine infection model, *F. oxysporum* persisted in the lungs of immunocompetent mammalian hosts in the form of chlamydospore-like survival structures.[7] After exposure to these ubiquitous fungi, although rare, the fungal survival structures might have the potential to initiate invasive infection.

The most common radiologic findings of *Fusarium* pneumonia in immunocompromised patients include nodules or masses, consolidations, and cavitary lesions with or without the halo sign.[8,9] These findings are non-specific, making it easy to misdiagnose *Fusarium* pneumonia as other conditions, such as neoplastic disease or granulomatosis with polyangiitis in immunocompetent patients[10] and other invasive fungal pneumonias such as *Aspergillus* pneumonia in immunocompromised patients.[11] Similarly as *Aspergillus*, *Fusarium* can invade the blood vessels and cause tissue necrosis. This mechanism of lung injury in *Fusarium* pneumonia presents radiologically as multiple pulmonary macronodules with internal hypoattenuating areas or cavities, occasionally with other radiologic signs of angioinvasion such as the halo sign.[8,9,12] The halo sign, observed when ground-glass opacity surrounds a pulmonary nodule, results from hemorrhage in the alveoli adjacent to the nodule or from perinodular inflammation. In immunocompromised patients, this sign is highly specific for early infection by an angioinvasive fungus.[13]

Fusarium pneumonia has been much less frequently described in immunocompetent patients than in immunocompromised patients. Specifically, only two published case reports described *Fusarium* pneumonia in apparently immunocompetent patients.[4,5]

In the first of these studies, CT revealed multiple small nodules, some consolidation and bronchiectasis, and mediastinal lymphadenopathy.[4] In the second report, CT revealed interstitial thickening predominantly in the subpleural area of the lungs, as well as mediastinal lymphadenopathy.[5] However, our case differs from these previous reports in that the CT findings resembled those typically observed in immunocompromised patients, namely multiple macronodules with cavitation and the halo sign.

Because the radiologic findings in *Fusarium* pneumonia are similar to those observed in other types of invasive fungal pneumonia, the radiologic diagnosis of *Fusarium* pneumonia is challenging. Histopathologic analysis can sometimes aid diagnosis; however, *Fusarium* species have a similar morphological appearance as *Aspergillus* species, and differentiation is sometimes difficult on histopathologic grounds alone, particularly for pathologists without extensive background knowledge of infectious disease histopathologic examination. In a previous study using fungal culture as the "gold standard," histopathologic misidentification of fungi was observed in 21% of patients.[14] To identify unique sporulation structures of *Fusarium* species, specialized examination by experienced microbiologists is required.[14] Similarly, our patient was initially diagnosed with *Aspergillus* infection via histopathologic analysis, but the diagnosis was changed to *Fusarium* infection after the use of microbiologic analysis. It is clinically important to distinguish *Fusarium* species from *Aspergillus* species because they have differing susceptibilities to pharmaceutical treatments. Typically, azoles are used as first-line antifungal agents for *Aspergillus* species; however, *Fusarium* species are usually more susceptible to amphotericin B than to the azoles.[6,15] A previous *in vitro* study reported that amphotericin B was the only drug with activity against *Fusarium* species.[15] The exact resistance mechanisms in *Fusarium* species are not entirely understood, but altered gene expression and effective drug efflux might be involved in azole resistance.[16]

In conclusion, we reported a rare case of *Fusarium* pneumonia in an immunocompetent patient. Chest CT revealed multiple nodules and masses and areas of consolidation. In addition, some lesions exhibited cavitation or internal hypoattenuating areas, and some were accompanied by the halo sign. These signs resemble those typically observed in immunocompromised patients with invasive fungal pneumonia. Our findings suggest that when invasive aspergillosis is suspected on the basis of radiologic and histologic findings, if the initial response to empirical antifungal treatment is poor, *Fusarium* pneumonia may be considered in the differential diagnosis. A definitive diagnosis can be established using microbiological analysis and fungal culture.

Ethics

The requirements for ethics approval and informed consent were waved by our institutional review board because our case report was anonymized and its public interest considerations outweighed possible harms.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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