

[CASE REPORT]

Fatal Invasive Pulmonary Aspergillosis Associated with Nonspecific Interstitial Pneumonia: An Autopsy Case Report

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Abstract:

Invasive pulmonary aspergillosis (IPA) usually occurs in patients with severe immunodeficiencies involving neutropenia. Underlying lung disease is a well-known risk factor of IPA; however, interstitial lung disease has not been recognized as a risk factor of IPA. We herein report a patient with fibrotic nonspecific interstitial pneumonia who experienced IPA without neutropenia. His IPA was fatal and showed unusually slow disease progression over one month. The computed tomography findings showed only nonspecific consolidation and no typical lesions suggestive of IPA. Finally, the autopsic findings revealed numerous *Aspergillus* fungi, neutrophilic pulmonary necrosis, and vessels invaded by *Aspergillus* fungi.

Key words: invasive pulmonary aspergillosis, nonspecific interstitial pneumonia, autopsy, prednisolone, cyclosporine A, immunocompetent

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Introduction

Invasive pulmonary aspergillosis (IPA) usually occurs in severely immunocompromised patients, including those with neutropenia, hematological disorders, hematopoietic stem-cell transplantation, or solid-organ transplantation (1, 2). IPA progresses rapidly, and the mortality rate is high (3). Although the development of IPA in patients who have not received severe immunosuppressive drug therapies is uncommon, IPA in those with chronic obstructive pulmonary disease (COPD) has been described recently (3, 4). It is likely that the existence of underlying lung disease is a risk factor of IPA.

We herein report a patient with fatal IPA associated with fibrotic nonspecific interstitial pneumonia (f-NSIP).

Case Report

A 78-year-old man underwent flexible bronchoscopy 2 years previously to evaluate his shortness of breath. Computed tomography (CT) showed reticular markings, slight traction bronchiectasis, lobar volume loss, and ground glass opacification (GGO) on both sides of the lungs. All autoantibodies that could be inspected at that time were negative. The bronchoalveolar lavage fluid revealed a cell count of $11 \times 10^5/\text{mL}$, and lymphocytes were dominant (62%). From these clinical and radiological results, the final diagnosis was f-NSIP, and prednisolone (PSL) 20 mg/day (approximately 0.5 mg/kg) was administered. However, as PSL was tapered over the following two years, the symptoms of shortness of breath worsened and were accompanied by increased GGO on chest CT findings (Fig. 1a). The dosage of PSL was 30 mg/day, and cyclosporine A (CsA) 100 mg/day was supplemented.

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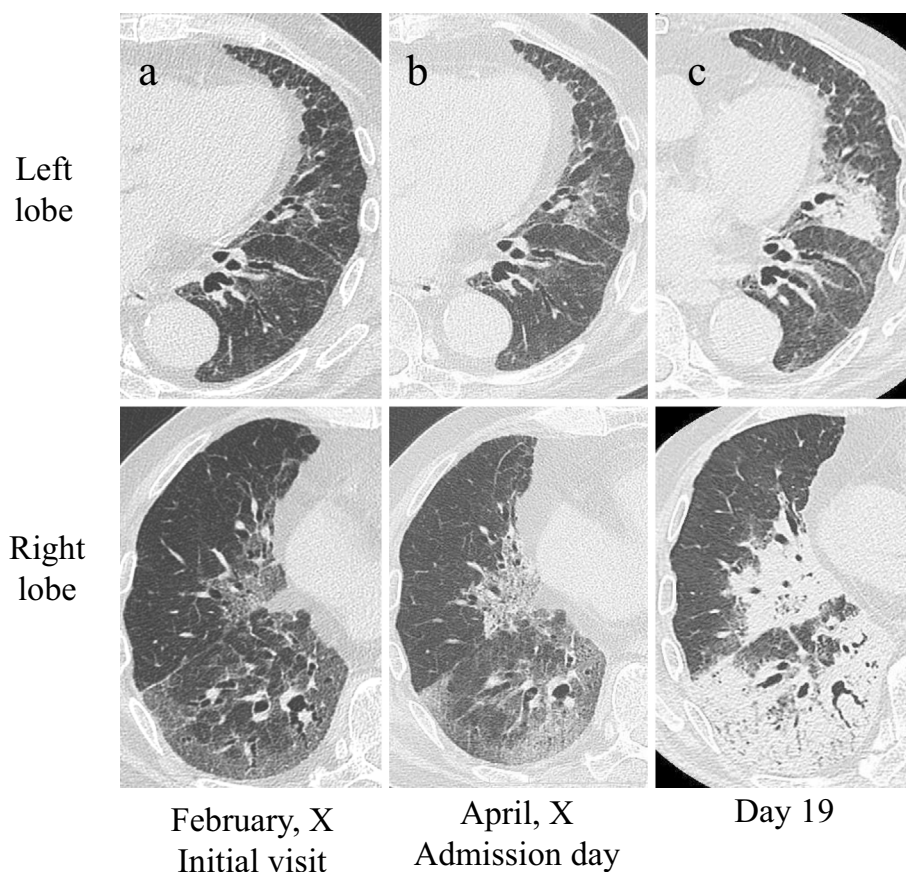


Figure 1. CT images of the development of pulmonary aspergillosis according to the lobes of the lungs. Chest high-resolution CT (HRCT) at the initial visit to our institute (a). Chest CT showed slightly expanded GGO accompanied by bronchiectasis (b). Chest CT on day 19 shows that GGO in both lungs had changed into nonspecific consolidation, and the area had spread (c).

Two months after intensification of the treatment, his respiratory condition deteriorated, and he was hospitalized. His subjective symptom was only cough without dyspnea. His arterial oxygen tension was 56.5 Torr, arterial carbon dioxide tension was 40.5 Torr on room air, and serum Krebs von den Lungen-6 (KL-6) was 2,628 U/mL on the day of admission. His hemoglobin A1c was elevated to 7.1%, indicating the development of steroid-induced diabetes mellitus (DM). Chest CT showed slightly expanded GGO with bronchiectasis (Fig. 1b). A pulmonary function test revealed a forced vital capacity (FVC) of 1.88 L, a percent predicted FVC 60.5%, and percent decreased diffusing capacity of carbon monoxide 42.3% at admission. CsA was increased to 150 mg/day for the disease control of NSIP.

The oxygen requirement further increased with deterioration of the chest CT findings on day 10 of admission. He was diagnosed with acute exacerbation of interstitial pneumonia, so high-dose corticosteroid (CS) therapy (methyl PSL 500 mg/day) was administered from days 11 to 13.

On day 14, the patient had a fever with excretion of a large amount of sputum, so antibiotics were administered. However, the fever did not lessen, and his respiratory condition deteriorated further. Chest CT showed that the GGO in both lungs had changed to consolidation, and the area had

spread by day 19 (Fig. 1c). β -D glucan, serum *Aspergillus* antibody, and *Aspergillus* antigen were 10,300 pg/mL, positive, and >5.0, respectively, and sputum culture revealed *Aspergillus* species. IPA was diagnosed, and antifungal agents were initiated; however, his respiratory condition was not improved. Although he underwent tracheal intubation, he ultimately died of respiratory failure on day 33. The clinical course is shown in Fig. 2.

A pathological autopsy revealed that both sides of the lungs were heavy and that necrotic lesions were observed macroscopically (Figs. 3a and 3b; arrows). Elastica Van Gieson (EVG) stain of the basal part of the left inferior lobe revealed homogeneous interstitial inflammation, fibrosis with thickening of interlobular septa, and no honeycomb lesions, findings that were compatible with f-NSIP (Fig. 3c). Many *Aspergillus* fungi were detected on the fibrotic parts and in airspaces (Fig. 3d). There were many lesions of bronchial pneumonia in the inferior lobe of the right lung (Fig. 3e). Some *Aspergillus* fungi had invaded the pulmonary arteries (Fig. 3f).

Discussion

Our report underscores the fact that the clinical course

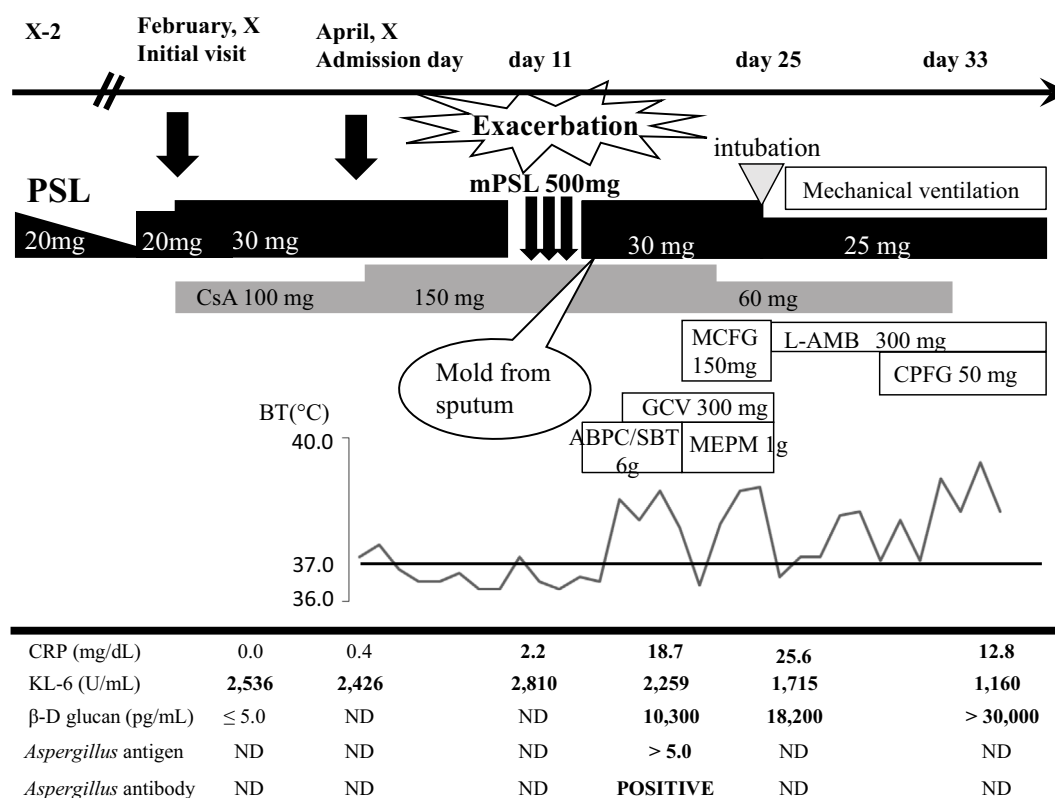


Figure 2. Clinical course and laboratory data. Our patient underwent high-dose corticosteroid therapy from days 11 to 13. Mold was detected from the sputum several times, and the β -D glucan levels became extremely elevated. The diagnosis was invasive pulmonary aspergillosis. Despite the use of antifungal agents, the patient ultimately died of respiratory failure on day 33. PSL: prednisolone, mPSL: methyl prednisolone, CsA: cyclosporine A, MCFG: micafungin sodium, L-AMB: liposomal amphotericin B, CPGF: caspofungin, GCV: ganciclovir, ABPC/SBT: ampicillin sodium/sulbactam sodium, MEPM: meropenem, BT: body temperature, CRP: C-reactive protein, KL-6: Krebs von den Lungen-6, ND: no data

and radiological manifestations of IPA in our patient were atypical because of underlying interstitial pneumonia.

Typical IPA is characterized by rapid disease progression within a few days and unique CT findings, including halo or air-crescent signs. However, IPA in our patient gradually progressed over the month after hospitalization. The time course was longer than for typical IPA. The relatively slow progression was atypical for IPA, and the unusual manifestation delayed the diagnosis and treatment. Furthermore, the chest CT findings in our patient showed nonspecific consolidation or GGO without halo or air-crescent signs. Therefore, we were confused as to whether acute exacerbation of interstitial pneumonia or infectious pneumonia had developed.

Generally, IPA occurs in patients who have been administered intensive immunosuppressive therapies that cause neutropenia. Many reports have noted that a major risk factor of IPA is prolonged neutropenia, as neutrophil phagocytosis is related to the biological defense mechanism in the lungs (2, 5). However, the development of IPA in our patient was unassociated with neutropenia; that is, he had a significant number of neutrophils. However, he had been administered CS and CsA. These medications suppressed the function of phagocytosis in neutrophils and alveolar macro-

phages and inhibited neutrophils from wandering in inflamed lesions. Because IPA is caused by inhaled conidia of *Aspergillus* floating in the air, deteriorated ciliary movement is a risk factor for IPA. The ciliary movement of the respiratory tract in the present patient was debilitated due to interstitial pneumonia, and this decline in pulmonary clearance by damaged cilia might have allowed *Aspergillus* fungi to colonize lungs. In addition, our patient had steroid-induced DM as well. A previous report showed that patients with DM were at a greater risk of developing respiratory tract infections than those without DM (6). The polymorphonuclear neutrophil function is decreased in diabetic patients, which increases the danger of infectious events (7). We believe that these consecutive factors additionally induced the development of IPA in our patient.

The radiological and pathological findings of IPA differ from those of patients with neutropenia (8). The radiological findings in patients with preserved numbers of neutrophils are characterized by irregular infiltration corresponding to histologically typical bronchopneumonia filled with acute inflammatory exudates with fungal rapid multiplication in alveoli. These findings share some similarities with the radiological and pathological findings in our patient (Fig. 1, 3),

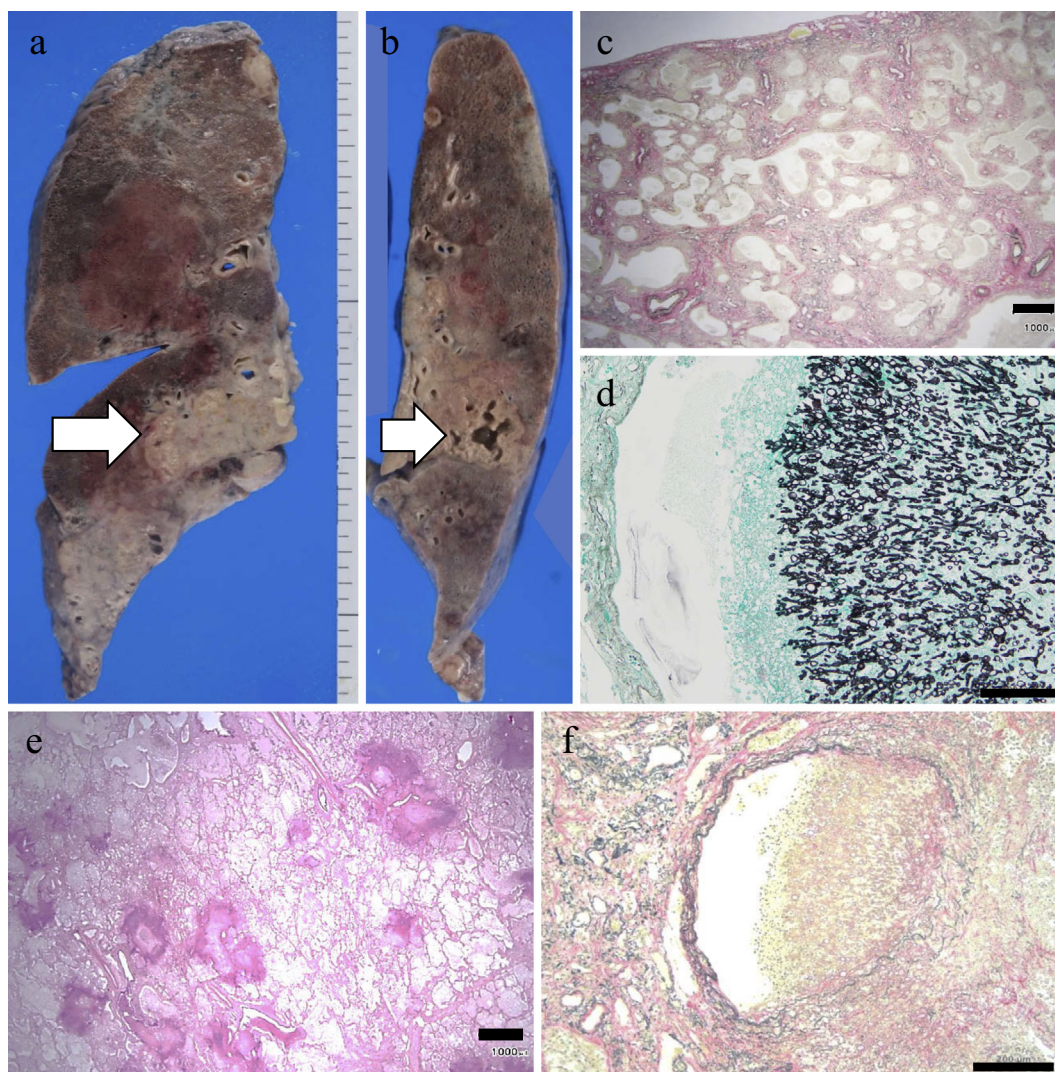


Figure 3. Pathological findings. Macroscopically, necrotic lesions were observed in the lungs [arrows, right (a), and left (b) sides]. EVG stain of basal part of left inferior lobe showed uniform interstitial inflammation and fibrosis, which is compatible with fibrotic nonspecific interstitial pneumonia (c: scale bar=1,000 μ m). There were numerous *Aspergillus* hyphae with Y-shaped branching on parenchyma and alveoli (Grocott's methenamine silver stain; d: scale bar=100 μ m). There were many lesions, such as bronchial pneumonia, in the inferior lobe of the right lung (e: Hematoxylin and Eosin staining, scale bar=1,000 μ m). *Aspergillus* hyphae invaded the pulmonary vessels (f: EVG stain, scale bar=200 μ m).

which were likely to have been caused by insufficient neutrophilic responses due to mild immunosuppression against *Aspergillus* infection.

Few case reports have noted IPA developing in patients with interstitial pneumonia (Table). No case has shown the typical radiographic signs of IPA, such as halo or air-crescent signs, although consolidation has been detected in all cases (9-12). These findings were also compatible with those in our patient. We should therefore not exclude the possibility of IPA based solely on nonspecific radiological findings.

The occurrence of IPA in patients with COPD has recently been reported in similar cases (3, 4, 13). In these patients, the ciliary movement was often injured by tobacco smoke and a number of infectious episodes. Damage to the

airways allows conidia to colonize the epithelial layers (13). It is believed that there are similarities between COPD and interstitial lung disease in terms of declined pulmonary clearance. Therefore, this suggestion emphasized the importance of underlying lung disease as a risk factor for IPA.

Another notable chest CT finding in our patient was GGO in the initial stage (Fig. 1). The GGO might be an initial lesion of aspergillosis; however, we were unsure whether the GGO indicated aspergillosis or NSIP. Checking the presence of *Aspergillus* antigen, also known as galactomannan, might be useful for diagnosing the disease in the early phase of IPA. The *Aspergillus* antigen is a polysaccharide found on *A. fumigatus* and secreted by growing hyphae. Marr et al. reported that the antigen might be useful for determining the likelihood of invading aspergillosis (14). We did not assess

Table. Review of 5 Cases of IPA Associated with IP.

No.	1	2	3	4	5 (present case)
Sex (age; years)	Male (56)	Male (71)	Male (79)	Female (75)	Male (78)
IP pattern	IPF/UIP	IPF/UIP	ND	ND	NSIP
Past medical history	Esophageal cancer	None	None	ND	DM, HT
WBC (NEU)	18,600 (17,763)/ μ L	ND	11,200 (ND)/ μ L	18,300 (15,189)/ μ L	13,400 (10,345)/ μ L
Treatment for IP	PSL (20 mg/day)	PSL (17.5 mg/day) + CsA (90 mg/day)	None	PSL (40 mg/day)	PSL (30 mg/day) + CsA (150 mg/day)
Administering mPSL pulse before developing IPA	+	-	-	-	+
CT image	Consolidation, GGO	Consolidation, fungus ball	Consolidation (Chest X ray)	Consolidation	Consolidation
Pathological findings of the lung	Abscess of <i>Aspergillus</i>	<i>Aspergillus</i> invading the pulmonary parenchyma	<i>Aspergillus</i> invading the pulmonary parenchyma, abscess of <i>Aspergillus</i>	<i>Aspergillus</i> invading the pulmonary parenchyma, necrosis	Abscess of <i>Aspergillus</i>
Outcome (cause of death)	Death (IPF acute exacerbation)	Death (ND)	Death (ND)	Death (ND)	Death (respiratory failure)
References	(9)	(10)	(11)	(12)	

CsA: cyclosporine A, CT: computed tomography, DM: diabetes mellitus, GGO: ground glass opacity, HT: hypertension, IP: interstitial pneumonia, IPA: invasive pulmonary aspergillosis, IPF: idiopathic pulmonary fibrosis, mPSL: methyl prednisolone, ND: no data, NEU: neutrophil, NSIP: nonspecific interstitial pneumonia, PSL: prednisolone, UIP: usual interstitial pneumonia, WBC: white blood cells

the presence of *Aspergillus* antigen at the initial visit in the present patient. If the positive conversion of the antigen can be identified in the early days, it might be a useful diagnostic tool in IPA.

The clinical course of developing IPA in our patient was similar to that of reactivation tuberculosis in patients with latent tuberculosis infection (LTBI). Reactivation tuberculosis can occur due to the use of immunosuppressive drugs. If our patient was indeed suffering from a latent *Aspergillus* infection similar to LTBI, then the use of CS and CsA might have triggered the development of IPA, similar to reactivation tuberculosis.

In conclusion, IPA with atypical manifestations can occur in patients with interstitial pneumonia. Constantly considering the potential presence of IPA can aid in the prompt diagnosis of such atypical IPA. Further reports should be accumulated to determine whether or not atypical IPA develops frequently in patients with interstitial pneumonia.

Author's disclosure of potential Conflicts of Interest (COI).

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