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Case Report

Resolution of secondary pulmonary alveolar proteinosis following treatment of rhinocerebral aspergillosis

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SUMMARY

Pulmonary alveolar proteinosis can be secondary to inhaled dust exposure, malignancy, and chronic pulmonary infections. However, pulmonary alveolar proteinosis secondary to extrapulmonary aspergillosis has never been reported. We report herein a case of pulmonary alveolar proteinosis secondary to invasive rhinocerebral aspergillosis. Neither immune modulators nor whole lung lavage was applied during the treatment course. The severe respiratory distress subsided, hypoxia resolved, and radiological infiltrates improved following the successful treatment of invasive rhinocerebral aspergillosis alone.

1. Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease with an estimated annual incidence of 0.36 and prevalence of 3.70 cases per million population.[1] The disease is sub-grouped into three types: congenital, idiopathic, and secondary. It is characterized by excess accumulation of diastase-resistant, periodic acid-Schiff (PAS)-positive granular lipoproteinaceous materials in the alveoli and terminal bronchioli due to the impairment of surfactant clearance by alveolar macrophages.[2,3] Aspergillosis is a common fungal infection of the paranasal sinuses in immunocompromised hosts, such as those with diabetes and patients with leukemia.[4] About 10% of the patients with invasive rhinal aspergillosis have central nervous system (CNS) involvement.[5] The mortality rate of rhinocerebral aspergillosis approaches 90%, even with vigorous surgery and antifungal chemotherapy.[6]

Secondary PAP accounts for less than 10% of the cases. Although it has been known to be associated with opportunistic infections, the development of PAP secondary to rhinocerebral aspergillosis in an immunocompetent patient has never been reported. Our case demonstrates the possible reversibility of secondary PAP after the resolution of the underlying causative infection and highlights the importance of early recognition in the treatment of rhinocerebral aspergillosis.

2. Case report

A 71-year-old woman presented to our hospital due to progressive exertional dyspnea and dry cough. She had also suffered from intermittent pulsatile headache, gustatory change, and postprandial vomiting for 2 months and had been treated for bacterial sinusitis with tension headache at local hospitals. There had been a 12-kg body weight loss within the past 10 months. The patient was a non-smoker and had no co-morbidities.

On admission, the patient was conscious. Her temperature was 37 °C, pulse rate 66 beats per minute, respiratory rate 20 breaths per minute, blood pressure 102/72 mmHg, and oxygen saturation 76–86% on room air. There was a left periorbital swelling, redness, ptosis, and pupil dilatation. Left third, fourth and sixth cranial nerve palsies were suspected. Chest examination disclosed fine crackles in the late inspiratory phase. Other physical and neurological examinations were unremarkable. Hemogram and blood biochemistry studies were within the normal range, except for an elevated lactate dehydrogenase level (LDH; 707 U/l, normal range 230–460 U/l). Serum tumor marker studies revealed elevated carcinoembryonic antigen (CEA; 18.6 ng/ml, normal <5.0 ng/ml) and carbohydrate antigen 19-9 (49.2, normal <37 U/ml). Blood gas analysis showed hypoxemia on room air (PaO_2 49.7 mmHg and $PaCO_2$ 35.5 mmHg). Autoimmune serology studies, sputum cytology and cultures were negative.

A standing chest radiography (CXR) showed bilateral diffuse interstitial infiltration and alveolar opacities (Fig. 1A). High-resolution computed tomography (HRCT) of the chest revealed

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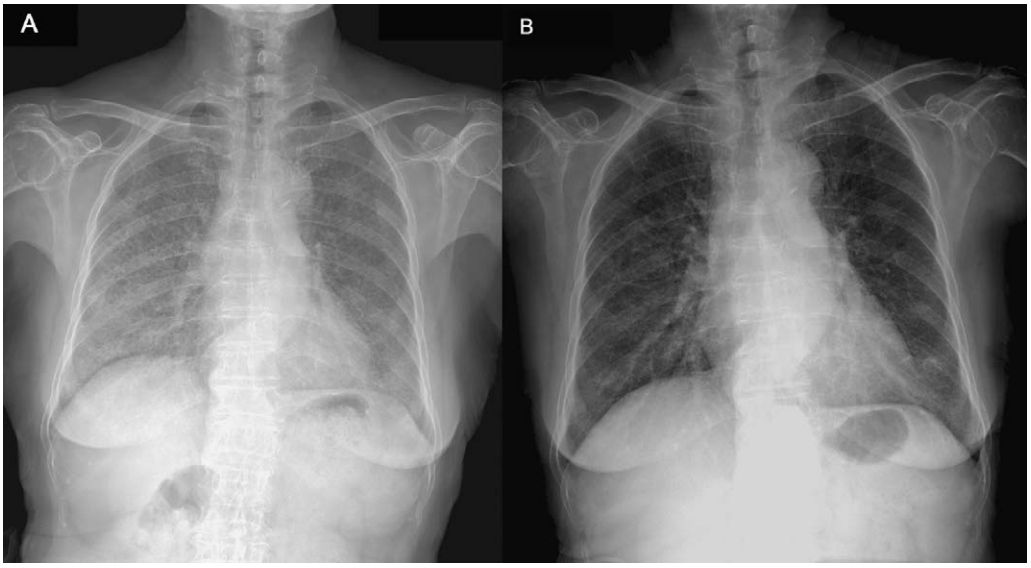

Fig. 1. The initial chest X-ray showed bilateral diffuse interstitial infiltration and alveolar opacities (A), which resolved after the successful treatment of rhinocerebral aspergillosis (B).

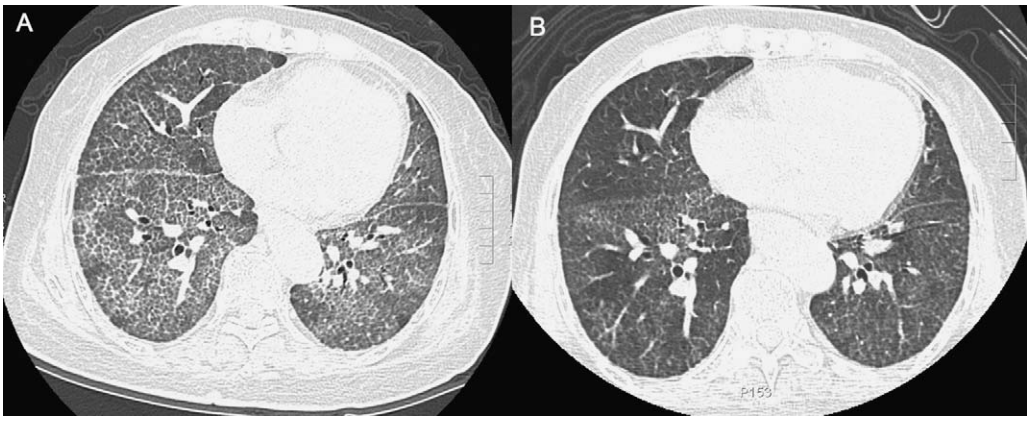

Fig. 2. The initial high-resolution computed tomography of the chest showed bilateral interlobular septal thickening on a background of ground-glass opacity in a crazy-paving pattern (A), which improved significantly after a 5-month antifungal therapy (B).

bilateral interlobular septal thickening on a background of ground-glass opacity in a crazy-paving pattern (Fig. 2A). A pulmonary function test disclosed a mild restrictive ventilatory defect with severe impairment of carbon monoxide diffusing capacity (DLCO). Brain magnetic resonance imaging (MRI) showed a 2.4 × 1.5 cm infiltrative mass at the left orbital apex, with left cavernous and left sphenoid sinus involvement. The tumor had a heterogeneous contrast enhancement and was with intermediate signal on both T1WI and T2WI images. Pulmonary alveolar proteinosis or bronchioloalveolar carcinoma was the initial differential diagnosis of the pulmonary lesions, and a sinonasal cancer, metastatic cancer, neurogenic tumor, or infectious process was the first impression according to the brain imaging findings. A video-assisted thoracoscopic lung biopsy and transethmoid sphenoid sinus biopsy were arranged. Histopathology studies from the pulmonary alveoli of two different lobes (right middle and right lower lung) showed diffuse filling with PAS-positive granular eosinophilic materials, indicating pulmonary alveolar proteinosis (Fig. 3A). In addition, there was no evidence of pulmonary infection, such as viral inclusion bodies, bacterial, fungal or mycobacterial infections, found on pathological studies or microbiological cultures. Results of sinus biopsy showed aggregation of septated, sharp-angled branching hyphae, and rhinocerebral aspergillosis was confirmed by microbiological culture (Fig. 3B).

Systemic antifungal therapy with liposomal amphotericin B (3–5 mg/kg/day, adjusted according to renal function status) and oral voriconazole (200 mg every 12 h) was administered after the tissue diagnosis. Monthly transethmoid surgery for sphenoidectomy, necrotic tissue debridement, and optic decompression was performed in the following 2 months. Transnasal endoscopy-assisted pus suction was done at two-week intervals. A brain MRI was carried out every 4 weeks. Although the lesion initially progressed with enlargement of size, occlusion of the left cavernous internal carotid artery, and small parietal infarcts, the patient's headache, vomiting, and left eye ptosis subsided; ophthalmoplegia and orbital apex syndrome improved; the gustatory abnormality recovered after 4 months. A brain MRI performed at the end of 5 months revealed a decreased lesion size. The antifungal combination therapy was administered for 5 months, followed by maintenance oral voriconazole therapy (200 mg every 12 h).

Taking into consideration the severity of the invasive rhinocerebral aspergillosis, no whole-lung lavage was performed throughout the treatment course, despite the initial poor oxygenation

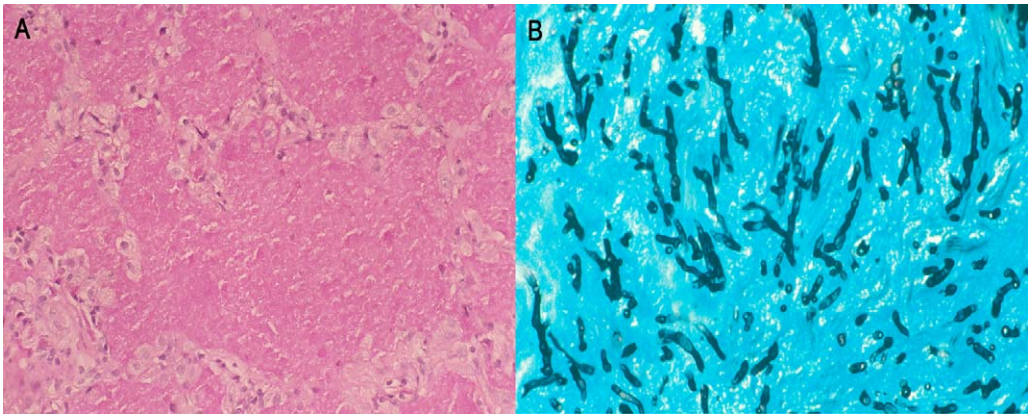

Fig. 3. (A) Histopathology of the lung showed diastase-resistant periodic acid-Schiff-positive eosinophilic granular material filling alveoli with intact interstitial architectures (periodic acid-Schiff stain, original magnification ×66). (B) Histopathology of the sphenoid sinus biopsied specimen showed aggregation of septated, sharp-angled branching hyphae (Grocott's methenamine silver nitrate stain, original magnification ×132).

status. Although the patient's dyspnea and oxygenation deteriorated in the first 2 months and she was dependent on a simple O_2 mask (40–98%, 8–10 l/min) to maintain the SpO_2 around 88–92%, her condition stabilized later under systemic antifungal therapy. At 4 months of antifungal therapy, the patient could tolerate an O_2 cannula (2 l/min) with the SpO_2 around 95%. At the end of 5 months, the patient could tolerate room air well, with an SpO_2 around 100% and the dyspnea resolved. A follow-up CXR (Fig. 1B) and chest HRCT (Fig. 2B) at 5 months showed marked improvement. Lung function tests revealed only mild impairment of DLCO. The patient made an uneventful recovery.

3. Discussion

PAP is a disease of macrophage dysfunction presented by poor phagocytosis of invasive pathogens. Pathophysiological mechanisms are involved in three ways: (1) by inhibiting ingestion of phagocytic particles; (2) by decreasing the rate of ingestion; and (3) by decreasing phagolysosome fusion. Alveolar macrophage dysfunction may increase the risk of an opportunistic 'pulmonary' infection, such as pulmonary aspergillosis. To our knowledge, this is the first report of secondary PAP associated with invasive extrapulmonary aspergillosis.

PAP usually presents with progressive dyspnea and a nonproductive cough. Pulmonary function tests typically reveal a restrictive pattern with disproportionate reduction in diffusion capacity. HRCT demonstrates thickening of interlobular septa with a ground-glass background in a crazy-paving appearance. Diagnosis of PAP is based on histopathological study.[3] Serum LDH, CEA, cytokeratin 19, mucin KL-6, and surfactant proteins A, B, and D may be elevated in patients with PAP.[7]

Secondary PAP can be associated with hematological malignancies, immunodeficiency disorders, inhaled chemicals, and opportunistic infections, with hematological malignancies being the most frequent.[8–10] Resolution of PAP has been reported in these patients whose hematological malignancies have been cured by either chemotherapy or stem cell transplantation.[11,12] Thus, it has been hypothesized that secondary PAP can resolve following treatment of the underlying disease.

The opportunistic organisms reported to be associated with PAP include Nocardia, mycobacteria, cytomegalovirus, *Pneumocystis carinii*, and Aspergillus.[9,10,13] Most of these infections are confined to the lungs, attributed to alveolar macrophage dysfunction and the nature of surfactant as being a good culture medium.[3] There are few reports of disseminated atypical Mycobacterium infections without pulmonary involvement[14] and primary cerebellar nocardiosis[15] in PAP patients. Moreover, all the reported cases in the literature concerning PAP and aspergillosis are in patients with hematological malignancies. The Aspergillus infections in these have been limited to the lungs,[16,17] except for one case in whom systemic aspergillosis was defined at autopsy.[18]

The clinical manifestations of rhinocerebral aspergillosis, such as facial tenderness and nasal obstruction, are often subtle, and a high degree of suspicion is needed to make an early diagnosis.[19] Periorbital swelling, ophthalmoplegia, and orbital apex syndrome signify orbital invasion; cavernous sinus and CNS involvement can develop rapidly.[19] Treatment of rhinocerebral aspergillosis includes extensive surgical debridement, irrigation of the affected cavity, and systemic antifungal therapy.[20] It has been reported that only 8.8% of patients with CNS involvement respond to amphotericin B.[21] Liposomal amphotericin B is an alternative and the dose should exceed 3 mg/kg in CNS infections.[22] The efficacy of caspofungin remains undetermined,[23] while voriconazole has been reported to be superior to amphotericin B and to have a good CNS penetrating ability. According to a cohort study, 35% of the patients partially responded to this drug and 31% of the patients remained alive after 390 days.[24]

In the patient reported here, fungal sinusitis was not initially disclosed and it progressed rapidly to invasive rhinocerebral aspergillosis. She presented to our hospital with respiratory distress, and physical examinations as well as imaging studies disclosed the coexisting diseases. No evidence of pulmonary aspergillosis was identified by chest images, histopathological studies, or cultures. Surprisingly, the pulmonary condition improved dramatically, both radiologically and clinically, following the successful treatment of rhinocerebral aspergillosis.

Our case demonstrates that PAP can resolve following the successful treatment of an underlying infectious disease. The case also highlights the critical impact of clinical alertness for the early diagnosis and management of rhinocerebral aspergillosis. Searching for a possible underlying etiology of PAP should be emphasized before it is categorized as idiopathic.

Conflict of interest

No conflict of interest to declare.

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