Rapid Formation of *Aspergillus mycetoma* in a Patient Receiving Corticosteroid Treatment. Serial Radiographic Observation Over Two Months

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**Abstract**

This study presents the case of rapidly progressing pulmonary aspergillosis in a 47-year-old woman who had healed cavitations of pulmonary tuberculosis in the right upper lobe. She had been treated for pulmonary tuberculosis seven years prior to admission. The initial manifestations of the disease on admission included cough, dyspnea, hemoptysis, pulmonary infiltrate, and renal failure. As anti-myeloperoxidase anti-neutrophil cytoplasmic antibodies (MPO-ANCA) were positive, she was diagnosed with ANCA-associated vasculitis and treated with corticosteroids. This treatment resulted in remission of the vasculitis. However, she developed new pulmonary symptoms and an enlarged cavitary lesion associated with the rapid formation of a fungal, ball-shaped shadow that was serially observed by radiological analysis. Pulmonary resection was finally performed because of acute progressive respiratory failure due to massive recurrent hemoptysis. A subsequent pathological analysis revealed a mass of hyphae with acute-angle branching, features consistent with *Aspergillus*, within the cavitary lesion, and she was diagnosed with pulmonary aspergillosis. The rapid development of pulmonary aspergillosis associated with the formation of an *Aspergillus mycetoma* should be attributed to the loss of normal immune mechanisms due to immunosuppressive treatment.

**Key words:** MPO-ANCA, aspergilloma, chronic necrotizing pulmonary aspergillosis, immunosuppression, renal failure

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**Introduction**

The clinical use of corticosteroids has expanded over the past few decades due to an increase in the number of cases requiring immunomodulation to treat various kinds of chronic disease (1). Control of the inflammation and the other aspects of the immune response result in severe immunosuppression, which may lead to infectious complications due to depressed resistance to a wide variety of infective agents (2). In this report, we describe a case of pulmonary aspergillosis associated with anti-neutrophil cytoplasmic antibodies (ANCA)-related vasculitis in a 47-year-old woman with the rapid formation of an *Aspergillus mycetoma* during a period of less than a few weeks. The patient had a past history of tuberculosis with healed cavities.

**Case Report**

A 47-year-old woman was admitted to our hospital in January 2005 with progressive fatigue, cough, fever, dyspnea, and hemoptysis. One month previously, she had visited another hospital with complaints of fatigue, persistent cough with blood-tinged sputum, and febrile episodes. She also had been treated for pulmonary tuberculosis seven years before admission. Although she had persistent cavities in the right upper lobe (Fig. 1), her sputum cultures of *Mycobacterium tuberculosis* became negative by medication and had remained negative until the previous year. No data regarding her previous renal function was available.

On admission, she was pale with periorbital and leg edema. Her blood pressure was 176/86 mmHg, pulse was 98
beats/min, respiratory rate was 20 breaths/min, and temperature was 37.6°C. Her oxygen saturation was 93% on room air, and bilateral rales were heard over the lung bases. Results of laboratory tests revealed a hemoglobin level of 6.9 g/dl, hematocrit of 19.9%, white blood cell count of 17500/μl, blood urea nitrogen of 56 mg/dl, serum creatinine of 3.51 mg/dl, and creatinine clearance of 7.0 ml/min. Serum electrolyte levels were as follows: sodium, 142 mmol/l; potassium, 4.8 mmol/l; and chloride, 108 mmol/l. A urinalysis showed active sediments with 50 to 100 red blood cells per high power field along with red blood cell casts. Blood gas values (breathing 28% oxygen) were PaO2 of 87 mmHg, PaCO2 of 36 mmHg, pH of 7.37, and bicarbonate of 21.1 mmol/l. A plain chest radiograph revealed a bilateral alveolar infiltrate pattern that was most noticeable in the right field, and a computed tomography (CT) scan of the chest demonstrated thick-walled cavities in the right upper lobe with diffuse alveolar consolidation affecting the entire right lung field and the left lower lobe (Fig. 1). ANCA with a perinuclear indirect immunofluorescence pattern and anti-myeloperoxidase activity (MPO-ANCA) were detected in the serum, reaching levels of 940 ELISA units (EU) (normal, <10 EU). Additional laboratory analyses revealed neither antiglomerular basement membrane antibodies nor proteinase 3 (PR3)-directed ANCA, while the complement levels were also found to be within the normal limits. The clinical picture suggested pulmonary-renal syndrome due to systemic vasculitis affecting the kidneys and lungs. A diagnosis of MPO-ANCA-associated vasculitis was made, and intravenous pulse therapy with methylprednisolone (mPSL) of 500 mg was given for three days followed by 0.8 mg/kg prednisolone (PSL) per day orally. Although recovery of renal function seemed to be temporal, prompt resolution of hemoptysis and chest radiography findings occurred with a decrease in levels of MPO-ANCA, which became negative after eight weeks of treatment (Fig. 1 and 2). At that time, however, the patient experienced a recurrence of frank hemoptysis. A chest radiograph showed the right apical cavity to have both pleural thickening and an irregularly shaped opacity projecting into it (day 64). CT scan also showed a round mass in the dependent portion of a large cavity in the posterior part of the right upper lobe, suggesting a mycetoma formation (Fig. 1, day 68). Eight days after beginning the steroid treatment, fluconazole (FLCZ, 100 mg per day), double tablets of trimethoprim-sulfamethoxazole (160 mg of trimethoprim, 800 mg of sulfamethoxazole; 2 times a week), and gargling with a 20× dilution of amphotericin B (100 mg/ml) were started for antimicrobial prophylaxis, although the rationale for the use of these drugs remains to be determined (3, 4). In addition to the exacerbation of her hemoptysis, the C-reactive protein levels became positive around on day 60. Therefore, we made a putative diagnosis of pulmonary aspergillosis, and on day 72 the patient was started on a treatment with intravenous micafungin sodium (MCFG) at a dose of 150 mg per day. She was intubated and placed on a mechanical ventilator on this day due to acute progressive respiratory failure owing to massive hemoptysis. Sputum cultures performed on days 72 and 74 revealed Asper-
Figure 2. Changes in the MPO-ANCA titer, in the counts of neutrophil and CD4 positive lymphocyte, and C-reactive protein (CRP). MPO-ANCA titer decreased and became negative after eight weeks of treatment. Although the patient was not neutropenic, absolute CD4 T-lymphocyte count was less than 250/μl when a CT scan revealed an aspergilloma in the cavitary lesion (day 68).

Figure 3. A histological analysis of resected pulmonary tissue. A: Photomicrograph of a specimen of the incised mycetoma, showing septate hyphae with acute-angle branching, which are features consistent with *Aspergillus*. B: Granulation tissue coated with a layer of fibrin-like exudates. The tissue specimen shows numerous blood vessels, edema, and a loose extra-cellular matrix associated with the infiltration of inflammatory cells. It was unclear whether or not *Aspergillus fumigatus* had invaded the pulmonary parenchyma. Periodic acid-Schiff stain (scale bar is indicated in each panel).

gillus fumigatus.

On day 93, pulmonary angiography and selective bronchial angiography were performed to delineate the sight of bleeding and to facilitate surgical decisions. The pulmonary vasculature seemed normal; however, a large tortuous right bronchial artery was seen running towards the diseased right upper zone. This artery was selectively embolized, and a right pneumonectomy was finally performed on day 105. The excised tissue included a 5×4×2.3 cm cavity containing a pasty brown substance. Histological examination of the resected right pulmonary tissue revealed an aspergillus mycetoma containing many necrotic aspergillus mycelia with exudative material (Fig. 3). Postoperative recovery was uneventful; however, her renal function deteriorated and she was started on a periodic hemodialysis program.

**Discussion**

The clinical presentation and pathological spectrum of pulmonary aspergillosis depend on the underlying structural
abnormalities of the lung and the immune status of the host (5). The most common and most recognized form of pulmonary involvement with Aspergillus is an aspergilloma. It is often a complication of cavitary lung disease caused by tuberculosis, sarcoidosis, or necrotizing pneumonia, as these cavities provide an environment conducive to saprophytic colonization (i.e., mycetoma formation) (5, 6). Of these diseases, pulmonary aspergillomas most commonly develop in preexisting tuberculous cavities. A British survey of 544 patients with tuberculosis showed that aspergillomas occurred 17% of the time (7). Although the process of pulmonary aspergillosis development has not yet been fully established, several studies reported that the time period required for formation of the pulmonary aspergilloma ranged from months to more than ten years and the average period was a few years, although the etiology of the underlying cavitary lung disease varied (8, 9). An aspergilloma may exist for long time without causing symptoms, although hemoptysis is a common occurrence (5).

Another form of aspergillosis that may be associated with mycetoma formation is chronic necrotizing pulmonary aspergillosis (CNPA) (10). It affects patients with altered local defenses resulting from underlying lung diseases such as previous pulmonary tuberculosis and chronic obstructive lung disease. It may also occur in mildly immunosuppressed patients with diabetes, poor nutrition, or low-dose corticosteroid treatment (11). The form of *Aspergillus* associated with CNPA triggers the inflammatory process that leads to tissue necrosis and cavity formation. The eventual formation of the mycetoma that is often present in this form of aspergillosis is a secondary phenomenon. Cough, fever, sputum production, and weight loss were the most commonly reported symptoms in the cases with CNPA (10, 12).

The present patient’s previous medical history of tuberculosis necessitated that radiological analysis be performed before admission. This imaging revealed the existence of open healed tuberculosis cavities without apparent evidence of mycetomas (Fig. 1). However, serial radiological observations after the initiation of corticosteroid treatment for ANCA-associated vasculitis (which would have predisposed our patient to CNPA) showed a growing of caviary lesion associated with the rapid formation of a spherical fungal shadow and an infiltration shadow around the cavity in right upper lobe within a few weeks. Since her hemoptysis worsened and her C-reactive protein level increased, we considered that she might actually have CNPA rather than an aspergilloma.

CNPA has been classified as a form of invasive aspergillosis distinct from the more classic forms of the condition such as aspergilloma, allergic bronchopulmonary aspergillosis, and acute pneumonic and disseminated aspergillosis. However, reports documenting the overlap of the various characteristics of pulmonary aspergillosis suggest a continuum of the same pathological mechanism (9, 10). It is therefore not surprising that our patient displayed overlapping manifestations of both an aspergilloma and CNPA. Indeed, we confirmed the presence of a mass of septate hyphae with acute-angle branching, features consistent with *Aspergillus* in the pre-existing cavity in the right upper lobe of resected lung. In addition, infiltration of inflammatory cells and extensive granulation tissue formation coated with a layer of fibrin-like exudates were observed within the wall of the cavity. We theorized that the corticosteroid treatment and pre-existing tubercular cavitary lesion had synergistically influenced the rapid progression to pulmonary aspergillosis. This conjecture partly explains why we failed to report the necrotizing granulomatous lesion located in the resected pulmonary tissue, (13). Since we neglected to measure the serum IgG antibodies to *Aspergillus*, which are positive in almost all cases of aspergillosis, it is unclear whether or not our patient was infected with *Aspergillus* before the initiation of the corticosteroid treatment (5).

The significant aspects of our patient’s presentation on admission were her renal issues and pulmonary hemorrhaging. No abnormal findings suggesting the presence of a pulmonary neoplasm or infectious disease were demonstrated by a sputum analysis (including cytology, Gram staining, and culturing). We also did not detect serum aspergillus antigens. This constellation of findings places the illness in the category of pulmonary-renal syndromes. Primary pulmonary-renal syndromes include Goodpasture’s syndrome, systemic lupus erythematosus (SLE), and small-vessel vasculitis. Our patient was positive for MPO-ANCA, which are known to be autoantibodies directed against cytoplasmic constituents of neutrophils (14). The association of ANCA with microscopic polyangiitis is well established, and ANCA can also be detected in other types of systemic vasculitis (such as Wegener’s granulomatosis) and occasionally in patients with rheumatoid arthritis, SLE, or inflammatory bowel disease (14). In the present case, there is no supporting evidence suggesting the presence of these diseases. Therefore, we concluded that MPO-ANCA-associated vasculitis plays a major role in the development of pulmonary-renal syndromes, although we failed to determine a pathological diagnosis because she refused a renal biopsy. Indeed, a radiological analysis on admission revealed a thick-walled cavitary lesion with diffuse alveolar consolidation. A prompt resolution of the radiological findings occurred after the initiation of treatment with corticosteroids (Fig. 1).

Corticosteroids exert anti-inflammatory and immunosuppressive effects via several pathways. These actions are accompanied with changes in the circulatory kinetics of leukocytes, alterations in the function in inflammatory cells, and modification of soluble mediators (15). Among these changes, neutrophilia is one of the characteristics of the effect induced by the administration of corticosteroids because of an increased intravascular half-life, increased bone marrow release, and decreased transfer from the circulation to extravascular site of inflammation. Neutrophilia is accompanied by a decrease in CD4 T-lymphocytes because of selective migration to the bone marrow and spleen (15). These effects on the intravascular leukocyte pool mitigate inflam-
matory and immunologic reactions, a favorable effect; however, these effects also diminish the participation of these inflammatory cells in eliminating microbial invaders. Although the distribution of neutrophils is considered sensitive, these cells seem to be relatively refractory in their function. On the other hand, cells of the monocyte-macrophage series are functionally sensitive to corticosteroids and exhibit reduced chemotaxis and killing activity (15). Therefore, it is reasonable to consider that monitoring of the number of lymphocytes, especially CD4 T-lymphocytes, may reflect the current condition of the immune system in patients receiving immunosuppressive agents including corticosteroids.

It is reported that a reduced helper T-cell count seems to result in severe infectious diseases with a significant risk of mortality, and that CD4 T-lymphocytopenia <250/μl was the best predictor for future infections in patients receiving chronic immunosuppressive treatment (16, 17). Our patient was not neutropenic (Fig. 2), but the rapid progression of pulmonary aspergillosis associated with mycetoma formation seemed to be implicated in the disturbed immune system suggested by the depletion of CD4 T-lymphocyte. Indeed, several studies of pulmonary aspergillosis have shown a dysfunction of macrophages and neutrophils, which are thought to provide natural immunity to aspergillus infections. This dysfunction included an impaired neutrophil oxidative burst in patients with reduced CD4 T-lymphocytes (18-20). There have also been several reports of pulmonary aspergillosis in patients with acquired immune deficiency syndrome with severe CD4 T-lymphocyte depletion (21, 22).

References
