CASE REPORT

Nodular invasive tracheobronchitis due to Aspergillus in a patient with systemic lupus erythematosus

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Nodular or pseudomembranous tracheobronchitis due to infection by Aspergillus species is an uncommon presentation of invasive aspergillosis. Most cases have been described in severely immunocompromised hosts. We describe the case of a 23-year-old woman, with recently diagnosed systemic lupus erythematosus, who developed worsening respiratory function. Bronchoscopy revealed rapid development and progression of multiple nodular plaques in her trachea and bronchi. Endobronchial biopsy demonstrated invasive fungal infection with tissue necrosis and the presence of hyphal elements consistent with aspergillosis. To the best of our knowledge, this is only the second report of fulminant invasive tracheobronchitis due to Aspergillus in a patient with an autoimmune disease. Lupus (2002) 11, 325–328.

Key words: aspergillosis; tracheobronchitis; systemic lupus erythematosus

Introduction

Pulmonary aspergillosis has been described in many immunocompromised patients, and can present as saprophytic colonization, allergic bronchopulmonary aspergillosis, aspergilloma and invasive aspergillosis. A form of locally invasive aspergillosis, invasive tracheobronchitis, has recently been described. Originally described in an AIDS patient, invasive tracheobronchitis can take the form of either locally invasive nodules of Aspergillus lining the trachea or can progress to a pseudomembrane extending over the trachea and bronchial tree. Similar forms of invasive aspergillosis have also been described in lung and bone marrow transplant recipients, patients with hematological and solid organ malignancies, and after chronic steroid treatment. Less than 30 case reports of invasive aspergillosis associated with systemic lupus erythematosus (SLE) have been reported. Only one of these reports described locally invasive tracheobronchitis occurring during a prolonged ICU stay, in a patient with a known, potential occupational exposure to Aspergillus. We report a second case of rapidly progressive, nodular invasive tracheobronchitis due to Aspergillus in a patient with SLE, who had received steroids and cyclophosphamide for less than 1 week and had no known exposure risk factors.

Case report

A 23-year-old woman was transferred to our intensive care unit for evaluation and management of shock, acute renal and liver failure, and respiratory distress. She had been well until September 1999, when a workup for oligoarthritis revealed an ANA titer of 1:640, but no malar rash or renal disease. Five months later, she presented to a local emergency room, where she was found to be hypotensive and had a witnessed tonic–clonic seizure. She required intubation, mechanical ventilation and vasopressor therapy. Her laboratory examination revealed a serum sodium of 113 mEq/l, creatinine 2.6 mg/dl, hematocrit 27%, white blood cell count 10x10^3 cells/mm^3, platelet count 55x10^3 cells/mm^3, AST 5000 IU, INR 1.6, and PTT 64s. Physical examination upon arrival revealed prominent facial edema, a distended...
abdomen with an enlarged liver, and active bleeding from sites of indwelling intravenous catheters. Fiberoptic bronchoscopy performed on the day of admission revealed erythematous and friable mucosa throughout the airways, but no endobronchial lesions. Bronchoalveolar lavage (BAL) fluid was grossly unremarkable. She received empiric fluconazole and piperacillin/tazobactam, and was started on cyclophosphamide (750 mg), high-dose methylprednisolone (1000 mg/day), and plasmapheresis for presumed severe SLE flare and antiphospholipid antibody syndrome.

Lupus serologies from the outside hospital drawn the day before transfer showed an ANA titer of 1:1280, the presence of anticardiolipin and double-stranded DNA antibodies, a C3 level of 44 mg/dl (normal 83–239 mg/dl) and a C4 level of 3 mg/dl (normal 10–63 mg/dl). Blood cultures drawn at the outside hospital on the day of her transfer grew *Neisseria sicca*, and blood cultures drawn at our hospital grew *Candida albicans*. Initial fungal stains of her BAL fluid demonstrated both yeast and mold, and high-dose penicillin and amphotericin B were started. BAL cultures ultimately grew *Candida albicans* and *Aspergillus fumigatus*.

Repeat fiberoptic bronchoscopy performed on ICU day 7 revealed diffuse whitish plaques with a cobblestone appearance throughout the trachea and bronchi. These lesions progressed to near confluence by ICU day 9 (Figure 1 A and B). Endobronchial biopsy revealed the presence of fungal forms with hyphae invading necrotic bronchial walls. Gomori’s methenamine-silver (GMS) staining demonstrated branched hyphae typical of *Aspergillus* spp. (Figure 1 C and D). Her condition progressively worsened and, in spite of aggressive therapy, she developed multiple organ system failure and died on ICU day 9.

**Discussion**

Infections with *Aspergillus* spp. have been described only rarely in SLE. Invasive aspergillosis more commonly occurs in patients with hematologic and other malignancies (often following bone marrow transplantation), AIDS, immunosuppression from chronic corticosteroid therapy, or after solid organ transplantation. An analysis of 23 cases of invasive

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**Figure 1** Fiberoptic bronchoscopy showing extensive, nodular white plaques presenting a cobblestone appearance throughout the airways. (A) Main carina and (B) right mainstem bronchus. (C) Endobronchial biopsy showing fungal hyphae within necrotic bronchial wall tissue (GMS×400). (D) Nodular mycelia-like aggregates that radiate in a ‘sun-burst’ arrangement (GMS×100). **Inset**: high power magnification showing branched, septate hyphae of *Aspergillus* species; (GMS×400).
aspergillosis in patients with SLE revealed high-grade disease activity (not defined), neutropenia (< 1000 cells/mm³), use of steroids or other cytotoxic agents, and the presence of bacterial co-infection as risk factors. In one series of eight cases of invasive aspergillosis, corticosteroids were administered at the time of Aspergillus infection; six of these patients had been given cyclophosphamide upon admission to the hospital. Despite antifungal therapy, the overall mortality was greater than 95%.

Early diagnosis of invasive aspergillosis may be important for implementation of appropriate therapy. Blood cultures are usually negative, and positive sputum cultures are often considered to represent contamination or colonization. In patients with a high index of suspicion, bronchoscopy with cytology and cultures from bronchoalveolar lavage have been shown to be > 90% specific. Unlike invasive aspergillosis involving lung parenchyma, invasive Aspergillus tracheobronchitis can usually be directly visualized and biopsied during bronchoscopy. The abnormalities exist as a continuum, ranging from erythematous and edematous tracheal mucosal ulcers, to multiple 2–3 mm raised cream-colored nodules or plaques lining the distal trachea or bronchi, to the presence of a pseudomembrane of fibrinous exudate. Endobronchial biopsies reveal the presence of narrow-angled hyphal forms, with invasion of underlying tissue. Only about 7% of patients with invasive aspergillosis have isolated invasive tracheobronchitis in the absence of parenchymal disease. In general, fungal tracheobronchitis is a benign disease discovered incidentally at autopsy. However tracheobronchitis caused by Aspergillus can invade and progress rapidly with a mortality rate of approximately 40–100%. Much like parenchymal invasive aspergillosis, neutropenia (< 1000 cells/mm³), protracted courses of corticosteroids, and broad-spectrum antibiotics have been correlated with development of invasive tracheobronchitis.

The role of corticosteroids and immunosuppressants in the evolution of invasive aspergillosis has been studied in animal models of the disease. Berenguer and colleagues have demonstrated that invasive aspergillosis is different in granulocyticotic rabbits, when compared to rabbits immunosuppressed with a combination of cyclosporin A and corticosteroids. Granulocyticotic animals had a higher mortality, more intra-alveolar hemorrhage, and extensive infiltration and angioinvasion by hyphae, whereas immunosuppressed rabbits demonstrated extensive neutrophil and macrophage infiltrates, minimal hemorrhage, and a paucity of angioinvasion or hyphae. These results are consistent with the finding that steroids impair macrophage-mediated inhibition of Aspergillus spore germination. Interestingly, it appeared that cyclosporin A alone did not contribute to the progression of invasive aspergillosis unless added to corticosteroid treatment. Together, these data suggest that the first line of host defense against Aspergillus conidia is mediated by pulmonary alveolar macrophages (suppressed by corticosteroids), and that the second line of host defense against Aspergillus hyphae is mediated by neutrophils (suppressed by cytokine-chemotherapy). The loss of both lines of defense in patients with autoimmune disease treated with steroids and cyclophosphamide may account for the rapidity of disease progression.

Although the patient we present did not have severe neutropenia (WBC nadir of 2.0), she was treated with corticosteroids, cyclophosphamide and antibiotics, and had a coexistent bacterial infection. These are known risk factors for the development of invasive aspergillosis and tracheobronchitis. This patient was given corticosteroids and immunosuppressants for less than 1 week, however, and it is possible that low complement levels may have played a role in her disease. The role of low complement levels in SLE and subsequent development of invasive aspergillosis has not been examined, although data suggest that complement may aid in phagocytosis of Aspergillus. The initial bronchoscopy showed no evidence of invasive aspergillosis, except for the growth of Aspergillus fumigatus from bronchoalveolar lavage fluid. Given the rapid progression of her disease, the erythematous airways seen at the time of her initial bronchoscopy probably represented early signs of infection. She might have been so severely immunocompromised by SLE that she was infected with Aspergillus prior to receiving steroids or cyclophosphamide. The most impressive aspect of her disease was the rapidity with which the invasive tracheobronchitis progressed. Over the course of 9 days, her airway abnormalities progressed from erythema to the development of confluent nodular lesions of invasive Aspergillus. This form of invasive aspergillosis should be considered in patients with SLE who have sepsis and respiratory failure, and the diagnosis can be easily made by bronchoscopy.

Aspergillus can lead to several known complications depending upon the organ systems involved. Disseminated aspergillosis can effect the lungs, intestines, brain, kidney and liver in decreasing order of occurrence. Invasive aspergillosis involving the pulmonary system can lead to a variety of complications depending upon the extent of invasiveness. The most life-threatening complication is massive hemoptysis due to growth and invasion of hyphae into pulmonary vasculature for which supportive care and surgery
may be the only treatment options. In addition, the development of a pseudomembrane of necrotic debris from invasive tracheobronchitis may also lead to the complication of acute airway obstruction. As noted by Clark et al, invasive tracheobronchitis may lead to other sequelae that are rarely seen due to the fact that most patients die during the acute illness. These sequelae may include focal tracheal or bronchial damage leading to stenosis or localized bronchiectasis.

The fatal outcome in our patient is similar to other reported cases of invasive tracheobronchitis in which the rapid nodular overgrowth by Aspergillus was terminal despite appropriate therapy. The standard treatment for invasive aspergillosis is Amphotericin B. However, overlapping nephrotoxicity with immunosuppressive drugs used in solid-organ transplant patients can limit its usefulness. Therapy with antifungal agents such as amphotericin B in severely immunocompromised patients has been largely unsuccessful in treatment of invasive tracheobronchitis, although oral itraconazole did prove to be of benefit in a series of lung transplant recipients. New drugs with in vitro activity against Aspergillus are being developed, including the new imidazole voriconazole and a new class of antifungals termed echinocandins. This latter class of drug targets fungal cell wall synthesis by inhibiting ß-glucan synthase, an enzyme unique to fungi. The role of intravenous imidazole therapy, possibly in combination with amphotericin B to induce synergistic killing, is not well known. Future studies of these therapies may offer insight into more successful treatment of this disease.

References