Invasive Pulmonary Filamentous Fungal Infection in a Patient Receiving Inhaled Corticosteroid Therapy

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We report a case of invasive pulmonary filamentous fungal infection in a patient with chronic obstructive pulmonary disease who was treated with a conventional dose of inhaled fluticasone in the absence of other causes of immunosuppression. This case demonstrates the potential risk for opportunistic fungal infections in patients treated with high-potency lipophilic inhaled corticosteroids.

A 63-year-old male smoker who had chronic obstructive pulmonary disease, hypertension, coronary artery disease, and normal-pressure hydrocephalus that had been treated with a ventriculoperitoneal shunt presented with an asymptomatic cavitating mass (size, 3 × 3.5 × 4.5 cm) in the right upper lung (figure 1A). CT performed 5 months before presentation had revealed a small nodular lesion (diameter, <1 cm) in the right upper lobe; the appearance of this lesion was unchanged on a CT scan obtained at the time of presentation. Fine-needle aspiration revealed necrotic material that was nondiagnostic. Histopathologic examination of material obtained from a wedge resection revealed invasive filamentous fungal infection that was morphologically consistent with infection due to an Aspergillus species (figure 1B–D). Material obtained from the fine-needle aspiration and the wedge resection was not submitted for culture. Although this case satisfies the criteria for invasive filamentous fungal infection, an alternative scenario is that the patient had a sterile pulmonary infarction due to thromboembolism, followed by fungal infection of the necrotic regions. Therapy with the cyclodextrin formulation of itraconazole (400 mg given orally daily) was initiated for the treatment of possible residual microfoci of infection. The patient has experienced no recurrence of disease since undergoing surgical resection in November 2000.

The patient had no history of unusual or recurrent infections. He had been treated with a conventional dosage of inhaled fluticasone (440 µg twice daily) for >2 years, but he had not received systemic corticosteroids during this period. Because invasive filamentous fungal infections are rare in a healthy host, we attempted to identify an underlying immunodeficiency. The results of tests for the detection of HIV were negative. The patient had circulating leukocyte and differential cell counts that were within normal ranges. The CD4 cell count (1307 cells/µL), CD8 cell count (1858 cells/µL), and natural killer cell count (349 cells/µL) were also within normal ranges. Lymphocyte proliferative responses to multiple antigens (tetanus and measles-mumps-rubella antigens, streptolysin O, and Candida albicans) were normal. The results of neutrophil function assays, including evaluations of chemotaxis, NADPH oxidase activity, myeloperoxidase levels, and CD11b, were normal. In view of the lack of detection of a systemic immunodeficiency, we propose that the inhaled fluticasone predisposed to the development of invasive filamentous fungal infection.

Systemic corticosteroids have profound effects on the distribution and function of neutrophils, monocytes, and lymphocytes that predispose to opportunistic fungal infections. Corticosteroids reduce adherence of the neutrophils to the endothelium, thus inhibiting migration of the neutrophils to inflammatory sites, and they also inhibit neutrophil fungicidal activity [1]. Corticosteroids elicit peripheral blood monocytes and depress a number of monocyte functions, including chemotaxis, bactericidal activity, and production of IL-1 and TNF-α (reviewed in [2]). Corticosteroids inhibit T cell activation, leading to reduced proliferative responses and cytokine production, and they also induce a redistribution of lymphocytes (predominantly T cells) out of the circulation, leading to peripheral lymphocytopenia [3]. In patients with collagen vascular disease, the incidence of infectious complications increases when the adult equivalent of 20–40 mg of prednisone is administered daily for longer than 4–6 weeks [4, 5].

Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease treated with systemic corticosteroids is well documented, although uncommon [6]. However, inhaled corticosteroids previously were not thought to increase the risk of systemic infections, although local mucosal infections have been documented. Leav et al. [7] reported a case of invasive pulmonary aspergillosis in a patient with asthma and adrenal insufficiency who was treated with high-
Figure 1.  A, CT scan of the chest showing a mass in the right upper lobe.  B, Histopathologic examination showed a central area of necrotic pulmonary parenchyma consistent with an ischemic infarct. This was surrounded by a rim of palisaded histiocytes, lymphocytes, plasma cells, and scattered eosinophils. Adjacent parenchyma exhibiting interstitial fibrosis with a mixed lymphohistiocytic and plasma cell infiltrate (hematoxylin-eosin; original magnification, ×40).  C, Numerous basophilic hyphae within the necrotic tissue (hematoxylin-eosin; original magnification, ×200).  D, Silver staining (Grocott-Gomori methenamine–silver nitrate; original magnification, ×400) showing that the hyphae were septated with 45-degree branching, consistent with Aspergillus species.

dose inhaled fluticasone (1760 μg daily). In contrast, our patient was treated with a standard dosage of inhaled fluticasone (440 μg twice daily) commonly used in clinical practice.

Pulmonary alveolar macrophages are the first line of host defense against Aspergillus infection targeted against the inhaled conidia, whereas neutrophils are targeted against the invasive hyphal stage. Given that high-potency inhaled fluorinated corticosteroids, such as fluticasone, are lipophilic, a slow rate of
clearance from the lung would be expected [8], which may further depress local pulmonary alveolar macrophage and neutrophil function. In addition to causing immunosuppression, corticosteroids have also been shown to directly stimulate the growth of *Aspergillus fumigatus* in vitro, possibly via sterol-binding proteins produced by the fungus [9].

The case report presented here and the report by Leav et al. [7] sound a note of caution regarding the long-term use of highly potent inhaled corticosteroids for patients with chronic obstructive pulmonary disease vis-à-vis the risk of development of opportunistic respiratory fungal infections.

**References**