Increasing Incidence of Invasive Pulmonary Aspergillosis and Its Early Diagnosis

**Key words:** fungal infection, drug-induced neutropenia, cefepime, ritodrine, halo sign, amphotericin B

Invasive pulmonary aspergillosis (IPA) is characterized by the invasion of normal lung tissue by *Aspergillus* organisms, usually resulting in significant tissue damage and necrosis. IPA most commonly develops in patients with impaired host defense. Its incidence has increased steadily in recent decades as more patients receive potent immunosuppressive agents in the course of therapy for malignancy or to prevent the rejection of transplanted organs (1).

IPA also occurs following exposure to certain medications not typically considered to be immunosuppressive. In this issue of the Journal, IPA was found in a puerperant with drug-induced neutropenia (2). The two drugs incriminated in the development of neutropenia were cefepime (a new cephalosporin antibiotic) and ritodrine (a β-sympathomimetic agent used for tocolysis). Neither of these drugs by themselves is considered to be immunosuppressive.

Neutropenia is a major predisposing factor for the development of IPA (3). The role of neutrophils in the innate host defense against *Aspergillus* is well documented in vitro (4) and in vivo (5). Recently, a case of IPA associated with anti-tumor necrosis factor (TNF) α therapy in Crohn’s disease was reported (6). TNFα plays a key role in recruiting neutrophils to the lungs in response to pathogens such as *Aspergillus fumigatus* (7). In both normal and neutropenic mice, antibody-mediated neutralization of TNFα is associated with an increase in mortality in animals challenged intratracheally with *Aspergillus fumigatus* (8).

The mortality rate from IPA is very high, exceeding 85% despite the best available therapy (9, 10). Survival of infected patients is improved by early diagnosis and the prompt initiation of therapy. However, long delays can result if the clinical suspicion of IPA must await confirmation by positive fungal cultures. Alternative methods to support the clinical diagnosis of IPA are available. Early evidence that a patient has IPA is provided by CT scans showing the development of a “halo sign”. This consists of a halo of ground-glass attenuation surrounding a soft tissue nodule (11). The “halo” is caused by hemorrhage of a central infected nodule that has become necrotic (12). In a prospective study of 30 patients with prolonged neutropenia, nodular lesions on plain chest radiographs, and the clinical suspicion of IPA, the halo sign was the single most effective method for confirming the diagnosis of IPA (13). In this patient group, IPA was present in 22/30 individuals (determined histologically and/or microbiologically). The presence of the halo sign on CT had a high sensitivity (16/22) and specificity (8/8). However, the halo sign was not universally present in patients with IPA (6/22), and can be found in subjects with other infectious diseases (and some non-infectious processes). Moreover, neutropenic patients are also at increased risk of developing fungal infections other than aspergillosis.

It is suggested that amphotericin B should be added to antifungal regimens whenever a neutropenic patient with cancer remains febrile despite 4–7 days of treatment with antibacterial agents (14). The rationale for the empiric addition of amphotericin B in this situation includes i) the increased likelihood that neutropenic patients will develop fungal infection, ii) the high rate of mortality from systemic fungal infection in these patients and iii) difficulty in culturing fungi from patients prior to systemic dissemination. The imidazoles (particularly fluconazole) may have prophylactic efficacy in this regard, but their spectrum of activity is narrower than that of amphotericin B and fluconazole is not effective against *Aspergillus*. Amphotericin B thus should be considered the mainstay of therapy for disseminated Candida and Aspergillus infection in the neutropenic patients.

In this report, two characteristic radiographic findings of IPA—the halo sign and air-crescent sign—were observed. The air crescent sign is typically associated with healing nodules, and results from cavitation of these lesions and their subsequent development of air crescents. The patient in this report was treated with itraconazole, which is a reasonable alternative to amphotericin B for the therapy of IPA (15). The patients received itraconazole after the development of air crescents. The good outcome is likely attributable to the development of IPA by an otherwise immunocompetent patient who was suffering from drug-induced neutropenia for a limited period of time. Considering the high mortality of patients with IPA, early initiation of antifungal therapy based on CT halo is advocated.

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References