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CONCISE ARTICLE

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Acremonium strictum Pulmonary Infection in a Leukemic Patient Successfully Treated with Posaconazole After Failure of Amphotericin B

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Abstract A severely neutropenic patient with chronic lymphocytic leukemia developed a diffuse bilateral pulmonary infection while receiving a therapeutic daily dosage of intravenous amphotericin B for *Candida glabrata* esophagitis. Computed tomography of the chest showed numerous lung nodules, ground glass areas and a pleural effusion. Biopsy of one nodule demonstrated hyaline septate hyphae. Multiple sputum cultures grew *Acremonium strictum*. Increasing the dose of amphotericin B and the addition of itraconazole did not resolve the infection. Change of treatment to posaconazole given orally at 200 mg four times/d resulted in progressive improvement leading finally to cure after 24 weeks of therapy. Treatment with posaconazole was clinically and biologically well tolerated.

Introduction

Acremonium (formerly *Cephalosporium*) spp. belong to the hyaline hyphomycetes. They are ubiquitous environmental contaminants typically found in soil and are commonly involved in superficial infections such as onychomycosis and keratitis or in mycetoma [1]. Invasive infections are less common and only a few have been related to *Acremonium strictum*. Reports of invasive infection include fungemia in a leukemic child, meningitis in a patient with Guillain-Barré syndrome receiving prolonged steroid therapy, brain abscess in a cancer patient and pulmonary or disseminated infections in patients with hematological disease [1, 2, 3, 4, 5, 6, 7]. The outcome of invasive infection from *Acremonium strictum* was usually poor; five deaths occurred among seven reported patients.

Acremonium spp. display little susceptibility to antifungal agents [1]. Fluconazole and flucytosine are ineffective. Some strains are susceptible to amphotericin B and to itraconazole. Recent in vitro data suggest that newer azoles may be effective against *Acremonium* spp. [8]. We present a case of severe pulmonary infection in a leukemic patient. The infection developed and progressed while the patient received amphotericin B. A change of therapy to posaconazole, a new broad-spectrum triazole available as an oral solution, was successful.

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Case Report

A 61-year-old woman, diagnosed with chronic lymphocytic leukemia 6 years earlier, was treated intermittently with chlorambucil. She was admitted to the hospital for persistent fever despite oral antibiotic therapy with clarithromycin followed by ciprofloxacin. She complained of retrosternal pain. Clinical examination showed multiple enlarged lymph nodes, oral thrush and several mouth ulcers. There was no evidence of hepatosplenomegaly.

Blood counts revealed severe neutropenia (neutrophils, 0/µl), lymphocytosis (lymphocytes, 61,940/µl) and moderate anemia (hemoglobin, 84 g/l) but no thrombocytopenia (platelets, 289,000/µl). Immunophenotyping of the lymphocytes was consistent with chronic lymphocytic leukemia. A bone marrow biopsy confirmed the complete absence of granulocytic lineage, massive lymphocytic infiltration and fibrosis. The patient was also severely deficient in immunoglobulins (IgG, 3.17 g/l; IgA, <0.23 g/l; IgM, 0.39 g/l).

Initial empiric therapy combined ceftriaxone, fluconazole and valacyclovir. The patient also received an infusion of immunoglobulins (1 g/kg). Culture of an oral swab grew both *Candida glabrata* and herpes simplex virus. Endoscopy revealed biopsy-proven esophageal candidiasis. A biopsy also grew *Candida glabrata*. Fluconazole therapy was changed to oral (4 g as oral suspension) and intravenous amphotericin B (0.5 mg/kg/d) after results of the cultures had been obtained. After 10 days of intravenous amphotericin B, the patient continued to be febrile and complained of retrosternal pain. The dosage of amphotericin B was then increased to 0.9 mg/kg/d.

Despite the increased daily dosage, the patient remained febrile. Although the upper digestive tract candidiasis improved and herpes lesions healed, she developed a cough, chest pain and a left pleural rub. A chest radiograph showed diffuse bilateral infiltrates

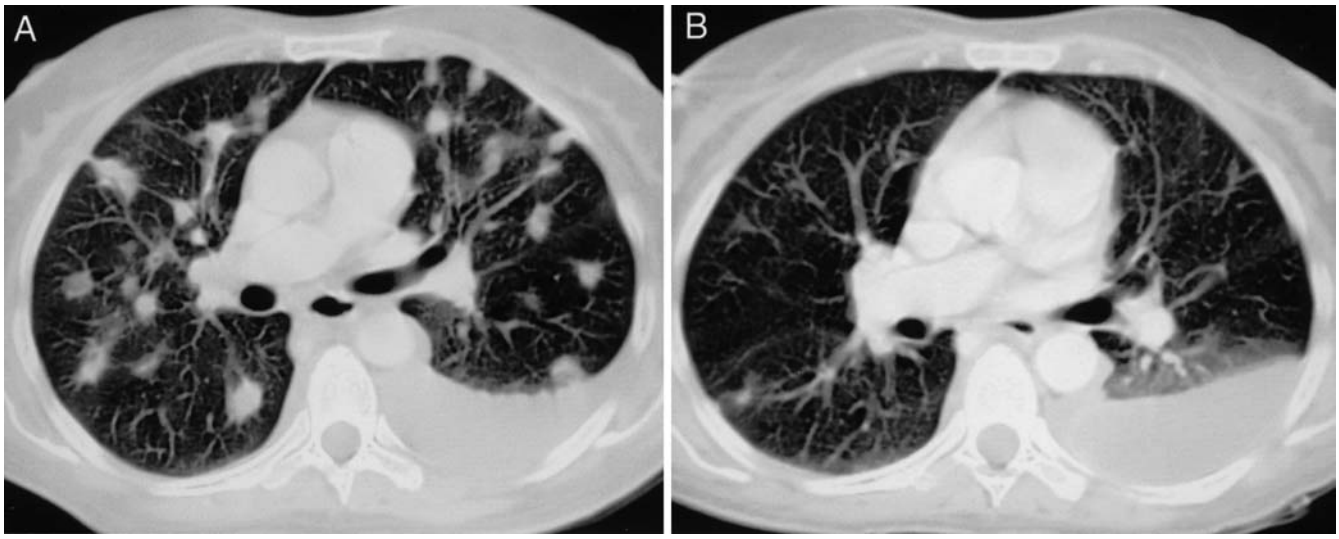

Fig. 1A, B Chest CT scan. **A** Baseline: multiple nodules disseminated in both lungs and left pleural effusion. **B** After 24 weeks of therapy with posaconazole: nearly complete disappearance of the pulmonary nodules; persistence of a left pleural effusion

Table 1 Minimum inhibitory concentrations (MICs) for various antifungal agents against the *Acremonium strictum* isolate

Incubation time	MIC (μg/ml)			
	Posaconazole	Itraconazole	Fluconazole	Amphotericin B
24 h	1	2	64	0.5
48 h	8	>8	>64	8

and a left pleural effusion. Computed tomography (CT) demonstrated multiple bilateral nodules with no halo sign, patchy ground glass areas and a left pleural effusion (Fig. 1). Itraconazole (600 mg/d) was added to the amphotericin B therapy. Granulocyte-colony stimulating factor was administered in an attempt to increase neutrophil counts, but was not successful.

As sputum cultures were still negative after 1 week of culture, a CT-guided fine-needle biopsy of one nodule was performed. Histopathological examination showed hyaline septate hyphae, but because the quantity of biopsy material was insufficient, no culture was done. On the basis of histologic proof of invasive fungal pulmonary infection together with continuous clinical and radiological signs of worsening infection, the patient gave her informed consent to be included in a salvage protocol with posaconazole.

At this time, the patient was still severely neutropenic. She had received a total cumulative dose of intravenous amphotericin B of 1250 mg given over 29 days in addition to 9 days of itraconazole therapy. Antifungal treatment was switched to oral posaconazole (200 mg four times/d). After 11 days of incubation, the initial sputum culture grew a filamentous fungus that was identified as *Acremonium strictum*. Six additional sputum specimens, obtained over the next 5 weeks after therapy with posaconazole had been initiated, also grew *Acremonium strictum*. Several pleural fluid cultures were negative.

After 3 weeks of posaconazole therapy, a CT scan of the chest showed slight improvement although the patient still had a mild fever. As the patient remained neutropenic and had a documented response to the change in antifungal therapy, we decided to begin intravenous chemotherapy combining fludarabine and cyclophosphamide supported by granulocyte-colony stimulating factor. This chemotherapy regimen resulted in the patient's unexpected complete recovery from neutropenia within 3 weeks.

After 21 weeks of posaconazole therapy, a chest CT scan showed nearly complete disappearance of the pulmonary nodules but persistence of the pleural effusion (Fig. 1). A second course of chemotherapy was administered, and the patient was discharged from the hospital. Antifungal therapy was continued for a total of 24 weeks. The final CT scan showed only a persistent pleural effusion. The patient was alive without any sign of infection 20 months after the end of therapy.

Despite concomitant cytotoxic chemotherapy, no clinical adverse effect with posaconazole was observed. With the exception of the patient's recovery from cytopenia related to chronic lymphocytic leukemia, there was no significant laboratory change during the 24-week course of posaconazole therapy.

Mycological Findings

Direct examinations of three sputum samples showed numerous hyaline septate hyphae. Sputum was cultured on Sabouraud chromogenic agar media (Candida ID; bioMérieux, France), incubated at 35°C for 7 days and then at 27°C. *Acremonium strictum* grew after 7–17 days of incubation. Species identification was based on morphological criteria after subculture on 2% malt agar medium incubated for 5 days at 27°C. After 7 days, colonies appeared moist and orange with a reverse turning to orange. Microscopic examination showed slender hyaline septate hyphae with slender phialides (20–60×1.4–2.5 μm) arising from the mycelium or from simple or occasionally branched short conidiophores. Phialides produced cylindrical smooth-walled hyaline conidia (3.3–5.5× 0.9–1.8 μm) that remained grouped in slimy heads.

Minimal inhibitory concentrations were estimated using a broth dilution method that followed the National Committee for Clinical Laboratory Standards recommendations for filamentous fungi (M.G. Rinaldi, Clinical Laboratory Science, University of Texas Health Science Center, San Antonio, TX, USA). Results appear in Table 1.

Table 2 Summary of *Acremonium strictum* invasive infections published in the literature that includes the present case

Reference	Age (y)	Sex	Underlying condition	Site of disease	Treatment	Patient outcome
[1]	60	F	bronchoalveolar carcinoma	brain	none	died
[2]	7	M	acute lymphoblastic leukemia	blood, intravenous thrombus	amphotericin B, flucytosine, surgery	cured
[3]	15	M	chronic granulomatous disease	lung	amphotericin B, ketoconazole	cured
[4]	9	M	Guillain-Barré syndrome	CSF	amphotericin B	died
[5]	62	M	myeloma	lung, kidney, spleen, skin,	amphotericin B, flucytosine	died
[6]	45	M	chronic granulocytic leukemia, blast crisis, neutropenia	blood, skin	amphotericin B	died
[7]	20	NR	multiple trauma	lung, skin	none	died
Present case	61	F	chronic lymphocytic leukemia, neutropenia	lung	amphotericin B, itraconazole, posaconazole	cured

NR, not reported; CSF, cerebrospinal fluid

Discussion

As with most other filamentous fungi, diagnosis of invasive *Acremonium* infection is difficult. Early diagnosis often requires the use of invasive procedures. Noninvasive samples are typically positive only in advanced disease. Furthermore, *Acremonium* spp. grow slowly. To ensure detection of a positive sample, cultures must be kept for at least 2 weeks. The high incidence of poor outcome may in part be related to this lengthy delay in diagnosis.

In most cases reported in the literature, speciation was not done. When strains have been identified, *Acremonium strictum* and *Acremonium kiliense* are most frequently involved [1, 2]. Other identified species include *Acremonium falciforme, Acremonium roseo-griseum, Acremonium alabamense* and *Acremonium recifei*.

There is no standard treatment for invasive *Acremonium* infection. According to the literature, deoxycholate or a lipid formulation of amphotericin B was given to 24 of 32 patients who received antifungal therapy [1, 2]. Regardless of the treatment given, 12 (38%) patients failed therapy. Five of the seven patients with an identified invasive *Acremonium strictum* infection died (Table 2).

In vitro susceptibility tests showed low minimal inhibitory concentrations at 24 h for posaconazole and amphotericin B. At 48 h, the minimal inhibitory concentrations were significantly higher for both antifungal agents. For itraconazole the minimal inhibitory concentrations at 24 and 48 h were above the usual range of the serum levels obtained in patients.

The efficacy of posaconazole has been investigated both in vitro and in vivo. In vitro, posaconazole has shown potent activity against a broad spectrum of common and uncommon yeasts, dimorphic fungi and molds [8, 9]. In vitro posaconazole has been found to be very active against all species of *Aspergillus* at lower concentrations than itraconazole and amphotericin B. Posaconazole shows comparable to greater efficacy relative to amphotericin B or itraconazole in models of murine aspergillosis [10, 11, 12]. Posaconazole also demonstrates efficacy in various animal models of other invasive fungal infections [10, 12, 13, 14].

We have presented the successful outcome of a patient treated with oral posaconazole despite massive bilateral pulmonary infection and previous failure on lengthy amphotericin B and itraconazole therapy. These results are encouraging in that, even in a difficult-to-treat patient population with a history of failure on other therapies, this case provides anecdotal evidence that posaconazole is safe and effective. Similar favorable responses to posaconazole were observed in patients with proven or probable invasive fungal infections refractory to standard therapy. Response rates to posaconazole in these patients with aspergillosis, fusariosis, cryptococcosis, candidiasis and phaeohyphomyces ranged between 44% and 80% after 4–8 weeks of treatment [15]. Our positive results against an uncommon and particularly severe infection in a difficult treatment scenario are encouraging and underscore the potential for this new azole.

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