Case Study: Posaconazole Treatment of Disseminated Phaeohyphomycosis Due to *Exophiala spinifera*

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A 41-year-old woman with no known immunosuppression experienced a 12-year period of a relapsing phaeohyphomycosis. Despite administration of multiple courses of therapy with standard antifungals, sustained clinical remission was not achieved. A partial response was seen initially with the combination of itraconazole and flucytosine therapy, but the patient did not respond to subsequent treatment. During the patient’s pregnancy, the mycosis became disseminated, with lymphadenopathy and fever, and was considered life threatening. Despite receipt of parenteral amphotericin B therapy, the patient did not show a clinical response. After premature delivery by cesarean section, treatment with oral posaconazole suspension (800 mg/day) was started. The patient’s condition improved within 1 week after initiating treatment; therapy was continued for 13 months. During posaconazole treatment, the patient showed a complete clinical response, with negative results of fungal cultures.

The term “phaeohyphomycosis” [1] defines subcutaneous or systemic mycoses caused by dematiaceous fungi, which, in their parasitic form, occur as septate hyphae, spherical cells, or yeast-like elements with dark brown cell walls [2]. A wide range of organisms can cause phaeohyphomycosis; >100 species and >60 genera of fungi have been implicated [3]. *Exophiala spinifera*, a dematiaceous fungus infrequently isolated in phaeohyphomycosis, was first identified in a sample of a nasal septum lesion obtained from a patient with tuberculosis and was initially referred to as “Phialophora spinifera” [4]. By 1992, 6 cases of phaeohyphomycosis involving *E. spinifera* had been established [5].

*E. spinifera* is a cosmopolitan fungus that lives on plant debris. Its morphological and culture characteristics are very similar to those of *Exophiala jeanselmei*. In recent years, several new cases of phaeohyphomycosis caused by *E. jeanselmei* and *E. spinifera* have been reported, both in humans and cats, and have exhibited a variety of clinical patterns, including subcutaneous pseudocystic lesions, peritonitis, and systemic infections [1, 6–15]. A report of 5 serious cases caused by dematiaceous fungi noted not only that infection due to this group of organisms is increasing, but also that species such as *E. jeanselmei* are exhibiting unusual manifestations [16].

The combination of a triazole antifungal agent (e.g., itraconazole or fluconazole) and flucytosine therapy, with or without surgical excision, has been used successfully to treat subcutaneous dematiaceous infection in adult patients [2, 5, 7, 10, 11, 14, 17, 18]. In vitro susceptibility studies of antifungal agents have shown that fungi of the *Exophiala* genus are susceptible to azoles, terbinafine, and flucytosine [19–21]. Posaconazole, a new triazole in clinical development, exhibits the broadest spectrum of antifungal activity of the newer antifungal agents (e.g., voriconazole and ravuconazole) [22] and is highly active against *Exophiala* species [12]. In both in vitro experiments and animal...
models, posaconazole demonstrated superior activity against dematiaceous fungi [23, 24]. In isolates recovered from 9 patients with *E. jeaneselmei*, the activity of posaconazole was equal to or greater than that of amphotericin B, itraconazole, and voriconazole [12]. These preclinical data suggest that posaconazole may be a rational choice for the treatment of serious infections due to *Exophiala* species. We summarize a case of disseminated phaeohyphomycosis caused by *E. spinifera* that was successfully treated with posaconazole.

**PATIENTS AND METHODS**

In October 1990, a 32-year-old white woman was referred to the mycology unit of Francisco Javier Muñiz Infectious Diseases Hospital (Buenos Aires, Argentina) with clinical signs and symptoms consistent with disseminated phaeohyphomycosis. Previous medical history was significant for asthma, which had been controlled with intermittent courses of oral corticosteroid therapy ~10 years before presentation, and congenital renal agenesis. She did not use tobacco products or drink alcohol and did not appear to have any hormonal or congenital immune disorders.

Initial physical examination revealed an afebrile patient in good general health. An erythematous, slightly papular skin plaque with definite borders (area, 2 × 2.5 × 2.5 cm) was present on the right side of her forehead, and similar, smaller lesions were identified in both inguinal folds and the left elbow. A chest radiograph showed right side, superior mediastinal lymphadenopathy. Lymphadenopathy was noted also in the right preauricular, carotid, and inguinal nodes. Abdominal ultrasonography revealed left-kidney agenesis. Results of electrocardiographic analysis and hematologic tests were within normal limits, and no humoral or cellular immunodeficiencies were identified. Immunoglobulin concentrations were normal, with the exception of low IgA levels. Because the patient’s sister also had phaeohyphomycosis (due to *Alternaria tenuis*) and had 2 children with Down syndrome, genetic screening was performed, but no abnormal findings were observed.

Results of tests for Chagas disease, toxocariasis, and other fungal and parasitic infections were negative. Direct microscopic examinations of a skin biopsy specimen and a needle aspirate obtained from a cervical lymph node revealed dark, septate, branching hyphae and dark spherical elements, which looked like chlamydospores. Cultures yielded several dark colonies. A metabolic antigen and a cytoplasmic antigen from the organism were prepared according to techniques previously described in the literature [25]. Results of immunodiffusion tests in agar gel with both antigens indicated an active infection.

At the end of November 1990, treatment with itraconazole (200 mg/day po) and flucytosine (5 g/day po)—a regimen typically used at our institution for treating chromoblastomycosis—was initiated for treatment of disseminated phaeohyphomycosis due to an unidentified organism. Three months after the initiation of therapy, the skin lesions disappeared, the preauricular adenopathy significantly decreased in size, and only palpable adenopathy of the right carotid chain persisted. Microscopic examination of a specimen of the carotid lymph node obtained during biopsy revealed dark septate hyphae and globular chlamydospores. Eventually, the fungal pathogen was identified as *E. spinifera* [4], on the basis of both macroscopic appearance of the fungus in culture and microscopic examination of fungal morphology (figure 1). This identification was confirmed by Michael McGinnis (University of Texas at Galveston) using similar techniques. Therapy was continued for a total of 8 months.

During the next several years, the patient experienced multiple relapses and received various antifungal therapies, with the duration of remissions decreasing over time (table 1). In June 1999, at the age of 41 years, the patient became pregnant, and the mycosis increased in severity over the next several months. At this time, itraconazole therapy was discontinued, and treatment with amphotericin B (50 mg/week iv) was initiated; higher amphotericin B doses could not be administered because of anemia (hemoglobin level, <10 g/dL), hypokalemia, and renal agenesis. A premature delivery by cesarean section was performed in November 1999. The baby was of normal weight for gestational age and did not have obvious lesions. At the time of delivery, the patient was febrile (temperature, 38.6°C) and had vegetating, verrucous lesions on the upper limbs and back, generalized lymphadenopathy, and small papules on the forehead and thighs. The skin lesions were draining a purulent, foul-smelling exudate. The left knee was painful, immobile, and swollen because of a new joint effusion. Visual acuity was diminished, with diffuse, white-yellow exudative foci and flame-shaped hemorrhages in the left eye; similar lesions developed in the right eye. Results of laboratory tests revealed leukocytosis with eosinophilia, increased erythrocyte sedimentation rate, and anemia, and cultures of samples obtained from several lymph nodes and the skin revealed *E. spinifera*.

Because the patient’s disease was refractory to all available antifungal agents, salvage antifungal therapy was initiated with posaconazole suspension (800 mg/day po, given in 4 divided doses after meals). After 7 days of treatment, the patient was afebrile and markedly improved. Two weeks after initiating treatment, changes in the left eye suggested stable endophthalmitis, and, after 1 month, the left-knee swelling and pain had resolved, but an MRI showed a hypointense bone lesion. The patient was discharged receiving posaconazole suspension (400 mg b.i.d.).

After 2 months of posaconazole therapy, the disseminated suppurative lymphadenopathy and verrucous skin lesions had markedly improved. After 5 months, the generalized adeno-
Figure 1.  A, Histopathologic analysis of a lymph node biopsy specimen showing numerous giant cells with round brown bodies inside. (Hematoxylin-eosin stain; original magnification, ×400.) B, Microculture of *Exophiala spinifera*. (Lactophenol cotton blue stain; original magnification, ×1000).
pathy and skin lesions continued to improve, but the inflammation in the vitreous humor and macular zone of the right eye persisted, and the left eye exhibited a cicatrical focus. After 6 months, cultures of skin biopsy specimens were negative for fungi. After 7 months, only lymphadenopathy in the right axilla remained, and results of microscopic examination and culture of aspirated material were negative. However, microscopic examination of a skin biopsy specimen showed scarce spherical septate mycotic elements, with brownish pigment in the dermis. The patient underwent surgery on her left knee for an osteolytic lesion in November 2000, and microscopic examination of a tissue biopsy specimen revealed brownish hyphae compatible with phaeohyphomycosis; however, cultures of specimens obtained from the lesions showed no growth. Postoperatively, the patient continued to receive posaconazole therapy, with continued improvements in radiographic findings and results of clinical examinations, eliminating the need for a bone graft. By the middle of December, the skin and lymph node lesions had healed completely.

Clinical and mycologic cures were achieved within 13 months after initiating treatment with posaconazole for disseminated phaeohyphomycosis involving the eye and bone, in addition to the cutaneous and lymphatic systems. Posaconazole therapy was subsequently discontinued. Approximately 4 months later (April 2001), a small, fluctuating, left preauricular nodule was found, and specimens that were obtained for culture grew E. spinifera. Three months later, lymphadenopathy was evident in the left posterior cervical chain, and 2 mobile, enlarged lymph nodes were found in the right axilla. In November 2001, posaconazole therapy (400 mg b.i.d. po) was started on an outpatient basis and was continued at that dose at the time of writing. As of February 2003, maintenance therapy for a total of 24 months was planned. Since restarting posaconazole, the patient has had an excellent clinical and mycologic response, with no signs of active lesions. Posaconazole therapy has been well tolerated after a duration of exposure of 2 years.

**DISCUSSION**

Phaeohyphomycosis comprises a wide range of clinical manifestations and has a very poor prognosis. This infection affects both immunocompromised and immunocompetent hosts [2, 26, 27]. Regardless of the patient’s immune status, mortality rates for disseminated phaeohyphomycosis are high (79%) [3]. Because of the diversity of etiologic agents and clinical manifestations, a treatment of choice for phaeohyphomycosis is lacking [2, 5].

In our experience, phaeohyphomycoses do not respond well to therapy, and relapses are common. Current treatment primarily involves flucytosine in combination with amphotericin B or a triazole compound [17]. For this patient, we initially chose a treatment regimen normally used for chromoblasto-

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**Table 1. Chronology of clinical events for a patient with phaeohyphomycosis.**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Signs and/or symptoms</th>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct 1990</td>
<td>Initial presentation to mycology unit</td>
<td>Skin lesions and adenopathies of right carotid chain and groin areas</td>
<td>Itr, 200 mg/day; 5-FC, 5 g/day</td>
<td>Disseminated phaeohyphomycosis was diagnosed, and treatment was continued for 8 months</td>
</tr>
<tr>
<td>Sept 1993</td>
<td>Relapse</td>
<td>Adenopathies of right cervical chain, right preauricular node, and inguinal regions</td>
<td>Itr, 200 mg/day; 5-FC, 6 g/day (100 mg/kg per day)</td>
<td>Exophiala spinifera was cultured for the first time; Itr was increased to 400 mg/day after 4 months; and therapy was continued for 6 months, then discontinued because of GI upset</td>
</tr>
<tr>
<td>Dec 1993</td>
<td>Relapse</td>
<td>Multiple skin lesions and adenopathies of right carotid and supraclavicular fossae</td>
<td>AmB, total dose of 520 mg</td>
<td>AmB was discontinued because of hypokalemia and nephrotoxicity; and treatment with liposomal AmB failed</td>
</tr>
<tr>
<td>July 1994</td>
<td>Continued infection</td>
<td>Skin lesions</td>
<td>Itr, 400 mg/day; 5-FC, 6 g/day; Ran, 300 mg/day</td>
<td>Clinical remission was achieved after 8 months, and when 5-FC was withdrawn from the Argentine market in 1995, Itr was increased to 600 mg/day</td>
</tr>
<tr>
<td>Jan 1996</td>
<td>Relapse</td>
<td>Skin and ganglionic lesions</td>
<td>Multiple antifungal therapies*</td>
<td>No complete remission occurred with any therapy</td>
</tr>
<tr>
<td>June 1999</td>
<td>Pregnancy confirmed</td>
<td>Skin and ganglionic lesions</td>
<td>AmB, 50 mg/week</td>
<td>Mycosis became severe in August</td>
</tr>
<tr>
<td>Nov 1999</td>
<td>Emergency cesarean section performed</td>
<td>Vegetating, verrucous skin lesions, adenopathies, knee osteomyelitis, visual difficulties, fever, and abnormal results of blood chemistry tests</td>
<td>Pos, 800 mg/day</td>
<td>Clinical and mycologic cure was achieved within 13 months</td>
</tr>
</tbody>
</table>

*Multiple antifungal therapies included griseofulvin (1 g/day); Itr (400 mg/day), with 5-FC imported for this case; terbinafine (250 mg/day) and Itr (200 mg/day); fluconazole (300 mg/day); and terbinafine (500 mg/day).

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**NOTE.** AmB, amphotericin B; GI, gastrointestinal; Itr, itraconazole; Pos, posaconazole; Ran, ranitidine; 5-FC, flucytosine.
mycosis (i.e., itraconazole plus flucytosine), because the definitive identification of the pathogen was delayed. This regimen was clinically effective against the organism during the first 3 years of treatment but did not produce a definitive mycologic cure. Although our patient intermittently received ranitidine therapy for the treatment of gastritis, which can reduce itraconazole bioavailability [28], no improvement in her clinical status was observed once ranitidine therapy was discontinued. During subsequent relapses, itraconazole produced only partial and short-lived symptomatic responses (table 1), suggesting that the clinical effectiveness of itraconazole was diminishing.

In our patient, the fungal infection was limited and not life threatening, until she became pregnant. Pregnancy is often overlooked as a risk factor for infectious disease. Cell-mediated immunity is compromised during pregnancy, which protects the fetus but places the mother at risk for infection and malignancy [29]. The abrupt worsening of chronic fungal infection during pregnancy, particularly during the final trimester, is a common occurrence in systemic mycoses and other granulomatous infections [5]. However, we do not believe that delivery of the infant significantly contributed to the clinical improvements observed in this patient. During the 3 years before her pregnancy, our patient’s infection showed no signs of clinical remission, despite treatment with multiple antifungal agents. Clinical improvement occurred within 1 week after initiating posaconazole therapy, and resolution of all lesions and complete clinical remission occurred with continued treatment. It is unlikely that the magnitude of the observed clinical improvement would have occurred without posaconazole therapy.

Posaconazole is highly lipophilic, orally absorbed, and extensively distributed into tissues. Pharmacokinetic evaluations demonstrate that serum levels exceeding MICs of most fungal pathogens, even strains resistant to other azole antifungal agents, can be reliably achieved [30, 31]. Posaconazole is being studied for the treatment of a variety of fungal infections, and interim results from clinical trials are promising. In an open-label, multicenter study evaluating the efficacy and safety of posaconazole as salvage therapy for patients with invasive fungal infection, interim analysis of the first 51 patients demonstrated that the clinical response was ≥50% after 4 and 8 weeks of treatment [32]. In phase II and phase III trials involving immunocompromised patients, posaconazole had a safety profile similar to that of fluconazole [33, 34]. Our patient tolerated oral posaconazole therapy well and experienced no adverse events or abnormal results of biochemical tests. The clinical response observed in this patient during posaconazole therapy is notable and suggests that it may be an effective treatment for these mycoses.

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References

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