

BRIEF REPORTS

Successful Outcome of *Scedosporium apiospermum* Disseminated Infection Treated with Voriconazole in a Patient Receiving Corticosteroid Therapy

A disseminated *Scedosporium apiospermum* infection was diagnosed in a woman with severe asthma and treated with corticosteroids. This fungus is resistant to fluconazole and amphotericin B. The infection was refractory to itraconazole, but responded successfully to voriconazole. A review of the literature is provided.

Scedosporium apiospermum (the anamorph state of *Pseudallescheria boydii*) is a hyaline filamentous fungus, ubiquitously present in soil, sewage, and polluted waters. This microorganism is an uncommon cause of human infection. In normal hosts, it usually produces localized disease after penetrating trauma or aspiration of polluted water. However, in immunocompromised patients it may cause severe pulmonary or disseminated infections [1].

The management of invasive *S. apiospermum* infections is difficult because it has intrinsic resistance to many antifungal agents, including fluconazole and amphotericin B [2, 3]. Voriconazole is a new triazole antifungal agent derived from fluconazole. Previous in vitro studies have demonstrated its efficacy against yeasts and filamentous fungi, and in vivo data suggest that voriconazole is effective in the treatment of invasive aspergillosis [5, 6]. However, data on the potential utility of voriconazole in invasive infections caused by filamentous fungi of the genus *Scedosporium* are only anecdotal [4, 7, 8]. We report a case of disseminated *S. apiospermum* infection in a woman with asthma who was receiving corticosteroid therapy. The infection continued to progress despite therapy with itraconazole; it finally responded to voriconazole.

A 75-year-old woman with severe asthma, who was receiving low-dose maintenance corticosteroid therapy, was admitted to our institution because of increasing dyspnea, tachypnea, and nonproductive cough. The chest x-ray film obtained at admission was normal. An exacerbation of asthma was diagnosed, and the woman was treated with oxygen, bronchodilators, clarithromycin, and increasing doses of corticosteroids (up to 80 mg of methyl prednisolone [MP] per day).

Fifteen days later, the patient developed a temperature of 38°C, chest pain, and hemoptysis. WBC count was 14,900 cells/mm³ (93% neutrophils), and other analytical parameters were within normal limits. At this time, she was receiving 30 mg of MP per day. Chest x-ray films and CT scans revealed a cavitated

lung abscess of 2 cm in diameter in the upper lobe of the left lung (figure 1). Results of sputum stains and cultures for bacteria and mycobacteria were negative. Calcofluor staining of sputum samples and a lung aspirate, obtained by transthoracic lung biopsy, showed septate hyphae. After 2 days, on Sabouraud's-dextrose agar (Emmons modification of Sabouraud's media) with chloramphenicol plates, all those samples showed the growth of white cottony colonies, which later turned dark green. The presence of septate hyaline hyphae, ovoid conidia, cut off at the base and borne terminally on elongated simple conidiophores (figure 2), plus the absence of cleistothecia prompted its identification as *Scedosporium apiospermum*. Blood culture results remained negative. The patient had not received any antifungal agent previously.

Antifungal therapy with itraconazole was started (200 mg q12h po, later increased to 400 mg q8h). The itraconazole trough blood level was 5.6 µg/mL. Corticosteroids could be tapered to a dose of 8 mg of MP per day. After 7 days of antifungal therapy, fever and chills persisted, and a second CT scan disclosed new lung lesions. The patient developed multiple nodular subcutaneous lesions on which biopsies were performed. Biopsy specimens yielded *S. apiospermum*. Results of blood cultures, a CT scan of the CNS, and echocardiographic studies were negative. The susceptibility study was performed by a reference center (Centro Nacional de Microbiología, Majadahonda, Spain). The reported results were as follows: MIC for amphotericin B, 16 µg/mL; for flucytosine, 256 µg/mL; for ketoconazole, 2 µg/mL; for fluconazole, 64 µg/mL; for itraconazole, 2 µg/mL; and for voriconazole, 0.12 µg/mL.

It was decided to treat the patient with voriconazole (265 mg iv q12h for 40 days and 200 mg orally q12h for another 63 days) and with granulocyte colony-stimulating factor (G-CSF); voriconazole was then obtained for compassionate use. Significant clinical improvement was observed within a few days, and the size of skin and lung lesions progressively decreased. During this time, doses of MP ranged from 5 mg to 15 mg per day, depending on the respiratory situation of the patient. The drug was well tolerated, with the exception of a morbiliform exanthem and a mild elevation of liver enzymes (γ-glutamyl transferase, 307 IU/L; alanine amino transferase, 79 IU/L) that did not require the withdrawal of the medication. The patient is alive and has had no recurrence of the fungal infection 8 months later.

Scedosporium apiospermum is a saprophytic fungus isolated worldwide from soil and plant residues. Although the organism has shown low inherent virulence, an increasing number of invasive infections caused by this microorganism have been reported in the past few years, mainly in patients with hematological malignancies or in those who have undergone solid organ transplantation [9].

In this report, we describe a case of invasive lung infection disseminated to the skin in a patient with asthma who was

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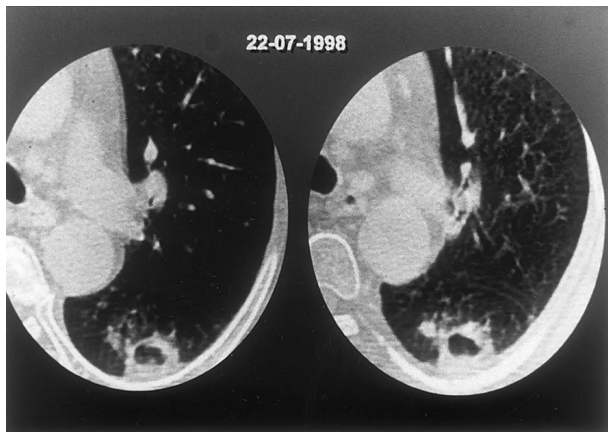


Figure 1. CT scan showing a new caviated lung lesion in the left lung. A transthoracic aspirate proved that it was caused by *Scedosporium apiospermum*.

receiving corticosteroid therapy as the only cause of immunosuppression. Extensive laboratory investigations failed to demonstrate any other cause of immunocompromise.

Recently, 3 cases of *S. apiospermum* infection have been reported in patients receiving chronic corticosteroid therapy (due to a nephrotic syndrome, chronic obstructive pulmonary disease [COPD] with bronchospasm and polymyositis) [10–12]. The 3 patients presented with subcutaneous nodules that had a sporotrichoid appearance. Although involvement of the lung or other internal organs could not be demonstrated in any of the patients, all finally died.

The correct diagnosis of *S. apiospermum* infection must be confirmed by the isolation of this fungus in culture, since both its histological appearance and its clinical presentation are quite similar to those of *Aspergillus* infection. A mistaken diagnosis can result in delayed or inappropriate treatment, considering that *S. apiospermum* is almost always resistant to amphotericin B [2, 4]. Microbiological diagnosis is easy to achieve because of its macroscopic and microscopic appearance in culture.

The treatment of choice for these infections has not been established. Surgical resection, when possible, and antifungal therapy with azole derivatives (mainly itraconazole) have been successful in some cases [8, 13, 14]. However, a recent report has shown no response of this fungus to itraconazole, despite in vitro susceptibility [11]. Our strain was resistant to amphotericin B (MIC, 16 $\mu\text{g}/\text{mL}$) [15], and treatment with itraconazole was ineffective despite apparently adequate plasma levels and tapering of the dose of corticosteroids, which made an alternative therapeutic approach necessary. Miconazole has been used to treat some cases of *S. apiospermum* infection. However, we did not consider using miconazole for our patient because of its high toxicity, the difficulty of obtaining it in an iv formulation (which is not commercially available), and the high rate of recurrence of infection and mortality [8].

Voriconazole is a new triazole with good in vitro activity against a range of molds, including *S. apiospermum* [3, 4], and treatment with voriconazole has resulted in a good clinical outcome for 2 patients with *Scedosporium* infection [7, 8]. In our case, voriconazole showed a good in vitro and in vivo activity and was able to control the disseminated *S. apiospermum* infection. The patient has not had a relapse, despite the new cycles of corticosteroid treatment that have been necessary during the 8 month follow-up period. More clinical studies are needed to establish the most efficacious therapeutic approach against these severe and difficult-to-treat fungal infections.

We cannot establish the independent influence of the use of G-CSF in our case, since treatment was started at the same time as treatment with voriconazole. G-CSF has been advocated as a potentially useful treatment for very severe fungal infections, even in patients without neutropenia. It increases neutrophil production and enhances polymorphonuclear cell-mediated killing of fungal pathogens in vivo, which implies that it may function as a biologic response-modifying agent and have a role in the treatment of opportunistic fungal infections. It should be used only for short-term treatments and for very severe cases, until more information is available.

For our patient, doses of corticosteroids were tapered from the beginning, but the evolution of the infection was poor despite treatment with high doses of itraconazole. It was never possible to withdraw corticosteroids due to exacerbations of asthmatic episodes.

In conclusion, *S. apiospermum* should be included in the differential diagnosis of invasive skin and lung infections in patients receiving corticosteroids, mainly when treatment with amphotericin B or itraconazole has failed. Voriconazole may well prove to be a suitable alternative therapy for *S. apiospermum* infections.



Figure 2. Blue cotton stain of *Scedosporium apiospermum* colony showing septate hyaline hyphae, with ovoid cauda cut off at the base and borne terminally on simple conidiophores.

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Rubella Susceptibility Predicts Measles Susceptibility: Implications for Postpartum Immunization

Measles and mumps antibody titers were measured in 262 pregnant women who were either positive ($n = 128$) or negative ($n = 134$) for rubella antibodies. Susceptibility to measles and mumps was detected in 4.6% (12/262) and 7.6% (14/184) of the women, respectively. Of the rubella-susceptible group, 8.2% were also measles susceptible, whereas only 0.8% of the rubella-immune women were measles susceptible. Susceptibility to mumps was evenly divided between rubella-susceptible (7.8%) and rubella-immune (7.4%) groups.

The goal of rubella immunization is the elimination of the congenital rubella syndrome (CRS). Protection from CRS is

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accomplished for the large majority of women in developed countries by routine childhood immunization(s) against rubella. A small number of women in their childbearing years, however, remain susceptible to rubella virus because of missed vaccinations (either intentional or unintentional) or vaccine failure. Prenatal screening of pregnant women for rubella antibodies is widely recommended to identify these susceptible women so that they can be offered vaccination postpartum. This strategy aims to eliminate the risk of CRS in the subsequent pregnancies. Whether to offer rubella vaccination alone or in combination with measles vaccine (MR) or measles and mumps vaccines (MMR) has only recently been considered by some national advisory bodies. For example, only the most recent recommendation of the Advisory Committee on Immunization Practices (ACIP) states that MMR vaccine should be offered to all rubella-seronegative women of childbearing age [1], whereas recommendation of the Canadian National Advisory Committee on Immunization calls simply for “rubella vaccination” in these women [2].

Young adults are now recognized as a population at risk for measles and mumps viral infections. This age group has not been protected by the recent introduction of 2-dose MMR vaccine policies for children and was not reached by mass measles vaccination strategies where such campaigns have been under-