Invasive Pulmonary Infection Due to *Scedosporium apiospermum* in Two Children with Chronic Granulomatous Disease

Nada Jabado, Jean-Laurent Casanova, Elie Haddad, Fabienne Dulieu, Jean-Christophe Fournet, Bertrand Dupont, Alain Fischer, Christophe Hennequin, and Stéphane Blanche

*Scedosporium apiospermum* is an opportunistic fungus in humans. The incidence of *S. apiospermum* infection in patients with acquired neutropenia (e.g., patients receiving chemotherapy and bone marrow transplant recipients) is steadily increasing. *S. apiospermum* has poor in vitro susceptibility to “conventional” antifungal agents, rendering the management of infections complex. Patients with chronic granulomatous disease (CGD) are highly susceptible to fungal infections, which are mostly due to *Aspergillus* species. We describe two children with CGD and invasive pulmonary infection due to *S. apiospermum*. Both patients were treated with antifungal therapy including azole derivatives (itraconazole or voriconazole) and surgical resection of infected tissues. These cases highlight that scedosporium infection can closely mimic aspergillus infection and should be considered in any case in which there is a failure to respond to appropriate “conventional” antifungal therapy. We also suggest that the emergence of this pathogen may have been favored by long-term use of amphotericin B in both patients.

Chronic granulomatous disease (CGD) is an inherited disorder characterized by an impaired respiratory burst of phagocytic cells due to deficient assembly in the NADPH oxidase [1]. Phagocytosis of microorganisms by neutrophils and monocytes occurs normally, but bacterial and fungal killing by phagocytic cells is defective [2]. Patients have recurrent infections beginning in the first year of life that usually involve the skin, lymph nodes, lung, liver, and gastrointestinal tract [3]. Primary prophylaxis with trimethoprim-sulfamethoxazole has been shown to be effective in reducing the frequency of bacterial infections in these patients [4], and IFN-γ therapy is used, with proven efficacy, for those who are severely affected [5]. However, fungal infections remain a major threat and are the leading cause of death in these patients. *Aspergillus* species are the most frequently encountered pathogens, and primary prophylaxis with itraconazole has been reported to reduce the incidence of fungal infections [6].

The genus *Scedosporium* has been associated with a wide spectrum of infections caused by two species: *Scedosporium apiospermum* (or *Pseudallescheria boydii*, the perfect stage of the fungus) and *Scedosporium prolificans* (formerly *Scedosporium inflatum*) [7]. *Scedosporium* species are hyaline filamentous pathogens of the Hyalohyphomycetes class, which also includes *Aspergillus* species and *Fusarium* species. These three pathogens share similar epitopes and are morphologically similar in terms of tissue [8]. The incidence of infections due to *Scedosporium* in patients with acquired neutropenia (e.g., patients receiving chemotherapy and bone marrow transplant recipients) or receiving immunosuppressive treatment (corticosteroids and cyclosporin A) has steadily risen in recent years [8–11]. One important feature of this emerging pathogen is its resistance to amphotericin B and flucytosine, the former being the “conventional” systemic antifungal chemotherapy given to immunocompromised hosts [10, 11].

**Case Reports**

**Case 1**

An 8-year-old boy with autosomal recessive CGD who had deficiency of the 47-kD cytosolic protein p47^{phox} [2] was admitted to Hôpital Necker Enfants Malades (Paris) in September 1995 because of high fever, cough, and tachypnea. He previously had two invasive pulmonary aspergillus infections in 1988 and 1993 that were both successfully treated with iv amphotericin B (1 mg/[kg·d]) for 1 month with progressive tapering over 1 year.

At the time of admission, a chest roentgenogram and CT scan showed the presence of a pulmonary abscess in the left lower lobe. The child had elevated inflammatory markers (neutrophil count, 10,000/mm³; erythrocyte sedimentation rate [ESR], 120 mm/h; and C-reactive protein level, 250 mg/mL) and a high titer of antibody to *Aspergillus* (>1:2,560 determined by ELISA), which had been previously negative. He was receiving treatment with oral itraconazole capsules (10 mg/[kg·d]) with repeatedly low serum levels (measured by HPLC) and trimethoprim-sulfamethoxazole prophylaxis (20 mg/[kg·d]). Invasive pulmonary aspergillosis was suspected;
he was treated with iv amphotericin B (1 mg/[kg \cdot d]) and flu-cytosine (200 mg/[kg \cdot d]), and itraconazole therapy was dis-continued.

After 1 month of treatment, extension to the chest wall with evidence of pleural and costal involvement was noted on a CT scan (figure 1). His titer of antibody to *Aspergillus* had, how-ever, fallen to 1:640, representing a significant drop of three dilutions from the level noted at admission. Sputum culture yielded *S. apiospermum*. Needle biopsy of the left pulmonary infiltrate was then performed and showed the presence of thin (2–3 μm) septate hyphae branched with sharp angles. Culture of the biopsy specimen yielded *S. apiospermum* (figures 2A and 2B). Serology for *Scedosporium* (cocounterimmunoelec-trophoresis) was performed on serum samples collected before and after admission; it was negative 1 year before admission, weakly positive at the time of admission (one band), and highly positive at the time of the pulmonary biopsy (three bands).

In vitro activity of antifungal agents against the *S. apiospermum* spores, tested by a microdilution method determining the MIC of the drug at which there was no visible growth of the isolate [12], demonstrated that the MICs of amphotericin B and flu-cytosine for the isolate were high (8 μg/mL and 12 μg/mL, respectively). The MICs of miconazole, voriconazole, and itraconazole were 0.3 μg/mL, 0.4 μg/mL, and 0.7 μg/mL, respectively, thus demonstrating their in vitro effectiveness against the isolate. Therapy with iv miconazole (50 mg/[kg \cdot d]) was started but had to be discontinued because of anaphylaxis due to the solvent (chremophor E). Treatment with high doses of oral capsules of itraconazole (30 mg/[kg \cdot d]) was begun but after 15 days had no effect on clinical symptoms (fever, cough, and chest abscess) and biological markers (ESR, neutrophil count, C-reactive protein level, and factor I level). Voricona-zole (UK 109-496) was then obtained on the basis of a compas-sionate protocol from Pfizer Central Research (Sandwich, En-gland), and the child was treated with oral voriconazole (10 mg/[kg \cdot d]) and subcutaneous IFN-γ (1.5 μg/[kg \cdot d]).

Systemic manifestations resolved, and a CT scan showed a marked improvement after 2 months of treatment. Titors of antibody to *Aspergillus* and antibody to *Scedosporium* became negative after 4 months of treatment. After 7 months of treat-ment, a pulmonary CT scan revealed a residual left pulmonary infiltrate with pleural and costal involvement. Trough and peak serum levels of voriconazole were still within the pharmaceuti-cal range (0.54 μg/mL and 5 μg/mL, respectively). Because of the CT findings, left-sided thoracotomy was performed, and the lower left lobe and the posterior parts of the seventh and eighth left ribs were removed. Histopathologic examination of the lung and rib tissue specimens showed the presence of multi-plle granulomas filled with periodic acid–Schiff stain–positive pathogens consistent with a persistent fungal infection. Cultures of these specimens were negative.

Treatment with voriconazole was continued for a further 8 months; a 4-month course of IFN-γ (1.5 μg/[kg \cdot d]) was added to the therapeutic regimen. One year after surgery, no new lesions were revealed by CT, and serology for *Scedosporium* was negative.

**Case 2**

A 13-year-old boy with X-linked CGD was admitted to Hôpi-tal Necker Enfants Malades in December 1995 because of high fever, tachypnea, and pulmonary abscesses. Until 1994, his disease had had an uneventful course, and he was receiving ketoconazole and trimethoprim-sulfamethoxazole prophylaxis. In 1994, invasive hepatopulmonary aspergillosis was suspected.
when the child presented with a lower right pulmonary abscess and a hepatic cavity that were seen on a CT scan. Titers of antibody to *Aspergillus*, which had previously been negative, were markedly elevated (1:640 determined by ELISA and three bands revealed by cocounterimmunoelectrophoresis). Ketocanazole prophylaxis was discontinued, and the child received therapy with iv amphotericin B (1 mg/[kg·d] for 1 month and then tapered doses over 16 months) and flucytosine (200 mg/[kg·d] for 6 months).

Fifteen months after the initial episode, the child presented with fever, hemoptysis, and tachypnea while he was still receiving maintenance therapy with amphotericin B (1 mg/kg two times a week). A CT scan showed persistence of the lower right pulmonary lesions with a second abscess in the right lung (figure 3). Serology for *Aspergillus* was negative. In contrast, serology for *S. apiospermum* was highly positive (four bands revealed by cocounterimmunoelectrophoresis). Retrospective serological analysis for *Scedosporium* revealed a recent rise in the titer of antibody. Treatment with iv miconazole (50 mg/[kg·d]) was initiated, but no improvement was observed after 15 days.

Right-sided thoracotomy was performed, and both pulmonary abscesses were removed. Histopathologic examination of abscess specimens showed necrotic granulomas with Grocott-Gomori methenamine–silver nitrate–positive, periodic acid–Schiff stain–positive septate hyphae (2–3 μm), some of which were in a sexually perfect stage compatible with infection due to *Scedosporium* species (figure 4). No exact identification of the pathogen was possible as culture of the lung specimen was negative probably because of ongoing antifungal therapy. With a combination of high doses of oral capsules of itraconazole (20 mg/[kg·d] for 1 month and then 10 mg/[kg·d]) and subcutaneous IFN-γ (1.5 μg/kg three times a week for 6 months) together with the surgical procedure, manifestations of the disease resolved. One year after surgery, the child was well; serology for *Scedosporium* was negative, and no new lesions were seen on a CT scan.

**Discussion**

*S. apiospermum* is the anamorph form of the fungus *P. boydii*, which is the causative organism of mycetoma [13–16]. The most commonly affected sites are the skin and lung in immunocompromised hosts [17–21], and allergic bronchopneumonitis and localized infections are most common in immunocompetent patients [9, 22]. A striking parallel exists between clinical manifestations of scedosporiosis and those of...
aspergillosis. Diagnosis of invasive infection is made on the basis of identification of the mold in a standard culture of a biopsy specimen of the infected tissue. Serum testing for antibodies to the pathogen may contribute to the diagnosis, even though this technique is not specific enough to diagnose infection due to S. apiospermum. Cross-reactions with Aspergillus and other pathogens and false-negative and false-positive results are possible [23, 24]. However, in patients with CGD, positive serology for Aspergillus is probably a good marker of an ongoing invasive fungal infection.

The usefulness of serology for other diseases, including cystic fibrosis (for which it mainly reflects fungal colonization) appears to be more limited. Serology is performed routinely for children who frequent the outdoors and serves as a baseline test for comparison for patients with symptomatic fungal infection and as an alarm trigger for asymptomatic patients whose serum antibody levels rapidly increase [25]. In case 1, the diagnosis of invasive pulmonary scedosporiosis was made by culture of infected lung tissue positive for S. apiospermum. In case 2, no definite diagnosis could be made as culture of infected lung tissue did not yield S. apiospermum probably because of treatment with miconazole. However, histological examination of the biopsy specimen and failure of amphotericin B therapy, together with the high titer of antibody to S. apiospermum and a negative titer of antibody to Aspergillus, strongly argue for invasive pulmonary scedosporiosis in this child.

Treatment guidelines for infections due to Scedosporium are not well established in the literature [8–11]. S. apiospermum is almost invariably resistant in vitro to amphotericin B and flucytosine [8–11]. Medical cures with azole derivatives have been attempted. Initially, intravenous miconazole was used; however, major side effects and a high rate of recurrence of infection and mortality occurred [26]. The successful use of itraconazole has been reported in a few cases [27–29].

Voriconazole is a new azole derivative with a spectrum of antifungal activity against filamentous fungi that is close to that of itraconazole. Its clinical and biological tolerance along with its effectiveness against fungal infections are still under evaluation. A recently reported study demonstrated its potentially high in vitro activity against emerging pathogens including isolates of Scedosporium species [30]. Treatment with these new azole derivatives helped control infection in our patients. However, both patients required surgical resection of pulmonary abscesses. These observations support findings of previously reported studies, which indicate that surgical resection should be performed whenever possible, especially when there are biological and/or radiological findings suggesting stagnation or if the infection has relapsed during administration of appropriateazole therapy.

A predisposing factor favoring this infection in our patients was long-term prophylaxis with itraconazole or ketoconazole, the selection effect of which is the emergence of resistant molds. Against this hypothesis is the fact that itraconazole has good in vitro activity against S. apiospermum [27–29], even if results of in vitro testing must be interpreted with caution as no good in vitro or in vivo correlation has been established. In addition, the relative initial ineffectiveness of itraconazole in case 1 could be because of the repeatedly low serum levels of itraconazole before admission (poor absorption of oral capsules and/or noncompliance) and/or because the duration of treatment with this agent was too short (15 days). The in vitro activity of ketoconazole against S. apiospermum is variable [8–11].

Both patients had previously received treatment for invasive aspergillus infection with amphotericin B without itraconazole over a long period, which could be another predisposing factor for scedosporiosis. Itraconazole prophylaxis was discontinued with the commencement of amphotericin B therapy because of concern about possible antagonism between the two molecules [31]. The hypothesis that the exclusive use of amphotericin B predisposed the patients to these infections is strongly supported by the lack of in vitro activity against most Scedosporium isolates and the poor in vivo therapeutic responses to this agent. Disseminated infection with P. boydii in a patient with CGD has been previously reported [32]. The child responded to treatment with iv miconazole followed by oral ketoconazole and IFN-γ therapy. No data regarding previous treatment of the child with amphotericin B, or other agents, were available.

It is also possible that the pulmonary aspergillus infections themselves contributed to the development of scedosporium infection, as infections due to this agent have been reported to develop as sequelae of pulmonary infections due to Aspergillus species [13, 24].

These cases highlight that scedosporium infection may mimic aspergillus infection and should be considered, and looked for, in any case in which appropriate “conventional”
antifungal therapy fails. The emergence of Scedosporium species causing infections along with other opportunistic molds [33] in patients with CGD is a matter of concern.

Acknowledgment
The authors thank Jane Peake for critically reading the manuscript.

References