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CASE REPORT

A fatal case of invasive fungal sinusitis by *Scopulariopsis acremonium* in a bone marrow transplant recipient

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Summary A fatal case of *Scopulariopsis acremonium* sinus infection in an allogeneic hematopoietic stem cell transplant patient is reported. Rapid vascular diffusion of the fungus to the major head vessels was observed, which led to subsequent repeated cerebral ischemia and death. The presence of hyphae in the right carotid wall might be considered an indirect sign of fungal blood diffusion in the absence of positive blood cultures. The infection developed during the course of prolonged voriconazole prophylaxis, which was found to be effective in the in vitro antifungal drug assay. This finding induced us to consider the capacity of this drug to reach infected paranasal sinuses, and the need in cases such as this of a combined systemic and local pharmacological therapy or a combined medical and surgical approach.

Introduction

Invasive fungal sinusitis is a potentially fatal disease that typically affects immunocompromised patients, such as those receiving intensive chemotherapy or undergoing an allogeneic hematopoietic stem cell transplantation (HSCT).[1–4] A wide range of causative pathogens has been described, with Aspergillus and Mucor remaining the most common agents.[3,5] The mortality as a result of this clinical entity varies depending on the underlying disease, site of infection, and antifungal management, and it remains very high – up to 60% by some estimates.[3,4] A late diagnosis often results in vascular invasion and spread of the infection to contiguous tissues, so worsening the prognosis and increasing the mortality.

Scopulariopsis spp are nondermatophytic fungi, cosmopolite and common soil saprophytes. *Scopulariopsis brevicaulis* is most frequently isolated in immunocompetent patients with onychomycosis and localized infections and is rarely reported as a causative agent of disseminated infection in

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immunocompromised patients.[6–11] Infection with *Scopulariopsis acremonium* has only been described in two immunocompromised patients.

We report herein a rare case of invasive fungal sinusitis caused by *S. acremonium* in a bone marrow transplant patient, which developed during antifungal prophylaxis with voriconazole.

Case report

In January 2005, a 50-year-old woman, originally from Cape Verde, but resident in Italy for approximately 10 years, received the diagnosis of IgG kappa, stage IIA multiple myeloma (total tumor burden 0.6–1.2 $\times$ 10^{12} cells/m^2, serum creatinine $<$2 mg/dl, or intermediate stage according to the Durie and Salmon staging system).[12]

From January to April 2005 she underwent four courses of combined chemotherapy and dexamethasone with subsequent partial remission of the disease. In May 2005, after mobilization induced by cyclophosphamide and granulocyte colony-stimulating factor (G-CSF), CD34+ cells (2.26 $\times$ 10^6/kg) were collected from her peripheral blood. In August 2005, the patient underwent to an autologous stem cell transplant.

In March 2006, she was admitted to the Hematology Stem Cell Transplant Unit and an allogeneic HSCT from her human leukocyte antigen (HLA)-identical brother was performed. As a conditioning regimen, she received a myeloablative regimen combining busulfan and fludarabine, and cyclosporine with methotrexate was used as prophylaxis against graft-versus-host disease (GVHD). The patient was discharged at day 17 after transplant in a good condition and in complete illness remission, with normal hematopoietic reconstitution of full donor origin. Prior to the transplant, a magnetic resonance image (MRI) of the paranasal sinuses showed a mucosal thickening of the left maxillary sinus, with polypoid formations.

In July 2006, the patient was readmitted to the Hematology Stem Cell Transplant Unit for biopsy-proven acute intestinal GVHD (Lerner grade III–IV), and treated with prednisone (2 mg/kg/day) and cyclosporine (3 mg/kg/day). During this hospitalization, due to the appearance of sinusitis and a suspicion of fungal disease, liposomal amphotericin B (3 mg/kg/day) was given for 21 days, followed by voriconazole (200 mg orally, every 12 hours) as antifungal secondary prophylaxis. No microbiological results were obtained from sinus swab cultures on this occasion.

In August 2007 (485 days after transplant) she was admitted to the hospital with acute blindness and edema of the right eyelid. She was on prednisone and mycophenolate mofetil for chronic intestinal GVHD, and was still on

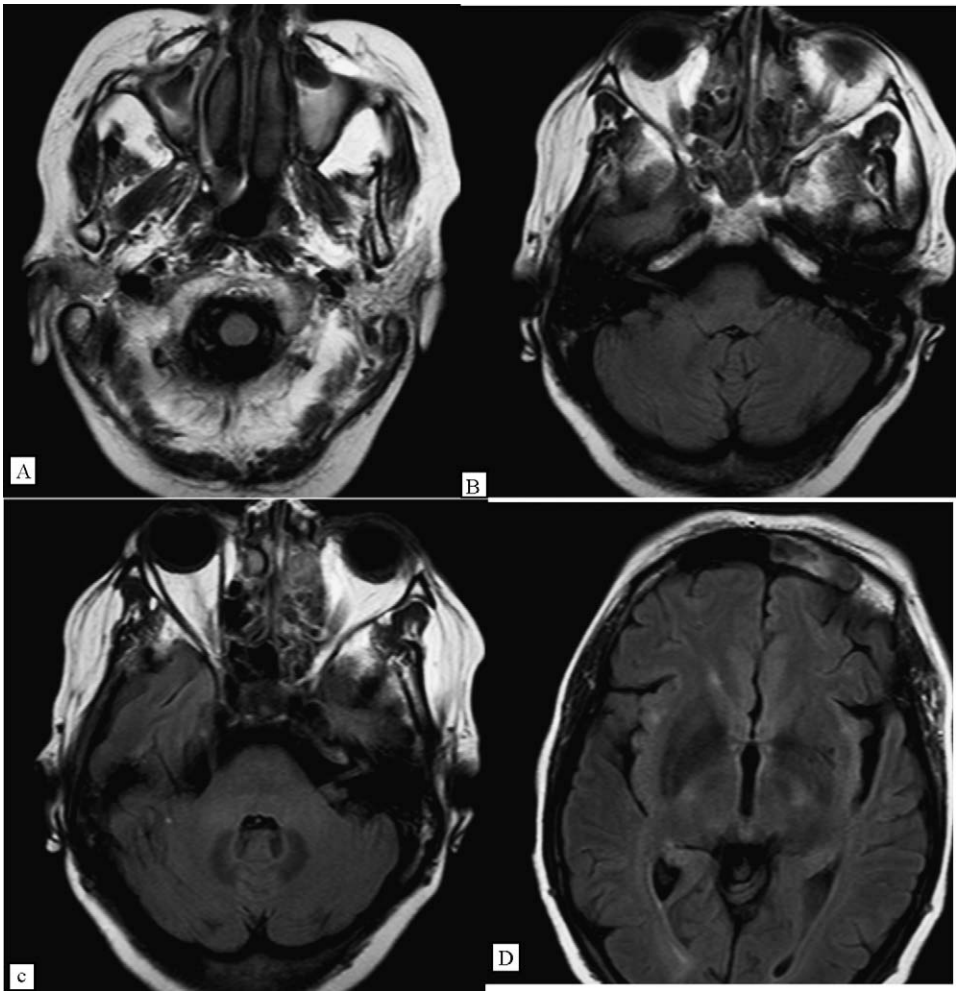

Figure 1 Magnetic resonance images showing evidence of mucosal thickening of the ethmoidal (A–C) and frontal (D) sinuses.

voriconazole. An MRI scan showed maxillary, ethmoidal, and frontal sinusitis (Figure 1), and an ocular fundus evaluation revealed an ischemia of the right retinal artery. Voriconazole was stopped and treatment with liposomal amphotericin B (3 mg/kg) and piperacillin/tazobactam was begun.

After 10 days of treatment, the patient developed complete left-sided hemiplegia, and a computed tomography (CT) scan showed a large cerebral ischemia of the right temporal area (Figure 2).

Fourteen days after admission, a culture from the sinus secretion grew *Scopulariopsis acremonium*. Susceptibility testing of the isolate was performed according to the broth microdilution method.[13,14] The minimum inhibitory concentrations (MICs) were determined using the reference procedure of the Antifungal Susceptibility Testing Subcommittee of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for spore-forming molds.[15] Amphotericin B, fluconazole, and itraconazole were found to be inactive in vitro against the isolate; however it was found to be sensitive to voriconazole (Table 1). As the infection developed during voriconazole prophylaxis, treatment with echinocandins (caspofungin) was started, but the patient died two days later due to a new episode of brain ischemia and hemorrhage.

Autopsy revealed the presence of thrombosis of the right carotid artery and of the middle cerebral artery, with the consistent presence of fungal filamentous hyphae in the vessel walls (Figure 3). Necrotic material and a polymorphonuclear infiltrate were found in the sinuses (Figure 4). The autopsy concluded that death was as a result of a septic embolism from sinus to arterial circulation, caused by *Scopulariopsis acremonium*.

Table 1 Antifungal susceptibility of the *Scopulariopsis acremonium* isolate

Antifungal drug	MIC (μg/ml)
Amphotericin B	2
Posaconazole	0.5
Fluconazole	256
Itraconazole	16
Ketoconazole	2
5-Flucytosine	64
Voriconazole	2
Caspofungin	1

MIC, minimum inhibitory concentration.

Discussion

Infections due to infrequently encountered fungi (e.g., hyaline molds, dematiaceous filamentous fungi, and zygomycetes) have become increasingly common in hematopoietic

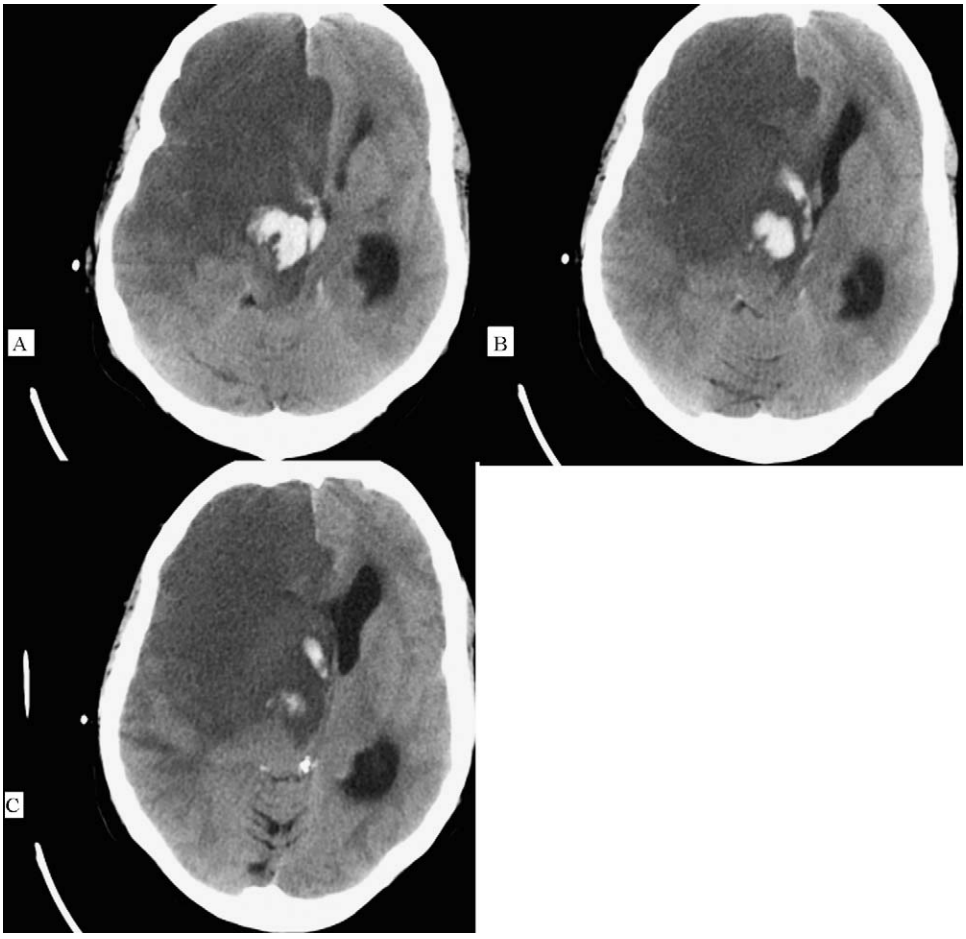

Figure 2 Axial computed tomography scan showing large right hemispherical brain ischemia (A—C).

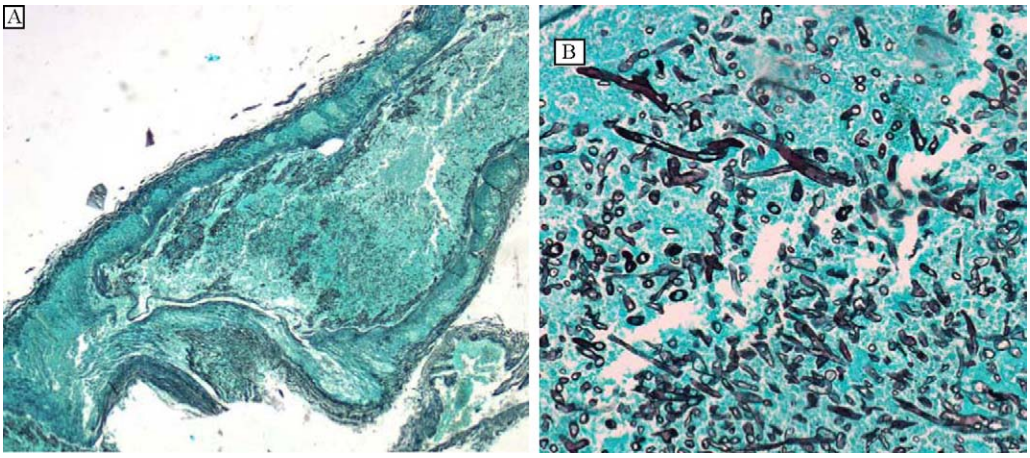

Figure 3 The carotid artery wall with evidence of thin, septate hyphae (Gomori methenamine silver stain; magnification (A) 4×, (B) 40×).

stem cell transplants.[16,17] This trend is worrisome given that opportunistic molds are often refractory to conventional antifungal agents and have innate resistance or erratic susceptibility to amphotericin B. All these factors account for the very low one-year survival (about 20%) of HSCT recipients with invasive mold infections.[16]

Mold infections are frequently disseminated to numerous other organs and tissues, and this is probably related to in vivo sporulation and the production of adventitious forms (hyphae, phialides, and phialoconidia) with a rapid vascular spread.[18] This suggested mechanism for the dissemination of infection could confer a particular virulence and resistance to treatment of these kinds of fungi.

Only two cases of infection by *S. acremonium* have been reported in the literature, one in a leukemic patient and one in a lung transplant patient.[11,19] The transplant patient had a fatal disseminated infection, while the leukemic patient had a sinusitis that was successfully treated with a combination of medical (amphotericin B plus itraconazole) and surgical (endoscopic sinus surgery) methods. In neither of the two cases was a hematogenous spread of the infection documented.

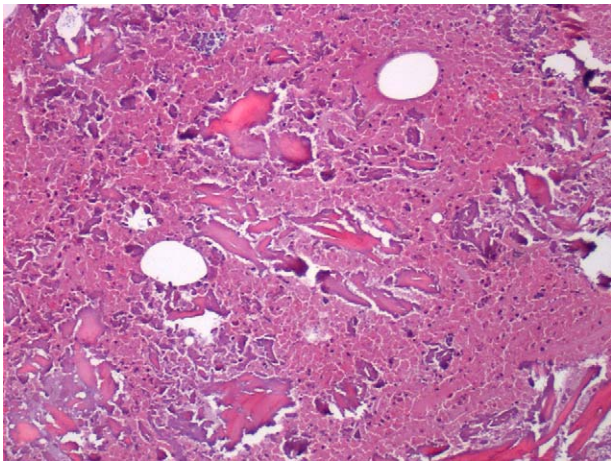

Figure 4 Fragment of the frontal sinus: evidence of bone necrosis and polymorphonuclear infiltrate (magnification 10×).

The clinical picture in our case was suggestive of a rapid vascular diffusion, with early involvement of the retinal artery and diffusion to the major head arteries. We had no positive blood culture; however, the presence of hyphal forms in the wall of the carotid could be considered a sign of vascular spread of the pathogen. The rapid vascular diffusion negatively influenced the clinical course in our patient.

The *S. acremonium* isolated in our case was found to be resistant to a large number of antimycotic drugs, and in particular to amphotericin B. There is a paucity of data regarding the in vitro antifungal susceptibility of *Scopulariopsis spp*;[13,20,21] however, a large number of clinical and environmental isolates have demonstrated a broad spectrum of resistance against antifungal agents.[21] Our patient developed *S. acremonium* infection while on prophylaxis with voriconazole, which in contrast to the other azole agents, was found to be effective in vitro. This finding could be explained by the possible limited diffusion of oral voriconazole or by insufficient penetration of the drug into the sinuses.

In conclusion, *S. acremonium* infection in HSCT patients is rare but can be a dramatic event due to the natural reduced sensitivity of the pathogen to antifungal drugs and its potential to spread rapidly by blood diffusion. Nasal sinuses as the site of infection make rapid diagnosis and treatment more difficult. Results of this study have led us to consider the use of combined systemic and local antifungal treatment and to evaluate the timing of a surgical approach in this kind of fungal infection, as has also been suggested by other authors.[22]

Early diagnostic procedures such as biopsy, or at the least endoscopic cultures, should be performed prior to starting empirical antifungal treatment in order to improve the outcome of this disease in the immunocompromised host.

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Given the death of the patient, the ethics committee of the hospital gave approval for the anonymous publication of this clinical case.

Conflict of interest statement: All authors declare no financial or personal relationships with other people or organizations that could inappropriately have influenced (bias) their work.

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