Disseminated Scopulariopsis brevicaulis infection in an allogeneic stem cell recipient: case report and review of the literature

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Abstract

A fatal case of disseminated Scopulariopsis brevicaulis infection in an allogeneic stem cell transplant recipient is described. The patient was initially thought to have pulmonary aspergillosis, on the basis of clinical signs and antigenaemia, but Aspergillus was not isolated by culture. Scopulariopsis brevicaulis was subsequently isolated from skin and then from sputum and stool. Further investigation revealed that the infection had spread from a primary pulmonary site to the skin. A review of the literature underscores the difficulty of diagnosing infections caused by such emerging fungal pathogens and the poor outcome of immunocompromised patients with non-Aspergillus mould infections.

Keywords: Antifungals, diagnosis, opportunist, Scopulariopsis, transplantation

Original Submission: 16 January 2009; Revised Submission: 7 April 2009; Accepted: 17 April 2009

Editor: M. Arendrup

Article published online: 15 July 2009

Clin Microbiol Infect 2010; 16: 508–512
10.1111/j.1469-0691.2009.02878.x

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Introduction

The ascomycete Scopulariopsis brevicaulis (teleomorph Microascus brevicaulis) is a soil saprophyte widely distributed in nature. It has been isolated from soil and from a wide range of plants and organic substrates [1]. In immunocompetent patients, S. brevicaulis has mainly been associated with onychomycosis, accounting for 1–10% of such infections [2,3]. It can occasionally cause cutaneous lesions [4,5] and more severe infections following traumatic or surgical injury [6,7]. During the last two decades, an increasing number of severe cases of S. brevicaulis infection have been reported in immunocompromised hosts, ranging from localized infections to invasive hyalohyphomycosis. Deep infections carry a poor prognosis, owing to diagnostic difficulties and the lack of a consensus therapeutic strategy. A combination of surgery and antifungal drug therapy seems to be the treatment of choice, but S. brevicaulis has been reported to be resistant to amphotericin B, terbinafine and azoles in vitro, and the indications for surgery are limited [8].

Here we describe a case of disseminated S. brevicaulis infection in an allogeneic stem cell graft recipient. Treatment with single-agent amphotericin B and with an antifungal drug combination (amphotericin B plus voriconazole) was ineffective. We also examine other reports of severe Scopulariopsis infections in immunocompromised patients, focusing on diagnosis and treatment.

Case report

In December 2006 a 38-year-old woman was admitted to Nancy hospital for acute myelogenous leukaemia. Seven months later, in June 2007, she underwent myeloablative conditioning and allogeneic peripheral blood stem cell transplantation from a mismatched unrelated donor. One month post-transplant, and despite graft-versus-host disease (GVHD)
prophylaxis with cyclosporin and mycophenolate, she developed acute GVHD and extensive chronic GVHD (gut, liver and skin) in October 2007. She was treated with steroids, a TNF-α antagonist and alemtuzumab. Posaconazole was used for antifungal prophylaxis.

In November 2007 she developed signs of Epstein–Barr virus-induced post-transplant lymphoproliferative disorder with pulmonary involvement. Computed tomography (CT) showed a lesion in the upper right lung evoking pulmonary aspergillosis (Fig. 1). Posaconazole was empirically switched to liposomal amphotericin B (3 mg/kg/day). After 2 weeks the lesion had shrunk, but she developed a pneumopathy a few days later. Presuming a bacterial infection, treatment with teicoplanine and ceftazidime was started and her condition improved. Since the patient’s serum was positive for Aspergillus galactomannan (index 0.57–2.03, twice weekly) (Platelia Aspergillus, Bio-Rad), liposomal amphotericin B (3 mg/kg/day) was combined with caspofungin (70 mg loading dose followed by 50 mg daily). On 7 January (day 190 post transplant) she developed necrotic cutaneous lesions on her legs and face, c. 2 mm in diameter with an inflammatory perimeter. Biopsy showed numerous septate hyphae by direct observation after Noir Chlorazol staining (Fig. 2a). Microscopic examination of histological sections stained with lactophenol blue, periodic acid–Schiff, haematoxylin–eosin (not shown) and Gomori-methamine silver revealed branching, septate hyphae and many vesicular swellings of different sizes (Fig. 2b–d). The dermis, hypodermis and subcutaneous vessels were invaded by numerous hyphae (Fig. 2b,c).

Opportunistic cutaneous fusariosis was suspected, as Fussarium is one of the most significant emerging fungal pathogens in the high-risk population to which this patient belonged. The dose of amphotericin B (3 mg/kg/day) was increased to 10 mg/kg/day and caspofungin was replaced by voriconazole (200 mg twice a day), based on recent published data [9].

To obtain the most accurate aetiological diagnosis possible and to avoid inhibition of fungal growth that would prevent identification, DNA was extracted from the biopsy specimen and successfully amplified with panfungal primers ITS1-ITS4 [10]. Molecular identification of S. brevicaulis was achieved by sequencing. Finally, cultures of the biopsy specimen grew whitish colonies after only 2 days on Sabouraud agar at 27°C. The colonies developed a brown powdery surface, with a reverse cream-coloured to brownish. Microscopic examination revealed hyaline anelloconidia, 3–4 μm in diameter, originating from penicillate flask-shaped conidiophores attached to hyaline septate hyphae. The conidia were mostly rough-walled with a truncated base and occurred in chains. The characteristic morphology of these conidia and conidiophores was consistent with S. brevicaulis (Fig. 1d). The isolate was sent to the Pasteur Institute in Paris for confirmation of the species identification and for susceptibility testing. The MICs were the following: amphotericin B, itraconazole and posaconazole ≥8 mg/L, flucytosine ≥64 mg/L, voriconazole 8 mg/L, and caspofungin 0.5 mg/L.

On 17 January, S. brevicaulis was detected in sputum using PCR and fungal culture. CT performed on 23 January showed worsening of the pulmonary lesions and the occurrence of bilateral renal lesions. During the following days the fungus was also isolated from stool. These results showed the dissemination of S. brevicaulis infection. The patient’s condition continued to worsen and she died on 29 January of multiorgan failure, 212 days after transplantation.

**Discussion**

We describe a case of widely disseminated S. brevicaulis infection in a woman with acute GVHD after stem cell transplantation. The patient was highly vulnerable to opportunistic infections, due to her severe immunosuppression, acute GVHD, and lengthy exposure to broad-spectrum antibiotics. Although significant advances have been made in the prevention of bacterial and fungal diseases in bone marrow transplant patients, the incidence of mould infections has increased in recent years [11]. The most common fungal pathogen in this setting remains Aspergillus. Less common fungi include Zygomycetes, non-Aspergillus hyalohyphomycetes (Fusarium sp., Scedosporium sp.) and phaeohyphomycetes (Exophiala dermatitidis, etc.) [12,13]. Human Scopulariopsis infections are relatively rare but are increasingly reported, particularly in immunocompromised hosts, with localized forms such as recurrent subcutaneous infections [14,15], pulmonary fungus ball [16], skin lesions [17,18], keratitis [19–21], endophthalmitis [6,22], and also pneumonia [23,24].
endocarditis [25–28], brain abscess [29], meningitis [30], and fatal disseminated infections [31–37].

As with other invasive hyalohyphomycoses, *Scopulariopsis* infections are difficult to diagnose, and this often delays appropriate therapy. Clinical manifestations cannot be used to distinguish between infections due to *Aspergillus* and other hyalohyphomycetes [37]. Cultures, including blood culture, are usually negative, and there are no commercial serological tests. Histopathological examination, the gold standard for the diagnosis of invasive mycoses, as well as direct mycological examination, reveal septate hyphae that are indistinguishable from those of other hyalohyphomycetes (*Aspergillus*, *Fusarium*, *Scedosporium*, etc.). Thus, many non-*Aspergillus* mould infections may be misdiagnosed as *Aspergillus* infection on the basis of clinical or histopathological features, as in the case reported by Wagner et al. (2005). Our patient was initially thought to have pulmonary aspergillosis on the basis of her clinical features and positive antigenaemia, even though *Aspergillus* was not isolated by culture. Subsequent isolation of *S. brevicaulis* from lesions of previously healthy skin suggested dissemination of the fungus from the lungs to the skin. In such cases, molecular tools may be particularly helpful for identifying the pathogen and hastening appropriate treatment [38].

A positive *Aspergillus* galactomannan test has previously been described in this setting [36]. The test detects galactomannan, which is widely distributed in filamentous fungi such as *Aspergillus* and *Penicillium*. In our patient the positive result may have been due to cross-reactivity with *S. brevicaulis* cell wall components, as no other fungus was isolated. Moreover, the patient had not been treated with piperacillin–tazobactam, which has been linked to false-positive galactomannan ELISA results [39]. The positive result is also consistent with haematogenous spread of *S. brevicaulis* from the lungs to the skin.

A similar case of secondary cutaneous infection by *Microascus* (a teleomorph of *Scopulariopsis*) from a primary pulmonary site has been described in a 12-year-old boy with acute myelogenous leukaemia who received autologous bone marrow transplantation [35]. The infection resolved after therapy with a colloidal dispersion formulation of amphotericin B (Amphocil). As in most other reports, lipid-amphotericin B therapy failed in our patient, as did voriconazole and also caspofungin lipid-amphotericin B combination therapy. Therapeutic approaches mentioned in the literature include debridement or excision of necrotic tissue plus prolonged single-agent or combination antifungal therapy [2,8,27,37,40,41].

In our case, the patient was receiving posaconazole for antifungal prophylaxis. The inefficacy of posaconazole in preventing rare pathogens that are less responsive to the most frequently used prophylactic drugs is noteworthy. *Scopulariopsis* infections are uncommon but may be encountered as breakthrough infections like other moulds in patients under antifungal prophylaxis. For example, cases have been published that occurred in patients under amphotericin B lipid complex [36,37]. Several breakthrough infections due to fungi other than *Scopulariopsis* have also been described in
patients under posaconazole prophylaxis (Rhizopus, Scedosporium prolificans, etc.) [42,43]. A recent paper has also reported the case of a woman with acute myeloid leukaemia who received 4 months of posaconazole for the labelled indication of prophylaxis of Candida and Aspergillus infections. The patient developed a fatal invasive sinus infection diagnosed as a mixed Aspergillus and Mucoar aetiology. Upon investigation it was found that the patient did not self-administer posaconazole as required in the product labelling. This may have led to drug failure in this patient. The disadvantage to oral administration of posaconazole is that it is not under medical control and may increase the risk of such breakthrough mycoses [44].

The strain isolated from our patient showed in vitro resistance to amphotericin B, itraconazole, posaconazole, fluconazole, and voriconazole. In a study of S. brevicaulis, all isolates were highly resistant to amphotericin B, itraconazole, posaconazole, voriconazole, terbinafine as well as caspofungin [45]. In some large in vitro studies, voriconazole was more effective than amphotericin B and itraconazole against S. brevicaulis [46,47]. Some combinations have shown synergy for S. brevicaulis isolates in vitro, including terbinafine plus fluconazol and itraconazole plus voriconazole [48]. Amphotericin B plus caspofungin, posaconazole plus caspofungin, and voriconazole plus caspofungin also showed synergy against some isolates [45]. Posaconazole plus terbinafine was synergistic for 68% of the isolates (2006). In contrast, few data are available on the clinical efficacy of combination therapy. In a case of a recurrent S. brevicaulis subcutaneous infection occurring 6 years after liver transplantation, a combination of surgery and long-term oral terbinafine resulted in a favourable outcome [14]. In another case of invasive sinonasal infection by S. candida, the patient survived after treatment with colony-stimulating factor, amphotericin B and itraconazole, without undergoing radical surgical debridement [23]. Isidro et al. [25] recommended initial empiric use of intravenous amphotericin B, alone or in combination with voriconazole or itraconazole, when Scopulariopsis is identified in a clinical specimen. Outcome depends mainly on immune status, the time from onset to diagnosis, and the extension of the infection.

As in previous reports, this case emphasizes the need for early accurate aetiological diagnosis and for more effective therapeutic strategies for such potentially life-threatening fungal infections.

Acknowledgements

The authors thank F. Dromer and O. Lortholary (Centre National de Référence de la Mycologie et des Antifongiques) for helpful discussion of this case, and D. Young and T. Dunham for editorial assistance and English checking.

Transparency Declaration

The authors do not have any relationship that may constitute a dual or conflicting interest.

References

19. Ragge NK, Dean Hart JC, Easty DL, Tyers AG. A case of fungal keratitis caused by Scopulariopsis brevicaulis treatment with antifungal


