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CASE REPORT

Fatal *Scopulariopsis brevicaulis* infection in a paediatric stem-cell transplant patient treated with voriconazole and caspofungin and a review of *Scopulariopsis* infections in immunocompromised patients

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Scopulariopsis brevicaulis is an airborne mould that causes 1–10% of cases of onychomycosis,[1,2] cutaneous lesions,[3] or severe soft tissue infection following traumatic or surgical injury in immunocompetent patients.[4,5] In this case we describe another dramatic presentation of *Scopulariopsis* species infection, widely disseminated infection, in a child after stem-cell transplantation with graft versus-host-disease who failed lipid amphotericin B therapy as well as voriconazole plus caspofungin combination therapy. We also review 12 cases of *Scopulariopsis* species infection in immunocompromised patients.

Case report

We report a 10-year-old African-American male who was diagnosed with acute myelogenous leukaemia in January, 2000. After failing induction chemotherapy he underwent an HLA-identical matched sibling bone marrow transplant on 28 March, 2000. He engrafted on day +13, but a repeat bone marrow examination revealed recurrent leukaemia. He then received a peripheral blood stem-cell transplant on 9 November, 2001 and 9 December, 2001 from his brother, and post-transplant infectious complications included *Staphylococcus aureus* bacteraemia and isolation of *Candida krusei* and *C. glabrata* from a tongue culture. He had persistent fever but his cytomegalovirus hybrid capture was repeatedly negative, and thoracic computed tomographic images were unremarkable.

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Eight months after his stem-cell transplant his underlying leukaemia was under control and he was no longer neutropenic, but he was undergoing intensive corticosteroid, infliximab (2 months), and daclizumab (2.5 months) therapy for grade IV gut and liver GVHD. At that time he developed a black, ulcerative lesion in the bandage area near his former central line exit site, which was clinically suspicious for cutaneous aspergillosis (Fig. 1). There was no evidence of onychomycosis. For the previous 5 months he had been on amphotericin B lipid complex (ABLC) at 5 mg/kg/d, so we replaced this with voriconazole (6 mg/kg/dose loading dose, followed by 4 mg/kg/dose maintenance dosing) combined with caspofungin (70 mg loading dose, followed by 50 mg daily maintenance dosing). A biopsy of the lesion showed septate hyphae by KOH examination and grew *S. brevicaulis* in pure culture. Histological examination revealed numerous septate true hyphae, many vesicular swellings of various sizes, and vessel invasion. In a few instances, structures that appeared clearly to be conidia were seen, indicating that adventitious sporulation had occurred. Conidiogenous cells (annellides) were not seen.

After two days on combination antifungal therapy he began to deteriorate clinically, requiring increased mechanical ventilation assistance and increased ionotropic support. Numerous new cutaneous lesions appeared on the skin after 4 days of therapy. Six days after initial biopsy culture, a blood culture was positive for *S. brevicaulis*. After a total of 11 days of combination antifungal therapy support was withdrawn. Autopsy revealed a severe disseminated fungal infection involving the heart, lungs, kidneys, thoracic cavity, and skin. In vitro testing of the isolated fungus was performed according to a modification of the NCCLS M38-P guidelines. The minimum inhibitory concentration (MIC) for amphotericin B was 16 μg/ml, caspofungin 8 μg/ml, and voriconazole 4 μg/ml. Macrodilution checkerboard testing revealed an in vitro synergistic interaction with voriconazole and caspofungin with a fractional inhibitory concentration index of 0.25.[6]

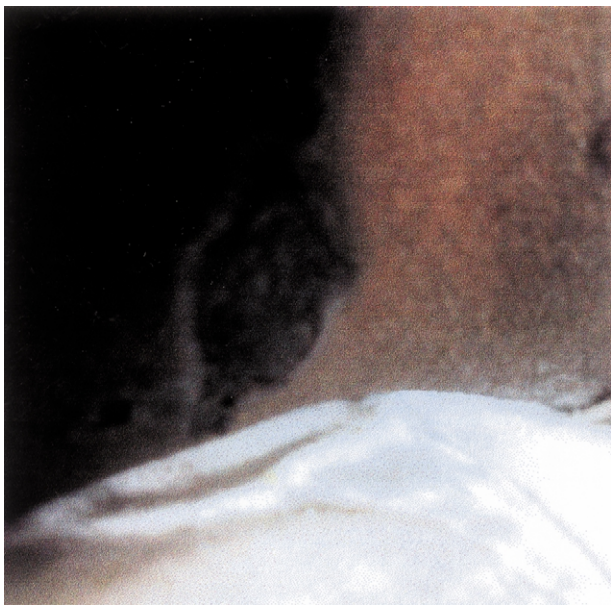

Figure 1 Skin lesion near previous intravascular catheter exit site.

Discussion

The genus *Scopulariopsis* accommodates species that can be pathogenic but which mainly are isolated from soil, food, paper, and other organic materials.[7] *Scopula* implies 'branches' or 'broom' in Latin, and the primary shape is a conidial-bearing structure resembling a brush. Eight species of *Scopulariopsis* have been reported as causing infection in humans (*S. acremonium*, *S. asperula*, *S. flava*, *S. fusca*, *S. koningii*, *S. brevicaulis*, *S. brumptii*, and *S. candida*), with five of them causing only onychomycosis. Some species of *Scopulariopsis* have either *Microascus* or *Kernia* teleomorphs (sexual states) and have been reported under these names as human pathogens.[8,9] The majority of human cases of *Scopulariopsis* species infection have been due to *S. brevicaulis*. Histopathologic findings show hyphal morphology indistinguishable from species of *Aspergillus*, *Fusarium*, and *Pseudallescheria*.[10]

Clinical manifestation of *Scopulariopsis* species infection in an immunocompromised patient can vary. Infection can present as a recurrent red-wine coloured, exophytic, ulcerative subcutaneous lesion not associated with any pain or itching, and without fever or lymphadenopathy.[11] One patient already on amphotericin B due to *Candida esophagitis* developed periungual erythema and tenderness followed by development of a black necrotic lesion adjacent to a toenail[10] while another patient developed a nodular skin lesion just before discharge.[12] In a report of two patients undergoing bone marrow transplantation with invasive *Scopulariopsis* species infection, both were presumed to have aspergillosis until *Scopulariopsis* species infection was identified microscopically by observation of annellides that formed a single or branching penicillus bearing distinctive conidia.[13] In our patient it appears that the fungus was introduced into skin and then vessels through trauma at a catheter site. It is possible that it

Table 1 Reports of immunocompromised patients with *Scopulariopsis* infection.

Underlying condition	Infection	*Scopulariopsis* species	Therapy	Outcome	Year	Reference
AML	Pneumonia	*Scopulariopsis* species	Amphotericin B for 47 days	Expired	1984	[27]
Allogeneic BMT	Pneumonia, brain abscess	*Scopulariopsis* species	Amphotericin B for 31 days	Expired	1987	[13]
Allogeneic BMT	Masoiditis	*Scopulariopsis* species	Surgery, amphotericin B for 16 months ketoconazole for 3 months	Expired	1987	[13]
Allogeneic BMT	Invasive toenail infection	*S. brevicaulis*	Surgery, amphotericin B for 4 months	Expired	1989	[10]
AIDS	Cutaneous	*Scopulariopsis* species	Itraconazole for 8 weeks	No change	1993	[28]
Liver transplant	Cerebral abscess	*S. brumptii*	Amphotericin B for 6 weeks	Expired	1994	[12]
Non-Hodgkin's lymphoma	Sinusitis	*S. candida*	Surgery, G-CSF, amphotericin B + itraconazole for 6 months	Alive	1994	[29]
Autologous BMT	Skin lesion, pneumonia	*Microascus cirrosus*[a]	Amphotericin B for 22 days, then amphotericin B colloidal dispersion for 'several weeks'	Cured, expired AML	1995	[30]
Chronic granulomatous disease	Suppurative granulomata	*Microascus cinereus*[a]	Amphotericin B for 10 weeks	Resolved	1995	[31]
AML	Sinusitis	*S. acremonium*	Surgery, amphotericin B for 3 weeks, itraconazole	Alive	1998	[32]
Allogeneic BMT	Brain abscess	*Microascus cinereus*[a]	Surgery, ABLC 30 days, then ABLC + itraconazole for 'several months'	Cured, expired GVHD	2000	[33]
Liver transplant	Recurrent subcutaneous lesions	*S. brevicaulis*	Surgery, terbinafine for 2 years	Cured	2000	[11]

AIDS, acquired immune deficiency syndrome; BMT, bone marrow transplant; AML, acute myelogenous leukaemia; G-CSF, granulocyte colony-stimulating factor; ABLC, amphotericin B lipid complex; GVHD, graft versus host disease.

[a] Teleomorph of *Scopulariopsis*.

gained entry through introduction into skin under adhesive bandage, a phenomenon that has previously been shown with Zygomycetes infection.[14]

Most antifungals have limited in vitro activity against *Scopulariopsis* species, including general inactivity with both amphotericin B and itraconazole.[8,15–18] Terbinafine has shown activity against *S. brevicaulis*,[19] but in nail infection models neither terbinafine nor itraconazole totally inhibit growth.[20] A large in vitro study with voriconazole showed superior activity over amphotericin B and itraconazole.[21] However, another in vitro study of 25 clinical isolates of *S. brevicaulis* isolated from skin and nails reported general inactivity with six different antifungals, including voriconazole.[22] Promising results include a report of terbinafine showing in vitro synergy with fluconazole, itraconazole, and voriconazole against isolates of *S. brevicaulis*.[23]

Most clinical experience with treatment of *Scopulariopsis* species infections focuses on onychomycosis,[1,2,24–26] forcing clinicians to extrapolate data to their immunocompromised patients. There are approximately a dozen published reports of immunocompromised patients with *Scopulariopsis* species infection (Table 1), and most succumbed to their infection. However, in many patients there was inadequate immunoreconstitution, a known essential component to combating an invasive fungal infection. Historically, treatment has largely consisted of amphotericin B or an azole, but now with an expanded antifungal armamentarium the clinician can attempt newer regimens for these often-recalcitrant infections. This is the first published clinical report of a patient treated with voriconazole and caspofungin, and while neither agent had excellent in vitro activity against this isolate, there appeared to be a positive interaction when both agents were used.

There are several important clinical points presented in this case. Although at times clinically indistinguishable, it is crucial to accurately distinguish between invasive *Aspergillus* and *Scopulariopsis* species disease. While amphotericin B and voriconazole have shown efficacy for invasive aspergillosis, *Scopulariopsis* species infections are more difficult to eradicate. This is clearly demonstrated in the review of previously published cases where amphotericin B therapy was often ineffective. In fact, our patient was on ABLC therapy at therapeutic doses for 5 months yet still developed invasive disease, forcing us to try a newer antifungal regimen. Despite in vitro synergy, our patient expired. However, he was only given 11 days of combination antifungal therapy, highlighting early diagnosis and immunoreconstitution as paramount to clinical success. Nonetheless, our in vitro checkerboard testing did show synergy with these two newer antifungals.

S. brevicaulis, like so many other once innocuous fungi, must now be included in the growing list of fungi able to cause disease in the immunocompromised patient. Our case illustrates how a severely immunocompromised patient living in the general environment and receiving antifungal prophylaxis will develop an unusual relatively drug-resistant superinfection. These types of emerging fungal infections are on the rise and will require creative management strategies. Presently there are limited therapeutic options, with many antifungals showing resistance. Clinicians will need to try unique newer therapies to combat the high mortality in the immunocompromised host, and we encourage the reporting of clinical experience using newer therapies in this difficult patient population.

References

1. Tosti A, Piraccini BM, Stinchi C, Lorenzi S. Onychomycosis due to *Scopulariopsis brevicaulis*: clinical features and response to systemic antifungals. *Br J Dermatol* 1996;**135**: 799—802.
2. Tosti A, Piraccini BM, Lorenzi S. Onychomycosis caused by nondermatophytic molds: clinical features and response to treatment of 59 cases. *J Am Acad Dermatol* 2000;**42**: 217—224.
3. Cox NH, Irving B. Cutaneous 'ringworm' lesions of *Scopulariopsis brevicaulis*. *Br J Dermatol* 1993;129.
4. Migrino RQ, Hall GS, Longworth DL. Deep tissue infections caused by *Scopulariopsis brevicaulis*: report of a case of prosthetic valve endocarditis and review. *Clin Infect Dis* 1995;**21**:672—674.
5. Sekhon AS, Willars DJ, Hawey JH. Deep *Scopulariopsis*: a case report and sensitivity studies. *J Clin Pathol* 1974;**27**: 837—843.
6. Lorian V. *Antibiotics in laboratory medicine*. Baltimore, MD: Williams and Wilkins; 1991.
7. Morton FJ, Smith G. The genera *Scopulariopsis* Bainier, *Microascus* Zukal, and *Doratormyces* Corda. *Mycol Pap* 1963; **86**:1—93.
8. Aguilar C, Pujol I, Guarro J. In vitro antifungal susceptibilities of *Scopulariopsis* isolates. *Antimicrob Agents Chemother* 1999;**43**:1520—1522.
9. Guarro J, de Hoog GS, Figueras MJ, Gene J. Rare opportunistic fungi. In: de Hoog GS, Guarro J, editors. *Atlas of clinical fungi*. Baarn, The Netherlands: Centraalbureau voor Schimmelcultures; 1995. p. 241—275.
10. Phillips P, Wood WS, Phillips G, Rinaldi MG. Invasive hyalohyphomycosis caused by *Scopulariopsis brevicaulis* in a patient undergoing allogeneic bone marrow transplant. *Diagn Microbiol Infect Dis* 1989;**12**:429—432.
11. Sellier P, Monsuez J-J, Lacroix C, et al. Recurrent subcutaneous infection due to *Scopulariopsis brevicaulis* in a liver transplant recipient. *Clin Infect Dis* 2000;**30**:820—823.
12. Patel R, Gustaferro CA, Krom RAF, Wisener RH, Roberts GD, Paya CV. Phaeohyphomycosis due to *Scopulariopsis brumptii*

in a liver transplant patient. *Clin Infect Dis* 1994;**19**: 198—200.
13. Neglia JP, Hurd DD, Ferrieri P, Snover DC. Invasive *Scopulariopsis* in the immunocompromised host. *Am J Med* 1987;**83**:1163—1166.
14. Mead JH, Lupton GP, Dillavou CL, Odom RB. Cutaneous *Rhizopus* infection: occurrence as a postoperative complication associated with an elasticized adhesive dressing. *J Am Med Assoc* 1979;**242**:272—274.
15. de Hoog GS, Guarro J, Gene J, Figueras MJ. *Atlas of clinical fungi*, 2nd ed. Utrecht, The Netherlands: Centraalbureau voor Schimmelcultures; 2000. pp. 276—282, see also pp. 902—916.
16. Szekely A, Johnson EM, Warnock DW. Comparison of E-test and broth microdilution methods for antifungal drug susceptibility testing of molds. *J Clin Microbiol* 1999;**37**: 1480—1483.
17. Pujol I, Aguilar C, Fernandez-Ballart J, Guarro J. Comparison of the minimum fungicidal concentration of amphotericin B determined in filamentous fungi by macrodilution and microdilution methods. *Med Mycol* 2000;**38**:23—26.
18. Regli P, Ferrari H, Buffard Y, Goudard M, Bastien J. Contribution a l'etude de la sensibilite de *Scopulariopsis brevicaulis* (Bainier) aux antifongiques. *Mykosen* 1983;**27**: 61—71.
19. Clayton YM. Relevance of broad-spectrum and fungicidal activity of antifungals in the treatment of dermatomycoses. *Br J Dermatol* 1994;**130**:7—8.
20. Richardson MD. Effect of Lamisil and azole antifungals in experimental nail infection. *Dermatology* 1997;**194**:27—31.
21. Espinel-Ingroff A, Boyle K, Sheehan DJ. In vitro activities of voriconazole and refernce agents as determined by NCCLS methods: review of the literature. *Mycopathologica* 2001; **150**:101—115.
22. Cuenca-Estrella M, Mellado E, Gomez-Lopez A, Monzon A, Rodriguez-Tudela JL. *Scopulariopsis brevicaulis*: a fungal pathogen resistant to broad-spectrum antifungal agents [Abstract M-1515] In: Program and abstracts for the 42nd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, (San Diego, CA), Washington, DC: American Society for Microbiology, 2002.
23. Ryder NS. Activity of terbinafine against serious fungal pathogens. *Mycoses* 1999;**42**:115—119.
24. Gupta AK, Gregurek-Novak T. Efficacy of itraconaozle, terbinafine, fluconazole, griseofulvin and ketoconazole in the treatment of *Scopulariopsis brevicaulis* causing onychomycosis of the toes. *Dermatology* 2001;**202**:235—238.
25. De Doncker PRG, Scher RK, Baran RL, et al. Itraconazole therapy is effective for pedal onychomycosis caused by some nondermatophyte molds in mixed infection with dermatophytes and molds: a multicenter study with 36 patients. *J Am Acad Dermatol* 1997;**36**:173—177.
26. Nolting S, Brautigam M, Weidinger G. Terbinafine in onychomycosis with involvement by non-dermatophytic fungi. *Br J Dermatol* 1994;**130**:16—21.
27. Wheat LJ, Bartlett M, Ciccarelli M, Smith JW. Opportunistic *Scopulariopsis* pneumonia in an immunocompromised host. *South Med J* 1984;**77**:1608—1609.
28. Dhar J, Carey PB. *Scopulariopsis brevicaulis* skin lesions in an AIDS patient. *AIDS* 1993;**7**:1283—1284.
29. Kriesel JD, Adderson EE, Gooch III WM, Pavia AT. Invasive sinonasal disease due to *Scopulariopsis candida*: case report and review of *Scopulariopsis*. *Clin Infect Dis* 1994;**19**: 317—319.
30. Krisher KK, Holdridge NB, Mustafa MM, Rinaldi MG, McGough DA. Disseminated *Microascus cirrosus* infection in pediatric bone marrow transplant recipient. *J Clin Microbiol* 1995;**33**: 735—737.
31. Marques AR, Kwon-Chung KJ, Holland SM, Turner ML, Gallin JI. Suppurative cutaneous granulomata caused by *Microascus cinereus* in a patient with chronic granulomatous disease. *Clin Infect Dis* 1995;**20**:110—114.
32. Ellison MD, Hung RT, Harris K, Campbell BH. Report of the first case of invasive fungal sinusitis caused by *Scopulariopsis acremonium*. *Arch Otolaryngol—Head Neck Surg* 1998;**124**: 1014—1016.
33. Baddley JW, Moser SA, Sutton DA, Pappas PG. *Microascus cinereis* (anamorph *Scopulariopsis*) brain abscess in a bone marrow transplant recipient. *J Clin Microbiol* 2000;**38**: 395—397.