Fatal Mycotic Aneurysms Due to *Scedosporium* and *Pseudallescheria* Infection

Adrian Ong,1 Christopher C. Blyth,2 Rosamma Bency,3 Mauro Vicaretti,4 Azian Harun,5 Wieland Meyer,5 Meena Shingde,6 Nicky Gilroy,1 Jeremy Chapman,3 and Sharon C.-A. Chen1,5*

Centre for Infectious Diseases and Microbiology, Westmead Hospital, Westmead, New South Wales,1 School of Paediatrics and Child Health, University of Western Australia, Perth, Western Australia,2 Department of Renal Medicine, Westmead Hospital, Westmead, New South Wales,3 Department of Surgery, Westmead Hospital, Westmead, New South Wales,4 Molecular Mycology Research Laboratory, Centre for Infectious Diseases and Microbiology, Westmead Millennium Institute, Sydney Medical School-Westmead Hospital, Westmead,5 and Department of Anatomical Pathology, Westmead Hospital, Westmead,6 New South Wales, Australia

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Angioinvasive complications of *Scedosporium* infections are rare. We report two cases of mycotic aneurysm, following apparent localized infection, due to *Scedosporium apiospermum* and *Pseudallescheria boydii*. The thoracoabdominal aorta was affected in one patient, and cerebral vessels were affected in the other. Despite voriconazole therapy and surgical resection, the patients died. Previously reported cases are reviewed.

CASE REPORTS

**Patient A.** A 55-year-old male with diabetes mellitus who was the recipient of a kidney transplant from a living related donor presented in 2009 with a left index finger lesion, following a trivial gardening injury. Immunosuppressive treatment included mycophenolate mofetil (500 mg thrice daily), tacrolimus (3 mg twice daily), and prednisolone (10 mg daily), with a course of therapy with methylprednisolone (1 g daily for 3 days) in the preceding 6 months. A culture of material from the lesion grew *Scedosporium apiospermum* and *Pseudallescheria boydii*. The in vitro MIC of voriconazole was 1 μg/ml (5). X rays of the hand showed no evidence of osteomyelitis, and there were no abnormalities upon chest X ray and cerebral computed tomography (CT) scanning. He received 3 months of oral voriconazole (200 mg twice daily after a loading dose of 6 mg/kg twice daily), with unchanged immunosuppression, with apparent complete clinical response.

Nine months later, the patient developed progressive, severe flank and lower back pain. He was afebrile and his blood pressure was 190/100 mmHg. There was bilateral soft tissue tenderness of the mid-lumbar region but no vertebral or abdominal tenderness. A CT scan of the abdomen revealed non-specific thickening of the aortic wall at the level of the third and fourth lumbar vertebra (LV3 to LV4). Magnetic resonance imaging (MRI) of the thoracoabdominal-sacral vertebra showed destruction of LV4 without evidence of discitis between LV3 and LV4. A paravertebral abscess was observed extending from the 10th thoracic vertebra (TV) to the LV4 level (Fig. 1a), in addition to inflammatory aortitis with aneurysm formation of the aorta from the level of TV9 to LV4 (Fig. 1b).

Empirical therapy with vancomycin, rifampin, and ciprofloxacin was commenced. Results from blood cultures were negative for bacteria and fungi. Drainage of the paravertebral abscess yielded 20 ml of purulent material; no organisms were seen on Gram or Ziehl-Nielsen staining. *S. apiospermum* and *P. boydii* were cultured after 14 days of incubation. A single, 1- by 2-cm subcutaneous nodule then appeared over the patient’s right wrist. Histopathological examination (Gromori-Grocott and periodic acid-Schiff [PAS] staining) of the excised lesion revealed granulomatous inflammation and septate hyaline fungal hyphae; *S. apiospermum* and *P. boydii* were recovered after culturing. Treatment with voriconazole was reinitiated (6 mg/kg twice daily and then 4 mg/kg twice daily) in association with a reduction in the intensity of the immunosuppressive regimen. Voriconazole serum levels were checked regularly (trough levels were between 2 and 3 mg/liter after reaching steady-state).

Serial MRI imaging of the spine demonstrated progressive enlargement of the aneurysm extending from TV10 to LV4. Urgent surgical resection and bypass of the aneurysm was performed. An 8.8-cm-diameter thoracoabdominal aortic aneurysm extending from the distal thoracic aorta to inferior to the native renal arteries (type V Crawford aneurysm) (31) with a sealed rupture at the distal thoracic aorta was identified. The aneurismal aorta was excised, and revascularization of the thoracic and abdominal aorta, celiac, and superior mesenteric arteries was performed using rifampin-soaked, gelatin-sealed Dacron grafts. Histopathological examination showed intimal fibrosis, fragmentation of elastic lamina, and multifocal granulomatous inflammation containing giant cells. Aggregates of PAS-positive fungal elements with branching septate hyphae and yeastlike structures were seen at the center of the granuloma (Fig. 2). *S. apiospermum* and *P. boydii* were grown from the diseased aorta. Unfortunately, the patient died 4 months
Species identification of all four *S. apiospermum* and *P. boydii* isolates (taken from finger, paravertebral abscess, cutaneous wrist lesion, and aortic wall tissue samples) was performed by standard morphological methods (7) and confirmed by DNA sequencing of the internal transcribed spacer (ITS1/2) region of the fungal rRNA gene cluster (8, 11). All isolates were identified as *S. apiospermum*, with 100% sequence similarity to the type strain of *S. apiospermum* sensu stricto (strain CBS 117407; GenBank accession number AJ 888416) (10, 12). Repeat susceptibility testing (5) revealed that the voriconazole MICs of all isolates were 1 \( \mu \)g/ml.

**Patient B.** A 48-year-old male with diabetes mellitus presented with severe headache, photophobia, left-sided visual loss, and dysphasia 4 weeks after a partial left mastoidectomy for a cholesteatoma. Physical examination revealed impaired vision (visual acuity, 6/60) of the left eye and palsies affecting the III, IV, VI, VII, and VIII cranial nerves. An MRI of the face and sinuses demonstrated marked erosion of the left petrous temporal bone with surrounding soft tissue enhancement on T2-weighted images. There was disease extension to the bony margins of the infratemporal fossa, pterygopalatine fossa, the apex of the left orbit, and encroaching on the left cavernous sinus, consistent with extensive skull base osteomyelitis. There were no intracerebral lesions.

Empirical intravenous ticarcillin/clavulanic acid, flucloxacillin, and metronidazole were commenced, and left functional endoscopic sinus surgery (FESS) was performed. Marked necrosis and invasion of bone and soft tissue with numerous septate fungal hyphae were seen on histopathological examination, and fungi, identified as *S. apiospermum* and *P. boydii* by standard morphological methods (7), were cultured from a bone sample. As for patient A, ITS sequence analysis of the isolate yielded a sequence with 100% sequence similarity to the type strain of *S. apiospermum* sensu stricto (see above) (10, 12).
Voriconazole (loading dose, 6 mg/kg daily, followed by 200 mg twice daily thereafter) was commenced. Serum voriconazole levels were not measured as therapeutic drug monitoring facilities were not available at that time. The patient received 12 weeks of ticarcillin/clavulanate and voriconazole. Although the headache resolved, the patient’s cranial nerve deficits persisted. Two weeks after cessation of therapy, the patient had a recurrence of severe headache. A gallium-67 citrate scan revealed persistent erosion of the left petrous temporal bone with new erosions extending into the right petrous temporal bone. He developed a subarachnoid hemorrhage into the basal cisterns and lateral ventricles. Magnetic resonance angiography revealed a right superior cerebellar artery (SCA) aneurysm with areas of ectasia of the posterior cerebral arteries, which is highly suggestive of aneurismal formation. Surgical clipping of the SCA aneurysm was complicated by extensive cerebellar infarction, and the patient died. Confirmation of mycological involvement was not possible (a postmortem was not performed); however, the aneurysm was very likely directly caused by *Scedosporium* infection.

**Discussion.** This report describes two cases of a fatal mycotic aneurysm implicating the fungus *S. apiospermum*. The causative role of this emergent pathogen was confirmed in patient A, and it is highly likely that it caused the aneurismal formation in patient B. Despite antifungal therapy and surgical resection, both patients died. Notable features of the cases presented herein include the insidious nature of bone involvement, with subsequent delayed presentation of aneurysmal dilation, and the aggressive extent of vascular invasion due to this pathogen.

Infections caused by *Scedosporium* and *Pseudallescheria* species are increasingly encountered in both immunocompromised and immunocompetent individuals (6, 17, 20, 29, 33). Mycotic aneurysms due to *Scedosporium* species are rare, however, with only 10 cases proven by biopsy specimens reported in the English literature (Table 1) (2, 3, 14, 15, 19, 20, 26, 28, 32, 36). These reports were identified through a Medline search for the terms “*Pseudallescheria boydii*,” “*Scedosporium apiospermum*”, and “*Scedosporium prolificans*” cross-referenced to terms that include “mycotic aneurysm,” “fungal aneurysm,” “infectious aneurysm,” “fungal,” and “aneurysm.” Case series describing infectious aneurysms or intracranial or aortic aneurysms were also scrutinized. With one exception, all patients with aneurysms caused by *Scedosporium* species were adults. Five (42%) had underlying malignancy and/or were organ transplant recipients; four of seven immunocompetent hosts had near-drowning accidents, and one suffered major trauma (Table 1). Both patients in the present report had diabetes mellitus; of
intracranial fungal aneurysms are most commonly caused by *Aspergillus* spp. (21, 34), while aortic aneurysms, in association with vertebral osteomyelitis, have been typically ascribed to *Salmonella* spp., other Gram-negative bacteria, and mycobacteria, with fungi (primarily *Aspergillus* spp.) comprising only 2.1% of cases in one series (25). Nonetheless, given the angio-invasive nature of *Scedosporium* and *Pseudallescheria* fungi (6, 17), careful investigation of any patient with invasive scedosporiosis with unexplained clinical symptoms that may be referable to a vascular cause is warranted. The majority of aneurysms caused by *Scedosporium* species (10/12 cases) (Table 1) have been reported to be caused by *S. apiospermum* and *P. boydii*. Access to DNA sequencing further enabled us to identify the causative pathogen as *S. apiospermum* sensu stricto. Recent genetic analyses have revealed *P. boydii* to be now separated from *S. apiospermum* as a distinct species and identified a new species of *Scedosporium* that would previously have been designated "*S. apiospermum*" (8, 10, 11). None of the isolates recovered from patients described previously (Table 1) were identified to the species level using molecular methods. Species identification of *Scedosporium* and *Pseudallescheria* species is important because of differences in virulence and antifungal susceptibility (11, 13).

A key feature of patient A's illness was the development of a large abdominal aortic aneurysm; two similar cases have been previously described but with less extensive involvement of the aorta (Table 1) (3, 28). In our patient, the aneurysm most likely developed as a result of direct invasion of the arterial wall from anterior spreading of vertebral osteomyelitis. Alternatively, infection may have originated from the aorta and then spread to the vertebra via the bloodstream; however, the absence of discitis (on completion of an MRI) mitigates against this hypothesis. Both purported routes of infection are consistent with the findings of one review of vertebral osteomyelitis that is coexistent with aortic pathology. In the event of a bony origin, anterior extension involving the aorta was identified to be the more typical situation (25). Aneurysms caused by *Scedosporium* species may also develop at unusual sites, including the hepatic artery (Table 1) (19).

We noted that intracranial aneurysms caused by *Scedosporium* and *Pseudallescheria* species have had a tendency to affect blood vessels at the base of the brain: seven of eight patients developed aneurysms in the posterior cerebral circulation, including patient B (Table 1) (21). We postulate that the apparent increased frequency of posterior circulation aneurysms may be related to direct anatomical spreading from infected mastoid air cells, malignant otitis externa, or invasive soft tissue and skull base osteomyelitis (as in patient B). While the spread of fungi from cerebral or meningeal infection is also possible (1, 16, 23), intracranial aneurysms complicating central nervous system scedosporiosis appears to be uncommon. There was no clinical evidence antemortem of endocarditis, although occult infection was not definitively excluded.

This report further underscores the mostly fatal outcomes (90% mortality) of this rare manifestation of scedosporiosis. This is consistent with the 80% mortality for fungal aneurysms of the internal carotid artery (all caused by fungi other than *Scedosporium* species) (18). The sole survivor in the cases we reviewed was an immunosuppressed patient infected with *S. prolificans* (Table 1). This patient was treated by surgical resection of the affected hepatic artery together with combined voriconazole and terbinafine therapy (19). Mortality rates of 79 to 100% have been reported for disseminated infection caused by both *S. prolificans* and *S. apiospermum* (4, 24).

A multidisciplinary approach with surgical resection of affected tissue and antifungal therapy is fundamental in managing patients with scedosporiosis (6, 20). A retrospective review of infected aortic aneurysms (only two cases were due to fungi) found that for those who had surgical treatment, the 1-year survival rate (90%), free of graft-related complications, was comparable to that reported for patients who had repair of noninfected aneurysms (27). However, early surgical outcomes were associated with significant morbidity, including ischemic colitis (27); indeed, patient A died following occlusion of the mesenteric artery graft. In another study of patients with vertebral osteomyelitis and infected aortic aneurysms, the best outcomes occurred for those who underwent surgical resection together with an extra anatomic bypass (25). The management of intracranial fungal aneurysms is also problematic. While there is general agreement that ruptured aneurysms should be immediately secured via either surgical means (as attempted in patient B) or endovascular aneurysm repair (EVAR) (22), unruptured infectious (predominantly bacterial) aneurysms have been treated medically with antimicrobials and followed by serial angiography (9, 30).

The decision to use voriconazole therapy was based on the *in vitro* susceptibility testing results and currently available clini-

cal information for the treatment of invasive scedosporiosis. Voriconazole is the preferred therapy for *S. apiospermum* and *P. boydii* infections (6, 35), although no recommendations regarding the optimal antifungal therapy or its duration have been established. Prolonged therapy is typically required. The complications of osteomyelitis and aneurysm formation in patient A did not manifest until 9 months after cessation of the initial course of antifungal therapy. Hence, careful follow-up of all high-risk patients for delayed complications, even with apparent clinical response, is critical. Although the clinical benefit of antifungal combination therapy has been reported for *S. prolificans* infections (6), a similar benefit has not been established for those due to *S. apiospermum* and *P. boydii*.

In summary, despite their rarity, mycotic aneurysms due to *Scedosporium* spp. are often fatal and may be delayed in their presentation. Clinicians should be vigilant for unusual manifestations of disease caused by this important pathogen. Early detection and prolonged antifungal therapy combined with surgical resection of the affected tissue are the cornerstones of management.

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REFERENCES


