**Scedosporium apiospermum** brain abscess treated with surgery and voriconazole

Case report


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✓ *Scedosporium apiospermum* is a fungus found in the soil and in contaminated water. Common cutaneous manifestations include Madura foot, a painless swelling on the sole of the foot. Invasive infection is usually associated with immunosuppression.

The authors present a 16-month-old immunocompetent boy who had a near-drowning event. Following this, he was severely disabled with spastic quadriplegia. Early computerized tomography scans revealed diffuse hypoxic injury. Magnetic resonance images obtained 3 months after the initial event demonstrated multiple ring-enhancing lesions in the brain. Aspiration of the lesion was performed. *Scedosporium apiospermum*, the asexual form of *Pseudallescheria boydii*, was cultured. Conventional antifungal agents were commenced, with minimal effect. The child was subsequently treated with a new antifungal agent, voriconazole, a broad-spectrum triazole antifungal agent with good penetration into the cerebrospinal fluid. The patient improved, with a good radiological outcome and a moderate clinical outcome. The authors review the use of voriconazole for central nervous system infections and review the literature on *S. apiospermum* associated with near drowning.

**Key Words** • *Scedosporium apiospermum* • brain abscess • voriconazole • drowning • pediatric neurosurgery

*Scedosporium apiospermum*, the asexual form of *Pseudallescheria boydii*, is a fungus commonly found in soil, polluted water, and sewage. It is a true fungus belonging to the *Ascomycete* family. An opportunistic pathogen, it rarely causes systemic disease in humans without a predisposing factor. Infections of the CNS with this pathogen have rarely been described in the literature. Risk factors for CNS manifestations include immunosuppression and near drowning. Treatment with surgical drainage and the available systemic antifungal medication gave poor results. Voriconazole is a new antifungal agent that has good CNS penetration. We present the case of a 16-month-old child who suffered multiple brain abscesses following a near-drowning incident. Surgical drainage and voriconazole improved the outcome.

**Case Report**

*History.* This previously healthy 16-month-old boy was admitted to the hospital after being found submerged in a pond after 5 minutes. Basic life support was administered at the scene. At the local hospital, he experienced asystolic arrest for 25 minutes with a core temperature less than 31°C. His initial blood gas report showed a pH of 6.63, a PaCO₂ of 10.45 kPa, and a base excess of -29. He was resuscitated according to advanced pediatric life support guidelines. Neurologically, he had no response to painful stimuli but his pupils did react to light. He was subsequently transferred to the tertiary PICU.

*Initial Presentation and Treatment.* In the PICU, he experienced acute respiratory distress syndrome with pulmonary infiltrates requiring high-frequency oscillatory ventilation. Pseudomonas septicemia subsequently developed and the patient required treatment with cefazidime and gentamicin. He responded well to the antibiotic agents but required a tracheostomy. Despite a protracted course of antibiotics and consistently negative blood cultures, he continued to have a low-grade pyrexia. A lumbar puncture revealed no abnormality. Fungal cultures of the sputum, blood, and urine were negative at that time.

*Interim Follow Up.* Neurologically, his condition began to improve. He was able to flex to painful stimuli, open his
eyes spontaneously, and make incomprehensible noises. A profound spastic quadriparesis was noted. He started to have grand mal seizures on Day 7 in the PICU. An electroencephalogram showed generalized slow wave activity. A head CT scan demonstrated areas of low density within the deep gray matter compatible with hypoxic brain damage (Fig. 1). No visual evoked responses were demonstrated; the results of electoretinography indicated cortical blindness. Three months after the incident, the patient had a continuing spastic quadriparesis and low-grade pyrexia.

In view of these symptoms, a cranial MR imaging study was performed, demonstrating multiple ring-enhancing lesions in both cerebral hemispheres. These lesions did not have surrounding edema. The largest one was located in the right frontal lobe. A CT scan of these lesions was obtained after aspiration of the largest abscess (Fig. 1 right).

**Operations.** The boy was subsequently transferred to the regional neurosurgical unit, where a right frontal burr hole for evacuation of the largest abscess was performed. During the operation, 20 ml of thick white pus was extracted using a Dandy cannula. Postoperatively he was more alert, but he still suffered from spastic quadriparesis and cortical blindness.

Over the next 4 months he underwent multiple procedures for drainage or excision of these abscesses. The right frontal abscess required aspiration on three more occasions. The left occipital abscess required drainage on two occasions, as did the right parietal abscess. The left occipital abscess was drained on one occasion. Microscopy of the aspirates revealed fungal hyphae. The boy was placed on a regimen of itraconazole 110 mg twice daily and amphotericin B 11.5 mg once a day based on his weight of 11.5 kg. Culture of the aspirate grew *S. apiospermum*, which was sensitive to miconazole but resistant to itraconazole and amphotericin B. Because it had been withdrawn from the market, miconazole was not available from the UK or the US. Because of toxic side effects and lack of in vitro sensitivity, amphotericin B was discontinued but itraconazole was continued. The patient’s condition improved. He was discharged 4 months after his first operation (7 months after the initial incident).

**Postoperative Course.** A repeated CT scan obtained 3 months later demonstrated enlargement of the right frontal abscess and many other abscesses. The patient was still pyrexial, despite a prolonged course of itraconazole. The right frontal abscess was reaspirated. Other abscesses were not aspirated because they were located in eloquent parts of the brain. It seemed clear that the abscesses were not responding to the available antifungal chemotherapy or the aggressive surgical aspiration and excision.

A new triazole antifungal agent, voriconazole (Vfend; Pfizer Central Research, Sandwich, UK), was commenced on this admission. This drug was in Phase II of a clinical trial so was begun on compassionate grounds after discussion with Pfizer pharmaceuticals. A loading dose of 6 mg/kg was infused intravenously and was given every 12 hours for the first 24 hours. The dose was then reduced to 4 mg/kg. The infusions were administered via a central venous catheter over the course of 3 hours. The patient’s liver function was regularly monitored as was his visual acuity. The intravenous route was converted to an oral formulation soon afterward. The serum concentration of vo-
Riconazole was measured at regular intervals. The minimum inhibitory concentration was 0.39 mg/ml. He was treated with oral voriconazole for 18 months.

The patient was last seen in our outpatient department 5 years after the initial episode (30 months following the cessation of voriconazole). He has made a remarkable recovery, although he still requires botulinum toxin injections for spasticity in both of his lower limbs. His right upper limb has normal tone and his left upper limb has mild hypertonia. He has good functional use of his arms. He is able to sit unaided, no longer requires feeding through a gastrostomy, and is beginning to say words. His hearing is normal and his visual acuity is 6/12 in the left eye and 6/9 in the right eye. He can communicate and understand simple commands. He has been seizure free for more than 3 years and currently takes no medication. His most recent MR images demonstrate resolution of the abscesses (Fig. 2).

Discussion

Scedosporium apiospermum is an opportunistic pathogen that rarely causes invasive disease in humans. Histological differentiation is difficult because it is quite similar to other filamentous fungi. The organism forms slender, septate hyphae with parallel cell walls that are difficult to distinguish from Aspergillus species. Accurate diagnosis depends on the results of cultures.

Clinical manifestations include endophthalmitis, pneumonia, endocarditis, lung abscess, disseminated disease, and CNS disease.16 Manifestations in the CNS include brain abscesses, meningitis,14 and mycotic aneurysms.1 Predisposing conditions for invasive S. apiospermum include insulin-dependent diabetes mellitus,15 transplants,3 leukemia,2 systemic lupus erythematosus,7 lymphoma,17 and near drowning.1,4,6,8,9,12

Scedosporium apiospermum is a difficult organism to treat in the CNS. It often demonstrates resistance to many of the commonly available antifungal agents, including amphotericin B, itraconazole, and ketoconazole. These antifungal agents have poor penetration into the CNS. Micronazole can be administered intrathecally but it is no longer available in the UK or the US because of its side effects, even for compassionate use.

Voriconazole has been developed to broaden the spectrum of activity of fluconazole. As with all azole antifungal agents, voriconazole works by inhibiting the enzyme cyto-

Fig. 2. Axial T1-weighted MR image demonstrating resolution in the abscesses after treatment with voriconazole.
chrome P450 14a-demethylase. This enzyme is involved in the sterol biosynthesis pathway that leads from lanosterol to ergosterol. Voriconazole inhibits P450 14a-demethylase more effectively than do other antifungals. It has consistently lower minimum inhibitory concentrations to S. apiospermum compared with other antifungal agents. It can be administered intravenously or orally (with an oral bioavailability of 90%). Most important, it has much greater CNS penetration than do other antifungal agents, with CNS concentrations approaching 50% of serum concentrations. Important side effects include dose-related elevated hepatic enzymes, skin rash, and visual disturbance. It has recently received Food and Drug Administration approval (in May 2002) for use in treating invasive S. apiospermum. Voriconazole is now available in the UK for the same indication.

Of the 10 reports of S. apiospermum causing brain abscess following a near-drowning incident, our patient is the youngest case found (Table 1). It is also the only one in which voriconazole was used. The mean age of the patients in this group was 16 years old, with three patients younger than 5 years. The outcome following CNS infection with S. apiospermum is poor, with only three of the 10 patients surviving. The mean time to diagnosis of a S. apiospermum brain abscess was 43 days. It is interesting to note that indication of pulmonary infiltrates were found on the initial chest x-ray films of all of the patients. In addition, the majority of patients had multiple abscesses. Theories for transmission include direct inoculation through the paranasal sinuses or via the hematogenous route. The facts that most patients had multiple abscesses and that all patients had indications of pulmonary infiltrates on the initial chest x-ray films suggest hematogenous spread into the CNS.

Scedosporium apiospermum in the CNS should be treated with aggressive surgery in association with the correct antifungal medications. Voriconazole is a new antifungal agent that has shown promise in treating this condition. One should have a low threshold for investigating any patient for a possible brain abscess following a near-drowning incident and should ensure that fungal cultures are taken in these patients.

**Disclaimer**

None of the authors have any financial interest in voriconazole.

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Scedosporium apiospermum brain abscess


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