

CASE REPORT

Infection of the CNS by *Scedosporium apiospermum* after near drowning. Report of a fatal case and analysis of its confounding factors

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This report describes a fatal case of central nervous system pseudallescheriasis. A 32 year old white man presented with headache and meningismus 15 days after nearly drowning in a swine sewage reservoir. Computerised tomography and magnetic resonance imaging of the head revealed multiple brain granulomata, which vanished when steroid and broad spectrum antimicrobial and antifungal agents, in addition to dexamethasone, were started. Cerebrospinal fluid analysis disclosed a neutrophilic meningitis. Treatment with antibiotics and amphotericin B, together with fluconazole and later itraconazole, was ineffective. Miconazole was added through an Ommaya reservoir, but was insufficient to halt the infection. *Pseudallescheria boydii* was finally isolated and identified in cerebrospinal fluid cultures, a few days before death, three and a half months after the symptoms began. Diagnosis was delayed because of a reduction in the lesions after partial treatment, which prevented a stereotactic biopsy. Physicians should be aware of this condition, and provide prompt stereotactic biopsy. Confirmed cases should perhaps be treated with voriconazole, probably the most effective, currently available treatment for this agent.

Central nervous system (CNS) infections secondary to *Pseudallescheria boydii* or its anamorph *Scedosporium apiospermum*, a hyalohyphomycete fungus formerly known as *Petriellidium boydii*, *Allescheria boydii*, and *Monosporium apiospermum*,^{1,2} can occur in individuals with a deficient immune response, such as patients with diabetes or the immunocompromised.^{3,4} However, *P boydii* is a ubiquitous microorganism that can be found in soil, sewage, and the polluted waters of streams and ponds with still water.^{4,5} Although several sites of infection have been described in the immunocompromised, including the CNS, infection in the immunocompetent usually presents as a sinusitis, lung infection, or most often after traumatic inoculation through skin bruises, usually in the lower limbs, as a chronic suppurative infection known by the eponym "Madura foot".^{2,5} CNS infection in immunocompetent individuals is usually associated with: (1) near drowning, with aspiration of a large inoculum of the fungi through the respiratory tree, which probably reaches the CNS through haematogenous spreading;^{1,5} (2) extension from orbital infection;⁶ (3) direct inoculation;¹ (4) surgical procedures or ventriculoperitoneal shunting;^{7,8} (5) epidural anaesthesia;⁹ (6) sphenoidal sinusitis;¹⁰ and (7) the presence of diabetes mellitus.² In cases secondary to aspiration after near drowning, once in the bloodstream, fungi seed into several sites but develop mainly in the CNS where, after an incubation period, that may last

from the usual 15 days to up to 130 days. This type of infection causes granulomata or abscesses and neutrophilic meningitis.^{1,2,5}

"In cases secondary to aspiration after near drowning, once in the bloodstream, fungi seed into several sites but develop mainly in the central nervous system"

To date, few cases of CNS pseudallescheriasis have been described.² However, such a diagnosis must always be sought in individuals who have suffered near drowning in standing polluted streams, ponds of water or sewage, or pits with manure.

The case of a man who acquired a CNS *P boydii* infection after near drowning in a swine sewage reservoir is described. We will focus on the difficulties of establishing the correct diagnosis and of choosing the best therapeutic approach.

CASE REPORT

A previously healthy 32 year old white man presented to our hospital with a history of a chronic CNS infection. Three months before he had nearly drowned in a swine sewage reservoir. Approximately a week after being discharged he began to suffer from fever, headache, and nuchal rigidity. A computerised tomography (CT) scan of the head revealed two images suggestive of brain abscess or granuloma. Ceftriaxone, metronidazole, fluconazole, and dexamethasone were started. Clindamycin was substituted for metronidazole, the patient became asymptomatic, with his cerebrospinal fluid (CSF) examination revealing only 5×10^6 cells/litre, and he was discharged. Two weeks later the symptoms recurred. At this time, CSF examination revealed 1300×10^6 cells/litre. Mannitol, dexamethasone, vancomycin, rifampicin, cefotaxime, and carbamazepine were started, on standard doses. The fever abated promptly, and a low grade headache subsided. At this time, he presented horizontal nistagmus, left hemiparesis, urinary urgency, and mild joint pains. He also developed a carbamazepine induced dermatitis, so carbamazepine was withdrawn. He was then referred to our centre. An additional CT scan revealed multiple brain abscesses. Rifampicin (600 mg/day), ceftriaxone (2 g/day), metronidazole and vancomycin (2 g/day), clonazepam (3 mg/day), and dexamethasone (16 mg/day) were maintained. Two days later, the patient became confused and presented a generalised seizure. His haematogram revealed a pronounced leucocytosis of $17\,800 \times 10^6$ cells/litre (51% neutrophils and 36% lymphocytes). His CSF was purulent, with 2820×10^6 cells/litre (24%

Abbreviations: Abbreviation: CNS, central nervous system; CSF, cerebrospinal fluid; CT, computerised tomography

monocytes and 76% neutrophils), total protein of 0.67 g/litre, and glucose of 2.11 mmol/litre. Although CSF examination was negative for fungi, pseudallescheriasis was suspected because of the history of near drowning in a manure reservoir. On the following day vancomycin, rifampicin, and metronidazole were discontinued, and cefepime was substituted for ceftriaxone. Amphotericin B (70 mg/day), oral itraconazole (200 mg twice daily), intravenous co-trimoxazole (three times a day), and phenytoin were started. A stereotactic biopsy was planned, but could not be carried out because a new CT scan revealed a reduction of the size and loss of definition of the brain lesions. Amphotericin doses were tapered to 20 mg every other day, according to creatinine blood concentrations. The dexamethasone dose was reduced to 8 mg/day, but was then tapered to 12 mg/day. During the next few days the symptoms recurred, and vancomycin, metronidazole, and dexamethasone were reintroduced. The patient improved. A new CSF examination disclosed 794×10^6 cells/litre (21% monocytes and 79% neutrophils), total protein of 0.832 g/litre, and glucose of 2.27 mmol/litre. CSF indirect immunofluorescence and enzyme linked immunosorbent assay for cysticercosis were negative. Co-trimoxazole was discontinued, and the dexamethasone dose reduced, but the patient worsened in the next few days. A CSF examination carried out at this time disclosed 1413×10^6 cells/litre (26% monocytes and 74% neutrophils), total protein of 0.662 g/litre, and a glucose of 2.11 mmol/litre. At this time, his haemoglobin was 0.105 g/litre, his haematocrit was 0.325, and the leucocytosis persisted at $13\,500 \times 10^6$ cells/litre (73% segmented, 5% bands, 15% lymphocytes, and 7% monocytes). His creatinine, which had previously reached 159.12 $\mu\text{mol/litre}$, returned to 106.8 $\mu\text{mol/litre}$, and his γ glutamyltransferase was 174 U/litre. Co-trimoxazole was reintroduced, and the clinical picture improved. Blood cultures yielded negative results, and CSF latex reactions for cryptococcal capsular antigens and CSF cultures for common and anaerobic bacteria and for free living amoeba were also negative. Alanine aminotransferase rose to 1.53 ukat/litre , glucose to 8.55 mmol/litre, and his prothrombin time rose to 13.6 seconds (88%). A new CSF examination was not helpful. After the third week of hospitalisation itraconazole was substituted for fluconazole. At this time his condition started to deteriorate. A new CT scan of the head showed slightly enhanced hypodense lesions in the white matter of the left frontal and the right parietal lobes. CSF pleocytosis increased to 2858×10^6 cells/litre (88% neutrophils and 12% monocytes), with a glucose of 1.11 mmol/litre, and a total protein of 0.87 g/litre. Small papular skin lesions ensued. An adverse drug reaction to co-trimoxazole was suspected and the drug was withdrawn. Analysis of the skin lesion disclosed an acute inflammatory process associated with dermatophytosis. At this time, his CSF revealed an increase in leucocyte count to 3178×10^6 cells/litre (10% monocytes and 90% neutrophils), glucose 0.67 mmol/litre, and total protein 0.79 g/litre. Amphotericin B (0.3 mg) and hydrocortisone (10 mg) were administered intrathecally, on alternate days, leading to an amelioration of the CSF parameters (1418×10^6 cells/litre; 18% monocytes, 72% neutrophils; total protein of 0.790 g/litre; glucose of 6.7 mmol/litre).

In spite of previous negative CSF immunological reactions to *P boydii*, *S apiospermum* was isolated from cultures of his CSF that had been carried out in Sabouraud, BHI, and Mycobiotic agar, incubated at 30°C. Cultures grew in the Sabouraud agar and later in the BHI agar, as a brownish and grey airy mycelium reversing dark grey. Microcultures revealed hyaline hyphae and isolated or grouped pyriform conidia in the extremities of simple or branched conidophores,

disposed laterally to the hyphae, a pattern characteristic of *S apiospermum*.

The patient's condition worsened. There was mild fever, confusion, and productive cough. A chest x ray was normal. He had pains in his left knee. At this time, he was taking dexamethasone (8 mg/day), clonazepam (1 mg/day), phenytoin (300 mg/day), cefepime (4 g/day), vancomycin (1.5 g/day), metronidazole (1.2 g/day), fluconazole (400 mg/day), and amphotericin (30 mg intravenously, which was reduced because of nephrotoxicity to 0.3 mg intrathecally on alternate days). He developed a complex partial status epilepticus and intravenous phenobarbitone was added to the regimen. CSF analysis revealed 5824×10^6 cells/litre (10% monocytes and 90% neutrophils), glucose of 0 mmol/litre and a total protein of 0.122 mg/litre. His electroencephalogram revealed a slow background activity, more pronounced on the right side. He became stuporous. Intravenous itraconazole (400 mg/day) was substituted for oral fluconazole, and vancomycin, cefepime, and metronidazole were discontinued. A left sided hemiparesis and bilateral abducens palsy ensued. A CT scan of the head revealed moderate hydrocephalus with periventricular enhancement. An external ventricular shunt and an Ommaya catheter were placed. The patient became confused and disoriented, in spite of improvement of CSF parameters (1838×10^6 cells/litre; 90% neutrophils, 10% monocytes; total protein of 0.830 g/litre, glucose of 1.39 mmol/litre). Ventricular fluid contained only 106×10^6 cells/litre; 22% monocytes, 78% neutrophils; total protein of 0.380 g/litre, and glucose of 3.72 mmol/litre. A few doses of miconazole were obtained for intrathecal administration. In the following days the ventricular CSF became progressively purulent. Seizures recurred and confusion increased. The patient died three and a half months after the symptoms were first noticed.

DISCUSSION

CNS pseudallescheriasis nearly always proves fatal, even when it occurs in previously healthy individuals. Of 29 cases reviewed, only seven patients survived. Of these, six were immunocompetent, although one of them had diabetes.

Currently, because of the small case series, there are no well defined predictors for survival. Patients who survived were submitted to surgical draining procedures of discrete lesions,¹¹ and some were also treated with intravenous and intrathecal miconazole¹² or amphotericin B,¹³ alone or combined with miconazole⁶ or ketoconazole.¹⁴ Some surviving patients were treated with high dose intravenous miconazole,^{1 6} and two were treated with voriconazole.^{8 15} Although the data are limited to a single case, the response to voriconazole seemed to be quicker and more sustained than the response to other antifungal agents, a finding attributable to its high fungicidal activity and its ability to cross the blood-brain barrier.⁸

“The main problem remains the attainment of an early diagnosis, the lack of which prevents prompt appropriate treatment and thus probably compromises the outcome”

When our patient was admitted, the diagnosis of CNS pseudallescheriasis was strongly suggested, not only because of the history of near drowning, but also because of the preceding pulmonary infection and a latent period of approximately two weeks. However, immersion in polluted waters may lead to infection of the CNS by free living amoeba, such as *Acanthamoeba* spp and *Naegleria* spp,¹⁶ and exceptionally by *Aspergillus* spp.¹⁷ Further diagnostic difficulties are the usual lack of appearance of *P boydii* in CSF stained smears, the lengthy time taken for the fungal colonies to grow in Sabouraud cultures, and the false negative immune reactions on serum and CSF, probably explained by the high

Take home messages

- We report a fatal case of central nervous system pseudallescheriasis in a 32 year old white man after nearly drowning in a swine sewage reservoir
- Diagnosis was delayed because of a reduction in the lesions after partial treatment, which prevented a stereotactic biopsy
- This case highlights the need for early diagnosis by stereotactic biopsy
- It is our opinion that confirmed cases should be treated with voriconazole, probably the most effective, currently available treatment for *Pseudallescheria boydii* infection

genetic variability of this species.^{18 19} Furthermore, false positive CSF latex reactions to cryptococcus capsular antigens may occur, confusing the diagnosis.⁵

However, the main problem remains the attainment of an early diagnosis, the lack of which prevents prompt appropriate treatment and thus probably compromises the outcome. In our case we identified two further diagnostic difficulties, namely: (1) the loss of definition of the granulomata/abscesses after treatment was started, which we attributed to steroid treatment because the symptoms were greatly reduced after it was introduced; and (2) a partial and fluctuating response to fluconazole, itraconazole, and to co-trimoxazole. Steroid treatment was effective in treating intracranial hypertension, but a diagnostic stereotactic biopsy had to be cancelled, thus postponing the definitive diagnosis until the terminal phase of the disease. Consequently, early access to a more appropriate antifungal treatment, such as voriconazole, could not be obtained. Although experience based on a single case cannot lead to definitive conclusions, it is our opinion that in cases like the one presented here, an early stereotactic biopsy should be performed, in view of the potential benefits of obtaining a precise diagnosis.

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