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# *Scedosporium apiospermum* as a rare cause of central skull base osteomyelitis

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ABSTRACT

We report a case of *Scedosporium apiospermum* mold causing ear infection, central skull base osteomyelitis and finally, occlusion of carotid artery in a 48-year-old diabetic man. The exact diagnosis was established and the severity of the disease understood several months after the onset of symptoms. Despite of appropriate antifungal therapy, and repeated surgical and otological procedures, the infection progressed to fatal cerebral infarction.



## 1. Introduction

*Scedosporium apiospermum* (teleomorph state *Pseudallescheria boydii*) is a mold commonly found in the environment. It is capable of causing invasive infections in both immunocompromised and competent individuals [1–3]. In patients with normal immune system, *S. apiospermum* typically causes local infections such as skin ulcers or arthritis [3] but as a result of immunosuppression, the pathogen can invade to vessel walls and blood circulation and cause disseminated infection [4,5]. *S. apiospermum* has a predilection to the central nervous system (CNS) and patients with brain abscesses have been reported [5,6]. Neutropenia, use of corticosteroids, and diabetes are risk factors for opportunistic *Scedosporium* infections [1,3–5]. Treatment is challenging and requires immune system reconstruction, aggressive surgical treatment and prolonged antifungal treatment. Guidelines rely on the experience gathered from single case reports. Voriconazole (VCZ) is suggested as the first line therapy of infections caused by these multidrug resistant molds [7].

Central skull base osteomyelitis (SBO) is a rare life-threatening condition originating from external auditory canal or less frequently from sinonasal infections [8–10]. It is defined as an osteitis of the temporal bone and skull base, including the bony labyrinth, the medial part of the petrosa, the sphenoidal and occipital bones and the clivus, even reaching the infratemporal fossa [11]. The infection may spread through the skull base forming granulomas and abscesses in the brain tissue and also lower cranial nerves can get affected [12,13]. In the diagnosis of SBO and its complications magnetic resonance imaging (MRI) is the most important method [14]. The most frequent etiology of SBO is bacterial but 20% to 50% are fungal [8]. Fungal SBO is most often caused by *Aspergillus* spp. [15].

We report a patient with *S. apiospermum* ear infection, central SBO, and finally, mycotic occlusion of the internal carotid artery (ICA) leading to death.

## 2. Case

A 48-year old man had suffered from type I diabetes for 35 years. His blood glucose had been poor for years. He had several diabetic complications including retinopathy and nephropathy. Hemodialysis had been started in September, 2013. He was using oral prednisolone 20 mg daily for painful chronic calcification wounds on his legs.

In December, 2013 (day 0), the patient complained of pain in his right ear. On the examination, there was an occluding mass inside the ear canal. Pathological anatomical diagnosis (PAD)

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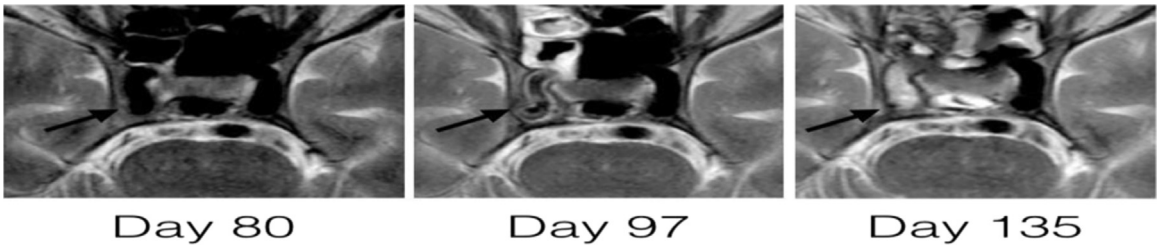


**Fig. 1.** MRI showing the evolution of the right ICA (arrow) infiltration at the level of cavernous sinus. On day 80 there is no visible infiltration and vessel walls are normal. On day 97, vessel walls are thick and the flow in the ICA seems to be slower. On day 135, the whole right ICA is occluded by non-enhancing material which was later proven to be of fungal origin.

showed an ulcer with granulation tissue. Bacterial cultures remained negative but no fungal tests were performed. Computed tomographic scanning (day 20) showed large soft tissue mass inside the mastoid sinus, middle ear and bony ear canal with bone erosions in the right jaw joint. Although the PAD suggested an abscess with fungal hyphae inside, no systemic antimicrobial treatment was commenced. Because of the worsening headache, drainage of the right ear, and temporal impairment of the left upper limb function, he visited the emergency, in February 2014 (day 80).

He had no signs of an acute infection, but complained of double images. Right-sided abducens nerve paresis was observed. C-reactive protein was 33 mg/l (normal $< 10$ mg/l), and white blood cell count $8.0 \times 10^9$/l (normal $3.4–8.2 \times 10^9$/l). MRI showed a cerebral lesion that was interpreted as ischemic or infective. There was a suspicion of vessel wall inflammation in the right ICA at the level of skull base (Fig. 1). The cerebrospinal fluid (CSF) contained no leukocytes but protein was elevated at 800 mg/l (normal 150–450 mg/l). Fungal polymerase chain reaction (PCR) showed weak positivity for *Aspergillus nidulans* considered as a contamination by the laboratory. Fungal and bacterial cultures remained negative.

Empirical treatment with intravenous (iv) ceftriaxone, iv vancomycin, oral rifampicin, and iv fluconazole (FCZ) 400 mg daily was started. Neurological symptoms were suspected to be due to partial seizures resulting from a cerebral infarction. He needed opiates because of severe headache.

On day 97, MRI revealed progression of infective areas in the skull base. Inflammation of the right ICA wall was stronger with occlusion and aneurysmatic enlargement which was suspected to be mycotic. On the right frontal and parietal lobes, multiple small focal abscesses were detected (Fig. 1). Due to the worsening situation and the PCR finding of *A. nidulans* FCZ was switched to oral VCZ (200 mg bid). Ceftriaxone was switched to meropenem. On day 101, an operation involving right sphenoidal and ethmoidal sinuses as well as right medial and superior conchae, was performed. PAD showed no fungal hyphae but a possibility of a healing fungal infection.

A mold was isolated from a sample taken from the sphenoidal sinus and was identified as *S. apiospermum* on the basis of typical colony morphology and shape of the conidiophores. The identification was confirmed by matrix-assisted laser-desorption-ionization time-of flight (MALDI-TOF) mass spectrometry, using Microflex LT instrument, MALDI Biotyper software version 3.1 and Filamentous Fungi Library database version 1.0 (supplied by Bruker Daltonics, Bremen, Germany). Specimen preparation was carried out as described by Schulthess et al. [16]. Antifungal resistance testing was performed at the Mycological Unit of the Clinical Microbiology Laboratory of Helsinki University Hospital (HUSLAB). The isolate showed minimum inhibitory concentrations of 0.38 for VCZ, 4 for posaconazole (PCZ), 32 for itraconazole and 12 for amphotericine B. The serum concentration of VCZ with both oral and iv (200 mg bid) administrations remained markedly below the suggested therapeutic concentration 2–5.5 mg/l. On day 121, VCZ dosing was switched back to oral 300 mg bid. VCZ concentration reached the level of 1.7 mg/l and patient's markedly improved condition made us to believe in the ongoing therapy. On day 135, MRI showed disappearing of the cortical lesions but the skull base involvement remained unchangeable. The non-enhancing mass occluding the ICA was larger (Fig. 1). The patient was discharged to an outpatient hospital on day 149 with oral VCZ and meropenem. He had no pain or problems with his ear and was scheduled for regular visits to the departments of infectious diseases and otolaryngology.

On day 162, patient's liver function tests (LFTs) appeared to be elevated: gamma-glutamyl transpeptidase 3722 U/l (normal 15–115 U/l), alkaline phosphatase 1291 U/l (normal 35 – 105 U/l), alanine aminotransferase 88 U/l (normal 10–70 U/l), and bilirubin 41 μmol/l (normal $< 21$ μmol/l). Meropenem was discontinued with no improvement on LFTs. On day 174, VCZ was switched to oral PCZ (400 mg bid) with no improvement on LFTs. The serum PCZ concentration of 0.4 mg/l (0.1–5 ml/l) was reached. Finally, antifungal treatment was discontinued because of the concern for patient's liver. An attempt was made to acquire isavuconazole (ICZ), a new azole-group antifungal at phase III clinical trials, probably with equal effectiveness but fewer side effects than the older azoles. MRI showed that cortical abscesses had almost disappeared and infective changes in the skull base were improving. However, the right ICA occlusion was still present and the non-enhancing mass in the vessel lumen was now almost at the level of middle cerebral artery (MCA) bifurcation.

On day 207, the patient contacted the emergency because of headache and dizziness. On examination, he still had abducens nerve palsy. CSF analysis revealed $2021 \times 10^6$/l leukocytes, indicating meningitis. Bacterial and fungal cultures and PCRs remained negative. Next day, the patient's condition collapsed, he was unconscious, rejecting pain with extension. MRI revealed an occlusion of the ICA at the level of MCA bifurcation. There was a suspected rupture of proximal right MCA with intracerebral hematoma and a large brain infarct of the corresponding MCA area. ICZ (received for compassionate use) was instituted but continued only two days before the patient died on day 212. Postmortem findings were consistent with previous investigations: skull base and vessel wall of the ICA were affected by fungal infection as seen also on histological sections (Fig. 2). *S. apiospermum* was cultured from both structures but not from the brain tissue. Massive cerebral infarction had led to brain herniation and to the death of the patient.

## 3. Discussion

Fungal central SBO is a rare condition and most often caused by *Aspergillus* spp. [15]. The fungal hyphae of *Aspergillus* and *Scedosporium* cannot be differentiated in microscopical examination and culture remains the gold standard for the diagnosis. *S. apiospermum* is extremely rare as a cause of central SBO, and has been rarely reported. Our patient did not have severe immunosuppression but

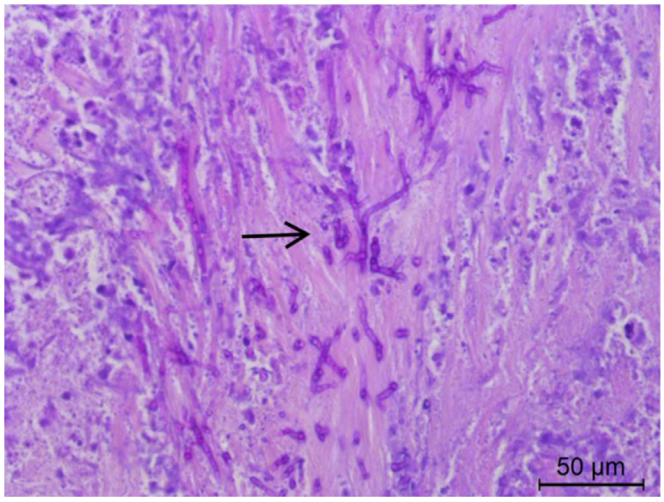


**Fig. 2.** Photomicrograph of the ICA, PAS staining. Fungal hyphae (arrow) are seen among arterial wall smooth muscle cells and necrotic debris.

suffered from diabetes and terminal uremia and was using oral prednisolone. Previously, patients with underlying HIV infection and central SBO caused by *S. apiospermum* have been reported [17,18]. One of these was successfully treated with itraconazole and the other died without effective treatment [17,18]. As in other mold infections, the severity of the underlying condition and degree of immunosuppression markedly influence on the outcome of the patient. Vasoo et al. treated their 51-year-old diabetic patient with right-sided otorrhea, cranial nerve palsies and SBO caused by *S. apiospermum* with VCZ for six months. Despite of extensive bony erosions, their patient remained in remission without further antifungal medication [19]. The possibility of this rare fungal infection should be recalled, because the treatment of severe fungal infections with amphotericine B will not be effective.

In the present case, the diagnosis was made very late mainly because the possibility of such a rare condition had not occurred to anybody's mind. Samples for fungal culture should have been taken in December, 2013. FCZ was started as a part of an empiric treatment because fungi were considered to be partly involved. FCZ is not effective against filamentous fungi why the treatment choice was not optimal. If amphotericine B had been started, it would have not worked either. Infectious disease specialist was engaged in the treatment in the middle of February, 2014. VCZ concentration did not reach optimal level either with iv or oral administration possibly due to the patient being a fast metabolizer. We do not know how PCZ would have worked if the patient had received it earlier. So far, there is much less experience on the use of PCZ against *S. apiospermum* infections but successful reports exist [6,7] and at least, therapeutic concentration was reached in our case. ICZ came too late to be able to influence on the disease progression.

The patient had elevated LFTs which finally lead to the cessation of the antifungal treatment, and presumably to the exacerbation of the infection. As seen also in one comparable previous case report, molds tend to evade vessels [2]. Due to the diffuse spread of the infection through bone, vessel, and brain tissues, radical surgery was not possible either in the present or the previously published case [2].

The outer ear infection initially detected and treated was only the tip of the iceberg. During treatment, the mold infection was irresistibly spreading inside the right ICA leading to the fatal rupture of the proximal MCA. Retrospectively, we can see how the process progressed despite of the apparently effective treatment with VCZ (Fig. 1). Hyperbaric oxygen might be an option as an adjunctive therapy but it was not used in our case. The prognosis of disseminated *S. apiospermum* infection is dismal with the mortality rate of CNS infection being 74% according to case reports [5]. Although our case represents rather local spread than wider dissemination, this patient case with an unhappy ending highlights the insidious nature of *Scedosporium* infection.

## Conflict of interest

There is none.

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