CASE REPORT

TREATMENT OF A BRAIN ABSCESS CAUSED BY *SCEDOSPORIUM APIOSPERMUM* AND *PHAEOACREMONIUM PARASITICUM* IN A RENAL TRANSPLANT RECIPIENT

Noppadol Larbcharoensub[1], Piriyaporn Chongtrakool[2], Chewarat Wirojtananugoon[3], Siriorn P Watchararanan[4], Vasant Sumethkul[5], Atthaporn Boongird[6] and Sopon Jirasiritham[7]

[1]Division of Anatomical Pathology, [2]Division of Microbiology, Department of Pathology, [3]Department of Radiology, [4]Division of Infectious Disease, [5]Division of Nephrology, Department of Medicine, [6]Division of Neurosurgery, [7]Division of Vascular/transplant Surgery, Department of Surgery, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Abstract. Cerebral mycosis is a significant cause of morbidity among immunocompromised populations. We present here a case of cerebral infection with *Scedosporium apiospermum* and *Phaeoacremonium parasiticum* in a 49-year-old renal transplant recipient. Fourteen years after renal transplantation, the patient presented with invasive pulmonary aspergillosis treated with intravenous liposomal amphotericin B. The patient had clinical and radiographic improvement. However, 6 weeks later, the patient presented with cerebral infection. Magnetic resonance imaging revealed multiple rim enhancing brain abscesses. Brain and cerebrospinal fluid cultures ultimately grew *Scedosporium apiospermum* and *Phaeoacremonium parasiticum*. The patient was treated with voriconazole for 6 months and had clinical and radiologic improvement. We believe this is the first reported case of co-infection of the brain with scedosporiosis and phaeohyphomycosis in a renal transplant recipient, who had received intravenous liposomal amphotericin B. Voriconazole may represent a new therapeutic option for these simultaneous infections in the brain.

Keywords: brain abscess, *Pseudallescheria boydii, Scedosporium apiospermum, Phaeoacremonium parasiticum, Phialophora parasitica*

Correspondence: Noppadol Larbcharoensub, Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok 10400, Thailand.
Tel: +66 (0) 2354 7277; Fax: +66 (0) 2354 7266
E-mail: Noppadol_l@hotmail.com

INTRODUCTION

Scedosporium apiospermum with its sexual anamorph *Pseudallescheria boydii* and *Phaeoacremonium parasiticum* (previously named as *Phialophora parasitica*) are ubiquitous filamentous fungi commonly

found in soil, sewage, and water (Castiglioni *et al,* 2002). Eumycetoma is the most common manifestation with both fungal organisms (Fincher *et al,* 1998; Castiglioni *et al,* 2002). They rarely infect the central nervous system causing brain abscesses. *S. apiospermum* brain abscesses have been reported and are usually seen in organ transplant recipients who receive immunosuppressive agents (Campagnaro *et al*, 2002; Castiglioni *et al,* 2002; Rogasi *et al*, 2007; Satirapoj *et al*, 2008). Only one case of a brain abscess caused by *P. parasiticum* has been reported (McNeil *et al*, 2011). Herein, the authors report the clinical, radiological, histopathologic and microbiologic features of co-infection in the brain with *S. apiospermum* and *P. parasiticum* in a renal transplant recipient. This case report was approved by the committee on human rights related to research involving human subjects at the Faculty of Medicine Ramathibodi Hospital, Mahidol University (ID02-54-55).

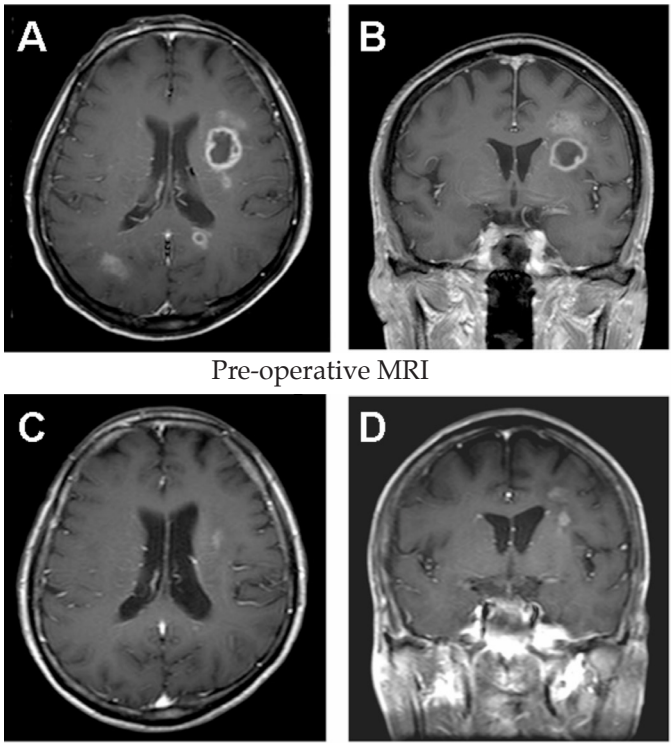

Fig 1–MRI shows multiple rim enhancing abscesses with perilesional vasogenic edema (1A: T1 axial view, 1B: T1 coronal view). Two months later the MRI shows resolution of the brain abscesses (1C: T1 axial view, 1D: T1 coronal view).

CASE REPORT

A 49-year-old man underwent cadaveric renal transplantation in 1993. The underlying diagnosis of this patient was chronic glomerulonephritis. His renal function was stabilized. He was taking daily immunosuppression with tacrolimus (FK506) and prednisolone. Fourteen years later, six weeks prior to admission, he contracted pulmonary aspergillosis. Serum galactomannan antigen was positive. Bronchoscopy was performed and histopathology revealed acute angle dichotomous branching septate hyphe. The lung tissue culture grew *Aspergillus fumigatus*. He was subsequently treated with intravenous liposomal amphotericin B. His pulmonary infection improved clinically and radiologically. However, within 6 weeks, he developed fever, intense headache over 72 hours and right-sided hemiparesis.

An upper motor neuron lesion was noted unilaterally. Laboratory studies revealed a hemoglobin of 8.9 g/dl, a hematocrit of 26.4%, a white blood cell count of 13,500/mm^3, a platelet count of 203,000/mm^3 and a serum creatinine of 2.8 mg/dl. An emergency computed tomography (CT) of the brain revealed multiple well-defined, thick walled hypodense lesions (18 Hounsfield units) with perilesional

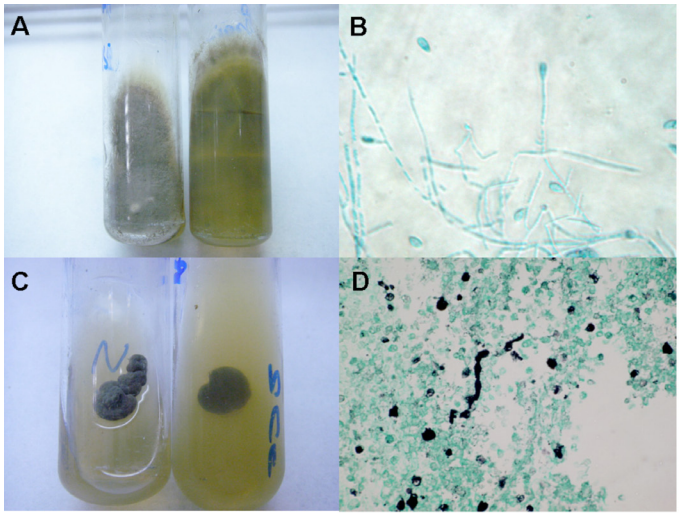

Fig 2–A 5-day-old fully grown colony of *S. apiospermum* on Sabouraud dextrose agar (2A). The colony was initially cottony and white but turned grey when older. The reverse was grey to black. A scedosporium asexual conidiation of *S. apiospermum* shows hyaline, septate hyphae and conidiogenous cells at the tip of the annellidic-flask-shaped conidiophores (2B, Lacto phenol cotton blue stain, x400). A 21-day-old colony of *P. parasiticum* on Sabouraud dextrose agar showing black, initially velvety radiating furrows, later developing hyphal fascicles, olivaceous-grey with a blackish reverse (2C). The sections of the brain abscess revealed beaded yeast-like fungi, morphologically consistent with *P. parasiticum* (2D, GMS stain, x200).

edema involving the centrum semiovale, left corona radiata, right occipital lobe and left splenium of the corpus callosum. Magnetic resonance imaging (MRI) of the brain revealed multiple rim enhancing cerebral abscesses with perilesional vasogenic edema (Fig 1). A cerebral abscess was diagnosed and surgical drainage was performed and samples sent for microbiology and histopathology. These showed multiple fungal elements with dichotomous branching septate hyphae and irregular, septate hyphal elements with beaded yeast-like forms.

A cultures of the brain abscess yielded *S. apiospermum* and *P. parasiticum*. *S. apiospermum* grew rapidly on Sabouraud's agar and produced floccose colonies that turned from white to dark-gray and smoky brown in 4 days (Fig 2). A slide culture showed unique morphological characteristics of this mould, presenting with hyaline, septate hyphae (2-4 m in diameter), with solitary, ovoid unicellular conidia, cut off at the base and borne terminally on elongated simple conidiophores. Concurrently, a graphium synanamorph was also seen showing erect, stiff, olive-brown bundles of hyphae, terminating in a brush of slender conidiogenous cells with annellidic conidiation. This type of conidiation produced smaller, less pigmented and more slender conidia compared with those of the scedosporium type. Both were truncated at their base, although the scedosporium types were more dominant. With the above mentioned characteristics, the isolate was phenotypically identified as *S. apiospermum*.

A culture of the cerebrospinal fluid (CSF) specimen in this patient yielded a dark-pigmented colony after 5 days of inoculation at 25°C. This moist colony grew moderately slowly and attained a diameter of 2-3 cm by 3 weeks of incubation. Its texture became wooly to velvety and heaped. The obverse was dark black and the reverse was iron-gray to black. Microscopic features using conventional slide culture techniques demonstrated dark-walled, septate (up to 5 m) hyphae, bearing rather long phialides located

terminally or laterally along the hyphae. The collarettes could hardly be seen due to their tiny, narrow parallel contours, characteristics that clearly differentiated them from the widely known *Phialophora verrucosa* and *Pleurostomophora richardsiae* (previously *Phialophora richardsiae).* The conidia were unicellular, hyaline, smooth and cylindrical in shape. These conidia sometimes accumulated in masses at the apices of the phialides, giving the appearance of a vase with a bundle of flowers. The length of the phialides seemed rather long, longer than 20 m and spine-shaped, which were the characteristics used for differentiate it from *Pleurostomophora repens* (previously *Phialophora repens)* in which the phialides are shorter than 20 m. Penicillate bushes of phialides, a unique characteristic of *P. repens,* could not be found in this isolate. Thus, this second isolate was morphologically identified as *Phaeoacremonium parasiticum.*

Intravenous voriconazole was given at a dose of 4 mg/kg every 12 hours. No antibacterial agents were given. Two months later, resolution of the brain abscesses was observed (Fig 1). The intravenous form of variconazole was then changed the oral form at a dose of 200 mg twice daily. The patient's central nervous system symptoms abated, and the infection continued to improve clinically and radiologically. The patient completed 6 months of oral voriconazole. He remained free of any signs of recurrence for 72 months after completion of therapy.

DISCUSSION

The cerebral mycosis is associated with many fungal organisms, including *Aspergillus* spp, *Candida* spp, and *Cryptococcus neoformans* (Larbcharoensub *et al,* 2007). Most cerebral mycoses are life threatening. The fungal species causing brain abscesses in solid organ transplant recipients is changing. *S. apiospermum* preferably affects solid organ transplant recipients, either with pathologic host defense alterations or those with severe drug-induced immunosuppression (Campagnaro *et al,* 2002; Castiglioni *et al,* 2002; Rogasi *et al,* 2007; Satirapoj *et al,* 2008). *S. apiospermum* brain abscesses have been reported and usually seen in kidney transplant recipients who receive immunosuppressive agents (Campagnaro *et al*, 2002; Castiglioni *et al*, 2002; Rogasi *et al*, 2007; Satirapoj *et al*, 2008). *P. parasiticum* is an uncommon emerging fungus causing cutaneous and subcutaneous infection in the renal transplant recipients (Fincher *et al*, 1988). Acquisition is usually through skin trauma or contamination of wounds. Secondary hematogenous dissemination may result in central nervous system (CNS) infection. However, only one case of brain abscess caused by *P. parasiticum* has been reported, in a patient with chronic granulomatous disease (McNeil *et al*, 2011). The authors believed that this was the first reported case of concurrent mycotic infection in a brain abscess with scedosporiosis and phaeohyphomycosis in a renal transplant recipient.

The specific diagnosis is difficult to make radiologically because the thick-wall hypodense lesion can be mistaken for both a brain abscess and a neoplasm, including a post-transplant lymphoproliferative disorder found in solid organ transplant recipients. The specific diagnosis is difficult to make histopathologically because *S. apiospermum* and *P. parasiticum* are indistinguishable from other mycoses in tissue sections and may produce infections similar to other cerebral mycoses. Therefore, the combination of a histopathological examination and tissues culture

are necessary to establish a definite diagnosis. Rapid molecular-based diagnostic methods are adjunctive tools. Prompt identification of fungal infections permits prompt antifungal treatment. It is crucial to make an early definitive diagnosis.

Scedosporiosis is frequently refractory to antifungal agents including amphotericin B, flucytosine, and fluconazole (Satirapoj *et al*, 2008). Intravenous miconazole, ketoconazole, and itraconazole with surgery appear to be effective for brain abscess (Castiglioni *et al*, 2002). Voriconazole has good CNS penetration and has emerged as a potential treatment option in cases of cerebral scedosporiosis (Nesky *et al*, 2000). Infection due to *P. parasiticum* is often susceptible to triazole antifungal agents, including itraconazole and voriconazole. However, cerebral phaeohyphomycosis has a high degree of mortality requiring early and aggressive therapy (McNeil *et al*, 2011). Further complicating this case was the renal transplant recipient, who was placed on amphotericin B for pulmonary aspergillosis. Breakthrough cerebral scedosporiosis and phaeohyphomycosis occurred. Therefore, voriconazole remains the drug of choice for the treatment of a patient with simultaneous cerebral *S. apiospermum* and *P. parasiticum* infection.

It is crucial to make an early definitive diagnosis because *S. apiospermum* is resistant to amphotericin B and itraconazole (Johnson *et al*, 1998; McGinnis and Pasarell, 1998), and *P. parasiticum* requires aggressive therapy. Voriconazole is the only therapeutic option for simultaneous infections with these two organisms. The duration of treatment has not been established. Long-term therapy may prevent recurrent infection. In this case, the patient completed a 6 month course of oral voriconazole. He remained free of any signs of recurrence 66 months after completion of treatment.

In conclusion, *S. apiospermum* and *P. parasiticum* should be considered in the differential diagnosis of cerebral mycosis and must be included in the expanding spectrum of life threatening opportunistic pathogens causing a brain abscess in solid organ transplant recipients, including renal transplant recipients. The emergence of infections due to *S. apiospermum* and *P. parasiticum* warrants a high index of clinical suspicion. Cerebral scedosporiosis and phaeohyphomycosis co-infection in a patient receiving intravenous amphotericin B may occur. Surgical biopsy with histopathological examination and tissue culture is the mainstay for a definite diagnosis. Surgical drainage of the brain abscess with adjuvant antifungal therapy is the cornerstone of management of the cerebral scedosporiosis and phaeohyphomycosis.

REFERENCES

Campagnaro EL, Woodside KJ, Early MG, *et al*. Disseminated *Pseudallescheria boydii* (*Scedosporium apiospermum*) infection in a renal transplant patient. *Transpl Infect Dis* 2002; 4: 207-11.

Castiglioni B, Sutton DA, Rinaldi MG, Fung J, Kusne S. *Pseudallescheria boydii* (Anamorph *Scedosporium apiospermum*). Infection in solid organ transplant recipients in a tertiary medical center and review of the literature. *Medicine* (Baltimore) 2002; 81: 333-48.

Fincher RM, Fisher JF, Padhye AA, Ajello L, Steele JC Jr. Subcutaneous phaeohyphomycotic abscess caused by *Phialophora parasitica* in a renal allograft recipient. *J Med Vet Mycol* 1988; 26: 311-4.

Johnson EM, Szekely A, Warnock DW. In-vitro activity of voriconazole, itraconazole and amphotericin B against filamentous fungi.

J Antimicrob Chemother 1998; 42: 741-5.

Larbcharoensub N, Srisuma S, Ngernprasetsri T, *et al*. Invasive fungal infection in Ramathibodi Hospital: a ten-year autopsy review. *J Med Assoc Thai* 2007; 90: 2630-7.

McGinnis MR, Pasarell L. In vitro testing of susceptibilities of filamentous ascomycetes to voriconazole, itraconazole, and amphotericin B, with consideration of phylogenetic implications. *Antimicrob Agents Chemother* 1998; 36: 2353-5.

McNeil CJ, Luo RF, Vogel H, Banaei N, Ho DY. Brain abscess caused by *Phaeoacremonium parasiticum* in an immunocompromised patient. *J Clin Microbiol* 2011; 49: 1171-4.

Nesky MA, McDougal EC, Peacock JE Jr. *Pseudallescheria boydii* brain abscess successfully treated with voriconazole and surgical drainage: case report and literature review of central nervous system pseudallescheriasis. *Clin Infect Dis* 2000; 31: 673-7.

Rogasi PG, Zanazzi M, Nocentini J, *et al*. Disseminated *Scedosporium apiospermum* infection in renal transplant recipient: long-term successful treatment with voriconazole: a case report. *Transplant Proc* 2007; 39: 2033-5.

Satirapoj B, Ruangkanchanasetr P, Treewatchareekorn S, Supasyndh O, Luesutthiviboon L, Supaporn T. *Pseudallescheria boydii* brain abscess in a renal transplant recipient: first case report in Southeast Asia. *Transplant Proc* 2008; 40: 2425-7.