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LETTER TO THE EDITOR

Successful treatment of invasive sphenoidal, pulmonary and intracerebral aspergillosis after multivisceral transplantation

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Fungal infections account for significant morbidity and mortality after solid organ transplantation. After liver transplantation, there is a reported incidence of 4–42% for fungal infections, which are predominantly caused by *Candida* species [1]. We report on the successful treatment of a very rare case of invasive sphenoidal, pulmonary and intracerebral aspergillosis after multivisceral transplantation.

A 34-year-old female patient with a history of complicated Crohn's disease since 1988, ultra-short bowel syndrome, liver cirrhosis, and renal failure underwent multivisceral transplantation (MVTx) and kidney transplantation in November 2003. Initial immunosuppression (IS) consisted of alemtuzumab [30 mg i.v. postoperative day (POD) 1], tacrolimus (trough levels 15–20 ng/ml for 4 weeks, then 8–10 ng/ml for 3 months, then 5–6 ng/ml), and steroids (500 mg i.v. POD 0 + 1; 250 mg POD 2, 100 mg POD 3, then rapid tapering over a period of 3 months until withdrawal). Anti-infectious prophylaxis consisted of sulfamethoxazole-trimethoprim and acyclovir for 6 weeks, without antifungal prophylaxis. The patient developed tissue-invasive cytomegalovirus (CMV)-enteritis (CMV-DNA 5000 copies/ml; CMV-pp65-Ag 4/100 000 cells), treated successfully with intravenous ganciclovir. She was discharged 5 months post-transplant with creatinine levels of 1.5 mg/dl. Acute cellular rejection of the intestine occurred 3 weeks later requiring methylprednisolone pulse therapy (3 × 1000 mg i.v.). Immunosuppression was enforced by sirolimus (2 mg once daily). A transient noninvasive CMV-infection (CMV-DNA 3200 copies/ml; CMV-pp65-Ag negative) was rapidly reversed by ganciclovir.

The patient then presented with severe left-sided temporal headaches resistant to analgesics 9 months post-transplant. Cranial CT and MRI scan showed left-sided sphenoidal and ethmoidal sinusitis (Fig. 1) with signs of osseous destruction of the lateral sphenoidal wall and inflammation of the adjacent dura mater. Transnasal left ethmoidectomy and sphenoidectomy were performed. Microbiological examination and histopathology confirmed tissue-invasive aspergillosis with *Aspergillus fumigatus*. Chest radiographics and CT scan demonstrated multiple focal lesions of varying sizes (Fig. 2). Bronchial fluid withdrawal by bronchioalveolar lavage and lung biopsy cultures grew *A. fumigatus*, sensitive to caspofungin, voriconazole, amphotericin B and flucytosine. Because of ongoing sirolimus treatment, voriconazole treatment was delayed; initial antifungal therapy comprised liposomal amphotericin B [5 mg/kg body weight (b.w.) i.v.] and caspofungin (50 mg i.v.). Two weeks after withdrawal of sirolimus, amphotericin B was substituted by voriconazole (6 mg/kg b.w. i.v.). Voriconazole serum levels were assessed once during initial therapy to assure sufficient therapeutic levels (1.5 μg/ml). After 3 months of combined antifungal therapy, the patient was discharged with voriconazole monotherapy (200 mg b.i.d orally). Owing to aggravating headaches and increasing signs for bone destruction, caspofungin was reinstituted again. After 4 weeks of combined intravenous antifungal therapy and still without improvement of headaches, the

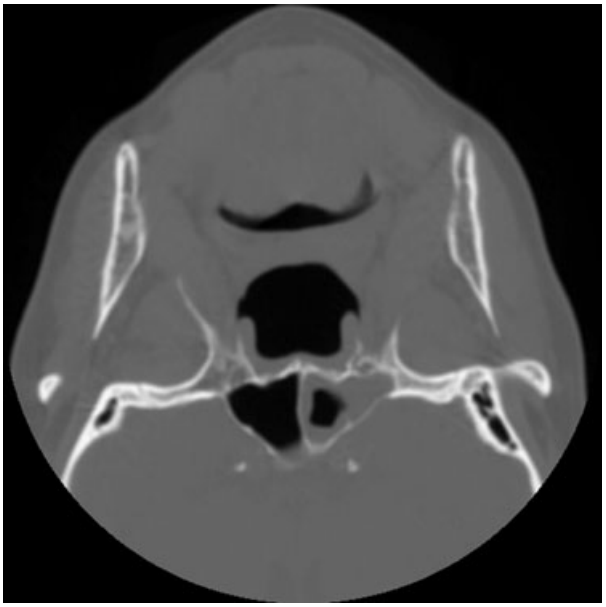

Figure 1 CT scan of the head with sinusitis of the left sphenoidal and ethmoidal sinuses and suspicion of osseous destruction of the lateral sphenoidal wall.

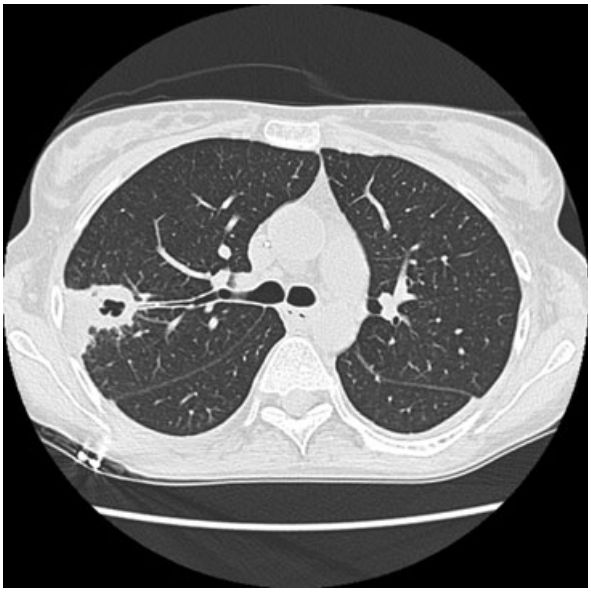

Figure 2 CT scan of the thorax with focal lesions indicative of invasive pulmonary aspergillosis in the right hemithorax.

patient recognized double visions caused by paralysis of the left abducens nerve. A cranial MRI scan showed invasive aspergillosis causing damage to the lateral wall of the left sphenoid sinus and affecting the cavernous sinus, abducens nerve, and left carotid artery (Fig. 3). Angiography revealed a stenosis of the left internal carotid artery (Fig. 4). Antifungal therapy was switched to liposomal amphotericin B (2 mg/kg b.w. i.v.) and flucytosine (500 mg i.v. t.i.d), immunosuppression was reduced. After 2 months, the pain subsided, double visions vanished and MRI showed a reduction of inflammatory alterations. The given antifungal regimen was continued for another 4 months, i.e. until August 2005. Since then, the patient has been recurrence-free. Kidney function has been stable over the entire post-transplant period.

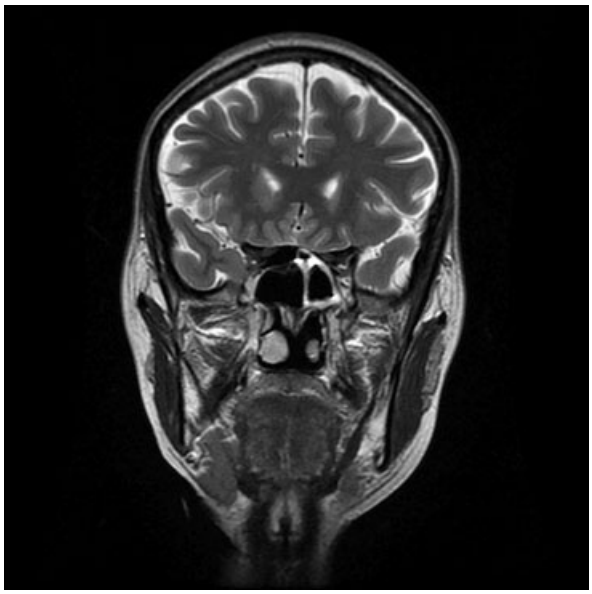

Figure 3 MRI scan of the head showing invasive aspergillosis and fungal osteitis of the lateral wall and the roof of the left sphenoidal sinus, and inflammatory alterations of the left cavernous sinus, internal carotid artery, and left abducens nerve.

There is an estimated 11–14% incidence of invasive aspergillosis in immunocompromised patients. Overall mortality was reported to be 50–60% [2]. Aspergillus sinusitis was associated with a mortality rate of approximately 25% [3], cerebral aspergillosis with a mortality rate of 65–90% [3,4]. However, there is very little data on the incidence of invasive aspergillosis after intestinal transplantation. Aspergillosis-related mortality after isolated or combined intestinal transplantation was reported as 1.5% in pediatric patients and 2.3% in adults respectively [5,6]. There are only anecdotal reports on successful treatment of invasive aspergillosis after MVTx [7].

Prolonged and profound neutropenia, CMV-infection, and intense immunosuppression particularly with the use of depleting drugs such as alemtuzumab have been identified as major risk factors [2,8,9].

Symptoms and clinical signs of aspergillosis are usually unspecific and appear late as described in the presented patient. An early diagnosis may be missed for a prolonged period of time because of the lack of high index of suspicion, and that explains tissue and bone invasion at the time of detection. Diagnosis depends on detection in culture or histology, as well as imaging techniques. For example, high resolution CT (HRCT) was shown to detect *Aspergillus*

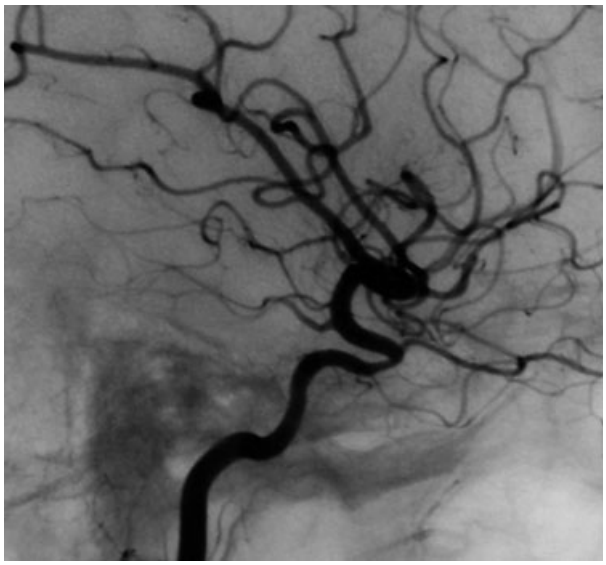

Figure 4 Angiography showing a stenosis of the left internal carotid artery.

pneumonia with a sensitivity and specificity of 87% and 57% respectively [10]. Screening methods such as antigen detection, e.g. for galactomannan, may improve early diagnosis of invasive aspergillosis. While selected trials showed a diagnostic sensitivity and specificity of up to 94% and 99%, respectively [11], other studies failed to show antigenemia preceding clinical diagnosis [12].

Amphotericin B was the gold standard for the primary treatment of aspergillosis until 2000 [13], but exerts considerable side-effects. Although liposomal amphotericin B and caspofungin have provided at least comparable efficacy despite higher tolerability [2], voriconazole has become the drug of choice for the primary treatment of invasive (cerebral) aspergillosis [14], because of its broad antifungal spectrum and the ability to pass the blood–brain barrier [15]. However, drug interactions may occasionally limit its use in transplant recipients, particularly in those receiving sirolimus [2]. Plasma drug level monitoring has not yet been recommended on a regular basis, however, appears reasonable in patients with serious *Aspergillus* disease because malabsorption and individual patterns of drug clearance may result in insufficient drug levels resulting in therapy failure [16]. Because of the high mortality of MVTx patients developing invasive aspergillosis, double- or triple-drug antifungal regimens are frequently preferred over single-drug treatment [7].

In the presented case, combination therapy with caspofungin and voriconazole only partially succeeded as first-line therapy of invasive pulmonary, sphenoidal and intracerebral aspergillosis. A complete and persistent response was finally achieved with liposomal amphotericin B and flucytosine. This study shows that individually ailored use of modern antifungals may be required in patients who have a very high mortality risk in invasive aspergillosis.

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