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CASE REPORT

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Lessons to be learned from a complicated case of rhino-cerebral mucormycosis in a renal allograft recipient

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Abstract Fungal infections still represent a serious complication after organ transplantation. Early diagnosis and aggressive treatment are crucial. Because of the many diagnostic problems involved, we present a case of mucormycosis – primarily affecting the paranasal sinuses with later intracranial extension – in a highly immunized recipient of a third renal transplant. Although fungal infection was suspected from various imaging techniques, only the detection of typical fungal hyphae in the infected tissue was diagnostic. Neither the blood tests and cerebrospinal fluid examinations performed nor cultures from maxillary sinus fluid were of any diagnostic help. Surgical debridement from a transnasal as well as an intracranial approach and systemic amphotericin B together with the discontinuation of immunosuppression after removal of the rejected graft were able to save the patient. This case stresses the importance of early diagnosis that can only be made from tissue biopsies and allows appropriate timely treatment.

Keywords Immunosuppression · Fungal infection · Rhino-cerebral infection · Mucormycosis

Introduction

Prevention of allograft rejection and infection are the two primary, inextricably linked prerequisites for successful organ transplantation. Especially in highly immunized patients, exposure to more aggressive immunosuppressive therapies to avoid rejection of the graft results in an increased risk of infection. Mucormycosis is a rare opportunistic fungal infection, but is increasingly recognized in the growing population of immunocompromised hosts [1]. Risk factors for mucormycosis include hematological malignancies and diabetes mellitus, in particular when associated with ketoacidosis [2]. Apart from the use of steroids and immunosuppressive agents in bone marrow and solid organ transplantation, broad-spectrum antibiotics, cytotoxic chemotherapy, and dialysis for uremic patients are predisposing factors [3, 4, 5].

Mucormycosis can appear in different clinical forms, i.e., rhino-cerebral, pulmonary, disseminated, gastrointestinal, cutaneous, and other rare forms [5]. The prognosis of the rhino–cerebral form is poor, with an overall mortality of up to 40–50% [6, 7] and residual defects in 70% of survivors [7]. In transplant recipients, the diagnosis of this rare opportunistic infection can be extremely difficult, in particular due to the anti-inflammatory effect of steroids included in most immunosuppressive regimens, obscuring some of the typical signs of infection. Because of the many diagnostic pitfalls encountered, a case of rhino-cerebral mucormycosis occurring shortly after renal transplantation is presented.

Case report

A 9-year-old male with chronic renal failure due to streptococcal nephritis received a cadaveric kidney transplant in 1986. When this graft failed, he was returned to dialysis and in 1989 was given a kidney from his mother, which functioned until 1994. Both grafts were lost due to chronic rejection. Since 1994 the highly immunized patient (98% preformed HLA antibodies) had been awaiting his third transplant. Finally, in December 1999 he received a cross-match-negative organ from a 26-year-old multiorgan donor.

Prophylactic immunosuppression consisted of tacrolimus, corticosteroids, and mycophenolate mofetil (MMF) together with an induction therapy with basiliximab apart from a series of nine prophylactic plasmaphereses. Perioperative antibiotic prophylaxis with piperacillin/tazobactam was given until postoperative day 3. Post-transplant anuria was thought to be due to acute tubular necrosis. Biopsy-proven acute rejection (Banff I) on day 7 after transplantation was treated with 500 mg methylprednisolone bolus therapy for 3 consecutive days. Under steroid therapy the patient developed hyperglycemia (fasting blood glucose levels between 150 and 200 mg/dl), managed by exogenous insulin. Ketoacidosis, however, was never observed.

On day 8 following transplantation, the patient for the first time complained of unilateral headache with nausea and pain of the hard palate, followed by pain on the right side of his face, ophthalmoplegia, and dysesthesia of the service area of the maxillary nerve. Upon clinical examination, only a livid discoloration of the palate about 1 cm in diameter was seen. Because of concomitant typical oral herpetic lesions, the patient was given acyclovir intravenously. On day 13 he began to develop a rapidly progressing state of coma. Cerebrospinal fluid (CSF) and EEG findings were abnormal, but nonspecific. Since neurotoxicity of acyclovir had to be assumed, possibly aggravated by MMF [8], both drugs were withdrawn immediately. Shortly thereafter the patient recovered from the comatous state, but presented with paraplegia of the lower limbs and fecal incontinence. Apart from opacification of all paranasal sinuses on the right side, cerebral MRI was uneventful, but a checkup 6 days later showed a 3-mm lesion in the occipital lobe with almost no ring enhancement. Spinal MRI detected a marked edema of the cauda equina and signs of spinal meningitis. Fungal infection and central nervous system (CNS) toxoplasmosis were considered as possible etiologies. Therefore, amphotericin B was started immediately at maximum dosage (1.5 mg/kg per day).

In the meantime, ongoing vascular rejection, which was histologically proven, and continuing anuria prompted us to remove the graft and withdraw immunosuppression on day 19. The postoperative course was complicated by recurrent bleeding from the urinary bladder. Despite antifungal therapy the CNS lesion increased to 7 mm in diameter and began to show a distinct enhancement of contrast medium. In addition, the patient's condition deteriorated further and he developed hyperacusis, visual disturbance, and a marked swelling of the right eyelid. Repeated serological blood and CSF tests, blood and CSF cultures, and swabs of the right maxillary sinus were of no diagnostic help. A CNS lymphoma was excluded since a hypoactive lesion was demonstrated by cerebral thallium-photon emission computed tomography (SPECT) and EBV-DNA in the CSF was negative.

Although the patient was seronegative for toxoplasmosis and tests for intrathecal antitoxoplasmic antibodies remained negative, amphotericin B was discontinued and replaced with pyrimethamine and sulfadiazine in combination with folic acid. A temporal lobe abscess with conspicuous contrast enhancement, meningeal inflammation, and extended erosion of the palate and maxilla as demonstrated by coronary CT scan (Fig. 1) led us to finally suspect rhino-cerebral mucormycosis on day 53 after the onset of symptoms. Definitive diagnosis was achieved by histological

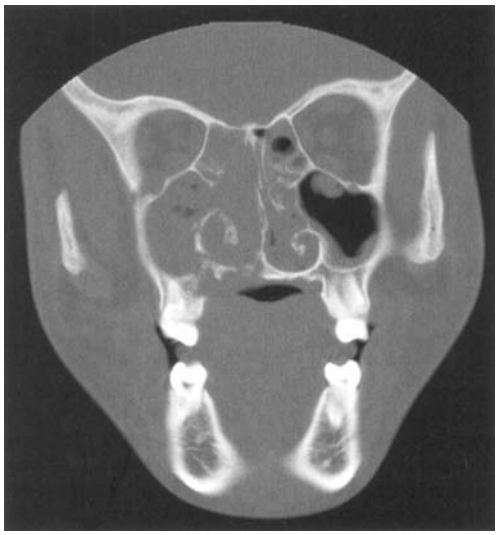

Fig. 1 Coronary CT scan with opacification of the right-sided sinuses and erosion of the palate and maxilla

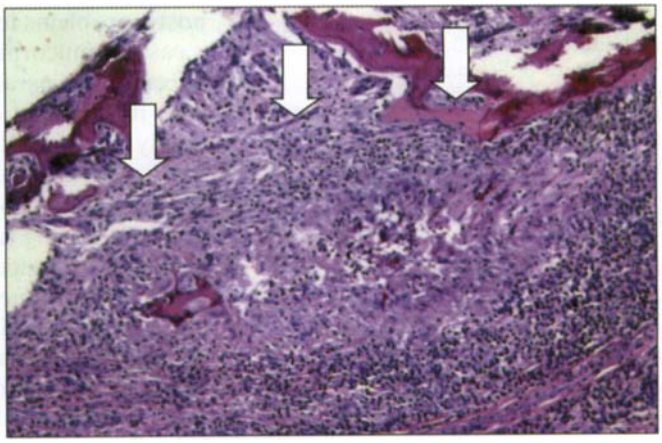

Fig. 2 Epitheloid granuloma adjacent to lamellar bone of the right sinus maxillaris

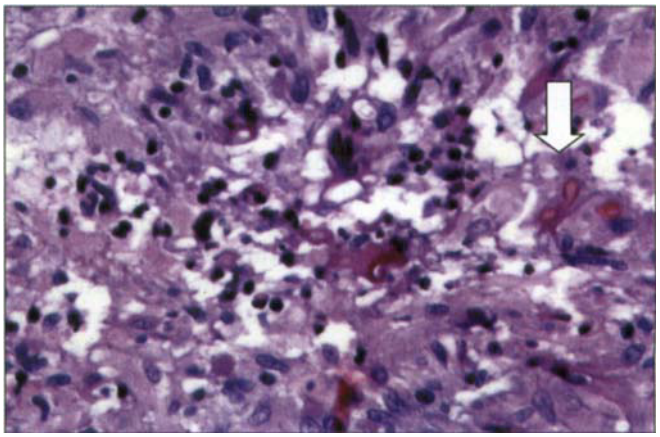

Fig. 3 High-power magnification with typical nonseptate hyphae

examination of scrapings and biopsies of necrotic nasal turbinates, revealing chronic granulomatous inflammation (Figs. 2 and 3) with typical nonseptate hyphae. The treatment consisted of aggressive surgical debridement of the nasal sinuses and temporal lobe abscess as well as intraoperative topical and, thereafter, systemic amphotericin B for 5 months. Following administration of amphotericin B at 1.5 mg/kg per day for 4 weeks, the dosage was decreased to 1 mg/kg per day for another 8 weeks since MRI detected no intracranial relapse. The patient thereafter continued on amphotericin B treatment (1 mg/kg every other day) for 2 more months and remained free of disease during the entire 5-month treatment period. While fecal incontinence still persists, hearing difficulties, impaired vision, eyelid swelling, and dysesthesia of the maxillary nerve disappeared and paraplegia improved. At this time, more than 3 years later, the young man remains without radiographic or clinical evidence of infection, has resumed his normal activities, and is doing well on dialysis. However, evaluation for a new transplant has still not been considered by the patient.

Discussion

Due to pharmacological immunosuppression, transplant recipients show defects in cell–mediated immunity and are therefore more susceptible to infections caused by intracellular microorganisms such as toxoplasmosis, herpes virus, and fungal species, the eradication of which is dependent on an intact T lymphocyte-macrophage system [9]. Patients at high immunological risk of allograft rejection due to preformed antibodies especially after induction therapy with antilymphocyte antibodies or high-dose corticosteroids for allograft rejection as well as plasmapheresis, causing an additional defect in humoral immunity, show an increased incidence of meningitis from these pathogens [9]. Nevertheless, immunity against mucormycosis is likely to occur at multiple levels, from the inhibition of spore germination by alveolar macrophages to the damage of hyphae by serum factors, alveolar macrophages, and neutrophils [5]. Severe immunosuppression, steroid-induced diabetes, broad-spectrum antibiotics, and dialysis must be considered the relevant predisposing factors for fungal infection in our patient. While in the immunocompetent host pathogenic fungi may produce only mild symptoms, severe neurological defects are seen in the immunocompromised patient after organ transplantation, where symptoms are masked by reduced inflammatory response under immunosuppression [9, 10]. Mucoraceae are ubiquitous fruit and bread molds, transmitted usually by inhalation of spores and associated with fungal brain abscesses. Less than 5% of the cases with mucormycosis are found in normal hosts [9]. In humans, mucor infections are most commonly linked to *Rhizopus spp.*, but in rare cases can be caused by a number of other genera like *Mucor*, *Rhizomucor*, *Absidia*, *Apophysomyces*, *Saksenaea*, *Cunninghamella*, *Cokeromyces*, and *Syncephalastrum spp.* [11]. In our case we were not able to identify the species.

In retrospect, the clinical presentation of mucormycosis in our patient was typical, with unilateral headache, facial swelling and pain, external ophthalmoplegia, and central nerve palsies. Acute paraplegia, however, is rarely seen in the early course of the disease. Contrast–enhanced MRI evidenced severe edema of the cauda equina, probably caused by spinal cord infarction due to vasculitis or mycotic thrombosis. Similar to *Aspergillus*, Mucorales characteristically spread into tissue by vascular invasion, leading to arterial thrombosis, tissue infarction, and necrosis [4, 5]. The occipital CNS lesion also has to be considered an early hematogenous dissemination. Only later on did the CT scan show bone destruction. The temporal lobe abscess is likely to have developed by contiguous expansion of the mucormycosis from the paranasal infected sinus. CSF examination and serological testing were abnormal, but nonspecific and therefore not helpful in establishing the diagnosis. We were further misled by the fact that the occipital CNS lesion worsened despite antifungal treatment. The fact that peripheral contrast media enhancement became detectable 1 week after cessation of immunosuppression can be explained by the anti-inflammatory effect of the steroids the patient received. Apart from fungal infection, toxoplasmosis was one of the differential diagnoses. Blood and CSF serology negative for toxoplasmosis is not an exclusion criterion for an acutely acquired toxoplasmosis in immunocompromised patients, particularly when neuroradiographic exams show iso- or hypodense lesions with or without ring enhancement after the administration of contrast material [9]. Likewise, systemic infection with *Listeria monocytogenes*, *Histoplasma capsulatum*, *Nocardia asteroides*, *Strongyloides stercoralis*, *Coccidioides immitis*, or EBV-associated post-transplant lymphoproliferative disease can cause similar clinical symptoms [10]. Lymphoma, however, have been reported to develop 33 months (3 weeks to 248.5 months) following transplantation [12]. Apart from the early onset of symptoms in our patient, an EBV-associated intracerebral lymphoma was excluded by the absence of EBV-DNA in the CSF and a negative thallium SPECT. According to the literature on the diagnosis of primary CNS lymphoma, the presence of increased uptake in the thallium SPECT and/or positive EBV-DNA has 100% sensitivity and 100% negative predictive value [13]. Although clinical and neuroradiological findings may be indicative, they are certainly not able to distinguish within the wide spectrum of CNS diseases. In many patients biopsy will be necessary to make the diagnosis [14]. A biopsy of the occipital CNS lesion in our case was discussed, but not performed because of the localization of the lesion close to the visual cortex. Sinus opacification, temporal lobe abscess, and extended osseous lesions made us suspect mucormycosis, which was confirmed by histological and

microbiological examination of paranasal bone scrapings showing typical nonseptate hyphae. Successful treatment of mucormycosis in this case consisted of high-dose amphotericin B (1.5 mg/kg per day) and aggressive surgery, including radical debridement through a combined intracranial-extracranial approach and local antifungal therapy. This bilateral access has been reported to offer a distinct advantage over a solely extracranial approach with regard to the incidence of CSF leak and disease recurrence [15]. The importance of surgery cannot be overemphasized because of the above mentioned propensity of the *Mucoraceae* to cause extensive tissue infarction by invasion of blood vessels, thus compromising the delivery of antifungal agents to the site of infection [15, 16]. The duration of amphotericin B treatment is empirical, and its use is limited by severe side effects such as nephrotoxicity. The lipid preparations of amphotericin B allow higher doses with lower systemic toxicity. However, after removal of the transplanted kidney nephrotoxicity was negligible and the substance was well tolerated by our patient. There is no evidence of a beneficial effect of monotherapy with any other antifungal agent as treatment of choice for this kind of infection. Caspofungin, a new antifungal agent of the echinocandin class [17, 18], has been shown to be effective against amphotericin-B-resistant *Candida* and *Aspergillus* infections. A synergistic effect of caspofungin with other antifungal substances might be possible because of its different mode of action, but clinical evidence is still lacking [19, 20]. Whereas posaconazole, ravuconazole, and voriconazole exhibit excellent in vitro activity against *Aspergillus spp.*, posaconazole and ravuconazole were more active than voriconazole against *Rhizopus spp.* and none of these new triazole derivates were active against *Mucor spp.* [21]. However, the clinical value of the in vitro data has still to be determined. It goes without saying that discontinuation of immunosuppression must be considered in recipients of non-vital organs.

Mucormycosis is a rare and frequently lethal opportunistic fungal infection in immunosuppressed subjects. It usually affects the face and predominantly the rhinocerebral region. Clinical and neuroradiological signs may be typical and highly suspicious, but often masked by drugs given in the post-transplant period. CSF and serological tests are usually abnormal, but nonspecific, while microbiological examination of paranasal swabs or fluid collection can even be without abnormalities. Histological examination showing tissue invasion by the fungus is diagnostic. Therefore, early diagnosis by an aggressive investigative approach to obtain tissue specimen is needed in order to reduce the high mortality and morbidity of this type of fungal infection by early surgical intervention combined with systemic antifungal therapy.

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