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Case Report of Sino-Orbital-Cerebral Mucormycosis in a Renal Transplant Patient

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Abstract **Case Report**

Mucormycosis is a rare but severe opportunistic fungal infection caused by Mucorales fungi, primarily affecting immunocompromised individuals. It is commonly seen in patients with uncontrolled diabetes, organ transplants, and conditions requiring immunosuppression. The infection can manifest in various forms, including rhino-cerebral, pulmonary, cutaneous, and disseminated types, with the classic presentation being rhino-sino-orbital involvement. Early diagnosis and treatment are critical for improving survival outcomes. This case concerns a 58-year-old female with a history of type II diabetes, diabetic nephropathy, and recent kidney transplantation. Two months post-transplant, she developed severe left-sided headaches, facial edema, and systemic symptoms. Initial diagnosis pointed to ethmoiditis and maxillary sinusitis, but due to worsening symptoms, further investigations revealed mucormycosis with Rhizopus Arrhizus confirmed through PCR. The infection rapidly progressed, leading to orbital and neurological involvement, and despite antifungal therapy with Ambisome and Isavuconazole, the patient's condition deteriorated, resulting in death one month after treatment initiation. Mucormycosis is particularly dangerous in immunocompromised patients due to rapid progression and high mortality rates. Early detection through histopathology or molecular methods like PCR is crucial. Treatment involves antifungal therapy, surgical debridement, and careful management of immunosuppression. Although amphotericin B is the most effective antifungal, adjusting immunosuppressive therapy remains a challenge, balancing rejection risk and infection control. This case underscores the importance of vigilance in diagnosing and managing mucormycosis, especially in transplant patients, where timely intervention can significantly impact outcomes.

Keywords: Mucormycosis, Kidney Transplant, Molecular Diagnosis, Mortality, Amphotericin B.

INTRODUCTION

Mucormycosis is an opportunistic infection caused by fungi from the Mucorales order, part of the Zygomycetes class [1]. Although the fungi and spores of Mucorales exhibit minimal intrinsic pathogenicity towards immunocompetent individuals, they can trigger an aggressive and fulminant infection in immunocompromised hosts [2]. This is most commonly seen in patients with poorly controlled diabetes, but also in cases of immunosuppression, such as leukemia, organ transplants (bone marrow or kidney), renal failure, or HIV infection[3]. It is a polymorphic disease with various clinical manifestations, including rhino-cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated forms [1]. The classic presentation is the involvement of the nasal mucosa with invasion of the paranasal sinuses and orbit in approximately 70% of cases, which can lead to extensive and devastating soft tissue damage, resulting in vascular thrombosis, with often fatal outcomes [4, 5]. The positive diagnosis of the condition is primarily based on histopathological analysis [6]. Additionally, the detection of circulating DNA by PCR in serum and biopsies allows for earlier diagnosis [7]. Therefore, it should be considered and sought in any diabetic or immunocompromised patient suffering from complicated rhinosinusitis. Surgical debridement or radical resection and the use of amphotericin B have significantly increased survival rates [6].

CASE PRESENTATION

This is a case of a 58-year-old female patient, with a medical history of hypertension, insulin-dependent type II diabetes complicated by diabetic retinopathy (treated with laser) and diabetic nephropathy at the stage of end-stage renal disease, who had been undergoing hemodialysis since September 2017 and underwent a kidney transplant from a cadaveric donor in September 2023. Induction therapy included anti-lymphocyte serum, resulting in complete lymphocyte

depletion. Maintenance therapy involved Tacrolimus, Cellcept, and corticosteroids. Immediate graft function was observed.

She was admitted to the emergency department two months after the kidney transplant with complaints of severe, left-sided headaches, insomnia, and symptoms resistant to first-line analgesics, along with a general decline in health, vomiting, and diarrhea. She was hospitalized in the nephrology department due to initial results indicating left-sided ethmoiditis with uncomplicated maxillary sinusitis, treated with amoxicillin-clavulanic acid. Despite this treatment, her condition worsened, with the development of seropurulent rhinorrhea from the middle meatus, prompting a negative bacterial culture following aspiration.

Ten days later, the patient returned to the emergency department with persistent pain, facial edema, biological inflammatory syndrome (leukocytosis of 11.63 x 10^9/L, CRP of 337 mg/L), and a CT scan showing left ethmoiditis and ipsilateral maxillary sinusitis with complete opacification. Given the refractory sinusitis and sepsis, she was transferred to the otorhinolaryngology department, where a meatomy and ethmoidectomy were performed, along with bacteriological and mycological cultures (**Fig 1**). Empiric antibiotic therapy was started with Meropenem and Linezolid.

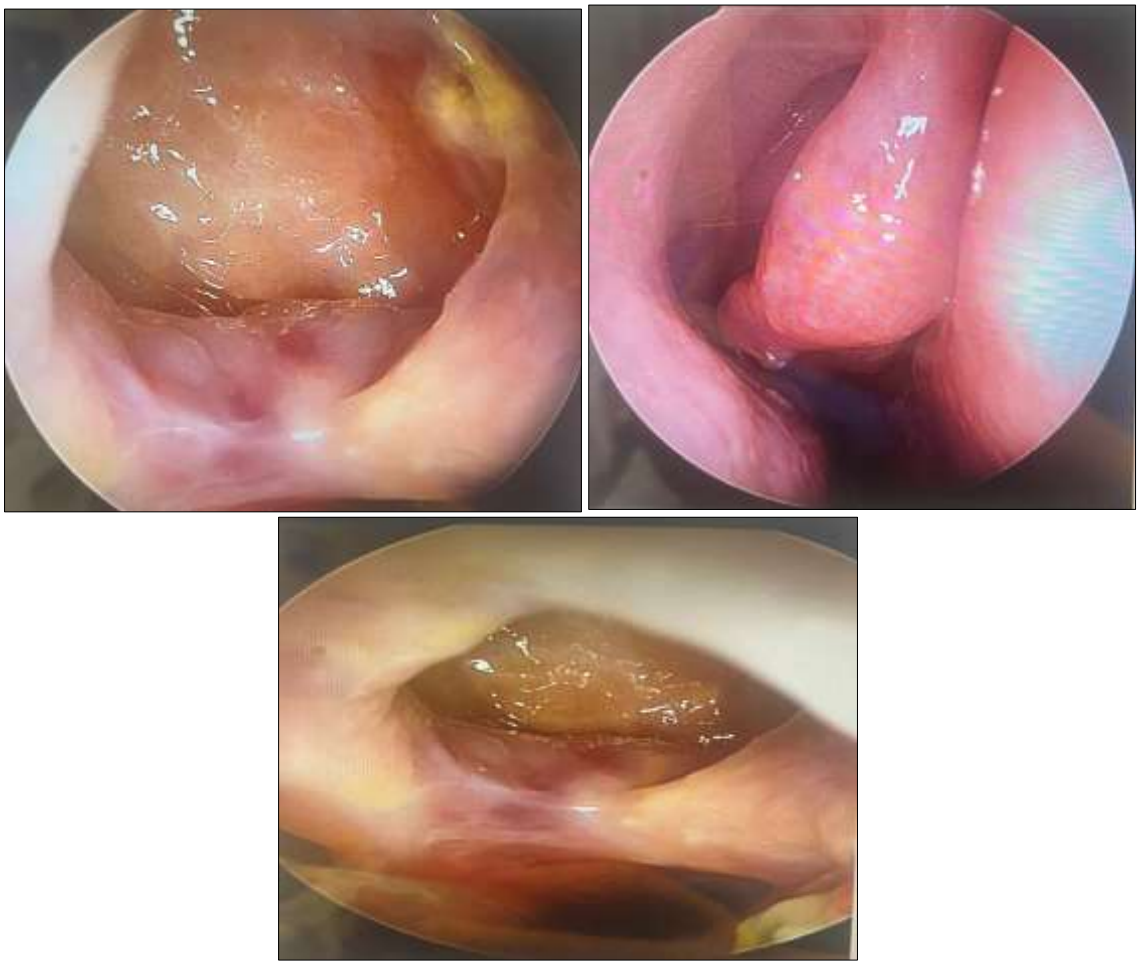

Fig 1

Due to the worsening facial edema, neurological deterioration, consciousness disturbances, and the appearance of stridor with diffuse laryngeal edema, the patient was transferred to surgical intensive care and intubated. An MRI was performed, which excluded cerebral venous thrombosis but showed persistent mucosal thickening and partial opacification of the sphenoid, ethmoid, and maxillary sinuses bilaterally (Fig 2). A lumbar puncture on the same day showed 16 elements with 2163 red blood cells, normal glucose and protein levels, and a positive PCR for mucormycosis (Rhizopus arrhizus). Complementary PCR tests on blood and ENT samples confirmed the same fungus. A diagnosis of mucormycosis with neurological involvement was made, and antifungal treatment with a combination of Ambisome and Posaconazole was initiated, followed by suspension due to liver enzyme abnormalities and the introduction of Isavuconazole. Cellcept was discontinued, and the tacrolimus target

levels were reduced (4-6 ng/ml). The patient's diabetes remained well-controlled post-transplant.

In the intensive care unit, the patient developed ventilator-associated pneumonia with Pseudomonas and Klebsiella pneumoniae and local extension of the mucormycosis, including orbital invasion, cerebro-meningeal spread, and optic nerve compression. The diagnosis of retro-septal cellulitis with optic nerve compression in the context of mucormycosis was made, with a poor visual prognosis and no surgical indication. Despite adequate antifungal therapy, the patient's overall and neurological condition worsened, leading to her death one month after the initiation of antifungal treatment.

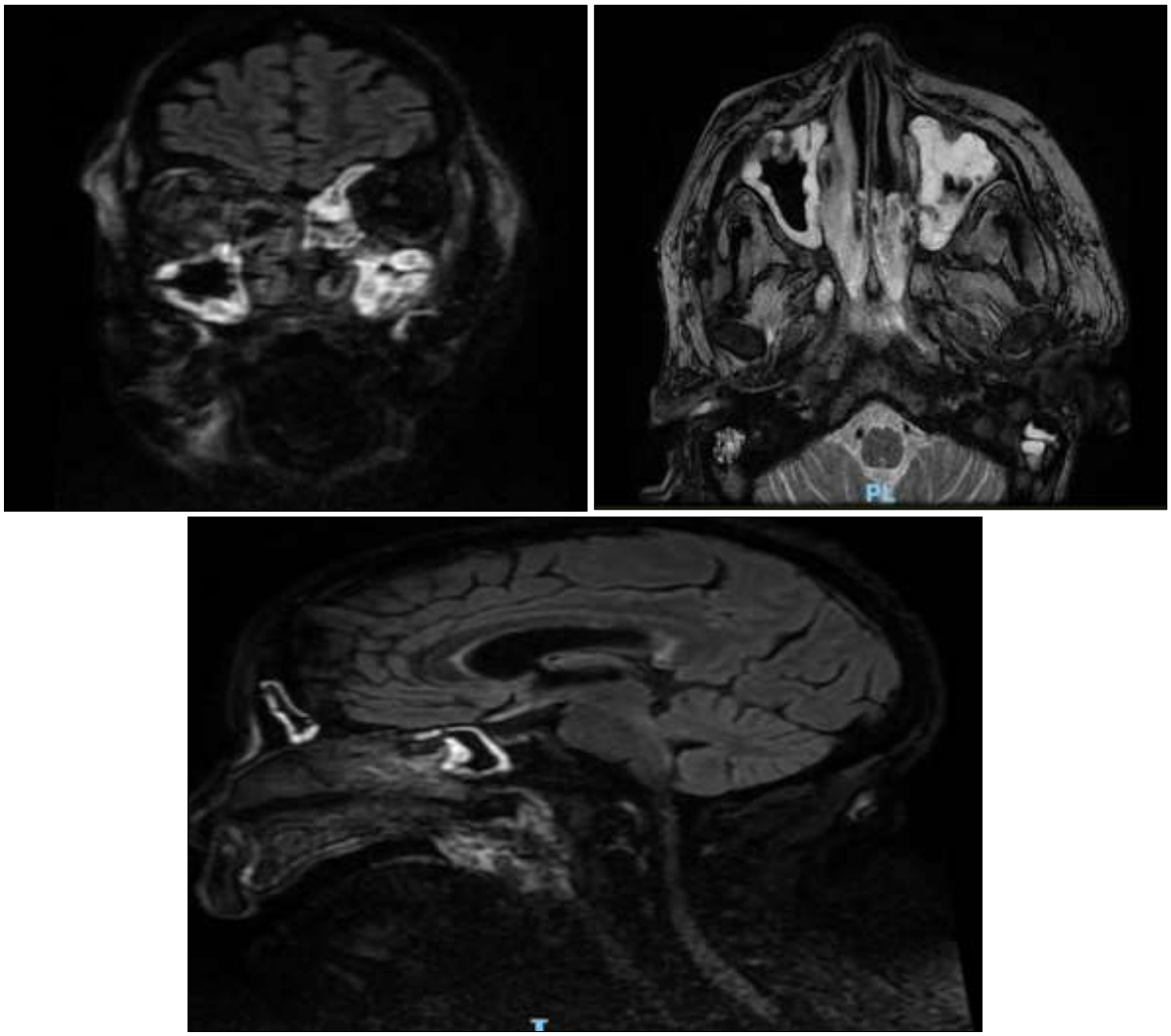

Fig 2

DISCUSSION

Mucormycosis is a rare but extremely severe fungal infection, primarily affecting immunocompromised patients, such as those who have undergone kidney transplantation. This infection is caused by filamentous fungi belonging to the Zygomycetes class and the Mucorales order. Among these, three genera are most frequently encountered: Rhizopus in 80% of cases (particularly *Rhizopus oryzae*), Mucor and Absidia [7, 8].

In this context, immunosuppression used to prevent transplant rejection is a major risk factor for the development of opportunistic infections, especially when combined with other comorbidities, such as diabetes, common in this patient population [9]. Diabetes promotes fungal growth due to hyperglycemia, and immunosuppressive treatment alters the inflammatory response, thereby affecting the body's ability to combat fungal infections. In our case, the patient exhibited these risk factors, facilitating the progression of the infection.

The clinical symptoms of rhino-orbito-cerebral mucormycosis are often insidious at first, with severe sinusitis, facial pain, and vision loss, which can be mistaken for less serious conditions. However, once neurological signs such as confusion or motor deficits

appear, it typically indicates the spread of the infection to the central nervous system [10].

The most important prognostic factor remains the speed of diagnosis and intervention. Studies demonstrate that early medical-surgical management after symptom onset can significantly improve the chances of recovery and survival [11].

The positive diagnosis of mucormycosis is primarily based on mycological culture and radiological and histopathological examination. Blood cultures or biopsies are generally negative, and positive cultures may sometimes be due to contamination rather than true infection. Direct mycological examination is rarely positive, and Sabouraud's medium cultures are often negative [12, 13]. However, the gold standard diagnosis is histology, which can be definitive and sensitive, but requires experienced personnel to differentiate mucormycosis from other fungal infections, especially aspergillosis [14]. Molecular techniques based on PCR offer a high potential for early-stage diagnosis, with the amplified target being species-specific and allowing for accurate diagnosis [15, 16].

The treatment of mucormycosis remains challenging, and the speed of intervention affects prognosis. A multidisciplinary approach is essential, combining the control of the underlying disease, surgical removal of infected tissues, and appropriate antifungal treatment. Amphotericin B remains the most effective agent [17]. In contrast, other drugs like voriconazole show no activity and might even promote mucormycosis [5]. In the management of rhino-cerebral mucormycosis, intravenous amphotericin B is used at a dose of 0.5 mg/day, complemented by intraventricular administration at 0.66 mg/day. In vitro studies on amphotericin B's activity against filamentous fungal infections report concentration-dependent effects starting at 2 µg/ml [18].

Managing immunosuppressants presents an additional challenge, as reducing their dose can promote graft rejection, while maintaining high levels increases the risk of infection. In our patient's case, a temporary reduction in immunosuppressive therapy was implemented due to the rapid progression of the infection.

Despite intensified treatment, the prognosis remains poor in cases of rhino-orbito-cerebral mucormycosis, with high mortality rates in this patient population [19].

CONCLUSION

Rhino-orbito-cerebral mucormycosis remains a formidable and difficult-to-treat condition, especially in kidney transplant patients. Early detection and multimodal management are crucial to improving prognosis. The medical team must be particularly vigilant for subtle clinical signs and the rapid progression of the infection to maximize treatment success and minimize the risks of fatal complications.

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