Isolated fungal sphenoid sinusitis with unilateral lateral rectus palsy six years post lung transplant

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ABSTRACT

Rhino-orbital-cerebral mucormycosis (ROCM) infections are rare and usually occur in patients with diabetes, malignancy, or organ transplantation. The most common presenting symptoms include facial pain and swelling, fever, and rhinorrhea. Mortality rates reach nearly 50%. Those with previous organ transplants typically present with sinus symptoms a few weeks to months after transplantation. A 75-year-old man presented with headache. His history was significant for bilateral lung transplantation in 2017. On his fourth presentation, he was admitted to the hospital for work up. Imaging showed small fluid levels within the right maxillary and sphenoid sinuses. Infectious work-up revealed no meningitis. On day three, the patient complained of diplopia on the right. His examination was significant for right lateral rectus palsy. Repeat imaging was performed and showed increasing fluid levels of the right maxillary and sphenoid sinuses, and the otolaryngology consultation service was consulted. Nasal endoscopy was significant for pink, vascularised mucosa with no obvious regions of pallor or necrosis. Endoscopic sinus surgery was performed. There were no findings suggestive of fungus but purulence of the right sphenoid grew Rhizopus. The patient's nerve palsy did not resolve and progressed to the contralateral orbit. Repeat nasal endoscopy continued to show healthy mucosa while MRI showed enhancement worrisome for meningitis. To our knowledge, this is the only reported case of fungal sphenoid sinusitis resulting in meningitis and death six years after transplant. Current literature documents fungal infection in post-transplant patients up to four years after surgery, with most occurring within the first year. Suspicion for fungal infection should remain high in this patient population.

Keywords: mucormycosis, lung transplant, sinusitis, lateral rectus palsy

INTRODUCTION

Mucormycosis is a rare but potentially lethal fungal infection that most commonly affects people with uncontrolled diabetes, various malignancies, organ transplants, or inherited immunodeficiencies.[1] The causative fungi are highly aggressive and can cause progressive disease through blood vessel and paranasal sinus invasion.[2] Consequences of these infections range from cranial nerve palsies to death with overall mortality rates reaching nearly 50%.[2] Despite its rapid progression and high mortality rate, diagnosis of invasive mucormycosis is frequently delayed due to the wide range of clinical manifestations, which are dependent on the severity of disease and the structures affected.[3] The most common forms of the disease are rhino-orbital-cerebral mucormycosis (ROCM) and pulmonary infections,[1] and the most common pathogen is *Rhizopus arrhizus*.[4]

Although specific symptoms may vary, ROCM typically presents with nasal and sinus infection that progresses to orbital involvement and eventually cerebral involvement if left untreated. The most common presenting symptoms include facial pain and swelling, fever,

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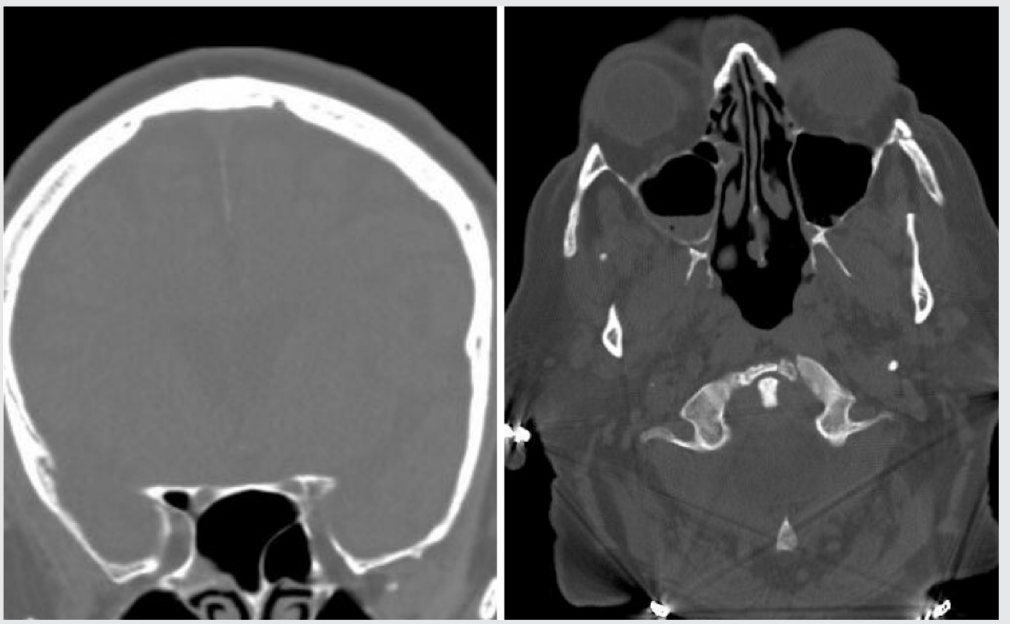

Figure 1. CT at initial presentation showing clear anterior sphenoid sinuses (left) and minimal air fluid level in the right maxillary sinus (right).

rhinorrhea, nasal ulceration, and epistaxis.[2] Unilateral and bilateral rectus palsy is also a rare finding with mucormycosis infections. In a review of isolated sphenoid sinusitis inflammatory disease (ISSID) and associated visual disturbances in 23 total patients, researchers found only 1 of 9 patients with fungal ISSID had unilateral cranial nerve VI involvement. 5 other patients with ISSID from other sources were found to have CN VI involvement.[5]

When these types of infections do occur in post-transplant patients, acute sinus symptoms typically present within a few weeks to months of the time of transplant.[6] One study conducted on mucormycosis in patients with liver transplants found that the majority of fungal infections post-transplantation occurred within the first 2 months.[7] This is a report of a 75-year-old man on immunosuppressive medication with an invasive *Rhizopus* infection with development of lateral rectus abducens palsies through the lateral walls of the sphenoid sinus 6 years following lung transplantation.

Case

This case began with a 75-year-old man with a past medical history of lung transplant 6 years ago with chronic immunosuppressive medication consisting of tacrolimus, prednisone, and azathioprine and stage 3 chronic kidney disease presenting to the emergency department (ED) for constant frontal headaches associated with photophobia, phonophobia, nausea, and visual disturbances. He was seen for headaches 3 times in the last 5 days that were relieved by various migraine cocktails and was subsequently discharged. Computed tomography (CT)of the head performed during the third ED visit demonstrated no acute intracranial pathology and small amounts of fluid in the sphenoid sinus and right maxillary sinus (Figure 1). On his fourth presentation at the ED, the patient was admitted for recurrent headache workup.

On initial workup of the patient, noncontrast magnetic resonance imaging (MRI) brain, CT with angiography of the head and neck, and infection panels were all negative. However, the patient developed progressive blurry vision, right lateral rectus abducens palsy, and right sided face and eye pain. A CT sinus displayed increasing air fluid level in the sphenoid and minimal air fluid level in the right maxillary sinus (Figure 2). The ENT service was consulted and did not find any evidence of pallor or necrosis in the nasal cavity or on the palate. The patient had an acute mental status change and increase in rhinorrhea on the 5th day of hospitalization. At this point, sinus endoscopy was performed due to worsening

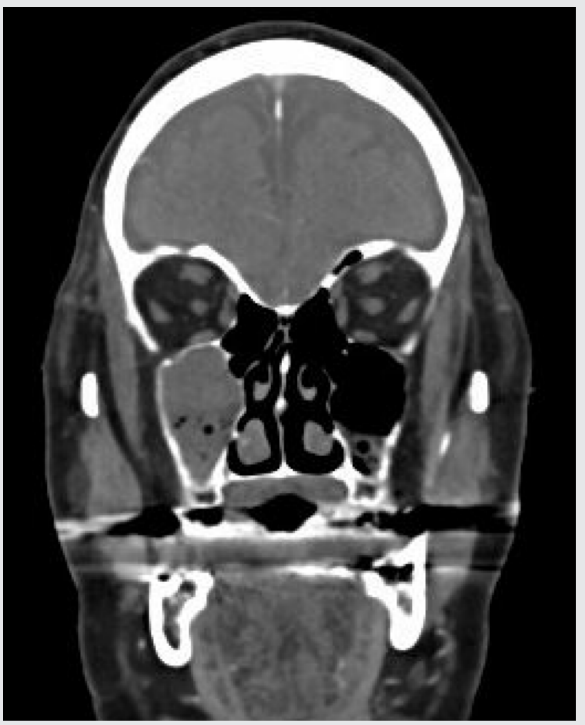

Figure 2. CT showing increasing air fluid levels in maxillary sinus.

disease and demonstrated purulence in the right maxillary sinus and right sphenoid sinus. Cultures were taken from the right maxillary and sphenoid sinuses and grew +1 Rhizopus.

Over the next week, the patient continued to decline and developed a left sided lateral rectus palsy despite an IV regimen of liposomal amphotericin B. Repeat endoscopy was negative for necrosis or hyphae. A repeat MRI was also performed and showed presumed invasive fungal infection with inflammatory infiltrate in the right lateral rectus, temporalis, and to a lesser extent the muscles of mastication and segment narrowing of the petrous internal carotid artery, intracavernous internal carotid artery, long segment abnormal mural enhancement of the right internal carotid artery within the carotid canal (Figures 3–4). No necrotic turbinates or non-enhancing mucosa was visualized. Despite continued aggressive medical management and another endoscopic debridement, the patient ultimately died from the infection.

Discussion

Mucormycosis is a relatively uncommon infection, with an estimated incidence of 1.7 cases per million in the United States.[8] It commonly affects patients with underlying disorders, such as diabetes mellitus, hematological malignancies, hematopoietic stem cell transplantation, and solid organ transplantation.[1,8] Common clinical manifestations are classified by the affected anatomic regions, which can be divided into sinus, pulmonary, cutaneous, gastrointestinal, and disseminated.[8] Mucormycosis affecting the sinus can be further divided into localized or extending into the

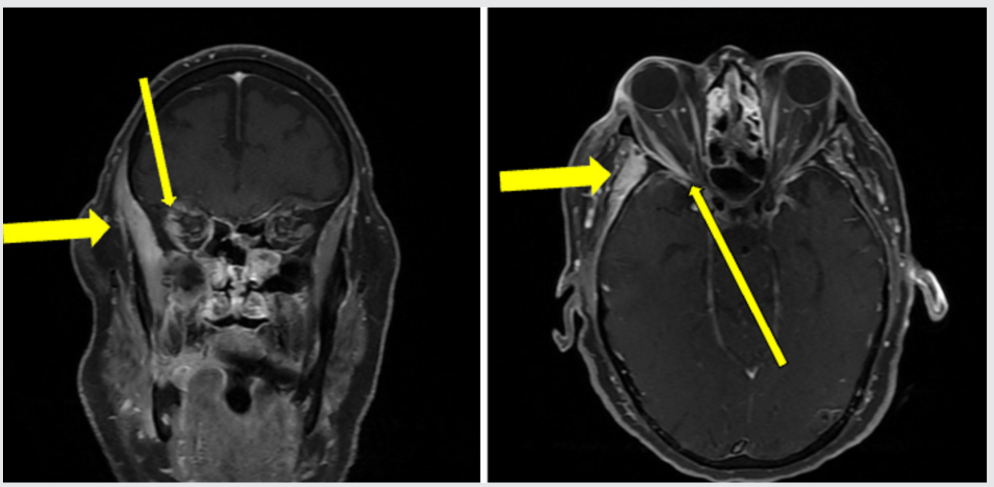

Figure 3. MRI showing asymmetric enlargement and enhancement of the right lateral rectus muscle, thin rim of enhancing abnormal soft tissue along the lateral aspect of the right orbit which extends almost to the level of the orbital apex (thin arrows), and enfacement within the right temporalis muscle (thick arrows).

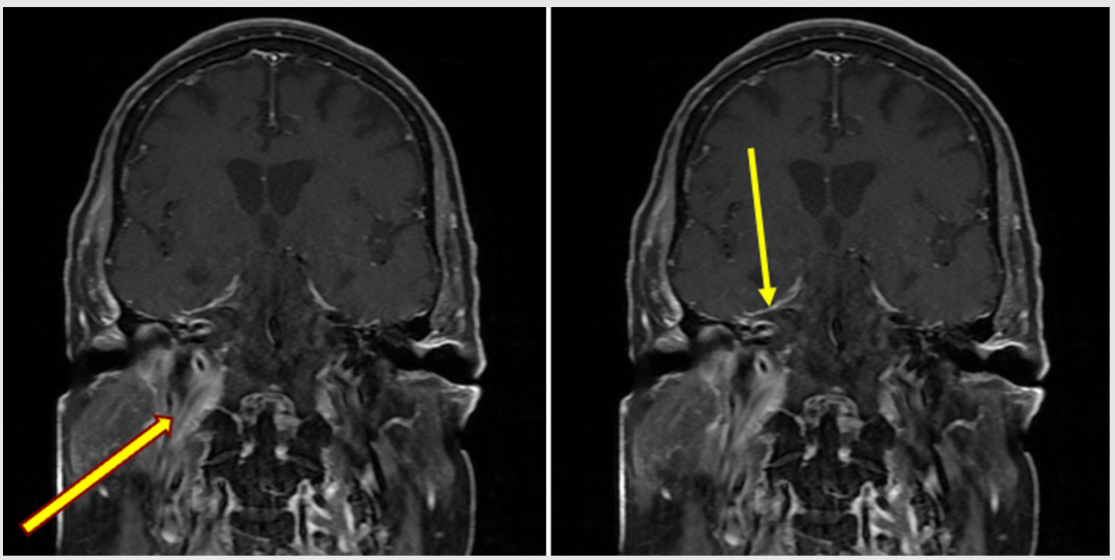

Figure 4. MRI showing edema within the right masticator space, deep to the right masseter muscle and within the infratemporal fossa (left) and segment narrowing of the petrous internal carotid artery, intracavernous internal carotid artery, long segment abnormal mural enhancement of the right internal carotid artery within the carotid canal (right).

orbit or brain.[8] Nasal endoscopy findings often show necrotic ulcers along the nasal mucosa and present with nasal congestion, bloody rhinorrhea, sinus tenderness, and retro-orbital headache.[2,8] Extension into the oral cavity may also occur, leading to painful necrotic ulceration on the hard palate.[8] Progression of the disease may result in facial or periorbital swelling, blurred vision, diplopia, and proptosis.[8] Specifically in solid organ transplant patients, sinus symptoms present within a few weeks to months.[6,7]

How are patient did not display any of the classic findings mentioned and had no evidence of pallor or necrosis in the nasal cavity or on the palate. Furthermore, our patient received a lung transplant 6 years prior to disease development. Due to the subtle initial presentation and apparent lack of risk factors, the patient was repeatedly discharged from the ED with only migraine medications.

Further workup of the patient revealed signs of disease in the sphenoid sinus with minimal maxillary sinus involvement with physical examination findings of blurry vision, right lateral rectus abducens palsy, and right-sided facial pain. While visual symptoms and facial pain are common, isolated lateral rectus palsy remains rare. In a study of patients with isolated sphenoid sinus disease, only 1 out of 9 patients presented with a defect of cranial nerve VI.[5] Furthermore, cranial nerve findings often result from involvement of the cavernous sinus, often affecting cranial nerves V and VII, leading to ipsilateral facial sensation loss, ptosis, and pupillary dilation.[9]

Diagnosis of rhinocerebral mucormycosis is often difficult, and up to half of the cases are diagnosed postmortem.[9] As seen in our case, imaging techniques often reveal only subtle findings of sinus mucosal thickening or thickening of extraocular muscles.[9] Similarly, the nasal mucosa may appear normal, as in our patient, because fungal invasion may precede clinically visible damage to the tissue.[9] Combined with the need for extensive diagnostic work-up and high mortality, initial empirical therapy with a polyene antifungal agent should be started.[9]

Treatment of mucormycosis can be difficult as antifungal therapy alone is often inadequate. Many fungal strains are highly resistant, and the drugs may display poor penetration into the infected tissue due to thrombosis and tissue necrosis.[9] As a result, surgical debridement is paramount and must be performed urgently. In a case series evaluating 49 patients with rhinocerebral

mucormycosis, mortality rate was 70% in patients who were treated with antifungals only versus 14% in those who also had surgery.[9] Finally, novel iron chelators and adjuncts such as hyperbaric oxygen therapy have shown benefits in various case reports, although further studies are needed to support their use fully.[9]

Conclusion

Due to the invasive nature and high mortality rate of *Rhizopus* infections, clinical suspicion of fungal ROCM must remain high in all patients with a history of solid organ transplantation presenting with refractory headaches, cranial nerve palsies, and other signs and symptoms of mucormycosis regardless of how long ago the procedure was done.

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