



Rhino-Orbital-Cerebral Mucormycosis: An Uncommon Cause of Stroke in Young Adults

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Received 21 December 2024;

Accepted 08 January 2025;

Published 12 January 2025

Abstract

Rhino-orbital-cerebral mucormycosis is an invasive fungal infection that primarily affects immunocompromised individuals, particularly those with haematological malignancies, organ transplant recipients, and uncontrolled diabetes. Following initial infection of the nose and sinuses, fungal vascular invasion and bone erosion can lead to the spread of the disease to adjacent tissues, notably the orbits and brain, with the potential for multiple cerebrovascular complications. Early diagnosis and prompt treatment initiation are crucial for effective disease control.

We report the case of a 29-year-old woman with a history of long-term uncontrolled type 1 diabetes, who was diagnosed with mucormycosis. Despite the absence of neurological symptoms initially, both computed tomography (CT) and magnetic resonance imaging (MRI) revealed ischaemic lesions in the left cortico-subcortical occipital, parietal, and frontal regions, caused by occlusion of the left cavernous internal carotid artery and left anterior cerebral artery. The patient later developed diplopia and underwent surgical intervention, prolonged antifungal therapy, and hyperbaric oxygen therapy, resulting in a slow but positive recovery.

This rare case of stroke in a young adult underscores the importance of excluding cerebrovascular complications in rhino-orbital-cerebral mucormycosis, even in the absence of neurological symptoms, to prevent further damage and morbidity.

Keywords: *rhino-orbital-cerebral mucormycosis; invasive fungal infection; ischaemic stroke; internal carotid artery occlusion; stroke in the young adult.*

Introduction

Mucormycosis is an invasive fungal infection [1,2] first described in 1885 by Pataulf [3], which can affect virtually any organ [4], although its more frequent presentations are pulmonary, rhino-orbital-cerebral, cutaneous, and, less frequently, gastrointestinal and disseminated disease [1,4-6]. It is caused by the inhalation of spores [3,5,7] from fungi of the order *Mucorales* present in the environment, with the most common agents being *Rhizopus* spp., *Mucor* spp., and *Lichtheimia* spp [1,3-5,8]. The incidence of this opportunistic infection has been increasing in recent decades [3,4,6,8], which is attributed to the rising number of immunocompromised patients, specifically those with haematological malignancies undergoing stem cell transplants, even though uncontrolled diabetes remains a major risk factor, particularly in developing countries [4-6].

A distinctive pathogenic feature of mucormycosis is vascular invasion by the fungal hyphae, leading to thrombosis, ischaemia, and tissue necrosis [1-3]. This can result in a stroke, especially when the cavernous sinus and internal carotid artery are involved [2,9,10]. Due to the severity of rhino-orbital infections, stroke symptoms may go undetected, which can leave patients out of the

window period for vascular intervention, resulting in poorer outcomes and higher mortality [11]. We present the case of a rapidly progressive rhino-orbital-cerebral mucormycosis that culminated in an ischaemic stroke in a young patient.

Case report

A 29-year-old woman with a medical history of type 1 diabetes mellitus for more than 20 years, poorly controlled, complicated by stage 4 chronic kidney disease and retinopathy, along with arterial hypertension, dyslipidaemia, chronic anaemia, biliary lithiasis, and depressive syndrome, was admitted to a local hospital for diabetic ketoacidosis, sinusitis, and a maxillary abscess of presumed odontogenic origin. Her symptoms were refractory to initial outpatient treatment with a 7-day course of amoxicillin-clavulanate. She was subsequently treated with levofloxacin and clarithromycin for 9 days, followed by a switch to ceftriaxone and clindamycin for 5 days.

Due to clinical worsening, she was transferred to a tertiary hospital where, on admission, physical examination revealed oedema in the left malar region and left lower eyelid, with a normal neurological exam. Blood tests showed leucocytosis (15,200/mm³)

with neutrophilia (12,130/mm³) and elevated C-reactive protein (82.4 mg/L). A nasolaryngoscopy performed by Otorhinolaryngology (ORL) revealed oedema of the left middle meatus. A computed tomography (CT) scan of the paranasal sinuses and orbits showed opacification of the left sphenoid sinus, left ethmoidal cells, partial opacification of the left frontal sinus and right sphenoid sinus, thickening of the left maxillary sinus, and areas of bone erosion in the walls of the left maxillary sinus and ethmoidal cells (see **Figure 1**). There was also thickening of the soft tissues in the left masticator space, subcutaneous malar space, and left orbit. A head CT identified a subacute left cortico-subcortical posterior parieto-occipital ischaemic lesion, suggestive of a watershed stroke, and thickening of the soft tissues in the nasopharyngeal cavity, with possible extension to the left carotid artery (see **Figure 2**).

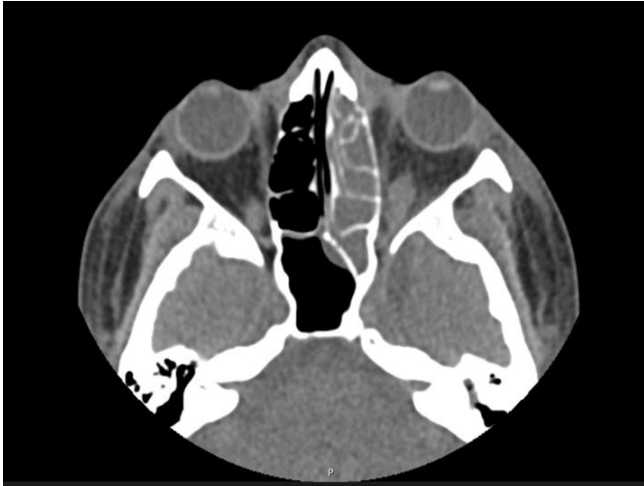


Figure 1: Paranasal computed tomography showing opacification of the left sphenoid sinus and left ethmoidal cells with areas of bone erosion.

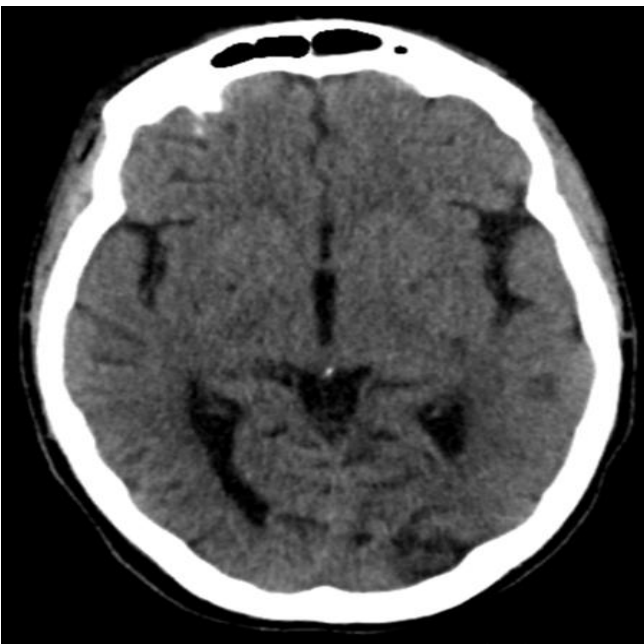


Figure 2: Cerebral computed tomography showing a subacute left cortico-subcortical posterior parieto-occipital ischaemic lesion.

Given these CT findings, invasive rhinosinusitis was suspected, and the patient underwent nasal endoscopic surgery, where granulation tissue and secretions were found and collected, and an ethmoidectomy and sphenoidotomy were performed. Antibiotic therapy was escalated to ceftazidime, isavuconazole, linezolid, and liposomal amphotericin B. Microbiological cultures isolated

Enterococcus faecium and *Candida glabrata*, while histopathology revealed necrosis and extensive fungal infiltration with large hyphae, consistent with *Mucor* spp. The patient completed a two-week course of linezolid and continued treatment with liposomal amphotericin B.

Head magnetic resonance imaging (MRI) showed multiple recent ischaemic foci in the left cortico-subcortical occipital, parietal, and medial frontal lobes, as well as the involvement of the corpus callosum, with an absence of patency of the left internal carotid artery and stenosis of the A1 segment of the left anterior cerebral artery (see **Figure 3**). A multidisciplinary discussion suggested that the ischaemic lesions were due to extrinsic compression of the cavernous portion of the internal carotid artery and anterior cerebral artery and antiplatelet therapy with acetylsalicylic acid was initiated. A neck and transcranial Doppler revealed reduced flow in the left middle cerebral artery due to proximal occlusion of the left internal carotid artery and stenosis of the left anterior cerebral artery.



Figure 3: Absence of patency of the left internal carotid artery on brain magnetic resonance.

On the 13th day of hospitalization, the patient developed diplopia, prompting a magnetic resonance venography that excluded cavernous sinus thrombosis and identified the extension of the infectious process to the left intra-orbital inferior space, explaining the ophthalmoplegia. She underwent another surgical intervention for debridement of the affected tissues and continued antifungal therapy with amphotericin B for 40 days, after which it was switched to oral isavuconazole due to worsening renal function. Concomitantly, the patient started hyperbaric oxygen therapy, completing a cycle of 20 days, with a subsequent MRI showing only slight improvement of the inflammatory process, which led to an extension of the hyperbaric sessions.

The hospitalisation was characterized by difficult metabolic control, largely due to the patient's poor cooperation with her diet plan, as well as episodes of worsening renal function requiring escalating diuretic doses. Psychological factors were significant, as the patient exhibited symptoms of depression due to the prolonged hospitalisation. After 66 days, she was discharged, still experiencing diplopia. She maintained isavuconazole therapy, underwent weekly follow-up with ORL, and had periodic imaging, with the last MRI showing a reduction in the inflammatory thickness of the ethmoidal cells, sphenoid sinus, and left orbital pavement.

Discussion

Although rare, mucormycosis is the third most common opportunistic fungal infection [8]. The increasing incidence in recent decades is concerning due to the rapid and potentially fatal

progression of the disease. The rise in cases is associated with the longer survival of immunocompromised patients and advances in diagnostic techniques, especially in developed countries [3,4,6,8]. On the other hand, India remains the most affected developing country, with an estimated disease burden 70 times higher than the global average [3]. In India, there was a peak in mucormycosis cases during the second wave of the COVID-19 pandemic [11]. The most common causative agent is *Rhizopus* spp., accounting for over 70% of cases, followed by *Mucor* spp. and *Lichtheimia* in Europe and the Americas, while *Apophysomyces* is the second more common agent in India [3,4,6,8]. In our case, *Mucor* spp. was identified, consistent with existing literature.

This disease predominantly affects immunocompromised individuals, particularly those with haematological malignancies (especially when neutropenic), recipients of solid organ and haematopoietic stem cell transplants, patients undergoing chemotherapy or prolonged high-dose corticosteroid therapy, and those with uncontrolled diabetes and ketoacidosis [1,2,5-8].

Mucormycosis can have various presentations depending on the site of inoculation [1,3,5]. Rhino-orbital-cerebral and pulmonary infections are caused by inhalation of fungal spores [1,3-7], which in immunocompromised hosts can overcome phagocytosis [3,7] and bind to host cell glucose-regulated protein 78 kDa in nasal cells through spore coating proteins [1,3,6]. This allows cell invasion and eventually angioinvasion, a hallmark of mucormycosis, leading to thrombosis and tissue necrosis [1,3,6]. In patients with ketoacidosis, hyperglycaemia impairs normal defence mechanisms [1,3,6,7], and the release of iron from binding proteins increases free serum iron, promoting fungal invasion [1,3].

The nasal mucosa is the usual site of infection, from where the disease can spread to the paranasal sinuses and orbit, eventually reaching the central nervous system, either through erosion of bone structures or by spreading along the nerve pathways or vasculature [3,6,10]. The symptoms typically begin with nasal manifestations, such as rhinorrhea, nasal congestion, sinus pain, fever, headache, and nausea [1,2,6]. However, as the infection advances, ocular symptoms may appear, including retro-orbital or periorbital pain, diplopia, blurred vision, and even amaurosis [1,2,4-7]. When the central nervous system becomes involved, patients may present with seizures, dizziness, altered mental status, and gait disturbances [1,2,6]. In the patient described in this case, the disease began with symptoms typical of sinusitis, including facial pain and nasal discharge. However, she did not immediately present with the orbital and neurological symptoms commonly associated with the disease. The progression of the infection was marked by oedema of the left lower eyelid, indicating orbital involvement, followed by the late onset of diplopia. This delay in symptom development made the diagnosis more challenging. In cases of mucormycosis, neurological symptoms may be masked by the severity of the infection and the rapid progression of the disease, as seen in this case.

Cerebrovascular complications in rhino-orbital-cerebral mucormycosis primarily result from vascular invasion [2,11], particularly involving the cavernous sinus, internal carotid artery, or basilar artery. Invasion of blood vessel walls can lead to arterial occlusion or formation of intravascular thrombi, as well as causing reactive vasospastic narrowing, all of which may lead to ischaemic stroke [9-14]. In cases of disseminated mucormycosis, infarctions in multiple territories are also possible, although rare [11]. Additionally, vasculitis can lead to aneurysm formation and subsequent subarachnoid haemorrhage [2,9,10,12].

The prevalence of cerebrovascular complications in rhino-orbital-cerebral mucormycosis varies between studies. S. Pandey *et al.* [10] reported the presence of ischaemic stroke in 25% of 44

patients, while D. Ramachandran *et al.* [11] identified brain ischaemia in 42% of 26 patients in a prospective observational study. Symptoms of stroke varied from hemiparesis, aphasia, ophthalmoplegia, loss of vision, and altered mental status [7,9,10,11,13,14]. The most common infarction pattern was watershed infarcts, primarily affecting the border zones of the anterior circulation [11,13,14], with the ophthalmic artery and cavernous internal carotid artery being the most frequently affected vessels [10,11].

Most of these patients had a prior COVID-19 infection, which likely contributed to a prothrombotic state, further increasing the prevalence of infarctions [10,11,13,14]. There was no difference in conventional risk factors between patients with or without stroke [11,14], but patients with stroke had a more infiltrative fungal infection with affection of ethmoid and frontal sinuses as well as cavernous sinus and internal carotid artery involvement, and higher inflammatory markers [11,14], including d-dimer, white blood cell counts, neutrophil/lymphocyte ratios, blood urea nitrogen/creatinine ratio.

Interestingly, our patient did not initially present neurological signs but later developed diplopia, which indicated the progression of the infection to the orbit. This delayed manifestation of orbital and neurological symptoms may have contributed to the delayed diagnosis and vascular involvement observed on CT and MRI.

Early diagnosis of mucormycosis, especially in cases with cerebrovascular involvement, is critical for improving outcomes. Since early symptoms can be nonspecific and often resemble other severe sinus infections, a definitive diagnosis relies on detailed radiological studies and tissue biopsy to observe the characteristic fungal hyphae. CT scans may show sinus thickening and opacification in the early stages, with bone erosion in later stages [2,4-7]. MRI is more sensitive for detecting orbital and brain involvement, including cavernous sinus thrombosis, internal carotid artery occlusion, and perineural spread [5,9,12,14]. MRI is therefore the recommended imaging modality to exclude cerebrovascular complications and should be performed early, particularly in high-risk patients such as diabetics with mucormycosis [5,12].

The treatment of mucormycosis includes a combination of reversal of risk factors (including hyperglycaemia, neutropenia, corticosteroid treatment), surgical debridement of affected tissues and antifungal therapy [3-7,15]. Liposomal amphotericin B is the first-line antifungal agent [3,5-7,15], although posaconazole and isavuconazole are also used as first-line or salvage therapies [5,15]. The duration of antifungal treatment depends on clinical response and can extend for several weeks to months [5-7]. In this case, the patient was treated with liposomal amphotericin B for several weeks, followed by oral isavuconazole due to renal function deterioration. Surgical intervention is critical for debridement of necrotic tissue, which may require multiple surgeries. The goal is to remove as much of the affected tissue as possible to limit the spread of infection and prevent further complications, sometimes resulting in deformity [3-7]. Adjunctive therapy with hyperbaric oxygen therapy is frequently recommended as it promotes the release of growth factors to improve angiogenesis and wound healing [3-6,15].

Despite aggressive treatment, the prognosis for mucormycosis remains poor, with mortality rates ranging from 40% to 80%, especially when there is brain involvement [1,5,7]. The presence of ischaemic stroke or vascular involvement significantly worsens the prognosis, and patients often experience long-term sequelae [9]. Accordingly, our patient was submitted to prolonged anti-fungal therapy, surgical debridement and hyperbaric chamber sessions, with slight improvement after more than 2 months. The

inadequacy of glycaemic control, in which psychological factors played an important role, was a factor that contributed to the difficulty of treatment.

Conclusions

This case highlights an uncommon cause of ischaemic stroke in young adults that should be considered and ruled out not only in the presence of sudden neurological changes but also in cases of invasive sinusitis in immunocompromised and diabetic patients. Mucormycosis presents diagnostic and therapeutic challenges, with its incidence increasing, although mortality rates remain high. Timely recognition of mucormycosis is still an issue due to its nonspecific clinical signs, as also seen in this case, where the patient had already undergone two antibiotic regimens before the fungal infection was identified. Cerebrovascular events in mucormycosis lead to significant morbidity and mortality, emphasizing the importance of early symptom recognition and prompt MRI screening. In this case, the absence of early neurological signs contributed to the delayed diagnosis, although an early MRI might have identified the lesions and allowed for earlier intervention.

Declarations

Ethics approval and consent to participate

Consent was given by the patient for the writing of this article.

List of abbreviations

CT: Computed tomography
ORL: Otorhinolaryngology
MRI: Magnetic resonance imaging

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding Statement

The authors were not funded by any institution.

Authors' contributions

MMV was involved in patient care, collected and analysed the patient data and wrote the manuscript. MSM and SB collected and analysed patient data and were major contributors in reviewing the manuscript. SC, MM and LS were involved in patient care and were major contributors in reviewing the manuscript. MCF was a major contributor in reviewing the manuscript. All authors read and approved the final manuscript.

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