CLINICAL VIGNETTE

Angioinvasive Mucormycosis Masking as Stroke

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Introduction

Mucormycosis is an invasive fungal infection that can severely affect immunocompromised individuals. In diabetic patients, it most commonly has a rhinocerebral presentation. Diagnosis can be difficult as many of the symptoms are nonspecific, but once suspected, the extent and location of infection is confirmed with imaging. Treatment consists of a combination of high-dose antifungals and surgical debridement. We present a patient with poorly controlled diabetes who initially presented with neurologic deficits concerning for stroke and on further imaging was found to have invasive mucormycosis sinusitis with cavernous sinus involvement and angioinvasion of the right ICA.

Case Presentation

A 56-year-old female with type two diabetes mellitus and hypertension presented to the emergency department with right facial pain and swelling, right facial droop, and left upper extremity weakness. A code stroke was activated. Initial imaging showed a right MCA/ACA borderzone infarction as well as occlusion of the cavernous segment of the right ICA with diminished flow to the R ophthalmic artery and concern for invasive sinusitis (Figure 1). Upon further questioning she reported several weeks of sinus symptoms. Urgent ENT evaluation noted, an eschar with extensive necrotic tissue in the right nasal cavity. Frozen section from bedside biopsy was notable for fungal elements which were later confirmed on permanent section to be mucormycosis-rhizopus species. On day 1 of hospitalization she was taken to the OR for debridement and started on high-dose amphotericin and micafungin per infectious disease consultant. Serial imaging over several days noted progression of disease including involvement of the right optic nerve and orbital apex (Figure 2), with exam notable for loss of vision in the right eye and complete CN V palsy prompting further surgical debridement of necrotic tissue in the OR. Given the degree of orbital involvement, extensive discussion between subspecialists including oculoplastics and neurosurgery led to continued medical management with every-other-day retrobulbar amphotericin injections, started on day 15 of hospitalization. Her antifungal therapy was broadened to include isavuconazole in addition to amphotericin and micafungin on day 16. Fungal invasion progressed despite triple therapy and serial imaging on day 22 noted development of a R-ICA saccular mycotic aneurysm. On day 23 she was more somnolent. Stat imaging noted both intraventricular and subarachnoid hemorrhages thought to be due to the rupture of the mycotic R-ICA aneurysm. No surgical intervention was deemed appropriate and her family elected to transition her to comfort care on day 26, and she died on hospital day 28.

Discussion

Infection with mucormycosis can be devastating, particularly in diabetic patients with rhinocerebral disease and a delay in diagnosis. One multi-case review of 929 documented cases of mucormycosis found 39% of cases had sinus involvement, with higher prevalence of 66% in patients with diabetes.[1] As with our patient, the initial sinusitis can progress to the sino-orbital area (8%) causing facial numbness due to infarction of the sensory branches of the fifth cranial nerve and rhinocerebral involvement (21%) with angioinvasion. The prognosis for patients with rhinocerebral infection is poor. One study reported mortality rate of 62%.[1] Mucormycosis also has a high affinity for blood vessels and can cause thrombosis, necrosis, and resultant tissue infarction. Mycotic aneurysm formation can occur with invasion of the vessel wall as seen in our patient. Given the severity of this disease, when mucormycosis is suspected, current guidelines recommend early and extensive debridement, which can be disfiguring, and antifungal treatment, which can be toxic.[2] At the time of presentation our patient already had intracerebral and intravascular spread, increasing the likelihood of a poor outcome.

The combination of surgery and antifungals offers the most survival benefit (70%) compared to treatment with surgery alone (57%) or antifungals alone (62%).[1] Current guidelines for mucormycosis recommend systemic antifungal treatment with liposomal amphotericin B as the first line agent (unless preexisting renal compromise is present), in combination with early surgical treatment in the form of resection or debridement of infected or necrotic areas.[2] Patients with cerebral involvement, commonly require higher doses (10mg/kg per day) of intravenous liposomal amphotericin. Although there are no definitive studies to guide combination therapy with echinocandins,[2] our infectious disease team recommended initial dual therapy with micafungin due to the severity of our patient's presentation and lack of enhanced toxicity. Dose reduction is often required if renal toxicity develops from amphotericin B, which occurred for our patient on day 8 of therapy. Her dose was reduced to 7.5mg/kg which was maintained for the duration of her treatment due to a sustained increase in creatinine. In patients with disease progression or toxicity, intravenous

isavuconazole or posaconazole are recommended for salvage therapy.[2]

Our patient's treatment included discussion over exenteration versus retrobulbar amphotericin for her orbital involvement. Generally, exenteration can be justified in cases of advanced orbital involvement with total vision loss and ophthalmoplegia.[3] However, it is unclear whether exenteration confers a survival benefit, even in the presence of intracranial spread and rapid disease progression.[3] Retrobulbar amphotericin B injections are a minimally invasive treatment option but are considered an off-label use of this medication with little data on dosage, timing, or long-term adverse effects. It is generally only considered as an adjunctive treatment in patients who are already receiving systemic antifungal therapy, have had aggressive sinus debridement, and have had reversal of hyperglycemia and immunosuppression.[3] Ultimately, neither exenteration nor retrobulbar amphotericin B injections have been shown as superior and so retrobulbar amphotericin was chosen for our patient.[3]

Conclusion

Mucormycosis infections commonly present as sinusitis in patients with diabetes, but in those with delayed access to care can present with complications from further cerebral invasion including cranial nerve palsies from cavernous sinus involvement, stroke, and mycotic aneurysm formation. Patients with advanced disease require swift initiation of antifungal therapy and aggressive surgical debridement given the poor prognosis. With the invasive nature and spaces involved, treatment often requires interdisciplinary management between multiple specialties.

Figures

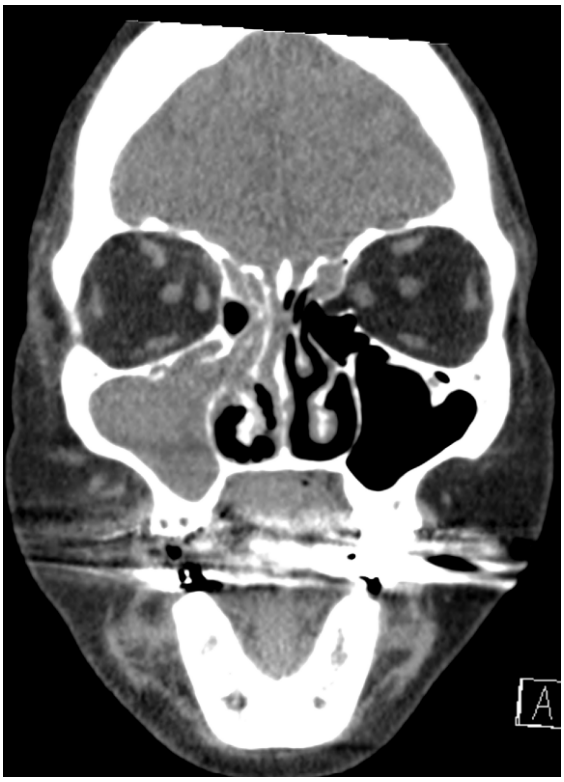

Figure 1: CT scan on presentation: Air-fluid levels and frothy appearance within the near completely opacified right maxillary sinus and right anterior ethmoid air cells. Partial opacification of the right frontal sinus with opacification of the right frontal recess.

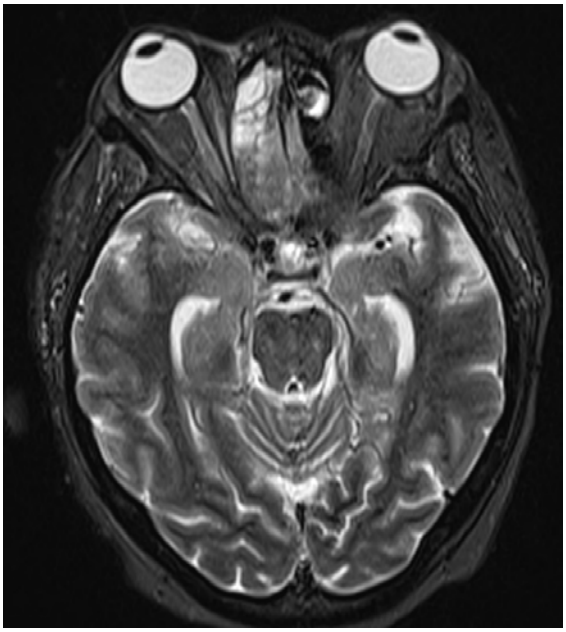

Figure 2: MRI after debridement: Seen are findings of prior endoscopic sinus surgery and evidence of invasive fungal sinusitis with involvement of the right orbital apex and likely associated right intracranial ICA.

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