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Isolated cerebral mucormycosis of the basal ganglia

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Abstract

Isolated cerebral mucormycosis is a rare fungal infection for which morbidity and mortality remain high despite prompt tissue diagnosis and antifungal treatment. Intravenous drug use is strongly associated with this condition. However, other risk factors classically associated with systemic mucormycosis, such as poorly controlled diabetes and an immunocompromised state, are seldom seen in cases of isolated cerebral involvement. Here, we present a rare case of isolated mucormycosis of the basal ganglia by *Rhizopus* in a patient with multiple risk factors. Diagnosis and treatment guidelines for isolated cerebral mucormycosis are also reviewed. Earlier detection and therapy are likely to lead to improvement in the course of this otherwise deadly disease.

Keywords

mucor; mucormycosis; isolated cerebral mucormycosis; *Rhizopus*; cerebral abscess

1. Introduction

Mucormycosis is a rare fungal infection most commonly caused by *Rhizopus* and *Mucor* organisms, which are ubiquitous in nature. A recent meta-analysis of 929 cases of mucormycosis since 1885 found that the most prevalent primary sites of infection were the sinuses, lungs, and skin [1]. Central nervous system (CNS) involvement occurred in 30% of cases, with 84% of these cases reflecting secondary seeding from another site. The most common source of secondary seeding was sinonasal infection with subsequent extension into the CNS, referred to as rhinocerebral mucormycosis. Only 16% of mucormycosis cases affecting the CNS demonstrated isolated involvement. Isolated cerebral mucormycosis is presumed to result from seeding of the brain during an episode of fungemia. The most

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significant risk factor for isolated cerebral mucormycosis is intravenous drug use [2, 3], and indeed isolated cerebral mucormycosis is the most common manifestation of mucormycosis in intravenous drug users [1]. Although diabetes and an immunocompromised state are risk factors for mucormycosis, these are classically associated with rhinocerebral and pulmonary mucormycosis, respectively, and have only rarely been reported in patients with isolated cerebral mucormycosis [1]. Here, we present a rare case of isolated mucormycosis of the basal ganglia by *Rhizopus* in a patient with multiple risk factors.

2. Case report

A 28-year-old man with poorly controlled type I diabetes, Crohn's disease aggressively treated with infliximab, and history of intravenous drug abuse presented to an outside hospital with subacute onset of severe headaches, neck pain, photophobia, nausea, vomiting, and temperature of 100.8 F. Initial exam did not reveal any focal neurological deficits but was notable for oral thrush. Cerebrospinal fluid from a lumbar puncture revealed glucose of 137 mg/dL, protein of 87 mg/dL, 125 leukocytes (82% polymorphonuclear leukocytes), 15 erythrocytes, and negative Gram stain. Laboratory studies were notable for diabetic ketoacidosis and elevated ESR and CRP. The patient was started on vancomycin, ceftriaxone, ampicillin, and acyclovir for empiric coverage of bacterial meningitis and herpes encephalitis. On hospital day 3, he developed left face, arm, and leg weakness. CT demonstrated a $5 \times 3 \times 3$ cm hypodense lesion in the right basal ganglia, with no involvement of the paranasal sinuses. MRI revealed a minimally enhancing lesion with avid diffusion restriction. On hospital day 4, the patient was transferred to our institution for further management. Antibiotic coverage was expanded to include metronidazole and amphotericin B for anaerobes and mucor, respectively. On hospital day 5, the patient's left arm weakness progressed to plegia. Repeat MRI showed progression of the brain lesion with increased enhancement and mass effect (Figure 1). MR spectroscopy revealed elevated lactate and choline and decreased N-acetyl aspartate peaks, while MR angiogram demonstrated no abnormalities of the intracranial vessels. CSF testing was negative for herpes simplex virus 1 and 2, varicella zoster virus, Lyme, West Nile virus (WNV), eastern equine encephalitis virus (EEE), and VDRL for syphilis. Serum testing was negative for human immunodeficiency virus, WNV, EEE, human herpesvirus 6, cytomegalovirus, treponemal IgG, Coccidioides antigen, galactomannan, and beta-D-glucan. Transthoracic echocardiogram revealed a patent foramen ovale but no valvular vegetations. Given the patient's declining condition, a biopsy of the basal ganglia lesion was pursued. An open biopsy was performed to obtain a maximal amount of tissue as requested by multiple consulting services. Due to possible involvement of the middle cerebral artery by the inflammatory process, a right frontal trans-sulcal approach rather than a transsylvian approach was employed. Histopathologic examination of biopsy samples revealed fungal forms with broad non-septate hyphae branching at wide angles, angio-invasion, fibrinoid necrosis of vessel walls, and prominent neutrophilic and lymphocytic infiltration (Figure 2 A-B). These findings were consistent with cerebral mucormycosis; subsequent culture was positive for *Rhizopus* organisms. The dose of amphotericin was augmented post-operatively with cessation of other antimicrobial drugs. Despite prompt treatment, the patient's neurologic status progressively declined, and he expired on hospital day 20 after his family

elected to pursue comfort measures only. Autopsy examination of the brain revealed a hemorrhagic abscess with necrosis and black/dark red spots centered in the right caudate, putamen, internal capsule, and thalamus with midline shift (Figure 2 C). Microscopically, broad-based fungal hyphae were seen within the brain parenchyma and blood vessels, with associated vasculitis, granuloma formation, chronic meningoencephalitis, and hemorrhagic necrosis, consistent with cerebral mucormycosis. No systemic fungal source was identified at autopsy, corroborating the isolated cerebral involvement.

3. Discussion

Isolated cerebral mucormycosis is a rare fungal infection strongly associated with intravenous drug abuse. Diabetes and an immunocompromised state have only rarely been reported in patients with isolated cerebral mucormycosis since these risk factors more commonly predispose to other patterns of infection, such as rhinocerebral or pulmonary mucormycosis [1]. The patient described in this case was not only an intravenous drug abuser, but also had poorly controlled type I diabetes, and was immunocompromised due to treatment of Crohn's disease with high doses of infliximab. Patients with multiple risk factors should not only arouse clinical suspicion for mucormycosis if symptomatic, but may also warrant close monitoring for the development of symptoms of this deadly condition.

Mortality of isolated cerebral mucormycosis exceeds 60% [1]. Early recognition and treatment improve morbidity and mortality from this condition, which is often diagnosed at autopsy [3]. Prompt diagnosis requires knowledge of relevant symptoms, signs, and risk factors for the development of isolated cerebral mucormycosis. Patients with isolated cerebral mucormycosis may present with subacute onset of headache (44%), fever (41%), hemiparesis (38%), and altered mental status (21%) [3]. Workup includes lumbar puncture and brain MRI. Characteristically, fungal infection will result in lymphocytic CSF pleocytosis with low glucose and elevated protein. In diabetic patients, serum glucose should be measured at the time of lumbar puncture so that CSF glucose can be interpreted relative to its predicted value of 60% of serum glucose levels. In addition to standard CSF analyses, recent studies have suggested that India ink staining of CSF and PCR-based analyses of RNA isolated from CSF may facilitate early detection of mucormycosis [4]. The majority of cases of isolated cerebral mucormycosis involve the basal ganglia, and MRI frequently reveals basal ganglia abnormalities such as thrombotic infarcts, mycotic emboli, and abscesses. The tendency for isolated mucormycosis to cause basal ganglia lesions may be due to the specific size of mucor sporangiospores, thought to facilitate distribution through the striatal arteries to the heavily vascularized basal ganglia [1]. The predilection of mucor for the basal ganglia may also be due to high levels of iron in this brain region, since iron has been shown to stimulate growth of mucor [5].

While the appearance of cerebral mucormycosis on imaging is often nonspecific, MRI features may include an irregular abscess cavity wall, intracavitary projections, and abscess cavity with avid diffusion restriction. MR spectroscopy may demonstrate presence of lipids, lactate, and amino acids, with depleted N-acetyl aspartate [6]. Ultimately, definitive diagnosis requires tissue sampling. While stereotactic biopsy has been effective in some cases [7], it may provide insufficient tissue to diagnose isolated cerebral mucormycosis in

others. As a result, open surgical biopsy may be advisable depending on the clinical scenario [3].

The standard treatment for isolated cerebral mucormycosis includes surgical debridement and amphotericin B. The extent of surgical debridement should be determined judiciously depending on the anatomic localization, extent of infection, and clinical context. Amphotericin B appears to be the most critical variable that affects the outcome of isolated cerebral mucormycosis. One study found that treatment with amphotericin B was the only predictor of survival, reducing mortality from 92% to 41%. Other factors, including age, gender, intravenous drug use, HIV status, treatment with surgical drainage, or treatment with steroids, flucytosine, or cytosine arabinoside did not significantly impact survival [2]. In suspected or confirmed cases of cerebral mucormycosis, amphotericin B should be dosed between 0.5 mg/kg/d and 1.0 mg/kg/d. While intrathecal administration of amphotericin B has been employed with variable success, it is not currently considered standard of care [7].

4. Conclusion

Isolated cerebral mucormycosis is a rare infection that is most often associated with intravenous drug use but should also be considered in patients with other risk factors for mucormycosis, such as poorly controlled diabetes or immunocompromise. Symptoms, CSF abnormalities, and imaging characteristics are non-specific, and definitive diagnosis requires sampling of involved tissue. Given the high mortality of isolated cerebral mucormycosis, high clinical suspicion in the appropriate context and prompt initiation of treatment with amphotericin are essential. Successful treatment also requires surgical management with debridement of infected tissue. Earlier detection and therapy are likely to lead to improvement in the course of this otherwise deadly disease.

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Figure 1.

Axial MR images five days after initial presentation. (A) T2-weighted FLAIR, (B) diffusion-weighted imaging, (C) T1-weighted post-gadolinium, and (D) apparent diffusion coefficient images reveal an isolated right basal ganglia lesion with sparse enhancement and avid diffusion restriction.

Figure 2.

(A) Hematoxylin and eosin stain of biopsy specimen at 200X magnification shows fungal forms of mucormycosis with classic broad, non-septate hyphae, and wide angles (arrows) with angio-invasion and fibrinoid necrosis of vessel walls (arrowhead).

(B) Biopsy specimen shows fungal forms (arrows) with prominent neutrophilic and lymphocytic infiltration (arrowheads), consistent with cerebral mucormycosis (H&E, 200X).

(C) Axial section from autopsy shows the hemorrhagic lesion with necrosis in the right caudate, putamen, internal capsule, and thalamus with midline shift.