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Orbitocerebral Mucormycosis in a Patient with Central Nervous System Lymphoma

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Abstract

A 61-year-old man with well-controlled diabetes mellitus type 2, cirrhosis from hepatitis C, alcohol abuse, and portal hypertension presented with painful vision loss and left orbital swelling. Imaging showed diffuse orbital, perineural, and pachymeningeal inflammation. He was initially diagnosed with neurosarcoidosis. However, cerebrospinal fluid analysis revealed central nervous system lymphoma, and lacrimal gland biopsy showed fungal organisms consistent with mucormycosis. We describe a case of Mucorales infection lacking sinonasal involvement and discuss the differential diagnosis and management of patients presenting with orbital and central nervous system inflammation from this uncommon fungal infection.

Precis

Due to its rapidly progressive and potentially fatal nature, orbitocerebral mucormycosis should be included in the differential diagnosis of orbital cellulitis in immunocompromised patients, even in the absence of sinonasal disease.

Keywords

orbitocerebral mucormycosis; orbital apex; central nervous system lymphoma

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Mucormycosis is a rare fungal infection that primarily affects immunocompromised patients and is acquired through contact with Mucorales fungal spores.¹ The most common underlying condition for patients with mucormycosis is diabetes, and 68% of patients with sino-orbital disease have diabetes.¹ Mucormycosis limited to the sinuses and orbits has a mortality of 24%, but once previously localized disease disseminates into the CNS, observed mortality increases to 98%.¹ Due to the high mortality rate upon CNS dissemination, prompt diagnosis and treatment is essential in those with suspected mucormycosis. All collection and evaluation of protected patient health information were HIPAA compliant.

Case Report

A 61-year-old Hispanic man with diabetes mellitus type 2, cirrhosis from hepatitis C, alcohol abuse, and portal hypertension presented with painful vision loss and left orbital swelling. He was treated with 10 days of broad-spectrum antibiotics for suspected orbital cellulitis prior to being transferred to our facility. On exam, vision was 20/25 OD and no light perception OS, with normal intraocular pressure OU. The left pupil was nonreactive with a relative afferent pupillary defect. Extraocular muscle movements were limited in all directions OS. Dilated fundus exam was normal OU, without disc pallor. The left eye had moderate periorbital edema and ecchymosis, chemosis, and relative proptosis (Fig. 1A). Patchy alopecia and eschars were seen on the scalp (Fig. 1B).

Post-contrast magnetic resonance imaging (MRI) of the orbits showed heterogeneous enhancement of the left orbit involving the intraconal fat, lacrimal gland, and optic nerve sheath. Inflammation extended to and through the orbital apex with pachymeningeal enhancement extending around the left lateral convexity of the brain and mesial temporal lobe. Edema and inflammation extended to the left temporalis muscle and overlying soft tissues (Fig. 2 and 3). There was no evidence of sinonasal involvement.

Broad-spectrum antibiotics were continued. Rapid plasma reagin, cytoplasmic anti-neutrophil cytoplasmic antibodies, antinuclear antibody, Sjögren's-syndrome-related antigens A and B, and immunoglobulin G4 were negative. Hemoglobin A1C was 5.9. White blood cell (WBC) count was 19,100. Serum angiotensin-converting enzyme (ACE) level was 121, and perinuclear anti-neutrophil cytoplasmic antibodies titer was 1:80. Lumbar puncture (LP) showed WBC 394, protein 67, and ACE 5. While results of the lacrimal gland biopsy and LP cytology were pending, a presumed diagnosis of neurosarcoidosis was made due to elevated serum ACE level, and intravenous (IV) methylprednisolone was started. The patient's mental status declined sharply, and repeat contrast MRI brain showed acute/subacute infarcts of the left caudostriatal nuclei with a new hemorrhagic stroke in the left basal ganglia (Fig. 4).

Lacrimal gland biopsy subsequently showed fungal organisms consistent with mucormycosis (Fig. 5); CSF cytology showed immunophenotyping consistent with a B- cell lymphoproliferative disorder. IV methylprednisolone was discontinued immediately, and micafungin and amphotericin B were started. Biopsy of his scalp lesions revealed fungal elements consistent with mucormycosis. Otorhinolaryngology performed nasal endoscopy, which showed normal pink mucosa with no signs of fungal involvement. The patient

declined despite treatment, and subsequent head computed tomography (CT) and MRI of the brain showed extensive ischemic changes with hemorrhagic transformation in the left temporal lobe and basal ganglia (Fig. 6). His family ultimately chose to withdraw care, and he passed on post-transfer hospital day 12, 29 days after the onset of his symptoms.

Discussion

Mucormycosis involving the orbit and CNS classically starts in the sinonasal tissues and is termed rhino-orbito-cerebral mucormycosis (ROCM).² Abdollahi et al reported sinus or nasal involvement in all 15 cases of their ROCM review, and Nithyanandam et al and Bhansali et al reported sinus involvement in all their cases, 34 and 35, respectively.²⁻⁴ In an analysis of 11 ROCM cases initially presenting with orbital apex syndrome by Jiang et al, all demonstrated sinus or nasal involvement on CT and rhinoscopy.⁵ Our patient presented with orbital apex syndrome due to orbitocerebral mucormycosis and lacked sinonasal involvement on CT/MRI or nasal endoscopy at any point during his clinical course. To our knowledge, there are only 2 other published cases of mucormycosis isolated to the orbits and CNS.^{6,7} Both of these cases had bilateral orbital involvement, making ours the first published case with isolated, unilateral orbitocerebral mucormycosis (PubMed search July 10, 2018 using combinations of search terms orbito-cerebral, orbital-cerebral, and orbitocerebral with mucormycosis, mucormycosis and zygomycosis).

When our patient presented, he was not presumed to be immunocompromised because his diabetes was well controlled. Once the diagnosis of mucormycosis was made, however, he was also found to have CNS lymphoma, which was likely the underlying condition predisposing him to the infection. His elevated serum ACE level was initially thought to be due to sarcoidosis, for which methylprednisolone was initiated. In retrospect, this elevation was most likely related to his diagnosis of liver cirrhosis, which is associated with elevated serum ACE levels.⁸ Glucocorticoids stunt the host immune response to Mucorales and increase blood glucose levels.⁹ Therefore, premature initiation of glucocorticoids before pathologic diagnosis can be deleterious in unknown cases of orbital and CNS inflammations, and fungal infections should be ruled out prior to administering glucocorticoids.

Definitive diagnosis of mucormycosis is based on histological examination of biopsy specimens, which is considered more sensitive than culturing.³ MRI is the preferred imaging modality for orbital disease and is useful in determining the extent of intracranial involvement.¹⁰ When MRI does not show a definitive abnormality, diffusion-weighted imaging (DWI) plays an important role in demonstrating optic nerve thickening and infarction. Ischemic optic nerve involvement manifests as high signal intensity along the nerve on DWI and a hypointense signal on apparent diffusion coefficient determination.¹¹

The standard pharmacological management of mucormycosis is with IV liposomal amphotericin B¹; however, the disease causes ischemic vasculitis with tissue infarction that lowers IV drug penetration. For this reason, aggressive surgical debridement is required in addition to antifungal therapy. There is minimal data on the benefit of orbital exenteration with respect to mortality in cases of orbital disease.¹² Controlling the underlying infectious predisposition helps reconstitute host defenses. This involves discontinuation of immuno

suppressants in iatrogenic cases and optimization of blood glucose and electrolyte disturbances in diabetic patients.¹⁰

Conclusion

Despite the majority of ROCM cases demonstrating sinonasal involvement, physicians should be alert to the potential for mucormycosis in all immunocompromised patients due to its rapid dissemination and frequently fatal nature. Mucormycosis should promptly be included in the differential diagnosis of orbital cellulitis and vision loss in these patients, even in the absence of sinonasal disease.

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Figure 1.
External photographs showed moderate periorbital edema with ecchymosis of the eyelids (A). Inspection of the scalp showed small scabs with patchy alopecia and erythema (B).

Figure 2. Brain magnetic resonance imaging at presentation. Coronal post-contrast images (A-C) depicted heterogeneous intraorbital enhancement involving the left lacrimal gland, intraconal fat, and optic nerve sheath. Edema and inflammation extended to the left temporalis muscle and overlying soft tissues.

Figure 3.
Pachymeningeal enhancement was present around the lateral convexity of the brain and as well as posteriorly through the mesial left temporal lobe and along the left tentorium (A, B).

Figure 4. Follow-up brain magnetic resonance imaging after change in mental status. Axial fluid-attenuated inversion recovery (A) and diffusion-weighted imaging (B) indicated acute/subacute infarcts of the caudostriatal nuclei and hemorrhagic stroke in the left basal ganglion.

Figure 5.

Lacrimal gland biopsy. A. Focal chronic inflammation of the acinar and periductal parenchyma consisting of lymphocytes and plasma cells (black arrow; hematoxylin and eosin, 10X:). B. Necrotizing granulomatous inflammation with central necrosis and aggregates of neutrophils and palisading histiocytes with multinucleated giant cells at the periphery (white arrows; hematoxylin and eosin, 10X:). C. Distinct fungal hyphal elements with an empty-looking appearance that are irregular in caliber (white arrows; hematoxylin and eosin, 40X). D. Distinct fungal hyphal elements were seen with periodic acid-Schiff fungal (PAS/F) stain (white arrow, 40X).

Figure 6.

A. Axial T2 fluid-attenuated inversion recovery from repeat magnetic resonance imaging of the brain showed expansion of left thalamic and basal ganglia infarct when compared to the previous scans. Axial (B) and coronal (C) computed tomography images of the brain without contrast showed ischemic changes with hemorrhagic transformation in the left temporal lobe and basal ganglia with midline shift and mass-effect upon the left lateral ventricle.