Perineural Spread of Rhinocerebral Mucormycosis

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Summary: An unusual pathway of local spread of rhinocerebral mucormycosis is presented with MR and pathologic correlation. Perineural extension, proved with pathology, followed the trigeminal nerve to the pons. Enhancement of the nerve was seen on MR.

Index terms: Brain, infection; Nerves, trigeminal (v)

Mucormycosis is a potentially devastating fungal infection in diabetic and immunocompromised hosts. Infection is acquired by inhalation of this ubiquitous organism, and multiple clinical syndromes have been described, including rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated (1).

The rhinocerebral form of this disease is one of the most common, and there is a characteristic pattern of spread. Fungal hyphae invade vessel walls with subsequent local thrombotic infarction (2). This process often progresses from the sinonasal cavity to the orbit, and later to the cavernous sinus. Direct spread through the cribriform plate may also occur (3). In addition, hematogenous spread from the cavernous sinus has been shown to occur with distant cerebral infarction or abscess. We present an unusual mechanism of mucormycosis invasion, perineural spread from the cavernous sinus to the pons.

Case Report

A 65-year-old diabetic man presented to another hospital with new right periorbital edema and facial swelling. There was right ptosis with total right ophthalmoplegia and visual loss. Blood glucose was 512 mg/dL. A computed tomography (CT) scan revealed soft-tissue opacification of the right maxillary sinus, right ethmoid sinuses, and right nasal vault, with bony destruction of the medial right maxillary sinus wall and bony nasal septum. Endoscopic biopsy with antrostomy and ethmoidectomy was performed, and a diagnosis of sinonasal mucormycosis was made.

The patient was transferred to our institution, and a repeat CT scan revealed right maxillary and ethmoid sinus opacification. In addition, there was questionable fullness of the right cavernous sinus, with abnormal infiltration of fat in the right orbit, pterygopalatine fossa, and infratemporal fossa (Fig 1A). The right cavernous carotid artery enhanced normally, with no evidence of thrombosis. The patient’s hyperglycemia was controlled with sliding-scale insulin, and intravenous amphotericin B was begun. The patient underwent right medial maxillectomy with right orbital exenteration. Extensive broad nonseptate hyphae with mixed inflammatory response were identified throughout the soft tissues of the orbit, diagnostic of mucormycosis (Fig 1B). There was ischemic necrosis and inflammation of the right optic nerve.

Though there were no new symptoms in the early postoperative period, a repeat CT scan demonstrated progressive enlargement of the nonenhancing right cavernous sinus, with occlusion of the right cavernous carotid artery (Fig 1C). Magnetic resonance (MR) confirmed the right internal carotid artery occlusion, but in addition revealed abnormal enhancement of a thickened right trigeminal nerve extending into the pons (Fig 1D and E). A left hemiplegia later developed and the patient subsequently died.

At autopsy there was brown discoloration of the right fifth nerve. Thrombosis was demonstrated in the right internal carotid and the proximal right middle cerebral arteries, with associated infarction of the right insular cortex. No evidence of leptomeningitis was seen, except in the region adjacent to the right middle cerebral artery distribution infarct. Microscopically, an area of necrosis within the right trigeminal nerve was demonstrated (Fig 1F), surrounded by an inflammatory infiltrate composed predominantly of plasma cells, macrophages, and multinucleated giant cells. In the necrotic fifth nerve and pons, scattered fragments of broad, nonseptate hyphae, morphologically consistent with Mucor, were identified.

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Discussion

The rhinocerebral form of mucormycosis may occur in any immunocompromised host, but there is a distinct predilection for diabetics (1). Treatment strategies include aggressive surgical debridement, intravenous amphotericin B therapy, and control of blood glucose. Central nervous system involvement may occur from hematogenous spread or direct invasion, and portends a bleak prognosis with 5-year survival rates of 20% to 45% (3).

The spread of rhinocerebral mucormycosis is somewhat predictable. From the paranasal si-

Fig 1. A, Coronal CT image with contrast reveals right maxillary and ethmoid sinus opacification. Abnormal infiltration of right orbital fat (white arrow), right infratemporal fat (black arrow), and right pterygopalatine fossa (not shown) is present. The right optic nerve is enlarged.

B, High power view of hematoxylin and eosin–stained orbital exenteration specimen demonstrates multiple broad, nonseptate hyphae (arrows) within necrotic orbital contents.

C, Axial CT image with contrast reveals postoperative changes of orbital exenteration. Expansion of the nonenhancing right cavernous sinus is present, with bulging lateral contour (white arrow). The occluded right cavernous carotid artery does not enhance. The normal enhancement of the left cavernous carotid artery is shown for comparison (black arrow).

D, Axial T1-weighted MR image (600/12/2 [repetition time/echo time/excitations]) with contrast reveals abnormal enhancement of a thickened right trigeminal nerve, with apparent extension into the pons (arrow). Note absence of right internal carotid artery flow void, confirming occlusion.

E, Axial T1-weighted MR image (600/12/2) with contrast, at a level slightly lower than D, confirms extension of enhancement into the pons, with central low signal intensity (short arrow). Note also the abnormal signal in the right Meckel’s cave (long arrow), indicating involvement.

F, Low-power view of Gomori-methenamine silver–stained right pons section reveals inflammatory changes, with dark-staining neovascularity at the right fifth nerve root entry zone (arrow). 4V indicates fourth ventricle.
nuses, *Mucor* fungi often invade the orbit and progress posteriorly into the cavernous sinus. Thrombosis of the cavernous sinus and cavernous carotid artery may then occur, and intracranial extension may be in the form of distal mycotic emboli or direct meningeal inflammation (4). The pathologic explanation of this *Mucor* invasion pathway is that the fungus has a propensity for growing along the walls of blood vessels, and in fact, *Mucor* has been called angiotropic (1). However, direct spread through the cribriform plate into the anterior cranial fossa may also occur, and it has been suggested that this represents perineural spread (5). Our case initially progressed from the orbit to the cavernous sinus in the usual manner, but during the patient’s hospital course, MR demonstrated perineural extension from the cavernous sinus to the pons along the right trigeminal nerve, with no other apparent meningeal or intraparenchymal brain involvement. Pathologically, spread of mucormycosis within the trigeminal nerve was confirmed.

Perineural spread of disease is commonly described in head and neck malignant neoplasms, particularly adenoid cystic carcinoma and squamous cell carcinoma (6). The trigeminal nerve and its branches are common sites of perineural spread of malignancy. Direct fungal infiltration of the seventh and eighth cranial nerves from the subarachnoid space of the internal auditory canal has been documented in the past, but it occurred in the setting of fulminating basal meningitis from *Cryptococcus* or *Aspergillus* organisms (7). In a different case report of mucormycosis, cavernous sinus occlusion by fungal hyphae was accompanied by local infiltration of the adjacent branches of the trigeminal nerve, but there was no fungal extension to involve the sensory ganglion (8). A more recent study showed direct intracranial extension from the cavernous sinus to the pons that resembled the perineural spread described in this work, but that patient survived the infection and pathologic demonstration of perineural spread was not available (4). Our case of perineural spread of rhinocerebral mucormycosis is distinct in that fungal elements involved the trigeminal nerve from the cavernous sinus to the pons, with no apparent fungal leptomeningitis.

The use of MR to evaluate rhinocerebral mucormycosis was reported in 1988 (4). For evaluation of perineural spread of tumor below the skull base, both CT and MR imaging provide adequate information, but MR is felt to be superior for skull base, cisternal, and brain stem perineural infiltration (6). It seems logical that this could be extrapolated to intracranial extension of fungal infections as well. Given the propensity for mucormycosis to gain access to the cavernous sinus, MR may prove to be the most useful technique for excluding perineural spread or other potential routes of intracranial fungal invasion.

References