

Neuronavigation-Guided Endoscopic Endonasal Resection of Extensive Skull Base Mucormycosis Complicated With Cerebral Vasospasm

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Abstract: A 24-year-old woman presented with double vision since 6 months. Examination revealed left eye ptosis and bilateral abducens nerve palsy. Brain computed tomographic scan and magnetic resonance imaging revealed a bone-eroding mass lesion located in the middle skull base, occupying the posterior ethmoidal cells, the planum sphenoidale, the sphenoid sinus, the lateral recesses of the sphenoid sinus, the pterygoid apexes, and the middle and lower clivus, with compression of the inferior wall of the cavernous sinus and the parasellar and paraclival parts of the internal carotid artery. The patient was operated on with extended endoscopic endonasal approach guided with neuronavigation. Total mass resection was achieved. Histopathologic examination revealed mucormycosis infectious mass. On postoperative day 5, the patient developed right hemiplegia, and brain imaging revealed left internal carotid vasospasm. After treatment, the patient improved and was discharged.

Key Words: Extended endoscopic endonasal approach, mucormycosis, neuronavigation, skull base, vasospasm

(*J Craniofac Surg* 2014;25: 1319–1323)

Mucormycosis is an invasive fungal infection with predilection for the paranasal sinuses.¹ Despite the advances in diagnosis and treatment, invasive rhino-orbito-cerebral infection is still the most lethal clinical form of the disease.^{2–4} The mortality rate is reported to be as high as 20% even if the diagnosis and aggressive treatment are not delayed.⁵

Despite these efforts, these approaches are still considered invasive, requiring various degrees of bone demolition and neurovascular manipulation. With the introduction of the functional endoscopic sinus surgery, endoscopic techniques and approaches were developed starting from diagnosing techniques^{6,7} to endoscopic endonasal transphenoidal pituitary⁸ and extended endoscopic skull base surgeries.^{9–14} The endoscopic endonasal approach to the midline skull base has become a popular approach for the surgical management of pathologic lesions occupying this region. This popularity was gained because of the advantages offered by this technique, such as minimal invasiveness, less neurovascular

retraction and thus lower risk for neurovascular injury, wide view of exposure, no disruption of the facial skeleton, and better postoperative performance of the patients with shorter hospitalization period.

In this report, we present a case of invasive skull base mucormycosis that was treated successfully with complete removal of the mass with neuronavigation-guided extended endoscopic endonasal skull base approach, and complicated with postoperative internal carotid artery (ICA) vasospasm, representing an interesting triad of rare disease, novel surgical technique, and unusual complication.

CLINICAL REPORT

A 24-year-old woman presented with double vision since 6 months. The patient had no significant medical history. On admission, the neurologic examination revealed left eye ptosis and bilateral abducens nerve palsy with total inability to move both eyes laterally. Brain computed tomographic (CT) scan revealed a mass lesion located in the middle skull base, occupying the posterior ethmoidal cells, the planum sphenoidale, the sphenoid sinus, the lateral recesses of the sphenoid sinus, the pterygoid apexes, and the middle and lower clivus. The mass was seen eroding the bones of the skull base and showing homogenous hyperdense signal with areas of air. Brain magnetic resonance imaging (MRI) showed a cystic mass lesion in the upper mentioned areas. The mass was extending to and compressing the inferior wall of the cavernous sinus and the parasellar and paraclival parts of the ICA. The mass was hyperintense on T1-weighted and hypointense on T2-weighted images, with homogenous enhancement with gadolinium on postcontrast images. The mass showed strong capsule enhancement around the mass. Brain magnetic resonance angiography (MRA) showed no abnormalities in the intracranial arteries (Fig. 1). On the basis of the radiologic appearance and location of the tumor, we applied extended endoscopic endonasal approach to remove the tumor guided with neuronavigation.

Operative Technique

The patient was placed in supine position, with the head in neutral position and with a 10- to 15-degree adduction toward the left shoulder to prevent the surgeon's lateral bending and to avoid fatigue. The operation was performed using Karl Storz 0- and 30-degree, 4-mm-diameter, 18-cm, and 30-cm rod-lens rigid telescopes (Karl Storz and Co, Tuttlingen, Germany). The endoscopic approach was aided by neuronavigation (Stealth Station Treon plus; Medtronic, Louisville, CO) (Fig. 2). The endoscope was introduced binostrally, bilateral middle turbinate resection was performed, and the sphenoid osseum was identified. The posterior portion of the nasal septum and the vomer were resected to expose the whole anterior wall of the sphenoid sinus and the clivus. In addition, the superior portion of the nasal septum was resected to expose the skull base (the floor of the posterior ethmoid cells).

After preparing the surgical corridor in the nasal step, the ostia of the sphenoid sinus were identified in the sphenoethmoidal recess. After large anterior sphenoidectomy, the optic protuberance was identified in

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Received December 3, 2013.

Accepted for publication January 17, 2014.

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The authors report no conflicts of interest.

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ISSN: 1049-2275

DOI: 10.1097/SCS.0000000000000786

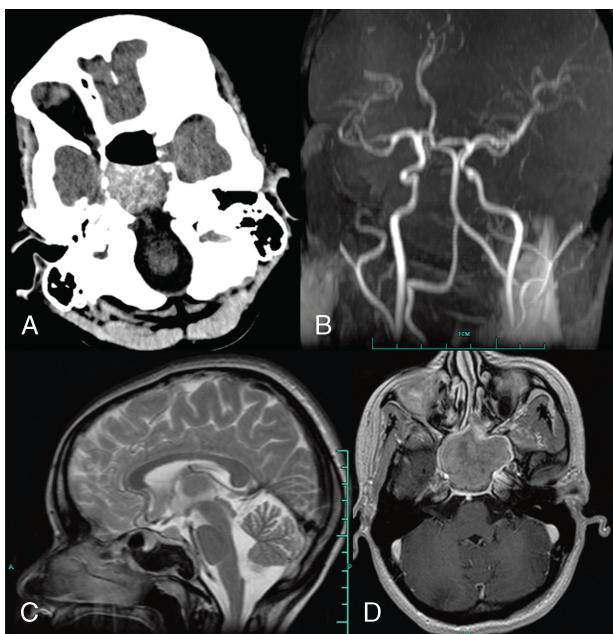


FIGURE 1. Preoperative neuroimaging demonstrating the skull base mass. A, Brain CT scan; B, brain MRA; C, sagittal T2-weighted brain MRI; D, axial postcontrast enhancing brain MRI.

the sphenoid roof. Using the anatomic landmarks in the sphenoid sinus roof and with the control of neuronavigation, the posterior ethmoidal cells located anterosuperior to the sphenoid sinus were resected until the lamina papyracea was exposed laterally; the roof of the posterior ethmoidal cells, superiorly; and the middle turbinate basal lamella, anteriorly (posterior to anterior approach).

With opening of the lateral recesses of the sphenoid sinus combined with the resection of the posterior ethmoidal cells, the pterygoid apex was exposed bilaterally, which is called the ethmoidopterygospheoidal (or

far lateral) approach. After exposure of the bone of the inferior part of the cavernous sinus and the middle cranial fossa, bone resection is continued laterally from the lateral border of the parasellar ICA until the level of the pterygoid apex. The vidian nerve (the sphenopalatine nerve) exits from the vidian canal, which is located in the pterygoid base, inferior to the ICA segment between the vertical paraclival segment and the horizontal petrous segment (lacerum segment). Thus, the vidian nerve is a good landmark locating the lacerum segment of the ICA at the turning point between the paraclival and petrous portions.

During bone resection to expose the sella, the clivus, the anterior skull base, and the pterygoid apex, the bone was found lytic and fragile. Underneath, a mass of soft grayish tissue with cystic areas filled with serous fluid was seen. During mass resection, the dura of the anterior skull base (planum ethmoidale), the planum sphenoidale, the sella, the inferior part of both cavernous sinuses, and the middle and lower clivus were exposed (Fig. 3). During the resection, an arterial bleeding was seen medial to the left parasellar carotid artery, at the level of the posterior carotid bend and lateral to the sella. This bleeding was controlled by coagulation. The extent of the resection was from the lower clivus inferiorly to the anterior ethmoidal cells superiorly and the both lateral recesses of the sphenoid sinus, the pterygoid apexes, and the paraclival carotid arteries laterally.

Postoperative Course

The patient was extubated, and immediate neurologic examination revealed new deficits. The first postoperative day brain MRI showed total resection of the mass (Fig. 4). Histopathologic examination revealed loose fibrovascular tissue lined by benign respiratory epithelium and containing aggregates of multinucleated giant cells engulfing fungal branching hyphae positive for periodic acid-Schiff (PAS) and surrounded by rich eosinophils infiltration. The same fungi were arranged in the perivascular array and diagnosed as mucormycosis (Fig. 5). Accordingly, 0.7 mg/kg per day of intravenously injected amphotericin B was started. In the third postoperative day, the bilateral abducens nerve palsy started to regress and the patient started to move the eyes to both sides. In the fifth postoperative day, the patient complained of right-sided weakness, and examination revealed hemiparesis with motor power of 3 of 5, which became total hemiplegia in the sixth postoperative day. Brain MRI showed ischemia in the left anterior internal capsule, the head of caudate nucleus, the anterior perforating area, and frontal subcortical areas. Brain MRA showed severe vasospasm in the left internal carotid (Fig. 6). Triple H (hypertension, hypervolemia, and hemodilution) therapy and 0.6 mL of low-molecular-weight heparin 1 dose daily were started. This therapy was continued for 10 days in which the patient showed motor improvement. The patient was

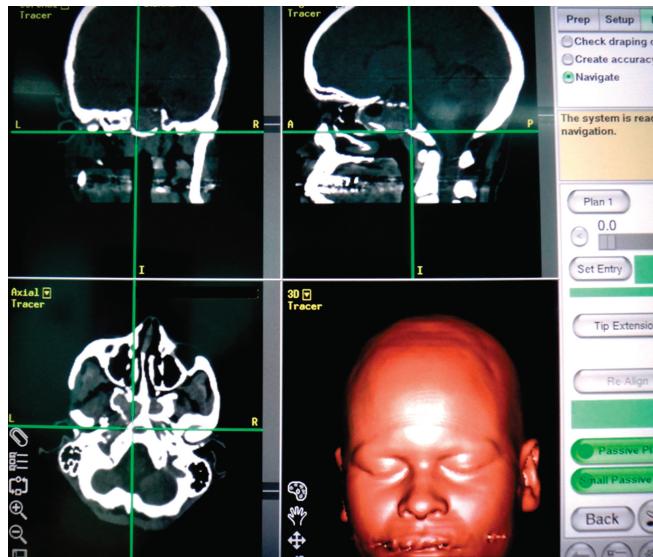


FIGURE 2. Application of intraoperative neuronavigation. Planning of the approach is demonstrated through the endonasal route toward the skull base mass.

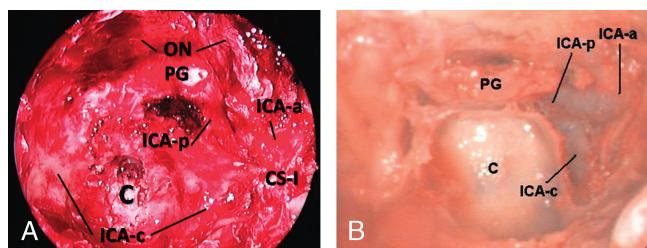


FIGURE 3. A, Intraoperative view showing the dura and related underlying structures after mass resection. B, An endoscopic endonasal cadaver dissection to the same area compared with the endoscopic view in A. C indicates clivus; CS-I, inferior wall of cavernous sinus; ICA-a, anterior bend of ICA; ICA-C, paraclival part of ICA; ICA-p, posterior bend of ICA; ON, optic nerve; PG, pituitary gland. Adapted from Abuzayed et al.¹¹

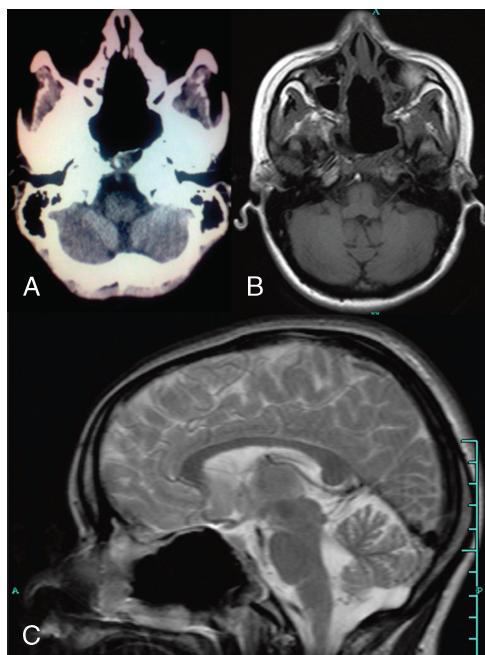


FIGURE 4. Postoperative neuroimaging demonstrating the total resection of the skull base mass. A, Brain CT scan; B, axial postcontrast enhancing brain MRI; C, sagittal T2-weighted brain MRI.

discharged with final motor power of 4 of 5, resolved abducens nerve palsy, and improved left eye ptosis.

DISCUSSION

Mucormycosis is an invasive fungal infection first described by Paulltauf in 1885.¹⁵ The causative agents of mucormycosis are the filamentous fungi of the Mucoraceae family of the order Mucorales, subphylum Mucormycotina, which are also found in normal human nasal flora.¹⁶ The most frequently isolated species is *Rhizopus oryzae* followed by *Rhizopus microsporus* and *Absidia corymbifera*.¹⁷ Infections by members of the order Mucorales are primarily opportunistic infections and represent the third leading cause of invasive fungal infections after *Aspergillus* and *Candida* species.¹⁸ The disease may present with various manifestations, but there is a predilection for the paranasal sinuses.¹⁸ Rhinocerebral mucormycosis is also referred to as rhino-orbito-cerebral mucormycosis in the respective literature to denote involvement of the orbital structures. Extension of the disease to the orbit and the brain is a grave concern and is often seen in

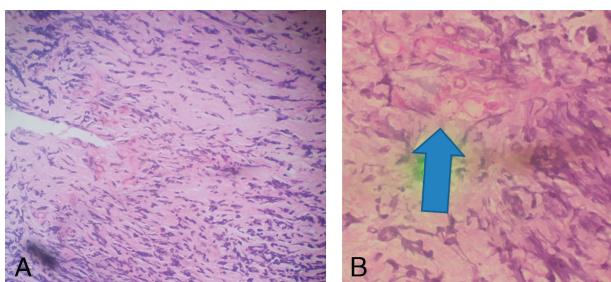


FIGURE 5. A, A photomicrograph showing PAS-positive fungal branching hyphae and surrounded by rich eosinophil infiltration. B, A photomicrograph showing the PAS-positive fungal hyphae arranged around and invading the perivascular area (arrow).

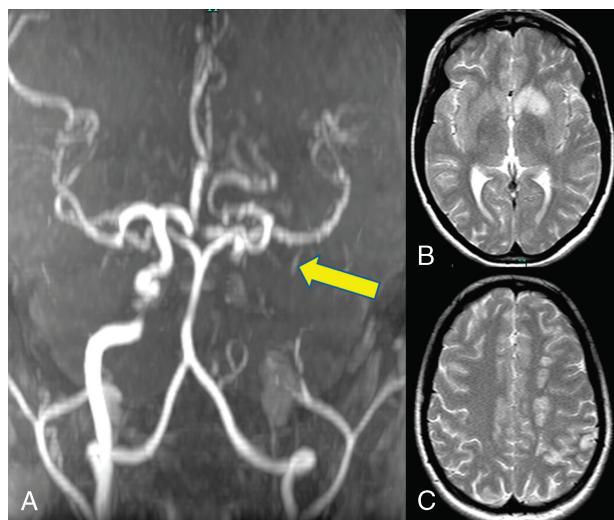


FIGURE 6. Neuroimaging at postoperative day 6 after development of the right hemiplegia, demonstrating left ICA vasospasm in the brain MRA (arrow), and the ischemic areas in the left anterior internal capsule, the head of caudate nucleus, the anterior perforating area, and frontal subcortical areas in axial T2-weighted brain MRI (B, C).

patients with immunosuppression.¹⁹ However, in our case, the patient had no significant medical history or history of possible exposure. All tests of our patient showed immunocompromised status.

The locoregional spread pathway of rhinocerebral mucormycosis has not been adequately described. Hosseini and Borghei²⁰ regarded the pterygopalatine fossa as a reservoir of the disease through which it can spread to neighboring structures including the retroglobal space of the orbit and the infratemporal fossa. On the contrary, angioinvasion by the fungi has been studied to a greater extent and is considered central to its ability to cause tissue necrosis and dissemination.^{21,22} In addition, invasive mucormycosis of the paranasal sinuses has an affinity for blood vessel walls and may cause cavernous sinus and ICA thrombosis, which were not evident in either of our cases; surrounding soft tissue infarction may also occur.²²

The common presenting symptoms and signs are headache, fever, acute sinusitis, decreased vision, unilateral periorbital or facial swelling, facial pain, alterations in mental state, and necrotic ulcer in the nasal or the oral mucosa.²³ Although rare, orbital apex syndrome, which presents with ptosis, proptosis, sensorial deficit, and visual loss, may be the initial manifestation of the disease.²⁴ In our case, our patient's first presentation was left eye ptosis and bilateral abducens nerve palsy, correlating with invasiveness of the disease.

Histopathologic examination of surgical specimens can confirm the clinical diagnosis with the appearance of right-branching aseptate hyphae, which are considered typical of Mucor species, along with evidence of angioinvasion and tissue necrosis.²⁵ Fungal cultures can provide further confirmation. However, a large number of false-negative results have been reported compared with direct histopathologic examination.²⁶ Speciation and susceptibility tests can also be ordered, although this information is more of scientific and epidemiologic interest with no clinical implications because the treatment plan is uniform in all cases.²⁷ Other laboratory diagnostic modalities include molecular detection of Zygomycetes, which has been available, but the results so far have been less than promising.²⁸ Cerebrospinal fluid analysis has also been reported as helpful in the diagnosis in few reports.²⁹ However, isolation of the fungi from blood cultures and cerebrospinal fluid should not be considered normal.²¹

Surgical intervention has been associated in large series with favorable outcome.^{30,31} However, no formal guidelines have been

formulated as to the timing and extent of appropriate surgical management.³² Reed et al³³ advocate an “aggressive-conservative” approach with frozen section-guided surgical exploration, sparing unininvolved orbital structures, whereas Nithyanandam et al³⁰ support a more aggressive approach with early excision of infected structures. Although orbital exenteration has been reported as helpful even in the context of intracranial spread, the topic of orbital exenteration has not been adequately studied, thereby necessitating individualization of surgical intervention.^{27,33} Irrigation of the surgical site with amphotericin B solution has also been proposed based on the vaso-occlusive nature of the infection, which leads to reduced delivery of antibiotics to infected areas.³⁴

The midline skull base is an anatomic area that covers the upper nasal and oral cavities, and it extends from the crista galli to the lower clivus.³⁵ This region is a site for a variety of pathologies, which are considered surgically challenging because of its critical location and neighboring neurovascular structures. Many transfacial and transcranial approaches were proposed,^{36–39} which are considered aggressive because of large incisions and flaps; facial skeleton disturbance; cosmetic problems; wide neurovascular manipulation and retraction; and patients’ difficulty in tolerating the surgery because of bad general condition, especially for those with oncologic pathologies. Surgeons started to seek more minimally invasive techniques to avoid these difficulties. Endoscopic visualization from “below” has offered the surgeons the possibility to reach the midline anterior skull base without skin incision and brain retraction and with minimal neurovascular manipulation.^{9–14}

As neurosurgeons, we found the posterior-anterior approach to be more suitable in performing ethmoidectomy and exposing the anterior skull base. The reason is that early identification of the sphenoid sinus and the sellar and parasellar regions, which are well known to neurosurgeons, can be achieved using this approach.⁹ Thus, early opening of the anterior wall of the sphenoid sinus and exposure of the sphenoid sinus roof with its anatomic landmarks, which the neurosurgeon is more familiar with, can help us to conserve orientation of the dissection direction toward the ethmoid sinus, with more controlled orientation to the critical neighboring neurovascular structures, with less risk for their injury. On the other hand, the anterior-posterior approach needs specific knowledge of the anatomy of the ethmoidal cells and in-depth experience in endoscopic sinus surgery, with good orientation while “moving” inside the ethmoidal cells, which the otorhinolaryngologists are most familiar with. The anterior skull base is exposed from the 2 medial orbital walls and optic nerves bilaterally, the sella posteriorly, and the frontal recesses anteriorly, which can provide us with good and wide access to many pathologies of this region. Early identification of anterior and posterior ethmoidal arteries is very important to avoid the risk for their injury and early devascularization of some tumors in this region.^{9,12,13}

The sellar floor is resected laterally toward the carotid protuberance to expose the parasellar portion of the ICA. This resection is continued laterally until the lateral border of the ICA, thus exposing the inferior part of the cavernous sinus. Both the anterior and posterior bends of the parasellar portion of the ICA are widely exposed.^{8,10} To expose the inferior portion of the cavernous sinus, the superior and middle turbinates and the posterior ethmoidal cells are removed (extended endoscopic endonasal transsphenoidal approach). The anatomic landmarks in the roof of the sphenoid sinus are valuable to determine the anatomic location of the cavernous sinus. The ICA, with its parasellar and paraclival parts, is delineated by the carotid protuberance, with the sellar fossa located medially. In addition, when the lateral septae of the sphenoid sinus exist, these are generally attached to the carotid protuberance and point to the location of the ICA.¹⁰ These important landmarks can help locate the intercavernous ICA and the cavernous sinus before bone resection and opening of the dura, which

offers a safer approach.¹⁰ Including the sellar fossa in the bone resection is preferred because wide exposure of the related structures avoids blind manipulation and creates a space for ICA retraction when needed. After exposure of the bone of the inferior part of the cavernous sinus and the middle cranial fossa, bone resection is continued laterally from the lateral border of the parasellar ICA until the level of the pterygoid apex. The vidian nerve (the sphenopalatine nerve) exits from the vidian canal, which is located in the pterygoid base, inferior to the ICA segment between the vertical paraclival segment and the horizontal petrous segment (lacerum segment).^{10,40} Thus, the vidian nerve is a good landmark locating the lacerum segment of the ICA at the turning point between the paraclival and petrous portions.^{10,40} When the opening of the vidian canal is required to expose the vidian nerve and/or approaching pathologies in the pterygopalatine fossa, drilling of the canal is recommended to be started from the inferior and the medial aspect of the canal because the ICA is located along the superior margin.^{10,40} This will decrease the risk for intraoperative injury of the ICA during drilling of the vidian canal. After identifying the vidian nerve, a triangular area lateral to the ICA can be identified. The base of this triangle is formed by the vidian nerve inferiorly with the apex pointing superiorly. The lateral arm of the triangle is formed by the medial pterygoid process, and the medial arm is formed by the parasellar ICA.

The endoscopic endonasal route offers a direct access to the clivus, compared with microscopic anterior approaches, with the lateral limit of the surgical corridor being the vidian nerve superiorly and the paraclival portion of the ICA inferiorly.¹¹ Thus, surgically challenging intradural and/or extradural lesions located anteriorly to the brain stem and the foramen magnum can be treated with this approach. In addition, because of the lateral exposure offered by angled lenses, this approach can offer resection of the lateral parts of the tumors without the need for lateral facial osteotomies. Another advantage of this approach is the lack of the need for soft palate splitting in contrast to transoral approaches, thus avoiding postoperative wound healing problems and facilitating early oral intake.

Inadvertent ICA injury occurs in 3% to 5% of skull base procedures, with an additional 1.9% of patients having carotid artery vasospasm.⁴¹ The timing of vasospasm after tumor resection is similar to that observed after aneurysmal subarachnoid hemorrhage and is optimally managed using similar interventions, including hyperdynamic therapy and/or endovascular injection of vasodilating agents. In our case, vasospasm developed in postoperative day 5. Although there was a possibility of vasculitis as a known complication of invasive mucormycosis,²³ the timing of the vascular occlusion and the good response to the vasospasm standard triple H therapy (hypertension, hypervolemia, and hemodilution) favored the diagnosis of vasospasm. A possible explanation of this complication is that it resulted because of the coagulation and thermal injury to the walls of the ICA or irritation of the ICA nerve plexus because it corresponds well to the side and the site of coagulation in the left parasellar carotid artery, at the level of the posterior bend and lateral to the sella.

Medical treatment of cerebrorhinal mucormycosis includes amphotericin B deoxycholate, which remains the only licensed antifungal agent for mucormycosis. However, lipid formulations of amphotericin B are considered a safe and efficient alternative.³² Liposomal amphotericin B in particular has been proven superior to amphotericin B deoxycholate, whereas amphotericin B lipid complex has been reported to be effective as part of a combination treatment with caspofungin.³³ Recommended starting doses for the lipid formulation of amphotericin are 5 to 7.5 mg/kg per day, with higher dosages (up to 10 mg/kg per day) recommended for central nervous system involvement.³² Iron chelation therapy and posaconazole should be considered in cases of refractory infection or polyene intolerance.³² Regarding the duration of treatment, Spellberg et al³² specify the

resolution of immunosuppression, radiographic signs, and clinical symptoms as the objectives of treatment. Deferasirox and deferiprone are new iron chelators, which, in contrast to deferoxamine, cannot be used by the fungi as siderophores.²³

Despite the advances in diagnosis and treatment, invasive rhino-orbito-cerebral infection is still the most lethal clinical form of the disease.²⁻⁴ The mortality rate is reported to be as high as 20% even if the diagnosis and aggressive treatment are not delayed.⁵ Besides prompt diagnosis and aggressive treatment, the extent of the infection and the prognosis of the underlying disease affect the survival, and this may explain why the mortality rates have been indicated up to 40% to 50% in the literature.^{4,5}

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