CASE REPORT

Lethargy and vision loss: successful management of rhinocerebral mucormycosis

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SUMMARY

Rhinocerebral mucormycosis (RCM) is an angioinvasive fungal infection most often caused by *Rhizopus oryzae*. It is usually associated with an underlying risk factor and is associated with a poor prognosis. There are no consensus guidelines on the optimal management of this aggressive disease; most management decisions are based on case reports and expert opinion. We report a successfully managed case of RCM in an insulin-dependent diabetic, initially presenting with a change in mental status, rapidly progressing to complete right eye blindness and ophthalmoplegia and complicated by multiple cerebral infarctions and abscesses. We describe the diagnostic approach and various therapeutic interventions undertaken to successfully manage our patient.

BACKGROUND

Mucormycosis refers to fungal infections caused by members of the Zygomycetes in the order of Mucorales,¹ of which *Rhizopus oryzae* is the most common human pathogen. Zygomycetes—aseptate hyaline moulds that reproduce by sexual and asexual means—are ubiquitous in the environment. There are several forms of disease. Rhinocerebral mucormycosis (RCM) is the most common clinical presentation, and diabetes mellitus (DM) is the most common risk factor. Other risk factors include immunosuppression, HIV, intravenous (IV) drug abuse, haematological malignancies and iron overload. The major host immune defences against mucormycosis are phagocytic mononuclear and polymorphonuclear cells. Patients with diabetic ketoacidosis (DKA) are particularly at high risk, as the phagocytes of affected individuals have defective intracellular killing mechanisms and impaired chemotaxis.^{2–3} Moreover, the acidosis accompanying patients with DKA helps to liberate iron from the body's stores making it readily available for the fungus, which is essential for the growth and development of mucorales.¹ Rapid progression of invasive mucormycosis results from its predilection for angioinvasion, which leads to thrombosis and subsequent tissue necrosis.⁴ The diagnosis is confirmed by observing the fungal elements in direct smears and histological sections. Management includes controlling the underlying predisposing factors, prompt administration of systemic antifungal agents and repeated aggressive surgical debridement.

CASE PRESENTATION

A 22-year-old woman with a medical history of insulin-dependent DM presented to the emergency

department with a 2-day history of a progressive change in mental status noted by her family members. This was associated with multiple episodes of epistaxis and a non-specific headache; further review of systems was difficult to elicit due to the patient's mental status. She has a known history of insulin non-compliance, with multiple prior admissions for DKA. Her social history is significant for active inhaled heroin abuse. Pertinent physical examination findings revealed that she was ill-appearing, lethargic and with tachypnoea and tachycardia. Her cardiopulmonary examination was otherwise normal. Her abdominal examination revealed normoactive bowel sounds and diffuse tenderness without guarding or rebound. Examination of the head and neck revealed dry mucous membranes and dry necrotic-appearing right nasal turbinates. Examination of the right eye and orbit revealed proptosis and ptosis (figure 1), ophthalmoplegia in all directions, non-reactive mydriasis (figure 2) and complete loss of vision. Fundoscopic examination of the right eye revealed a cherry red spot. Examinations of the left eye and the remainder of the neurological system were normal.

INVESTIGATIONS

Laboratory investigations revealed leucocytosis ($18.6 \times 10^3/\mu\text{L}$) with neutrophil predominance, hypokalaemia (3.2 mmol/L), hyperglycaemia (548 mg/dL) and anion gapped metabolic acidosis. Her urine analysis and drug screen revealed the presence of significant ketonuria and opiates. Initial CT without an intravenous contrast of the brain was performed to rule out an acute intracranial abnormality. This revealed mucosal thickening in the ethmoid sinus without bony destruction, along with opacification of the right-sided nasal cavity, without evidence of intracranial involvement.

Figure 1 Examination of the right eye showing evidence of proptosis and ptosis with evidence of cellulitis involving the upper and lower eyelids.

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Figure 2 Examination of the right pupil showing evidence of mydriasis.

DIFFERENTIAL DIAGNOSIS

Given the data available, the major differential diagnosis included DKA precipitated by an infectious process. The focus of our attention was to identify the source of infection causing the various clinical findings mentioned above. These included bacterial sinusitis, orbital cellulitis, dental abscess, RCM and aspergillosis. Other differentials that were entertained included cavernous sinus thrombosis and an orbital tumour. Therefore, a CT venogram (CTV) and a CT angiogram (CTA) were performed. The CTV was normal. The CTA revealed an abrupt cut-off of the mid-portion of the right ophthalmic artery (figure 3).

TREATMENT

The patient was admitted to the intensive care unit (ICU), and her DKA was managed according to the protocol with intravenous fluid infusions, an insulin drip, and careful replacement and monitoring of electrolytes. Blood cultures were drawn, and the patient was started on infusions of broad-spectrum antibacterial and antifungal agents, including vancomycin, cefepime,

Figure 3 CT angiography of the brain showing a total occlusion of the middle portion of the right ophthalmic artery.

metronidazole, micafungin and liposomal amphotericin B (LAmB). When the patient was taken to the operating room for endoscopic debridement of the necrotic mucosa of the right nasal cavity, fungal mycelia (figure 4A, B) debrided and biopsy specimens were taken for histological evaluation.

OUTCOME AND FOLLOW-UP

Focused assessments of the oral and nasal cavities were performed two times per day. The biopsy specimens obtained from the necrotic nasal mucosa revealed thick-walled, aseptate, hyphae 6–15 µm in diameter, confirming the diagnosis of invasive mucormycosis (figure 5). Her antibacterial agents were discontinued, and she continued to receive LAmB and micafungin, along with daily intranasal irrigations with amphotericin. Nevertheless, she developed left-sided hemiparesis. MRI demonstrated multiple acute infarctions without loss of sinus wall integrity (figure 6A, B). After three surgical debridements and daily intranasal amphotericin irrigation over 5 days, progressive intracranial involvement prompted complete orbital exenteration. On the 13th postoperative day, the patient's mental status again declined. MRI of the brain now demonstrated intracerebral abscesses resulting in obliteration of the fourth ventricle causing an obstructive hydrocephalus (figure 7). A ventriculostomy was placed, and incision and drainage of the abscess was completed. On subsequent neurological examination, the patient was stabilised, and radiographic progression of the disease halted. Ultimately, she was transferred to an acute inpatient rehabilitation facility on a prolonged course of dual antifungal therapy pending radiographic improvement. After 7 months on LAmB and micafungin, she continues to

Figure 4 (A) Endoscopic examination of the right nasal cavity prior to surgical debridement revealing mycelia and necrotic mucosa. (B) Endoscopic examination following surgical debridement of the nasal mucosa.

Figure 5 Gram stain of the tissue obtained during surgical debridement revealing thick, aseptate fungal hyphae branching at obtuse angles.

demonstrate slow neurological improvement, and radiographic resolution has begun.

DISCUSSION

Mucormycosis is a fungal infection caused by saprophytic fungi living on decomposing matter. The aetiological agent belongs to the family Mucoraceae of the class Zygomycete. The four most common genera associated with the disease in humans are *Rhizopus*, *Absidia*, *Cunninghamella* and *Mucor*. The most common pathogenic species is *Rhizopus oryzae* followed by *R. microsporus* and *Absidia corymbifera*.⁵ *Rhizopus* species alone account for 90% of RCM.⁶

Mucormycosis is a rare infection; therefore, its incidence is difficult to establish. A review of mucormycosis cases at one US cancer centre found that 0.7% of patients had mucormycosis at autopsy and calculated that 20 patients per 100 000 admissions had invasive disease.⁷ The 1-year cumulative incidence of mucormycosis has been estimated at ~4 cases per 1000 stem cell transplantations and 0.6 cases per 1000 solid organ

Figure 6 (A) MRI of the brain showing T2 abnormalities involving the right anterior medial temporal lobe, lower midbrain, lateral pons, middle cerebellar peduncle and scattered in the right cerebellar hemisphere. (B) Corresponding diffusion weighted imaging (DWI) signal abnormalities in the specified regions consistent with acute infarcts.

Figure 7 Contrast-enhanced MRI of the brain showing large rim-enhancing collections with regions of internal restricted diffusion, consistent with parenchymal abscesses in the right anterior medial temporal lobe and the right cerebellum extending to the brainstem.

transplantations, accounting for 7% and 2% of all fungal infections in these populations, respectively.⁸

When these fungi are introduced into the nares of patients with predisposing factors for invasive disease, they induce a fulminant infection.⁹ The most important of these predisposing factors are haematological malignancies, organ transplantation, poorly controlled DM, profound neutropenia, burn injuries and iron overload states. Uncontrolled DM, especially with DKA (as in our patient), increases the risk of invasive mucormycosis because acidosis, which inhibits the ability of iron to bind with the transferrin carrier protein, increases the amount of free iron available for scavenging by the fungus. Moreover, acidosis decreases neutrophil chemotaxis and phagocytosis, both of which are essential elements in the host defence against this pathogen.⁹

The classic initial sign of RCM is necrotic mucosa, classically as a dark patch, seen on the palate in a critically ill patient. This lesion results from angioinvasive hyphae that propagate after fungal spores have germinated in the nasal mucosa, resulting in a 'dry' gangrene appearance. Left unchecked, direct tissue invasion through the lamina papyracea of the ethmoid sinus, the roof of the maxillary sinus or the vascular branches supplying the orbit¹⁰ results in the clinical presentation of proptosis, unilateral painful ophthalmoplegia and rapidly deteriorating vision, as was seen with our patient.¹¹ When angioinvasion results in cavernous sinus thrombosis and/or internal carotid artery encasement, cerebral infarctions, mycotic abscesses and aneurysms, and haematogenous dissemination follow.¹² Tissue necrosis and thrombosis of blood vessels,⁴ such as the ophthalmic artery in our case, may occur rapidly even early in the course of disease. Blindness, cranial nerve palsies, and other motor and sensory deficits are major sequelae of the disease.

The morbidity and mortality rate of mucormycosis is high; the timeline from infection to death occurs in ~2 weeks due to

the rapidly progressive nature of this infection and limitations in the delivery of antifungal agents resulting from vaso-occlusive disease. Our patient developed multiple brain abscesses—a condition with mortality rates >80%—as an extension of her RCM.¹³ Early detection and aggressive therapy is imperative in the management of these cases. A high degree of clinical suspicion based on the presence of risk factors and compatible clinical findings should prompt the diagnostic work-up and initiation of empirical therapy. Histopathological examination of biopsy specimens confirms the clinical diagnosis with the presence of angioinvasive aseptate hyphae with right-angle branching, which are considered typical of mucor species, and tissue necrosis.¹⁴ In case reports, fine-needle aspiration (FNA) of paranasal masses may yield the diagnosis of mucormycosis; however, therapy should not be withheld pending results.¹⁵ Although cerebrospinal fluid (CSF) usually shows normal findings, an elevated opening pressure, modest neutrophilic pleocytosis, normal or slightly elevated protein levels and low glucose levels are suggestive of the diagnosis in a compatible clinical setting.¹⁶ After identifying fungal hyphae with India ink staining of CSF specimens, speciation can be determined by PCR assay 16s ribosomal RNA (rRNA) gene sequence analysis.¹⁶

Imaging modalities, such as CT and MRI, play an important role in assessing the degree of invasion. CT scans may reveal bone destruction, soft tissue inflammation, and air-fluid levels in the paranasal sinuses and orbit. Intracranial abscess appears on CT as a hypodense or ring-enhancing lesion that can be misdiagnosed as infarction or neoplasm. CT or MR angiogram (MRA) can reveal occlusion of major arteries of the head and neck. Typical MRI characteristics of sinonasal mucormycosis include a rim of soft tissue thickening along the paranasal sinuses with sinus opacification, air-fluid levels and obliteration of the nasopharyngeal tissue planes. Moreover, RCM is suggested by contiguous foci of non-enhancing nasal tissue, referred to as the 'black turbinate sign', when contrast is used. It is due to the angioinvasion of vasculature supplying the sinus mucosa.¹⁷

The treatment of RCM requires a multipronged approach, implemented simultaneously and empirically. First, efforts to control predisposing conditions should be aggressively pursued, including the correction of hyperglycaemic and acidotic states, reducing iron overload and reversing immunosuppression (if able). Similarly, aggressive early surgical debridement of the involved tissue is essential to reduce organism burden more quickly than chemotherapeutic agents would allow. In the case of intracranial abscess formation, lesions <2.5 cm can be aspirated or drained followed by 3 weeks of parenteral antibiotic therapy. Lesions >2.5 cm require 6–8 weeks of parenteral antibiotic therapy with complete excision.¹⁸

Though slower to curb the spread of infection than surgical debridement, early administration of active parenteral antifungal agents, even prior to confirmation of the diagnosis, increases the amount of chemotherapeutic agent delivered to affected tissues prior to extensive vaso-occlusion. The initiation of antifungal therapy within 5 days of presentation is associated with improved survival compared with the therapy initiated after 6 or more days.¹⁹ The polyene antifungals amphotericin B deoxycholate and its liposomal formulations are first-line agents for the treatment of RCM. Although no head-to-head trials comparing LAmB to conventional formulations have been performed, experts favour the use of LAmB. The rationale for this preference is that LAmB demonstrates greater penetration into the blood–brain barrier and sinuses may be safely administered over a longer period of time and is less nephrotoxic.^{20–23}

Newer reports of in vivo and in vitro studies indicate that combination therapy with a polyene backbone therapy may be beneficial. Options available for combination therapy include echinocandins, deferasirox, posaconazole and isavuconazole in addition to the polyene backbone. Combination therapy with LAmB and micafungin or anidulafungin demonstrated a survival benefit in neutropenic and DKA mice with disseminated mucormycosis.^{23 24} Several mechanisms have been proposed to explain the mechanism of improved efficacy with the addition of an echinocandin. First, it disrupts the β -glucan cross-linking of the cell wall improving the delivery of the polyene to the cell membrane. Second, it alters the virulence of the fungus, and finally, there is an enhanced host response.²¹

In addition, there are a number of adjunctive therapies that may be of benefit. Amphotericin nasal irrigation has been proposed as a potential treatment strategy to improve drug delivery to infected and ischaemic tissues.²⁵ If done early in the course of infection, this drug delivery method may prevent the need for disfiguring surgical procedures. In one small case series, only one of the seven patients treated with standard therapy plus topical amphotericin required orbital exenteration.²⁶ Owing to the low incidence of this infection, a paucity of data prohibits the determination of whether nasal irrigations impact morbidity and mortality. In addition to fungicides, the iron-chelating agent deferasirox has been used to decrease the availability of host iron for fungal growth,²⁷ with animal models demonstrating a survival benefit when used in combination with LAmB.²⁸ Adjunctive therapy with gamma interferon, G-CSF and GM-CSF may be considered for refractory invasive mucormycosis, though data are limited.^{29 30} Hyperbaric oxygen may also be beneficial as it limits fungal tissue invasion by reducing hypoxia and acidosis in ischaemic tissues that result from angioinvasive disease.³¹ However, limited studies are available to prove its efficacy and mortality benefit.

In summary, RCM is a devastating disease with a significant mortality and morbidity among survivors. Our case required an extensive multidisciplinary approach where multiple healthcare providers from different specialties, in addition to ancillary staff, were involved in the care of our patient. A high level of suspicion in a predisposed patient, along with early initiation of anti-fungal and surgical therapy while controlling the underlying predisposing factor was key in successfully managing our patient. Teamwork and communication among different providers allowed for prompt and early management. Moreover, the rarity of this disease makes it difficult for randomised controlled trials to be performed to establish the optimum management modalities. Most reports are based on animal models and case reports.

Learning points

- Rhinocerebral mucormycosis (RCM) is the most common presentation of mucormycosis, and should be suspected in patients with predisposing factors such as immunosuppression, haematological malignancies and uncontrolled diabetes mellitus.
- Correcting underlying predisposing factors along with prompt early combined medical and surgical therapy is associated with improved outcomes.
- Dual antifungal therapy may improve outcomes in patients with RCM.

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REFERENCES

- 1 Howard DH. Acquisition, transport, and storage of iron by pathogenic fungi. *Clin Microbiol Rev* 1999;12:394–404.
- 2 Ibrahim AS, Spellberg B, Walsh TJ, et al. Pathogenesis of mucormycosis. *Clin Infect Dis* 2012;54(Suppl 1):S16–22.
- 3 Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. *Clin Microbiol Rev* 2005;18:556–69.
- 4 Chamilos G, Luna M, Lewis RE, et al. Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989–2003). *Haematologica* 2006;91:986–9.
- 5 Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis* 2005;41:634–53.
- 6 Bakathir AA. Mucormycosis of the jaw after dental extractions: two case reports. *Sultan Qaboos Univ Med J* 2006;6:77–82.
- 7 Kontoyiannis DP, Wessel VC, Bodey GP, et al. Zygomycosis in the 1990s in a tertiary-care cancer center. *Clin Infect Dis* 2000;30:851–6.
- 8 Kontoyiannis DP, Marr KA, Park BJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. *Clin Infect Dis* 2010;50:1091–100.
- 9 Vaidyanathan V, Shetty K. Rhinocerebral mucormycosis: a series of 3 cases. *Ann Trop Med Public Health* 2012;5:591.
- 10 McLean FM, Ginsberg LE, Stanton CA. Perineural spread of rhinocerebral mucormycosis. *AJNR Am J Neuroradiol* 1996;17:114–6.
- 11 Thajeb P, Thajeb T, Dai D. Fatal strokes in patients with rhino-orbito-cerebral mucormycosis and associated vasculopathy. *Scand J Infect Dis* 2004;36:643–8.
- 12 Sehgal A, Raghavendran M, Kumar D, et al. Rhinocerebral mucormycosis causing basilar artery aneurysm with concomitant fungal colonic perforation in renal allograft recipient: a case report. *Transplantation* 2004;78:949–50.
- 13 Choir H, Lew J, Jackson I. Rhinocerebral mucormycosis combined with brain abscess. *Eur J Plast Surg* 1992;15:146–50.
- 14 Lass-Flörl C. Zygomycosis: conventional laboratory diagnosis. *Clin Microbiol Infect* 2009;15(Suppl 5):60–5.
- 15 Deshpande AH, Munshi MM. Rhinocerebral mucormycosis diagnosis by aspiration cytology. *Diagn Cytopathol* 2000;23:97–100.
- 16 Bengel D, Susa M, Schreiber H, et al. Early diagnosis of rhinocerebral mucormycosis by cerebrospinal fluid analysis and determination of 16S rRNA gene sequence. *Eur J Neurol* 2007;14:1067–70.
- 17 Safder S, Carpenter JS, Roberts TD, et al. The 'Black Turbinate' sign: an early MR imaging finding of nasal mucormycosis. *AJNR Am J Neuroradiol* 2010;31:771–4.
- 18 Mathisen GE, Johnson JP. Brain abscess. *Clin Infect Dis* 1997;25:763–79, quiz 780–1.
- 19 Skiada A, Lanternier F, Groll AH, et al. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). *Haematologica* 2013;98:492–504.
- 20 Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *N Engl J Med* 1999;340:764–71.
- 21 Reed C, Bryant R, Ibrahim AS, et al. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. *Clin Infect Dis* 2008;47:364–71.
- 22 Gleissner B, Schilling A, Anagnostopoulos I, et al. Improved outcome of zygomycosis in patients with hematological diseases? *Leuk Lymphoma* 2004;45:1351–60.
- 23 Spellberg B, Ibrahim A, Roilides E, et al. Combination therapy for mucormycosis: why, what, and how? *Clin Infect Dis* 2012;54(Suppl 1):S73–8.
- 24 Ibrahim AS, Gebremariam T, Fu Y, et al. Combination echinocandin-polyene treatment of murine mucormycosis. *Antimicrob Agents Chemother* 2008;52:1556–8.
- 25 Yohai RA, Bullock JD, Aziz AA, et al. Survival factors in rhino-orbital-cerebral mucormycosis. *Surv Ophthalmol* 1994;39:3–22.

- 26 Seiff SR, Choo PH, Carter SR. Role of local amphotericin B therapy for sino-orbital fungal infections. *Ophthal Plast Reconstr Surg* 1999;15:28–31.
- 27 Soman R, Gupta N, Shetty A, *et al.* Deferasirox in mucormycosis: hopefully, not defeated. *J Antimicrob Chemother* 2012;67:783–4.
- 28 Ibrahim AS, Gebermariam T, Fu Y, *et al.* The iron chelator deferasirox protects mice from mucormycosis through iron starvation. *J Clin Invest* 2007;117:2649–57.
- 29 Abzug MJ, Walsh TJ. Interferon- γ and colony-stimulating factors as adjuvant therapy for refractory fungal infections in children. *Pediatr Infect Dis J* 2004;23:769–73.
- 30 Roilides E, Farmaki E. Granulocyte colony-stimulating factor and other cytokines in antifungal therapy. *Clin Microbiol Infect* 2001;7:62–7.
- 31 John BV, Chamilos G, Kontoyiannis DP. Hyperbaric oxygen as an adjunctive treatment for zygomycosis. *Clin Microbiol Infect* 2005;11:515–17.

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