MAN WITH SWOLLEN EYE, BLURRED VISION, AND FEVERS IN THE SETTING OF NEWLY DIAGNOSED MDS

Rory Bowers, MD

Case Presentation

An 82 year-old male with a past medical history of prostate cancer, atrial fibrillation, gout, and recently diagnosed myelodysplastic syndrome presented with a chief complaint of left eye pain. The patient also reported peri-orbital numbness, swelling, and clear discharge as well as episodic blurry vision of his left eye. Over the previous two months he had been admitted to the hospital multiple times complaining of cough and high fevers and was subsequently treated with several courses of antibiotics for presumed pneumonia. During the initial admission for pneumonia he was noted to have a relative pancytopenia. A bone marrow biopsy was eventually undertaken revealing a diagnosis of myelodysplastic syndrome (MDS).

Prior to the current presentation, his facial numbness, erythema, and peri-orbital swelling had persisted over the period of three weeks. He was seen in an outpatient clinic, diagnosed with a periorbital cellulitis, and treated with a course of oral clindamycin, levofloxacin, and erythromycin eye drops. During his last outpatient follow up he was told to go directly to the emergency room secondary to the worsening appearance of his left eye. On current presentation he denied any fevers, chills, or sweats. He denied traumatic injury to his eye. He also denied headaches or other neurological complaints but occasionally experienced blurred vision in his left eye, which usually resolved spontaneously. He had significant pain around his left eye, which was worse with eye movements. He denied photophobia and noted that his symptoms had not improved over the past three weeks. In addition, he had continuous feelings of numbness across his left face. He denied sore throat, chest pain, recent weight loss, myalgias, or arthralgias. His cough had persisted since his diagnosis of pneumonia and was non-productive in nature.

His current medications were aspirin, erythromycin eye drops, levofloxacin, furosemide, digoxin, potassium chloride, metoprolol, clindamycin, and percocet. He had an allergy to penicillin, which had caused a rash in the past. He denied alcohol, tobacco, or substance abuse. A family history was notable for coronary artery disease and asthma.

On physical exam his vitals were noted to be the following: temperature 97.6° Fahrenheit, respiratory rate 20 breaths/minute, heart rate 87 beats/minute, blood pressure 160/90 mm Hg, and pulse oximetry of 95% on room air. He was noted to have prominent left periorbital swelling and erythema with a moderate amount of clear discharge. He had mild periorbital tenderness and his left sclera appeared injected. The pupils remained reactive to light and accommodation and his extra-ocular movements were intact. The visual acuity in the left eye was moderately reduced. His cardiac exam revealed only an irregularly irregular rhythm consistent with known atrial

fibrillation. His lungs had mildly decreased breath sounds at the right base but were otherwise clear. His abdomen was benign. He was neurologically intact with the exception of left facial numbness. He had mild lower extremity pitting edema bilaterally.

Laboratory tests revealed a mild pancytopenia: white blood cell count 3.6 B/L, hemoglobin 8.5 g/dL, and platelet count of 140 B/L. A comprehensive metabolic panel was grossly normal aside from a mildly elevated BUN and creatinine (21 U/L and 1.6 mg/dL, respectively). An orbital CT scan was quickly obtained due to the concern for a possible retro-orbital infectious process. The MRI scan revealed findings consistent with orbital cellulitis of the left eye with invasive sinusitis. The patient was emergently taken to the operating room for exploration and debridement of his maxillary, sphenoid, and ethmoid sinuses. Subsequent biopsies and cultures revealed a species of *rhizopus* fungi as the probable etiology of the patient's symptoms. He was diagnosed with invasive mucormycosis involving the left orbit and sinuses.

The patient underwent multiple surgical procedures on his sinuses and left orbit. Intraoperatively, he received irrigation to the affected region with amphotericin B. He also received systemic therapy with amphotericin until he was noted to have worsening renal function. He was subsequently started on oral posaconazole with plans for a prolonged course of treatment. Following improvement in his symptoms he was discharged home with appropriate follow up with ophthalmology and infectious disease.

Discussion

Mucormycosis refers to an infectious condition caused by a variety of spore-forming organisms belonging to the zygomycetes class of fungi. These organisms are ubiquitous in nature, commonly being found in organic substrates such as soil, plant matter, and animal feces. Humans are routinely exposed but due to the intact functioning immune systems of the host, clinical disease is rare. However, in certain susceptible individuals a much more severe form of disease presentation can occur.

An important point in the discussion of mucormycosis is the terminology used to describe zygomycete infections. The class of zygomycetes is broken down into two subclasses: mucorales and entomophthorales. Mucormycosis refers to infections caused by the mucorales subclass of organisms.¹ Within the mucorales subclass are multiple genera including mucor, rhizopus, rhizomucor, and absidia.

Mucormycosis was originally described in 1885 and up until the 1950s was considered an exceedingly rare diagnosis. However, with the sharp increase in certain susceptible populations (e.g.,

diabetics) over the past 50 years the diagnosis has become increasingly more common.²

Mucormycosis has been described in a variety of different presentations with multiple organ systems being affected. Cerebral, pulmonary, renal, gastrointestinal, cutaneous, disseminated, and ophthalmologic forms have all been described. Disease can often spread locally to involve surrounding tissues such as the sinuses in our patient. Infection typically begins with inhalation of zygomycete spores into the nasopharynx during an environmental exposure. In the immunocompetent host, these spores are typically caught by the cilia of the respiratory tract, expectorated, and are of no further significance. However, if intact immune mechanisms are lacking in a host, local infection may begin with the germination of the spores into fungal elements called hyphae. Localized sites of infection can spread aggressively and become angioinvasive resulting in tissue infarction.³ Infection may also spread to distant sites via hematogenous routes. Other potential sites for initial infection occur as a result of breakdown in the skin as seen in intravenous (IV) drug abusers or those with indwelling IV catheters. Most commonly patients possess some underlying risk factor for infection; however, case reports with no identifiable risk factor do exist.⁴

Susceptible hosts usually possess a defect in the function of their mononuclear or polymorphonuclear phagocytes.⁵ Other immunosuppressive conditions can also confer risk. The most prevalent groups of patients who suffer these infections include those with diabetes, hematologic malignancies, neutropenia, acidotic states, solid organ or bone marrow transplants, as well as those who abuse IV drugs and those who are currently on deferoxamine iron chelation therapy.^{2,5,6}

Iron chelation therapy presents an interesting susceptibility to mucormycosis organisms. All microorganisms require iron to survive, and zygomycete organisms are especially sensitive to this requirement. In the past it has been observed that patients who carried a diagnosis of iron overload and were treated with deferoxamine chelation therapy seemed to suffer higher rates of mucormycosis than other populations.¹ In the healthy patient, free available iron is scarce and difficult for organisms to obtain for growth as it is bound tightly with normal host proteins. However, in the patient with excess free iron (e.g., hemochromatosis), zygomycete organisms can exploit elevated levels of available free iron, and this can result in increased incidence of clinical disease. Even more susceptible is the patient being treated with deferoxamine. While this seems paradoxical, it is thought that zygomycete organisms can specifically use deferoxamine as a siderophore to sequester iron for growth thus promoting worsening disease.⁷ This phenomenon is not seen with other iron chelators. A similar susceptibility is found in patients with acidosis. This is believed to be secondary to the inability of proteins to effectively bind iron in acidotic environments.⁸ The

end result of this is additional free iron available to the invading zygomycete organisms.

Perhaps one of the most common examples of a susceptible host is seen in diabetics. The mechanisms of susceptibility are two-fold in these patients. Hyperglycemia is a known risk factor for neutrophil dysfunction and thus presents a risk for mucormycosis.⁹ In addition to this, the prominent acidotic states seen in patients suffering from diabetic ketoacidosis provide an optimal environment for mucormycosis infection.

Patient presentation is often dictated by the site of infection. Rhinocerebral mucormycosis is the most common form, comprising roughly 33% to 50% of all cases.¹⁰ Poorly controlled diabetics represent the major risk factor in this group.^{1,2} Patients often present with symptoms of sinusitis (e.g., headache, fever) combined with facial numbness secondary to involvement of the fifth cranial nerve. This can rapidly progress to involve surrounding tissues resulting in ocular involvement (e.g., blurred vision, proptosis, ophthalmoplegia, peri-orbital cellulitis), and in severe cases can advance into the central nervous system and surrounding vasculature often resulting in cerebral infarction secondary to carotid thrombosis or cavernous sinus thrombosis. A prompt diagnosis requires a high level of suspicion and an understanding of underlying risk factors for disease. Computed tomography (CT) and magnetic resonance imaging (MRI) may show non-specific evidence for soft tissue infection. Occasionally an eschar may be found on close examination of skin, nasal airways, or oral mucosa. Immediate consultation with an otolaryngologist is essential. While antifungal treatment is needed, survival and limitation of morbidity is usually dictated by prompt surgical debridement.

Pulmonary mucormycosis typically begins with inhalation of spores into the lungs; however, less common hematogenous and lymphatic spread from distant sites to the lungs has also been described. These patients most often are neutropenic, especially in the setting of chemotherapy and bone marrow transplant.⁵ Early complaints are often similar to pneumonia (e.g., fever, cough, dyspnea, and chest pain). More advanced disease can present with hemoptysis, often massive in quantity due to the angioinvasive nature of these infections.⁵ Diagnosis can be difficult due to non-specific symptoms and unreliable cultures. Because of these factors, tissue biopsy is usually required to confirm the diagnosis. Unfortunately mortality rates can range from 60% to 95% in pulmonary mucormycosis, with increasing mortality as the disease process becomes more invasive.²

Cutaneous mucormycosis usually presents with local infection that has resulted from the breakdown of the normal barrier defenses in immunocompromised hosts as seen with traumatic injury, needle injections, and severe burns.¹ Prognosis is good, and surgical therapy can be curative if pursued early; however, the potential for more severe disease is possible in cases left untreated.

Disseminated mucormycosis is perhaps the most severe form of zygomycete infection. Severe neutropenia, hematologic malignancies, iron overload, with or without deferoxamine therapy, and other forms of immunosuppression carry the greatest risk for this form of disease.¹ Disseminated disease can spawn from any primary site of infection in the body; however, pulmonary disease is the most common source.⁵ The prognosis for these patients is dismal due to near absence of treatment options. Surgical therapy is not an option as the spread of disease is well beyond a focal source.

Other forms of mucormycosis are rare. Gastrointestinal manifestations involving the stomach, colon and ileum have been described.⁵ Similar risk factors are thought to play a role in these cases. Isolated CNS disease is rare in the absence of another primary site of infection. It is commonly seen with IV drug abusers and may present with focal neurologic deficits.² Other isolated cases of different organ involvement have been described but the overwhelming majority of cases involve rhinocerebral, pulmonary, cutaneous, and disseminated forms.

The diagnosis of mucormycosis can be difficult due to the typically vague symptoms on presentation. Prompt diagnosis is of the utmost importance in terms of patient survival. An awareness of at-risk patient populations is needed in order to prevent a delay in confirming the patient's diagnosis. Cultures are unlikely to yield timely results and may be contaminated due to the ubiquitous nature of the zygomycete organisms. Ideally, a tissue biopsy is obtained from an affected region of the patient's body. Careful preparation of the specimen in the lab is important as typical grinding of specimens can destroy hyphal elements and delay diagnosis. Fine mincing of specimens is the suggested method for preparation and informing the lab of your suspicions will help in this matter. Laboratory diagnosis is based solely on microscopic appearance of hyphal elements. While thin, frequently-septated hyphal elements with regular branching suggest an alternative type of fungal species such as aspergillus, the identification of broad (5 to 15 micrometers), non-septated hyphal elements with irregular branching support a diagnosis of a zygomycete infection. Radiologic manifestations are unlikely to be diagnostic but can provide supporting evidence for a diagnosis. In the majority of medical centers there are no other methods of diagnosis in use such as PCR or serologic testing.

The treatment for mucormycosis is mostly surgical. Aggressive and complete resection of all infected tissue is vital to improving a patient's chance of survival. Surgical consultation should be obtained as soon as possible and patients may often require multiple procedures to obtain adequate margins of resection. Serial imaging of affected tissues is done to monitor disease progression and may help guide further surgical procedures. With the exception of the last few years, the mainstay of medical therapy consisted solely of amphotericin B for the treatment of

mucormycosis. More recently some experience with the use of posaconazole has expanded the options available to clinicians in the treatment of mucormycosis.^{11,12} While amphotericin B is known to carry multiple adverse effects including renal failure as seen in our patient, posaconazole is an alternative in patients who cannot tolerate amphotericin B.¹³ Posaconazole is available with oral dosing allowing for prolonged outpatient treatment which may be necessary in certain infections. Other antifungal medications possess little or no activity against zygomycete species and should not be used in any therapeutic regimen. The optimization or elimination of any predisposing risk factors (e.g., hyperglycemia, acidosis, neutropenia, etc.) should also be addressed as soon as possible to improve patient outcomes.

There is some interest in using iron chelation therapy as an adjunctive treatment to surgery and antifungal medications in the treatment of mucormycosis. Deferiprone (Ferriprox) is a potent iron chelator that has been used in thousands of patients outside the United States to successfully treat iron overload.^{14,15} Deferiprone, unlike deferoxamine, cannot be exploited by fungal species as a siderophore.¹⁶ This would potentially reduce free iron levels in patient serum, making it more difficult for fungal species to grow and reproduce. Ibrahim *et al*, in a rhizopus-infected DKA mouse model, were able to show significant improvements in survival of mice treated with deferiprone vs. placebo.¹⁶ The applicability in a human host is not proven at this time, and the use of deferiprone in the treatment of mucormycosis is available as compassionate use only.

The overall prognosis of patients diagnosed with mucormycosis is poor. Although outcomes have improved with the use of amphotericin B, mortality rates can approach greater than 80% in patients with pulmonary disease.² Disseminated mucormycosis can result in mortality rates approaching 90% to 100%.² Cutaneous disease, when addressed promptly with local surgical resection, carries the best prognosis with a greater than 90% survival rate.² In most cases overall survival will be largely dictated by the underlying risk factors as well as the timeliness of surgical intervention.

In summary, mucormycosis represents a highly lethal type of infection typically affecting specific patient populations. Immunocompromised patients, diabetics and especially patients with DKA, oncology patients, patients with iron overload and those receiving treatment with deferoxamine should be viewed as having elevated risk for mucormycosis. Prompt consultation with a surgical team is of utmost importance and should not be delayed for a confirmed diagnosis. Systemic therapy with antifungal medication such as amphotericin B or posaconazole should be instituted quickly but should be viewed only as adjunctive to successful surgical resection. Overall prognosis is poor in most forms of disease with the exception of mild localized cutaneous disease.

References

1. Kontoyiannis D, Lewis R et al. Invasive Zygomycetes: Update on Pathogenesis, Clinical Manifestations, and Management. *Infect Dis Clin N Am* 2006;20:581-607.
2. Roden M, Zaoutis T, Buchanan W et al. Epidemiology and Outcome of Zygomycosis: A Review of 929 Reported Cases. *Clinical Infectious Disease* 2005;41:634-653.
3. Greenberg RN, Scott LJ, Vaughn HH, Ribes JA. Zygomycosis (mucormycosis): emerging clinical importance and new treatments. *Curr Opin Infect Dis* 2004;17:517.
4. Sridhara SR, Paragache G, Panda NK, Chakrabarti A. Mucormycosis in immuno-competent individuals: an increasing trend. *J Otolaryngol* 2005;34(6):402-6.
5. Spellberg B, Edwards J, Ibrahim A et al. Novel Perspectives on Mucormycosis: Pathophysiology, Presentation and Management. *Clinical Microbiology Reviews* 2005;18:556-569.
6. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. *Clin Microbiol Rev* 2000;13:236-301.
7. Boelaert JR, de Locht M, Van Cutsem J, Kerrels V, Cantinieaux B, Verdonck A, Van Landuyt HW, Schneider YJ. Mucormycosis during deferoxamine therapy is a siderophore-mediated infection. In vitro and in vivo animal studies. *J. Clin. Investing.* 1993;91:1979-1986.
8. Artis WM, Fountain JA, Delcher HK, Jones HE. A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: transferrin and iron availability. *Diabetes* 1982;31:1109-1114.
9. Chinn RY, Diamond RD. Generation of chemotactic factors by *Rhizopus oryzae* in the presence and absence of serum: relationship to hyphal damage mediated by human neutrophils and effects of hyperglycemia and ketoacidosis. *Infect. Immun.* 1982;38:1123-1129.
10. Pillsbury HC, Fischer ND. Rhinocerebral mucormycosis. *Arch. Otolaryngol* 1977;103:600-604.
11. Greenberg RN, Mullane K, van Burik JA, et al. Posaconazole as salvage therapy for zygomycosis. *Antimicrob Agents Chemother* 2006;50:126-133.
12. Kok J, Gilroy N, et al. Early use of posaconazole in the successful treatment of rhino-orbital mucormycosis caused by *Rhizopus oryzae*. *Journal of Infection* 2007;55:e33-36.
13. Spanakis EK, Aperis G, Mylonakis E. New agents for the treatment of fungal infections: Clinical efficacy and gaps in coverage. *Clinical Infectious Diseases* 2006;43:1060-1068.
14. Hoffbrand AV, Cohen A, Hershko C. Role of deferiprone in chelation therapy for transfusional iron overload. *Blood* 2003;102:17-24.
15. Kontoghiorghes GJ, Neocleous K, Kolnagou A. Benefits and risks of defiriprone in iron overload in thalassaemia and other conditions: comparison of epidemiological and therapeutic aspects with deferoxamine. *Drug Saf* 2003;26:553-584.
16. Ibrahim A, Edwards, J et al. Deferiprone iron chelation as a novel therapy for experimental mucormycosis. *Journal of Antimicrobial Chemotherapy* 2006;58:1070-1073.