Hyperbaric Zygomycotic Infections

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Continuing Education Activity

Invasive zygomycosis, or mucormycosis, are a group of infections caused by fungi in the order Mucorales. The most common species that cause infection are the Rhizopus species from the Mucoraceae family. The disease is aggressive and commonly fatal despite appropriate treatment. Infection with mucormycosis is extremely rare in healthy individuals; infections occur almost exclusively in immunocompromised patients. It has an especially high predilection in diabetics who are in ketoacidosis, as the acidic environment contributes to fungal growth. This activity reviews the presentation of zygomycosis and highlights the role of the interprofessional team in the management of patients with this condition.

Objectives:

- Identify the etiology zygomycosis.
- Outline the presentation of a patient with zygomycosis.
- Summarize the treatment and management options available for zygomycosis.
- Outline interprofessional team strategies to optimize care coordination and care delivery to advance the diagnosis and treatment of zygomycosis and improve outcomes.

Introduction

Invasive zygomycosis, or mucormycosis, are a group of infections caused by fungi in the order *Mucorales*. The most common species that cause infection are the *Rhizopus* species from the *Mucoraceae* family. The disease is highly aggressive and commonly fatal despite appropriate treatment. It is extremely rare for mucormycosis to occur in healthy individuals. It almost always affects the immunocompromised- especially people with diabetes who are in ketoacidosis as acidic environment contributes to fungal growth.[1][2][3]

Etiology

These organisms are ubiquitous. They are found outdoors in soil and vegetation. They are also a common mold found in homes. One study from Denmark showed that it was present in 98% of samples taken from house dust. Studies have also shown the mold to be present on molded bread, other foods, dirty carpets, and vacuum cleaner systems.[4]

Epidemiology

Aggressive zygomycotic infections occur in immunocompromised individuals. Most commonly, they tend to occur in uncontrolled diabetics, especially those with ketoacidosis. They also occur in patients with malignancies, hematologic disorders, transplants, burns, or those receiving immunosuppressive medications. For reasons unknown, two-thirds of zygomycosis occurs in males. The occurrence is equal across race, age, and geography.

Pathophysiology

Mucormycosis, especially when caused by *Rhizopus arrhizus,* is an acute and rapidly fatal disease. These organisms can invade blood vessels and cause destruction quickly. The infection rapidly accelerates and extends into adjacent tissues and structures. Necrotic and black tissue develops in the nares, palate, or orbit. The organisms can invade vessels and initiate a clotting response that leads to infarction. This tissue death leads to acidosis, which continues to feed the growth and destruction of the fungal organisms. This lack of blood flow also

makes treatment with antifungals more difficult. Due to angioinvasion, the infection can quickly progress to fungemia and the disseminated form.

Histopathology

A biopsy of the affected tissue will show broad, nonseptate hyphae with right-angle branching.

History and Physical

There are several different classifications of zygomycosis: rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated. Rhinocerebral is the most common form and initially resembles sinusitis with congestion, sinus pain, and drainage. The exam will vary depending on how advanced the infection is. Patients may present with erythema, periorbital swelling, and black necrotic eschars. History and physical will also vary depending on the underlying immunosuppressive disorder. For example, a patient with diabetic ketoacidosis may present with nausea, vomiting, and abdominal pain.

Treatment / Management

The current standard of care for treatment includes aggressive surgical debridement and treatment with liposomal amphotericin B. If there is any suspicion for mucormycosis, amphotericin B should be initiated immediately. Correction of any underlying pathophysiology, such as diabetic ketoacidosis, should be done as well.[5][6][7]

Hyperbaric oxygen therapy (HBO) is commonly used for necrotizing soft tissue infections, chronic osteomyelitis, and compromised grafts and flaps. Hypoxia is a problem when it comes to nonhealing tissue. HBO allows for saturation of oxygen within the blood and hemoglobin and a 10-fold increase of dissolved oxygen in plasma. Oxygen delivery to compromised tissue is increased, and normal tissue oxygenation for healing is restored. Hyperbaric oxygen therapy has also been shown to improve vascularity and stimulate new blood vessel growth. These factors are important in zygomycosis because of the angioinvasive nature of the infection, tissue becomes hypoxic and blood vessels become thrombosed. In addition, zygomycosis patients often undergo extensive debridement surgery. In cases of rhinocerebral mucormycosis, patients can be left disfigured. Addition of postsurgical hyperbaric oxygen therapy could help the formation of granulation tissue and bone healing.[8][9][10]

Due to the rareness and severity of this rapidly progressive infection, it is extremely difficult to conduct randomized, controlled trials on human patients. Therefore, most of the research on using hyperbaric oxygen therapy for zygomycosis largely relies on case reports and retrospective studies. In a review of the literature done by Ferguson et al., 12 patients with rhinocerebral mucormycosis were investigated. They were all treated with surgery and amphotericin B. Half of the patients were treated with adjunctive hyperbaric oxygen therapy. Of the patients who did not receive HBOT, 4 out of the 6 patients died because of the infection. Of the 6 patients who received adjunctive HBOT, only 2 died. However, this case review is too small to draw any statistical conclusions.

One of the most interesting case reports comes from Couch et al. in which 2 diabetic patients with rhinocerebral mucormycosis were treated with adjunctive HBOT. A high fatality rate occurs when the cerebral extension of the infection occurs. Both patients were critically ill and had aggressive brain mucor abscesses and one patient even had total occlusion of the internal carotid artery. Despite surgical debridement and medical therapy, their infections progressed and HBOT was added as salvage therapy. Both patients had marked clinical improvement upon addition of HBOT. They each received treatments 6 days a week at 2.5 ATA for 90 minutes. One received 79 total treatments and the other received 85 treatments. Both patients remained disease-free 21 months after discharge. De La Paz et al. and Melero et al. also published case reports on successfully treating bilateral rhinocerebral mucormycosis with adjunctive HBO therapy. A more recent review of cases done in 2004 by John BV et al. explored the use of hyperbaric oxygen therapy in 28 cases. The HBO treatment sessions 90 minutes long at a pressure of 2 to 3 ATA, ranging from 90 to 120 minutes. In general, HBOT was not started until after surgical debridement. The survival rate was 86% with diabetic patients having a much higher survival rate of 94%. There is a

higher rate of survival when the underlying condition is correctable such as diabetic ketoacidosis. Conversely, 2 out of the 3 patients with malignancies died because of the infection.

Considering the pathophysiology of invasive zygomycosis, its high morbidity and mortality, and the benefits of hyperbaric oxygen treatment, it is reasonable to consider HBOT as adjunctive therapy in the treatment of this disease.

Differential Diagnosis

- Actinomycosis
- Anthrax
- Aspergillosis
- Brain abscess
- Cryptococcosis
- Cellulitis
- Colonic obstruction
- Ecthyma gangrenosum
- Fusariosis
- Nocardiosis

Prognosis

Even with prompt diagnosis and treatment, overall mortality rates average about 50%. Rhino-orbital-cerebral mucormycosis carries a much higher mortality rate. Some studies report anywhere from 30% to 80% depending on the underlying condition. Mortality is higher in patients who have hematological disorders or malignancies as their underlying conditions are more difficult to treat. The disseminated form has a mortality of over 90%. Patients who do survive are often left disfigured due to extensive debridement surgeries.

Enhancing Healthcare Team Outcomes

Mucormycosis is a life-threatening infection that is best managed by an interprofessional team that includes a pathologist, laboratory specialist, internist, infectious disease expert, ICU nurses, and a surgeon. These patients need immediate treatment and debridement of the necrotic tissues. HBO is used but only in stable patients. Antifungal agents need to be administered intravenously for weeks but despite optimal treatment, the infection carries a mortality of more than 50%.[11][12][13]

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