Fever and Headache in an Intravenous Drug User

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Zygomycosis refers to diseases caused by filamentous fungi from the class Zygomycetes. These organisms are ubiquitous in nature and can be found in soil as well as in decaying organic matter such as fruit and bread. Risk factors for zygomycosis include uncontrolled diabetes mellitus, hematologic malignancies, corticosteroid therapy, deferoxamine therapy, intravenous drug use, and malnutrition. Clinical manifestations include rhino-orbital-cerebral, pulmonary, cutaneous, disseminated, gastric, and isolated cerebral disease. Isolated involvement of the central nervous system is rare and is most often associated with intravenous drug use. This case report describes isolated cerebral zygomycosis in an intravenous drug user.

A young man with a history of anxiety, intravenous drug use, and chronic hepatitis B and C infections presented to the hospital with a one-day history of headache, fever, and chills. His family had noticed a fluctuating level of consciousness and hypersomnolence. Prescribed medications included clonazepam and methadone. The patient admitted to heroin use earlier that same day. Upon presentation, his initial vital signs included a temperature of 38°C, pulse 60/min, respiratory rate 18/min, and blood pressure of 115/58 mm Hg. He was confused and oriented to person and place only. The fundoscopic exam was unremarkable, and no nuchal rigidity was appreciated. The neurological exam demonstrated no abnormalities.

Laboratory values revealed a white blood cell count of 11,500/mm^3 (4,500-11,000/mm^3) with 59% (54%-70%) segmented neutrophils, 22% (0%-5%) bands, 8% (20%-40%) lymphocytes, and 11% (2%-8%) monocytes. Hemoglobin and hematocrit were 13.2 g/dL (13.0-16.0 g/dL) and 39.2% (37%-49%), respectively. Platelet count was 155,000/mm^3 (150,000-400,000/mm^3). Urinalysis was normal, and blood cultures were negative. An HIV test was non-reactive. Cerebrospinal fluid (CSF) analysis revealed a neutrophilic pleocytosis with 376 WBCs/mm^3 (differential: 96% segs, 1% lymphocytes, and 3% monocytes) and an elevated red blood cell count of 76/mm^3. CSF protein and glucose levels were within normal ranges, and Gram stain, India ink stain, bacterial culture, and cryptococcal antigen were negative. Chest radiographs revealed no acute cardiopulmonary abnormalities. A computerize tomographic (CT) scan of the head without contrast was notable for mildly asymmetric frontal horns of the lateral ventricles, a finding described as a normal variant.

Empiric treatment with ceftriaxone, ampicillin, vancomycin, and acyclovir for bacterial meningitis and herpes encephalitis was administered. The patient remained febrile, and his mental status failed to improve. He de-

CME INFORMATION

TARGET AUDIENCE

The May/June Clinical Case of the Month is intended for family physicians, general internists, medicine subspecialists, general practitioners, obstetricians-gynecologists, emergency medicine physicians, pediatricians, neurologists, radiologists, and psychiatrists.

EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be better able to identify and understand the pathophysiology, microbiology, clinical presentation, diagnosis, and treatment of cerebral zygomycosis.

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of 1 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

DISCLOSURE

Dr. Greene has nothing to disclose.
Dr. Richard has nothing to disclose.
Dr. Causby has nothing to disclose.
Dr. Beech has nothing to disclose.
Dr. Murphy has nothing to disclose.
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veloped asymmetric pupils, bilateral clonus, left-sided weakness, a left-sided facial droop, and a positive Babinski sign. A repeat CT scan of the head revealed rapid interval development of a large area of hypodensity involving the basal ganglia bilaterally and portions of the frontal horns bilaterally, as well as uncal herniation. Magnetic resonance imaging (MRI) demonstrated a large area of high signal predominantly within both basal ganglia which extended to the regions of the right and left frontal lobes (Figures 1 and 2). Liposomal amphotericin B was initiated due to concern for fungal infection.

On hospital day 7, the patient was unresponsive to pain and demonstrated extensor posturing. On hospital day 8, he expired. Postmortem examination of the brain revealed filamentous fungi with aseptate hyphae and irregular branching consistent with zygomycosis infection (Figures 3 and 4).

DISCUSSION

Zygomycosis infections are caused by a group of fungi from the class Zygomycetes. There are two orders within this class: Mucorales and Entomopthorales. The order Mucorales contains the genera *Rhizopus*, *Absidia*, *Cunninghamella*, *Rhizomucor*, *Saksenaea*, *Apophysomyces*, and *Mucor*. This order is responsible for most of the human infections from this class. The order Entomopthorales contains the genera *Conidiobolus* and *Basidiobolus*. Entomophthorales-associated fungi usually cause infections in normal hosts, and no known immunodeficiency predisposes to infection.[1] This order often causes chronic submucosal or subcutaneous infections of the nose, mouth, perinasal tissue, trunk, or extremities. For the remainder of the discussion, the terms zygomycosis and zygomycetes will refer to members of the order Mucorales.

The fungi of zygomycosis are ubiquitous in nature. They are found in soil, air, and decaying vegetation.[2] These organisms grow rapidly and produce large numbers of spores. They grow on most media in the laboratory (including sheep blood agar and chocolate agar) at temperatures from 25°C to 55°C. Oftentimes, no growth occurs from specimens of infected tissue, possibly due to the lack of septations of the zygomycetous fungi or to pre-culture disruption of tissue specimens. The hyphae of the fungi are broad in width measuring 5-50 microns in diameter, and they branch at irregular angles from 45°-90°. Most infections occur through inhalation of spores.[3] However, infections can also be acquired through disrupted skin barriers.[4] or from ingestion of contaminated foods.

Zygomycetes do not usually cause disease in healthy hosts. For disease to occur, there is usually some predisposing condition or underlying disease such as diabetes mellitus often with an associated metabolic ketoacidosis, trauma including burns, or immunocompromising states such as bone marrow and solid organ transplantation, malignancies including leukemia and lymphoma, graft-versus-host disease, corticosteroid use, chemotherapy, neutropenia, uremia including patients on deferoxamine chelating therapy, iron overload, intravenous drug use, and malnourishment.[3,5] Zygomycosis often results in ischemia, infarction, and necrosis of infected tissue secondary to hyphal invasion of tissue vasculature. Clinical manifestations of zygomycosis infection often depends on the site of infection and the host's underlying conditions. Clinical syndromes include rhino-orbital-cerebral, isolated cerebral, pulmonary, gastrointestinal, cutaneous, and disseminated zygomycosis. These syndromes will be discussed briefly below.

Rhino-Orbital-Cerebral Zygomycosis

Rhino-orbital-cerebral zygomycosis is the most common disease manifestation of zygomycosis. This infection is most commonly associated with ketoacidosis and poorly controlled diabetes mellitus. Occurrences in the immunosuppressed/leukemic patient populations are usually due to steroid use and/or concurrent diabetes mellitus. The most common isolated organisms belong to the *Rhizopus* species.

Rhino-orbital-cerebral infection begins as a result of inhalation of spores into the paranasal sinuses. Symptoms may include orbital erythema, fever, headache, facial pain, nasal stuffiness, dark nasal discharge, and sinus pain. The progression of symptoms may reflect the invasion of the organism to other areas such as the sinuses, palate, nose, eye, and brain. Spread to the palate may manifest as a black necrotic eschar while spread to the orbit/eye may result in the signs/symptoms of double

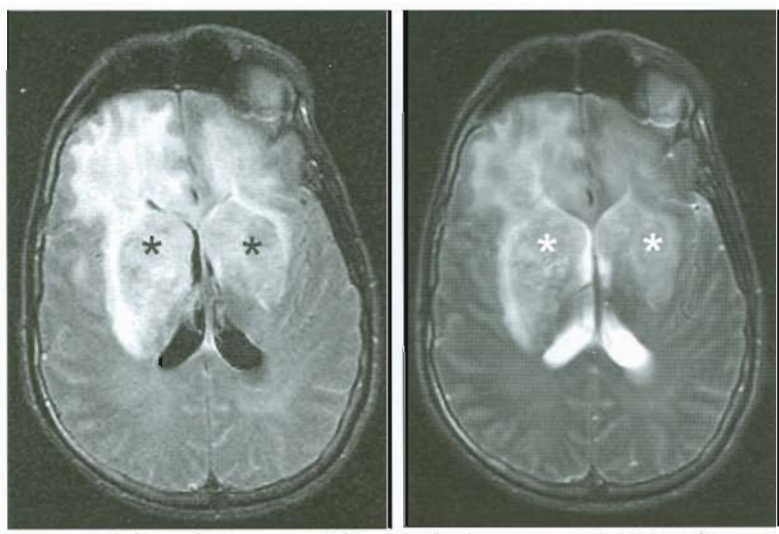

Figure 1 (left) and Figure 2 (right). Cerebral zygomycosis. FLAIR (figure 1) and T2-weighted (figure 2) images of the brain reveal diffusely abnormal signal intensity changes of the basal ganglia (*) as a consequence of fungal invasion. Inflammatory edema extends into the frontal lobes.

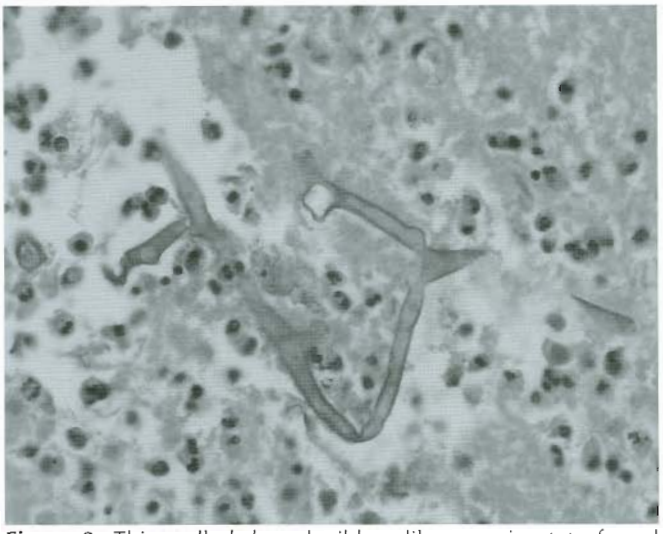

Figure 3. Thin-walled, broad, ribbon-like, pauciseptate fungal hyphae with right-angle hyphal branching within necrotic, acutely inflamed brain parenchyma. (Hematoxylin and eosin stain, 400X).

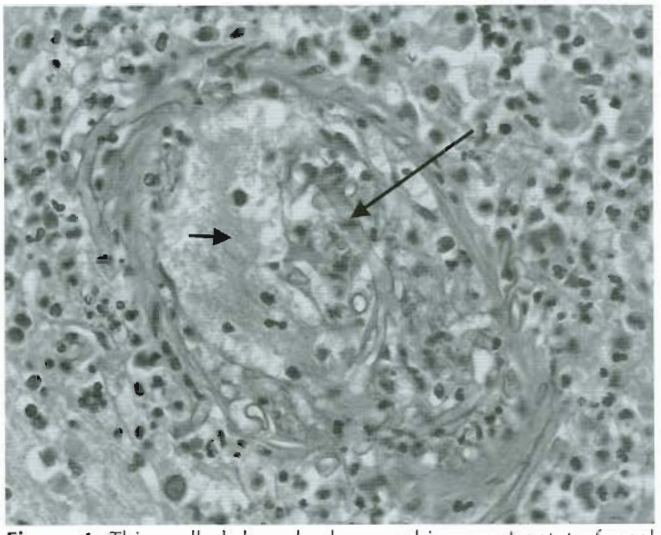

Figure 4. Thin-walled, broad, pleomorphic, pauciseptate fungal hyphae are present within the lumen and invade the wall of an intracerebral blood vessel (long arrow). Fibrin within the lumen of the blood vessel indicates early thrombus formation (short arrow). Fungal hyphae are also present within the surrounding necrotic, acutely inflamed brain parenchyma. (Hematoxylin and eosin stain, 400X). Reference: Chandler FW, Watts JC. Zygomycosis. In: Connor DH, Chandler FW, Schwartz DA, et al (editors). *Pathology of Infectious Diseases*. Stamford, Connecticut: Appleton and Lange; 1997:1113-1119.[24]

vision, loss of vision in the infected eye, periorbital swelling and cellulitis, lacrimation (discharge can be black and purulent), periorbital numbness, and proptosis. Mental status changes, including lethargy and coma, as well as cranial neuropathies are often signs of invasion into the brain. Progression through the brain may lead to cavernous sinus thrombosis and internal carotid artery thrombosis. Radiographs of infected sinuses can demonstrate fluid levels and opacification as well as bony involvement. CT scan or MRI helps determine the extent of the disease.

Isolated Cerebral Zygomycosis

Isolated cerebral zygomycosis is rare even among patients who are immunocompromised. Intravenous drug use (IDU) is the most important risk factor for developing isolated cerebral zygomycosis.[6] The fungus is thought to be injected intravenously or through an infected injection site. IDU is reported in over two-thirds of the cases with isolated CNS disease, and HIV infection alone does not appear to be an independent risk factor for developing isolated CNS disease.

The most common presenting symptoms in patients with IDU and isolated CNS disease include fever, lethargy, hemiparesis, and headache.[7] CSF findings are nonspecific. Pleocytosis is often present, usually manifesting a lymphocytic or neutrophilic predominance. CSF glucose is often normal, and protein levels may be normal or slightly elevated. CSF cultures and blood cultures are often negative.

Overwhelmingly, the most common site of involvement of isolated CNS zygomycosis in intravenous drug users is the basal ganglia.[8] Radiographic imaging of the brain with CT or MRI is variable and initially may reveal little-to-no contrast enhancement of lesions.[8] Diagnosis can be made by biopsy of the lesion; oftentimes, however, a diagnosis is not made until an autopsy is performed. Lesions similar in appearance are ascribed to bacterial abscesses, lymphoma, cryptococcosis, tuberculosis, and toxoplasmosis.[8] A combination of prompt surgical intervention and antifungal therapy, such as amphotericin B, should be pursued. Stereotactic biopsy of isolated central nervous system lesions followed by an extended course of antifungal therapy has been reported to result in favorable outcomes.[9] The mortality rate is approximately 63%.[6]

Pulmonary Zygmycosis

Pulmonary zygomycosis is the second most common manifestation of zygomycosis, and usually occurs in male patients with severe neutropenia, often in association with corticosteroid administration, i.e., patients with hematologic malignancies, lymphomas, and organ/bone marrow transplantation.[10] Patients with diabetes mellitus, renal transplants, and HIV infection have also developed lung infections with these fungi. Symptoms include fever, cough with hemoptysis, chest pain often described as pleuritic, and shortness of breath that typically persist in the setting of antibiotic administration. Chest radiographs are nonspecific and can demonstrate nodules, consolidation, and cavitation, often resembling pulmonary aspergillosis. The infection may cause infarction and extensive local tissue necrosis, and hematogenous spread to other organs can also occur.

Gastrointestinal Zygomycosis

The gastrointestinal (GI) tract is a rare site for zygomycosis. The most common sites of involvement include the stomach and the colon. The disease develops in transplanted patients or very malnourished individuals (usually infants) secondary to ingestion of food contaminated with fungal spores. Nonspecific symptoms/signs occur such as fever, abdominal pain, nausea, vomiting, bloody diarrhea, hematemesis, and melena. Gastrointestinal perforation requiring surgical intervention can complicate this infection.

Cutaneous Zygomycosis

Cutaneous and soft tissue disease most often results from direct inoculation, although hematogenous dissemination to the skin is also possible.[4] It is most often reported in patients with diabetes mellitus, leukemia, or organ transplants who have experienced burns or traumatic wounds, including post-surgical wounds. Infection often involves the extremities and may manifest cutaneously as nodules, ulcers, pustules, blisters, cellulitis, ecchymoses, or ecthyma gangrenosum-like lesions. Skin biopsy with histopathologic examination and cultures is required for diagnosis.

Disseminated Zygomycosis

Disseminated zygomycosis usually occurs in patients who are very immunosuppressed from hematologic malignancies (leukemia and lymphoma) or in patients receiving deferoxamine, corticosteroids, or chemotherapy. [5,10,11,12] Dissemination may occur from any site (lung and GI tract most commonly). Despite advances in medical and surgical therapy, the mortality rate approaches 100%.

DIAGNOSIS

Diagnosis of zygomycosis requires identifying the organism by biopsy of infected tissue. Cultures of infected tissue often are negative. Staining of infected tissue with haematoxylin and eosin, Gomori's methenamine silver, and periodic-acid Schiff can demonstrate aseptate hyphal elements invading blood vessels and exhibiting broad, irregular branching.[5] If no hyphal elements are seen but clinical suspicion for zygomycosis is high, the diagnosis should not be dismissed.

TREATMENT

Prompt diagnosis, surgical debridement when possible, and antifungal therapy are the cornerstones for management of patients with zygomycosis. The initial step in treatment involves correction of the predisposing condition. Hyperglycemia and metabolic acidosis should be controlled. Obtaining the optimal immune status in infected patients is essential. Reducing and/or withholding immunosuppressive drugs, such as steroids, is helpful when possible. Resolution of neutropenia can occur with the administration of granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF and G-CSF have also been used as adjunctive therapy in patients with zygomycosis who are non-neutropenic in order to enhance the antimicrobial activity of neutrophils.[13,14,15] Outcome of infections has been related to neutrophil recovery.[16]

Amphotericin B is the drug of choice for treatment of zygomycosis. Doses ranging from 1 to 1.5mg/kg/day of amphotericin B deoxycholate have typically been administered. The length of treatment is determined by the clinical response of the patient. Amphotericin B toxicity, especially nephrotoxicity, is a concern. Consequently, the lipid formulations of amphotericin B are increasingly utilized because of their reduced nephrotoxicity potential when compared to conventional amphotericin B deoxycholate. Posaconazole is a new antifungal triazole with a broad spectrum of activity. Data from an *in vitro* study have shown that posaconazole has efficacy comparable to amphotericin B against *Rhizopus* species, *Mucor* species, and *Absidia* species, and case reports of posaconazole use as salvage therapy for zygomycosis have been published.[16,17] Caspofungin, 5-FC and voriconazole do not demonstrate reliable activity *in vitro* against the agents of zygomycosis.[5] Of note, there are case reports of breakthrough zygomycosis in patients while on voriconazole.[18,19]

Aggressive surgical debridement is often required, especially in rhinocerebral and pulmonary infections. Necrotic tissue should be extensively removed, and serial debridements may be necessary. The operations can be disfiguring; however, chances of survival are often increased with surgery.

Hyperbaric oxygen (HBO) is thought to improve wound healing by decreasing tissue hypoxia, decreasing tissue lactic acidosis, and providing oxygen necessary for improved granulocyte function. HBO has been used as adjunctive therapy in rhinocerebral and soft tissue zygomycosis.[21,22] Benefit has yet to be established with this therapy, in part because of the small sample-size and non-randomization of patients in these studies.[23]

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CME QUESTIONS

To earn CME credit, read the preceding CME article and complete the registration, evaluation, and answer form on page 167. Mail or fax the registration, evaluation, and answer form to the Educational and Research Foundation. Answers must be postmarked or faxed prior to June 30, 2006. Participants must attain a minimum score of 75% to receive credit.

For each question, choose the one answer that is most correct.

1. All of the follo*wing statements about zygomycosis are true* except:
   a) Clinical syndromes include rhino-orbital-cerebral, isolated cerebral involvement, pulmonary, gastrointestinal, cutaneous, and disseminated zygomycosis
   b). Infections due to zygomycetes occur through inhalation of spores, through disrupted skin barriers, or from ingestion of contaminated foods.
   c) Rhino-orbital-cerebral zygomycosis is the most common disease manifestation of zygomycosis.
   d) Gram stain of infected tissue is the optimal stain for demonstrating the aseptate, broad, irregular branching hyphae of the angioinvasive Zygomycetes.
   e) Intravenous drug use (IDU) is the most important risk factor for developing isolated cerebral zygomycosis.

2. True or False? The fungi of zygomycosis are nosocomial in origin, and infections due to these organisms should only be considered in patients who are hospitalized or have been recently hospitalized.

3. True or False? Most patients with zygomycosis have a predisposing condition or underlying disease such as diabetes mellitus often with an associated metabolic ketoacidosis, trauma including burns, or immunocompromising states such as bone marrow and solid organ transplantation, malignancies including leukemia and lymphoma, graft-versus-host disease, corticosteroid use, chemotherapy, neutropenia, uremia, iron overload, intravenous drug use, and malnourishment.

4. All of the following statements are true *except*:
   a) Prompt diagnosis, surgical debridement when possible, and antifungal therapy are the cornerstones for management of patients with zygomycosis.
   b) Amphotericin B is the drug of choice for treatment of zygomycosis
   c) Two newer antifungal agents, caspofungin and voriconazole, are particularly effective against the agents of zygomycosis.
   d) Obtaining the optimal immune status in patients with zygomycosis is essential.