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Clinical presentation of zygomycosis

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Abstract

Zygomycetes are filamentous fungi with a worldwide distribution. This class of fungi encompasses two orders, i.e. the Mucorales and the Entomophthorales. Members of the latter are associated with chronic cutaneous and subcutaneous infections that are limited to the tropics and rarely disseminate to internal organs. The order Mucorales includes several species involved in rhinocerebral, pulmonary, cutaneous, gastrointestinal and other less frequent infections in immunocompetent and immunocompromised individuals, and is characterized by a tendency to disseminate. Portals of entry of zygomycetes are usually the lungs, skin, and gastrointestinal tract. A characteristic property of zygomycetes is their tendency to invade blood vessels and to cause thrombosis—processes that result in subsequent necrosis of involved tissues. Risk factors associated with zygomycosis include prolonged neutropenia and use of corticosteroids, solid organ or haematopoietic stem cell transplantation, AIDS, poorly controlled diabetes mellitus, iron chelation with deferoxamine, burns, wounds, malnutrition, extremes of age, and intravenous drug abuse. Recently, the widespread use of voriconazole for prophylaxis or treatment of aspergillosis in patients with haematological malignancies has been linked with a rise in the numbers of cases of invasive zygomycosis. As the symptoms, clinical signs and imaging findings of these infections are non-specific, a high index of suspicion is required for timely diagnosis. Early diagnosis, correction of the underlying predisposing factors, aggressive surgical debridement of all infected tissues and lengthy administration of antifungals are the only potentially curative options for this rare but emerging invasive fungal infection.

Keywords: Diabetes, Entomophthorales, immunosuppression, Mucorales, Zygomycetes, zygomycosis

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Introduction

Zygomycosis includes a variety of infections caused by the Zygomycetes, a class of fungi with a ubiquitous and worldwide distribution that is characterized by aseptate or paucisseptate hyphae, unlike fungi with distinct septate hyphae, such as *Aspergillus* spp. [1]. Zygomycetes are further subdivided into two orders, the Mucorales and the Entomophthorales, which produce distinct patterns of clinical manifestations. More specifically, the order Entomophthorales (*Conidiobolus* and *Basiodobolus* spp.) is associated with chronic cutaneous and subcutaneous infections that are almost exclusively limited to the tropics and rarely disseminate to internal organs [2]. For these infections, entomophthoramycosis is the correct term. On the other hand, the order Mucorales encompasses several genera (*Rhizopus*, *Rhizomucor*, *Mucor*, *Absidia*, *Apophysomyces*, *Cunninghamella*, *Saksenaea*, etc.) that are involved in rhinocerebral, pulmonary, cutaneous, gastrointestinal and other less common invasive fungal infections in both immunocompetent and immunocompromised individuals and have the tendency to disseminate. Mucormycosis is the correct term for infections due to fungi of this order. The term zygomycosis is used to describe any invasive infection due to zygomycetes, although it is frequently used interchangeably with the term mucormycosis [3].

The portals of entry of zygomycetes are usually the respiratory tract, the skin, and, less frequently, the gut. A characteristic property of zygomycetes is their tendency to invade blood vessels and cause thrombosis and necrosis of infected tissues [1]. In typical cases, the infection progresses rapidly, and unless the underlying risk factors are adequately and promptly reversed, in association with wide surgical resection of all necrotic areas and administration of amphotericin-based antifungal therapy, death occurs [4]. As is the case with other filamentous fungi, because of the low yield of blood cultures, biopsy of the affected sites is the mainstay of diagnosis.

Zygomycetes are unique among moulds in their ability to infect human hosts with a broader range of risk factors than other opportunistic moulds [3]. Thus, whereas infections due to *Aspergillus* spp. are almost exclusively limited to immunocompromised patients, many cases of zygomycosis have been reported in individuals with no apparent underlying immunosuppression.

Risk Factors

Risk factors associated with mucormycosis include prolonged neutropenia and use of corticosteroids, haematological malignancies (leukaemia, lymphoma, and multiple myeloma), aplastic anaemia, myelodysplastic syndromes, solid organ or haematopoietic stem cell transplantation, human immunodeficiency virus infection, diabetic and metabolic acidosis, iron overload, deferoxamine use, burns, wounds, malnutrition, extremes of age, i.e. prematurity or advanced age, and intravenous drug abuse [1–4]. Patients with solid tumours rarely develop zygomycosis. Several of these factors are common to immunocompromised individuals, whereas the association with metabolic factors, i.e. metabolic and diabetic acidosis, is quite characteristic of these emerging mycoses [5]. Recently, the widespread use of voriconazole in treating aspergillosis in patients with high-risk haematological malignancies or who undergo haematopoietic stem cell transplantation has been linked with a rise in cases of confirmed zygomycosis in many institutions worldwide. Physicians using voriconazole for prophylaxis or treatment of aspergillosis in profoundly immunocompromised patients should be aware of the risk of emergence of fungal pathogens that are intrinsically resistant to this azole, such as zygomycetes [6–14].

In the past, the most common underlying risk factors for invasive zygomycosis were poorly controlled diabetes mellitus with associated ketoacidosis, open wounds, and the use of deferoxamine to chelate iron or aluminium in patients with iron overload or on dialysis [15]. More importantly, a substantial number of cases were reported in individuals with no clear predisposing factors. Recently, a substantial increase in the numbers of cases of zygomycosis has been noted in profoundly neutropenic patients with high-risk leukaemia [16–27], in patients with myelodysplastic syndromes [28–30], and in haematopoietic stem cell [31–34] and solid organ transplant recipients [35–39]. Earthquakes and physical disasters, such as the 2004 tsunami in Southeast Asia, have also been linked with increases in the numbers of cases of cutaneous and subcutaneous zygomycosis due to traumatic inoculation of zygomycetes into wounds [40–42].

Clinical Manifestations

On the basis of organ(s) involvement, five major forms of invasive zygomycosis have been described, i.e. rhino-orbito-cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated, although rarer cases of zygomycosis, such as osteomyelitis and endocarditis, have been described. Roden *et al.* reviewed all published reports of zygomycosis in the English literature since 1885. A total of 929 eligible cases were reviewed. The mean age of patients was 38.8 years, and 65% of the patients were male. The most common types of infection were sinus (39%), pulmonary (24%), and cutaneous (19%). Dissemination developed in 23% of cases. The majority of patients with malignancy (92 of 154, 60%) had pulmonary disease, whereas the majority of patients with diabetes (222 of 337, 66%) had sinus disease [43]. Comparing primary sites of zygomycosis, skin and gut is more frequently affected in children compared to adults [44]. (In this Supplement, Roilides *et al.* review cases in neonates and children.)

Rhinocerebral zygomycosis

Rhinocerebral zygomycosis is characterized by involvement of the nose and paranasal sinuses, with frequent involvement of the maxillary sinus, the orbit, the cavernous sinuses, and the brain [20,26,30,45–48]. Although rhinocerebral zygomycosis occurs in immunocompromised patients, it is more common in patients with poorly controlled diabetes mellitus, and can be the first manifestation of the underlying metabolic abnormality. In diabetics with ketoacidosis, chemotaxis, adherence, spreading and oxidative burst of neutrophils are severely impaired, and this is associated with failure to suppress the germination of fungal spores and with an inability to kill proliferating hyphae [1]. Symptoms of zygomycosis of the paranasal sinuses are neither pathognomonic nor specific enough to distinguish zygomycetes from other pathogens causing rhinosinusitis. Nasal obstruction or congestion with noisy breathing, headache, odontalgia, maxillary pain and hyposmia or anosmia may be seen. Necrotic eschars in the nasal cavity, the turbinates or the palate, and necrotic facial lesions, signify aggressive angio-invasive infections. Orbital extension can lead to preseptal and orbital cellulitis, and is associated with chemosis, eyelid oedema, proptosis, blurred vision, double vision, worsening ophthalmoplegia, and, eventually, blindness. Intracranial extension is associated with a depressed level of consciousness. Intracranial complications include cavernous and, more rarely, sagittal sinus thrombosis, and epidural or subdural abscess formation. Obtaining biopsy specimens from necrotic lesions can help in making a rapid histological diagnosis, which is of paramount importance for

improving the clinical outcome. The mortality rate is extremely high, and is associated with delayed diagnosis and delayed institution of combined aggressive medical and surgical therapy.

Pulmonary zygomycosis

Pulmonary zygomycosis is more common in neutropenic patients with underlying haematological malignancies or who undergo haematopoietic stem cell transplantation. Its clinical and radiological features are indistinguishable from those of invasive pulmonary aspergillosis. Hence, patients present with prolonged fever that is unresponsive to broad-spectrum antibiotics, non-productive cough, pleuritic chest pain, and deteriorating dyspnoea. A friction rub may be heard on auscultation. Haemoptysis is an ominous symptom, and can be fatal, owing to erosion of a major lung vessel. The absence of fever does not rule out any pulmonary invasive fungal infection, especially in patients on corticosteroids. As with pulmonary aspergillosis, high-resolution chest computed tomography is the best method for determining the extent of pulmonary involvement, and demonstrates evidence of infection before chest radiographs. Halo and air-crescent signs are encountered in cases of zygomycosis, as in cases of pulmonary aspergillosis, and are non-specific. Nodular, segmental, lobar or cavitary lesions can occur. Chamilos *et al.* from the MD Anderson Cancer Center, using logistic regression analysis, showed two clinical parameters, i.e. concomitant sinusitis and voriconazole prophylaxis, to be significantly associated with pulmonary zygomycosis as compared with aspergillosis in patients with cancer, mostly haematological malignancies [49]. Among the radiological parameters, the presence of multiple (≥10) nodules and pleural effusion at the time of the initial chest computed tomography scan were also independently associated with pulmonary zygomycosis as compared with aspergillosis [49]. Pulmonary zygomycosis can spread to other organs if not promptly treated, and is associated with a high case-fatality rate.

Cutaneous zygomycosis

The skin is a less common site of secondary involvement in disseminated zygomycosis than with infections due to other opportunistic moulds. Hence, in the review by Roden *et al.*, haematogenous dissemination to the skin was rare [43]. On the other hand, primary cutaneous zygomycosis is associated with traumatic inoculation of the skin with zygomycetes in immunocompromised patients, burn victims, and patients with severe soft tissue trauma [16,17,35,50–61]. The clinical symptoms and signs of erythema and induration are non-specific and indistinguishable from those of any cutaneous or subcutaneous infection. Necrotic eschars are the diagnostic hallmark, and should prompt an immediate biopsy of the involved skin and subcutaneous fat. Zygomycetes are capable of extending rapidly along tissue planes, especially in neutropenic patients, and this property is associated with poor clinical outcome. In the Roden *et al.* review, 44% of cutaneous infections were complicated by deep extension or dissemination [43].

Gastrointestinal zygomycosis

Gastrointestinal zygomycosis is uncommon and has been mainly described in premature neonates, where it presents as necrotizing enterocolitis with a swollen, erythematous and tender abdomen. The disease is characterized by fungal invasion into the gut mucosa, submucosa, and blood vessels. Apart from prematurity, malnutrition, ingestion of contaminated food or of non-nutritional substances, severe underlying illness and immunosuppression are the most common predisposing factors. Few cases have been described in immunocompetent individuals. All parts of the gut can be affected, although more commonly the disease presents with an appendiceal, caecal or ileac mass or with gastric perforation that may be associated with an upper, frequently massive, gastrointestinal bleed [62–67]. Gastrointestinal perforation can lead to peritonitis with a high mortality rate.

Disseminated zygomycosis

Disseminated zygomycosis is usually the result of dissemination from invasive pulmonary disease, although it may originate from any of the primary sites of infection [68–70]. Most cases are diagnosed by post-mortem examination of profoundly immunosuppressed patients. However, several cases of disseminated zygomycosis have been described in immunocompetent individuals after life-threatening multiple injuries to various organs. The death rate approaches 100%.

Rare forms of zygomycosis

A rare manifestation of zygomycosis is a primary renal form that is usually confirmed at autopsy [71,72] Although rare, bilateral renal zygomycosis should be suspected in any immunocompromised patient who presents with haematuria, flank pain, and unexplained anuric renal failure. Rare manifestations of zygomycosis are involvement of the peritoneal cavity in patients undergoing peritoneal dialysis [57,73–75], brain involvement without rhino-orbital participation in leukaemic patients and intravenous drug abusers [76], and endocarditis in patients with artificial heart valves and rarely endocarditis on native heart valves. [77–79].

Conclusions

In conclusion, zygomycosis is becoming more frequent in today's era of highly active prophylaxis for *Aspergillus* spp. Different sites can be affected; symptoms are non-specific, and imaging findings are suggestive but not specific. Hence, a high index of suspicion is required for the timely diagnosis of this dreadful infection by physicians caring for immunocompromised individuals, but also caring for diabetics, sick premature neonates, debilitated elderly patients, those on peritoneal dialysis or deferoxamine chelation, and trauma victims. Early diagnosis, correction of the underlying predisposing factors, if possible, aggressive surgical debridement and lengthy administration of amphotericin B are the only potentially curative options for this rare but emerging invasive fungal infection.

Transparency Declaration

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