Cutaneous zygomycosis

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Abstract

The prevalence of cutaneous and soft tissue zygomycosis appears to have increased in recent years. We reviewed 78 case reports of cutaneous zygomycosis published from 2004 through 2008. Most patients with cutaneous zygomycosis have underlying conditions such as haematological malignancies, diabetes mellitus or solid organ transplantation, but a large proportion of them are immunocompetent. Trauma is the most common predisposing factor leading to zygomycosis in immunocompetent patients. If the patient is immunocompromised, the infection may disseminate. Cutaneous zygomycosis may be localized, may extend to deep underlying tissues, or may be disseminated. The most common clinical presentation is induration of the skin with surrounding erythema, rapidly progressing to necrosis. Histological examination and culture of soft tissue are important for the diagnosis of cutaneous zygomycosis. Treatment consists of surgical debridement, administration of antifungal agents (amphotericin B formulations and/or posaconazole) and, occasionally, hyperbaric oxygen. Mortality rates are approximately 30%.

Keywords: Cutaneous, Soft tissue, trauma, Zygomycosis

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Introduction

Zygomycosis has emerged as the third most common invasive fungal infection after candidosis and aspergillosis. It constitutes a group of infections caused by members of the class Zygomycetes, which is divided into two orders, Mucorales and Entomophthorales [1]. Although zygomycosis can involve any organ of the body, the most common clinical presentations are rhinocerebral, pulmonary, cutaneous and disseminated. The following is a review of cutaneous zygomycosis.

Epidemiology

The prevalence of cutaneous and soft tissue zygomycosis appears to have increased in recent years. A review of 929 cases by Roden et al. [2] included 176 cases (19%) of cutaneous zygomycosis. We searched PubMed for case reports of cutaneous zygomycosis published from 2004 through 2008 in English, selecting only articles describing cases in which the diagnosis had been confirmed by histology and/or culture, and identified 78 cases [3–65]. The large number of publications in recent years may reflect the greater awareness in the part of physicians of this infection, as well as publication bias, but there are also data which support an actual increase in the incidence of zygomycosis, mainly in patients with haematological malignancies [66]. In the review by Roden et al., cutaneous zygomycosis was the third most common clinical form of zygomycosis, after rhinocerebral and pulmonary forms [2]. In children, however, the skin is the most common site of infection with Zygomycetes [67]. In our review of 78 cases, 22 (28%) patients were children (0–14 years) and, of those, eight (36%) were ≤12 months old.

Most patients with cutaneous zygomycosis have underlying conditions such as haematological malignancies, diabetes mellitus or solid organ transplantation, but a large proportion of them are immunocompetent. In a review by Adam et al. [68], diabetes was present in only 26% of cutaneous cases and leukaemia and/or neutropenia in 16%. In the review by Roden et al. [2], of the 176 patients with cutaneous infections, 50% had no underlying conditions, whereas in our review of 78 patients, 31 (40%) were immunocompetent, 18 (23%) had a haematological malignancy, 10 (13%) had diabetes mellitus, five (6%) had received a solid organ transplant, four (5%) had received corticosteroids, while the remaining 10 (13%) had various other underlying diseases, including metabolic acidosis due to ureterointestomy, cirrhosis, prematurity, non-haematological malignancy, malnutrition and HIV infection.
Pathogenesis and Mode of Transmission

Zygomycetes can be acquired by inhalation, ingestion or direct inoculation. In cutaneous zygomycosis, the latter is by far the most common mode of transmission. A hallmark of these infections is the presence of extensive angioinvasion with resultant infarctions and tissue necrosis [69]. Intact mucosal and endothelial barriers serve as structural defences against tissue invasion and angioinvasion by Zygomycetes. These barriers can be disrupted by trauma, prior infection, cytotoxic chemotherapy, or maceration of skin by a moist surface [58], allowing high loads of sporangiospores to invade the dermis. The disease can be very invasive locally and can penetrate from the cutaneous and subcutaneous tissues into the adjacent fat, muscle, fascia and bone [69]. Depending on the immune status of the host, the infection can then be haematogenously disseminated to deep organs. There have been cases where a trivial trauma, such as that caused by the use of blood glucose self-monitoring equipment [55] or by a plant thorn [70], has led to fatal disseminated disease. Although dissemination from skin to other organs is relatively common, the reverse (i.e. dissemination to the skin) is very rare [69]. Roden et al. noted such reverse dissemination in only six cases (3%) [2].

Insect bites [19], stings [1] and even pecking by birds [65] have been implicated in disease transmission in cases of cutaneous and subcutaneous zygomycosis. Trauma in general is a major cause of zygomycosis, especially in immunocompetent patients. Besides the previously mentioned minor traumas, road traffic accidents [23,24,31,38,39] or crush injuries (by agricultural machines) [29] can lead to traumatic implantation of soil and subsequent zygomycosis. Zygomycosis has also been reported to occur as a result of injury in a natural disaster, such as the tsunami that struck Southeast Asia in 2004 [48] or the volcanic eruption which wiped out the town of Armero, Colombia in 1985 [71]. Another well-described cause of cutaneous zygomycosis is major burn injury, which, in addition to disrupting the skin barriers, confers significant immunosuppression of variable duration [5,46,52]. An increased risk for developing zygomycosis in the burn patient is the development of a condition called ‘burned stress pseudodiabetes’, which is marked by the occurrence of persistent hyperglycaemia and glucosuria [1].

In recent decades, zygomycosis has also emerged as a nosocomial infection. In our review, 28 (36%) of 78 patients had a hospital-acquired zygomycosis (Table 1). This type of zygomycosis has been associated with iatrogenic immunosuppression and a variety of medical devices or procedures, including antifungal prophylaxis, bandages [46], medication patches [70], and intravenous [33,41–43] or arterial [45] catheters. An outbreak of cutaneous Rhizopus arrhizus infection associated with karaya ostomy bags has been reported [35]. Karaya gum, a product derived from the sap of the Sterculia urens tree, was utilized to make the non-sterile adhesive of the ostomy bag used to affix the pouch to the abdominal surface.

Clinical Presentation

Cutaneous zygomycosis is subcategorized into three groups [2]. Patients in whom the infection is confined to the cutaneous or subcutaneous tissue are defined as having localized disease. Patients with invasion into muscle, tendon or bone are classified as having deep extension of infection and patients with cutaneous disease involving another non-contiguous site are defined as having disseminated infection. In Roden et al., 96 (56%) infections were localized, 43 (24%) were accompanied by deep extension and 35 (20%) were disseminated [2]. In cases occurring after 2003, equivalent numbers were 23 (32%), 38 (52%) and 12 (16%), respectively. Five cases were not included because the clinical presentation was not well described. In our review of 78 cases we found no dissemination from an internal organ to the skin.

Any area of the skin can be affected by zygomycosis. Although the upper and lower extremities are more often involved, there have been reports of cutaneous zygomycosis of the scalp [28,70], face [6,7,17,27], breast [18], thorax [37], back [23], abdomen [22,36], gluteal area [47] and perineum [42].

The clinical presentation of cutaneous zygomycosis varies. The disease may be gradual in onset and slowly progressive [54], or it may be fulminant, leading to gangrene and haematogenous dissemination [37,55]. In a report of cutaneous

<table>
<thead>
<tr>
<th>Mode of transmission</th>
<th>Cases before 2004 (%)</th>
<th>Cases from 2004 to 2008 (%)</th>
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<tbody>
<tr>
<td>Penetrating traumas</td>
<td>60 (34%)</td>
<td>31 (40%)&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Dressings</td>
<td>26 (15%)</td>
<td>6 (8%)</td>
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<tr>
<td>Surgery</td>
<td>26 (15%)</td>
<td>6 (8%)</td>
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<tr>
<td>Burns</td>
<td>11 (6%)</td>
<td>7 (9%)</td>
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<tr>
<td>Motor vehicle accidents</td>
<td>5 (3%)</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>Falls</td>
<td>5 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Not well described</td>
<td>42 (24%)</td>
<td>18 (23%)</td>
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<sup>a</sup>Of the 31 cases of penetrating trauma, 17 (55%) were nosocomial, related to intravenous, arterial or other catheters or needles.
zygomycosis caused by *Mucor hiemalis* in an immunocompetent child, the disease manifested as superficial lesions with only slightly elevated circinate and squamous borders resembling tinea corporis and was not diagnosed for 5 years [54]. Rubin et al. [45] described a case of superficial zygomycosis caused by *Rhizopus arrhizus*, which consisted of targetoid plaques with outer erythematous rims and echymotic or blackened necrotic centres; the authors suggested the name ‘bull’s eye infarct of cutaneous zygomycosis’. Similar descriptions have been reported by three other authors since 2003, for infections caused by *Cunninghamella bertholletiae* in one case and *Rhizopus* sp. in the other two [25, 32,44]. The differential diagnosis of targetoid cutaneous lesions includes multiple autoimmune diseases, drug reactions, infections, infiltrative diseases, neoplastic disorders, and primary skin diseases. In patients with open wounds, mucormycoses may have a cotton-like appearance resembling that of bread mould [21,39,57].

At the other end of the spectrum of clinical manifestations of cutaneous zygomycosis are necrotizing fasciitis and gangrene. In such cases, the infection may initially have the form of induration, blisters, pustules or necrotic ulcerations; it may rapidly progress, forming cutaneous abscess and necrosis of the deep subcutaneous tissues [12,29,57]. The lesions may mimic pyoderma gangrenosum [60], bacterial synergistic gangrene, or other infections produced by *Pseudomonas, Aspergillus, Histoplasma*, etc. When the disease is disseminated, the patient shows the general signs and symptoms of sepsis.

**Diagnosis**

Early diagnosis of zygomycosis is essential to improve the outcome. A necrotic lesion in an immunocompromised host should raise suspicion of zygomycosis. In a patient who has sustained a trauma, even if he or she is immunocompetent, zygomycosis should be included in the differential diagnosis, especially if there are necrotic elements, if the wound continues to expand despite broad-spectrum antibiotic therapy, or if a mould is observed on the wound edges. Biopsy of the lesions for histology and culture are necessary to establish the diagnosis. The biopsy specimen should be taken from the centre of the lesion and include subcutaneous fat, because moulds frequently invade blood vessels of the dermis and subcutis, resulting in an ischaemic cone at the skin surface [72]. Impression smears from the wound edges may also help in the diagnosis. Zygomyces are characterized by broad, mostly aseptate hyphae, with irregular branching that occasionally occurs at right angles. The identification of Zygomyces at the genus and species levels requires culture studies. However, in a high proportion of cases cultures do not yield a fungus. Cultures are negative in approximately 50% of cases of zygomycosis, including all sites of infection [2]. In our review of cases of cutaneous zygomycosis after 2003, 56 (72%) of 78 reported cases had a positive culture. The majority were *Rhizopus* spp. (24/56, 43%). The other isolates were *Absidia corymbifera* (12/56, 21%), *Apophysomyces elegans* (6/56, 11%), *Mucor* spp. (3/56, 5%), *Rhizomucor* spp. (3/56, 5%), *Cunninghamella bertholletiae* (3/56, 5%) and *Sakseae vasiformis* (4/56, 7%), and in one case the culture showed Mucorales. Recently, molecular methods have begun to be used in the diagnosis of zygomycosis; these may be very useful as an adjunctive diagnostic tool, especially in cases of suspected outbreaks [72].

**Treatment and Outcome**

Extensive surgical debridement in conjunction with systemic antifungal medication is the standard treatment of cutaneous zygomycosis. Surgical debridement consists of complete resection of necrotic and infected tissue, often with a cuff of apparently uninfected tissue. The wound must be closely monitored and at the first indication of disease progression, surgery must be repeated. In a series of zygomycoses in the upper extremities, patients underwent an average of ten surgical debridements (ranging from four to 20) [31]. Amputation is often necessary when the affected area is an extremity [5,31]. In cases of zygomycosis of the face, the operations may be disfiguring, necessitating plastic reconstruction.

Amphotericin B (AmB) is used for the treatment of zygomycosis. Liposomal AmB and other lipid formulations are widely used and allow the administration of higher doses (5–7 mg/kg) [69]. Posaconazole has recently been used successfully as salvage therapy for zygomycosis [39].

The prognosis in cutaneous zygomycosis is better than that in the other clinical forms of the disease, but mortality still remains at 31% [2]. Roden et al. found mortality rates of 10% in localized infection, 26% in cutaneous zygomycosis with deep extension and 94% in disseminated disease. In our review, the overall mortality rate was 30%, and specific rates were 4%, 29% and 83% in localized, extended and disseminated disease, respectively.

**Conclusions**

In summary, a high index of suspicion and early and aggressive management, making use of all available modalities, may improve the outcome of zygomycosis.
Transparency Declaration

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