Zygomycosis and diabetes mellitus

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Abstract

Zygomycoses are severe angio-invasive fungal infections that develop in immunocompromised and diabetic patients. Any episode of sinusitis not responding to short-term antibacterial therapy should evoke the diagnosis of zygomycosis in the latter population, especially in cases of a surrounding necrotic area. Appropriate diagnosis is obtained after careful direct examination of the sample and culture. Current therapy underscores the need to control glycaemia and acidosis in addition to the need for urgent administration of high-dose liposomal amphotericin B in combination with extensive surgery.

Keywords: Acidosis, diabetes, liposomal amphotericin B, sinusitis, surgery, zygomycosis


Introduction

Zygomycosis is a group of severe angio-invasive infections caused by common saprophyte filamentous fungi, the zygomycetes. These ubiquitous fungi can cause opportunistic infections with high lethality in diabetic patients. Whatever the route of contamination (inhalation of airborne spores, ingestion, or direct skin inoculation), the hyphae invade blood vessels, causing tissue infarction and necrosis [1–3]. In healthy individuals, innate immunity is sufficiently efficient to prevent infection, except in cases of massive contamination after traumatic inoculation of contaminated soil [4,5]. Patients with phagocytic dysfunctions due to neutropenia or ketoacidosis, or patients with high iron serum concentrations, are at high risk of developing zygomycosis [3]. These underlying conditions can influence the clinical presentation and outcome [1]. The rhinocerebral form of zygomycosis is the most frequently reported in the diabetic population.

In this article, we review data regarding diabetes-associated zygomycosis.

Epidemiology

The incidence of zygomycosis is seemingly increasing [6,7], at least in the population of patients with haematological malignancies. Several explanations are possible: longer survival of individuals with severe haematological malignancies, increased awareness of the infection on the part of physicians, improved diagnosis, and the prolonged use of voriconazole as prophylactic or empirical treatment in bone marrow transplant recipients [6,8,9]. Among 929 reported cases of zygomycosis in the literature, Roden et al. [4] showed that diabetic patients represented 36% of the total population, with type 1 diabetes representing 20% of the total number. Ketoacidosis was found in 48% of patients with type 1 diabetes and 34% of those with type 2 diabetes. The same authors also reported a decreased number of diabetic patients developing zygomycosis over time [4], a finding that is in marked contrast to the increased prevalence of diabetes in the world [10]. Such a decreased incidence of diabetes-associated zygomycosis led Kontoyiannis to speculate that the widespread use of statins in the diabetic population, at least in the Western world, might have resulted in the decreased rate of zygomycosis in this population [11]. Indeed, lovastatin has in vitro and in vivo activity against zygomycetes/zygomycosis [12,13], and statins are known immunomodulators that could help in the defence against zygomycosis [14].

However, through a collaboration between French public health authorities (Institut National de Veille Sanitaire) and the National Reference Centre for Mycoses and Antifungals, a population-based study of medical records of zygomycosis cases reported in France from 1997 to 2006 was performed to estimate the incidence of zygomycosis at the country
level. Eighty-four per cent of diabetic patients were aged more than 44 years, and a 9% yearly increase in the annual incidence rate of zygomycosis in the diabetic population was observed [15].

It is of note that, in a recent literature review of 157 zygomycosis cases occurring in children (0–18 years), diabetes mellitus was found in 15% (type I = 13%) and ketoacidosis in 10% [14,16].

A recent paper from a tertiary-care centre in North India also emphasized the emergence of diabetes-associated zygomycosis in the developing world. Indeed, 131 of 178 cases were observed in uncontrolled diabetic patients (73.6%), and, more importantly, zygomycosis led to a diagnosis of diabetes in 56 cases (42.7% of diabetes cases) [17]. A recent study collected 41 cases of rhino-orbital and rhino-orbito-cerebral zygomycosis between 1994 and 2006 in California. The authors reported that 83% of the patients had diabetes (only 59% had a known history of diabetes mellitus), and only 21% of 14 patients with corticosteroid-induced diabetes were receiving medication for diabetes [18]. Finally, among other high-risk populations that may develop zygomycosis, the presence of diabetes also influences the occurrence of the fungal infection. Indeed, during a prospective study involving patients with leukaemia and/or bone marrow transplantation, diabetes was found as an independent risk factor for the occurrence of zygomycosis [19]. In addition, Singh et al. recently showed that the presence of diabetes also significantly influenced the occurrence of zygomycosis in solid organ transplant patients [20].

**Pathophysiology of Diabetes-associated Zygomyosis**

Macrophages and neutrophils represent the major host cellular defences against zygomycetes. In addition to the neutrophil dysfunction classically reported during diabetes [21], low serum pH diminishes the phagocytic effect of macrophages and the chemotactic and oxidative burst of neutrophils, modifies the transferrin system (leading to more unbound iron, which is then utilizable by zygomycetes), and reduces the serum inhibitory activity against *Rhizopus* [21–24]. It is of note that a reduced neutrophil-related inflammatory response against *Rhizopus* has been described in diabetic rabbits [25]. A specific pathogenic role of hyperglycaemia itself has also been documented, in reducing the ability of macrophages to prevent *Rhizopus* germination [26]. In addition, ketones have been shown to alter the permeability of the blood–brain barrier [27], and this might contribute to the magnitude of cerebral involvement during diabetes-associated zygomycosis. Finally, it has been shown that diabetic mice are susceptible to an intra-ethmoidal challenge with $10^6$ *Rhizopus oryzae* spores, with 90% of diabetic mice dying (77% within 4 days) with viable fungi in brain and lungs, contrasting with the absence of death in control mice [23].

**Clinical Presentation of Zygomyosis in Diabetic Patients**

Among the diabetic population described by Roden et al., 66% presented with sinusitis, most often with cerebral (43%) or orbital (15%) involvement. Interestingly, no localized cerebral infection was observed in the diabetic population, suggesting that there is a nasal portal of entry in these patients. Lung involvement and cutaneous involvement were reported in 16% and 10% of cases, respectively. In another study, among 179 patients with sinus zygomycosis, 70% presented with ketoacidosis [28]. In the study from Reed et al., 83% of 41 patients with rhinocerebral zygomycosis were diabetics [18].

**Outcome of Diabetes-associated Zygomyosis**

The overall mortality of diabetic patients with zygomycosis reported in the literature is as high as 44% [4], and the subsequent death rate in children with ketoacidosis and zygomycosis is 25% [16]. However, more recent data from France have shown a case-fatality rate at hospital discharge of 9.2% in diabetic patients that remained stable over a 10-year period [15]. In cases of combination therapy using amphotericin B (AmB) and surgery, the survival rate was 79.6% in an Indian study involving mostly diabetic patients [17]. Overall, the case-fatality rate of patients with the rhinocerebral form decreases from 70% in patients treated with antifungals alone to 14% in patients who receive antifungals combined with surgical treatment [29].

**Contribution of Experimental Models to the Management of Diabetes-associated Zygomyosis**

Most experimental therapeutic data have been obtained in the diabetic ketoacidotic mouse model of disseminated zygomycosis designed by Ibrahim et al. from UCLA. In a first study, the investigators compared liposomal AmB (LAmB) (2, 5 and 7.5 mg/kg twice daily) with AmB (0.5 mg/kg twice
daily). High-dose LAmB increased the median survival time and overall survival, whereas the groups receiving low-dose LAmB and AmB had a survival time similar to that of controls. Thus, in this model, high-dose LAmB was more effective than AmB [30]. The same group then compared LAmB and AmB lipid complex (ABLCL) (7.5 and 15 mg/kg per day). In their model, LAmB [15] increased survival as compared to ABLCL (7.5 and 15 mg/kg per day), and LAmB, but not ABLCL (7.5 mg/kg per day), reduced the cerebral fungal burden. Thus, LAmB does better than ABLCL during experimental diabetes-associated zygomycosis [31]. The contribution of caspofungin was also examined. The authors showed that R. oryzae had an FKS gene, that caspofungin inhibited glucane synthase activity in crude R. oryzae membrane preparations, and, finally, that caspofungin at a low dose (0.5 mg/kg twice daily) improved the survival of mice infected with a small inoculum [32]. Interestingly, the same group also investigated the potential role of combination therapy with ABLCL (5 mg/kg per day) ± caspofungin (1 mg/kg per day). Combination therapy improved survival compared to monotherapy, whereas the combination arm failed to improve organ clearance. In this model, the prophylactic antifungal combination was not more effective than monotherapy [33].

In addition, the impact of iron chelation has been studied during diabetes-associated zygomycosis. Deferiprone exhibited fungastic activity at 24 h and fungidal activity at 48 h against R. oryzae, with an efficacy equivalent to that of LAmB in mice when measured by survival rate and brain fungal burden. In this model, free iron reversed protection. Another recent chelator, deferasirox (Exjade), was also effective (as measured by time to death/fungal burden) in ketoacidotic mice, was synergistic with LAmB, and increased the inflammatory response [34,35]. From a clinical perspective, in a preliminary case report, a 7-day oral course (15 mg/kg per day) of deferasirox as salvage therapy was effective in a diabetic patient with rhinocerebral zygomycosis [36].

Following the demonstration of posaconazole activity against zygomycetes in vitro and its potential efficacy in experimentally infected animals, the clinical potential of posaconazole in patients with zygomycosis was retrospectively evaluated in two studies in which the drug was given as second-line therapy in individuals who had been treated with other antifungals that were not tolerated or had an insufficient effect. Response rates of 60% in 91 patients and 79% in 24 patients, respectively, were reported [39,40]. It should be remembered that posaconazole can only be administered orally and carries the risk of drug–drug interactions, as is typical for the azole class of antifungal compounds [41]. Moreover, steady-state plasma levels are obtained only after 7–10 days of treatment [42]. Without representative data on first-line treatment, we consider that posaconazole should not be used as first-line treatment of zygomycosis. If the intravenous formulation of posaconazole becomes available, then a clinical trial comparing intravenous posaconazole with LAmB could be performed, and could provide potentially interesting perspectives on the management of zygomycosis.

The options and limitations of AmB deoxycholate (AmBD) and LAmB as first-line treatment for zygomycosis have been assessed in several retrospective analyses. A recent large retrospective survey, which included all cases of zygomycosis that had been described in the literature, reported a 61% survival rate for AmBD as compared with 69% for LAmB [43]. Two other retrospective studies evaluated the efficacy and safety of the alternative lipid formulations of AmB in the setting of second-line treatment of zygomycosis. The series of patients treated with ABLCL at a dose of 5 mg/kg per day was characterized by a wide variety of risk factors, and showed a 75% response rate for this drug [44]. AmB colloidal dispersion given in doses between 2 and 6 mg/kg per day gave an objective response in 60% of cases [45].

A recent study retrospectively compared patients treated with polyene for rhino-orbito-cerebral mucormycosis with those treated with a polyene–caspofungin combination [18]. The success rate was higher for patients treated with the combination. It is of note that 22 patients were treated with AmB lipid complex, which exhibits reduced central nervous system penetration in the rabbit model in comparison with AmB or LAmB [46].

Another recent study reported an increased mortality rate in haematology patients with zygomycosis for whom AmB-based front-line therapy was delayed (treatment initiation ≥6 days after diagnosis resulted in a two-fold increased mortality rate) [47], and extrapolation of these data to the diabetic population seems acceptable.

**Therapeutic Management of Diabetes-associated Zygomycosis**

Prospective therapeutic trials on the management of zygomycosis have not been reported. Most new antifungals, including voriconazole, are not active against zygomycetes [37], whereas polyenes and posaconazole display, at least in vitro, activity against zygomycetes [38]. Posaconazole has limited activity against certain zygomycetes. In a murine model of zygomycosis, posaconazole showed partial efficacy against *Mycocladus corymbifer* and a dose-dependent response effect in mice infected with *Rhizopus microsporus* [38].
In summary, lipid derivatives of AmB are probably more effective and better tolerated than AmBD in the treatment of zygomycosis. Whether higher dosages of LAmB would be of benefit for this indication remains unknown. Indeed, the area under the curve of LAmB is maximal at a dose rate of 10 mg/kg per day; at this level, the drug can saturate mononuclear cells and allow greater accumulation of AmB in the lungs, which are a major target of infection by the agents of zygomycosis [48]. Moreover, high doses of LAmB effected a clinical response in patients who failed to respond to conventional dosages [49,50]. In an attempt to provide an answer to the question of adequate dosing, we started in May 2007 a prospective national phase II multicentre study (‘Ambizygo’ trial) in France to evaluate the maximally effective and tolerated dose of LAmB (up to 10 mg/kg per day) as first-line treatment for zygomycosis in 27 adults and children. In addition, LAmB + iron chelation vs. LAmB is currently under investigation in patients with zygomycosis in the USA.

Conclusions

In conclusion, diabetes-associated zygomycosis is encountered with a variable epidemiology, according to country. Its pathophysiology remains incompletely understood, and diabetes now represents a significant risk factor in previously immunosuppressed patients. Rhinocerebral mucormycosis needs early recognition and strict control of glycaemia/pH, and benefits from high-dose LAmB and aggressive surgery followed by long-term oral posaconazole therapy.

Transparency Declaration

FL declares no conflicts of interest; OL is a member of the speaker’s bureau of Gilead, Schering Plough, Pfizer, Astelles and Merck.

References