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ORIGINAL ARTICLE

Palatal zygomycosis: experience of 21 cases

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OBJECTIVE: To present a clinical report of palatal zygomycosis, its epidemiological, mycological features, and our treatment experience.

DESIGN: Retrospective report.

SUBJECTS AND METHODS: This is a 25-year long retrospective trial of clinically and mycologically proven cases of zygomycosis. Some patients underwent a biopsy of the palatal lesion and autopsy. This study reports the treatment experience with amphotericin B alone and in combination with itraconazole and fluconazole.

RESULTS: Twenty-one cases (18.75%) of zygomycosis with palatal involvement were included in the study, from a total of 112 cases screened. Mean age was 36.5 years, with 18 adults and three children. The associated predisposing factors were: ketoacidotic diabetes (five type-1 and 15 type-2), and acute leukaemia in one patient. The clinical varieties were as follows: 19 cases of rhinocerebral (RC) involvement and two disseminated cases. Palatal ulcers occurred in 3/21 early cases (14.3%) and in 16/21 cases after the nasal involvement. All patients received amphotericin B; in four patients, it was combined with itraconazole and four with fluconazole. Clinical and mycological cure was achieved in 4/21 patients (19.04%).

CONCLUSION: Zygomycosis with palatal involvement occurs in around 18% of cases, usually associated with RC modalities; it has an acute and generally lethal course.

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Keywords: zygomycosis; mucormycosis; palatal; ketoacidotic diabetes; rhinocerebral; *Rhizopus*

Introduction

Zygomycosis is an opportunistic infection caused by a series of fungi of the *Mucorales* group, with the genus *Rhizopus* as predominant. They are ubiquitous fungi, usually harmless, characterized by causing acute rhinocerebral (RC), pulmonary, cutaneous, gastric and disseminated manifestations. Pathologically, the disease involves thrombosis, vascular invasion, ischaemia and infarctions. It occurs primarily in decompensated patients with diabetes of both types, and in immunocompromised patients, particularly in those with neutropenia or in transplant recipients treated with corticosteroids. *Mucorales* by regulating cause lesions in pre-disposed patients (Warnock and Richardson, 1982; Rinaldi, 1994; Eucker *et al*, 2001; Damante and Fleury, 1998; Jayalakshmi *et al*, 2007).

Zygomycosis is a rapidly progressing disease favoured by pre-disposing factors; it involves an acute course and is a classical nosocomial condition. The prognosis is usually poor, with high-mortality rates, which are influenced by the timeliness of diagnosis, and above all, by the patients' status. The oral (palatal) involvement has been reported since the first descriptions of the disease and is reported relatively frequently in the literature.(Van Der Westhuijzen *et al*, 1989; Jones *et al*, 1993; Kyrmizakis *et al*, 2002; Jayachandran and Krithika, 2006; Auluck, 2007). Our purpose was to present a clinical retrospective report, its epidemiological, mycological features, and our treatment experience.

Subjects and methods

This is a 25-year retrospective report (1982–2006) of zygomycosis with oral involvement at the palatal level. The case history of all patients was taken and the disease was proven by means of mycological tests, as follows: direct KOH (20%) examination; cultures with the routine Sabouraud dextrose agar and yeast extract agar media, incubated at 28°C for 5–7 days. The colonies grown were identified based on their macromorphology and micromorphology (reproduction modalities) and thermal tests. A biopsy of the palatal region was taken in some patients and, in cases of death, some of them underwent autopsy (with previously obtained consent). Plain X-rays were obtained in all patients and in some of them, plain computed tomography and helical computed tomography were also performed.

Once the proven diagnosis of zygomycosis was made, comprehensive treatment was started to

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stabilize the patients' pre-disposing factors; therapy with amphotericin B (Amb) at a dose of 0.5–0.75 mg kg^{-1} day^{-1} was instituted, and the corresponding control tests (renal and liver function tests and blood tests) were performed. In some patients, the above mentioned therapy was combined with itraconazole (200–400 mg day^{-1}) or fluconazole (200–400 mg day^{-1}), as concomitant therapy, or as maintenance therapy in case of patients with many side effects of AmB treatment (renal).

Results

During the study period (25 years), a total of 112 cases of RC and disseminated zygomycosis were proven, 21 of which (18.75%) had oral involvement at the palate level, and constituted the cases reported herein. Nineteen cases had only palatal involvement and two had involvement of the palate, the alveolar buccae and the maxilla. Fifteen of the 21 cases were classified as black necrotic ulcers and 6/21 were white necrotic ulcers. Table 1 shows the main patients' demographics.

Table 1 shows that 18/21 cases were adults, two adolescents and three were children <15 years of age.

Table 1 Demographic data

Data	*Cases (%)*
Age	
Youngest	8 years
Oldest	68 years
Mean	36.5 years
Standard deviation	17.73 years
Gender	
Male	12 (57.2)
Female	09 (42.8)
Age groups	
Adults	18 (85.7)
Children	3 (14.3)
Occupation	
Scholars	3 (14.3)
Employees	10 (47.5)
Home	6 (28.6)
Students	2 (9.5)
Duration of disease	
Shortest	5 days
Longest	18 days
Mean	8.3 days
Pre-disposing factor	
T-1/KA diabetes	5 (23.8)
T-2/KA diabetes	15 (71.5)
Leukemia (T2-ALL)	1 (4.7)
Clinical form	
Rhinocerebral	19 (90.4)
Disseminated	2 (9.6)
Mycological tests	
Direct exam	21 (100
Culture	20 (95.2)
Aetiology	
Rhizopus oryzae	12 isolates (57.1)
Rhizopus microsporus	1 (4.7)
Mucor circinelloides	5 (23.8)
Absidia corymbifera	2 (9.4)
Histopathology	
Biopsies	5 (23.8)
Autopsies	3 (14.3)

T-1, type-1; T-2, type-2, KA, ketoacidotic; T2-ALL, type-2 acute lymphoblastic leukaemia.

The cases of children and adolescents had ketoacidotic type-1 diabetes (KA-T1D). Of the 16/21 adults, 15 had KA-T2D and one had type-2 acute lymphoblastic leukaemia (T2-ALL). Palatal ulcers developed from two clinical presentations, 19/21 cases with the RC variety (RC) and 2/21 with disseminated varieties, which also started as RC. When both patients and their families were questioned, they reported a mean course of disease of 9.5 days, and the onset of the palatal ulcer occurred after 5 days in the earliest case and after 21 days in the latest one. Moreover, the palatal involvement was reported as having an independent onset in 3/21 cases (14.3%), and after the nasal manifestations (sinusitis) in 16/21 cases (85.7%) (Figures 1 and 2).

Table 2 shows the outcomes of treatment response. All cases received background therapy with standard AmB, except for one, who got liposomal AmB (L-AmB). In 8/21 cases, the treatment was combined with triazole derivatives; in four with itraconazole and in four with fluconazole. Surgical lavage was performed in four cases. Complete treatment response occurred in 4/21 cases (19.04%); the remaining patients, or 80.96%, had treatment failure, and all of them died. The four cured cases had RC involvement, all of them associated with ketoacidotic diabetes (3, T-2 and 1, T-1). Three of the cured patients were adults and one was a child.

Concerning side effects, 20/21 cases had various renal alterations and in five of them AmB was discontinued. Triazole agents did not have any side effects.

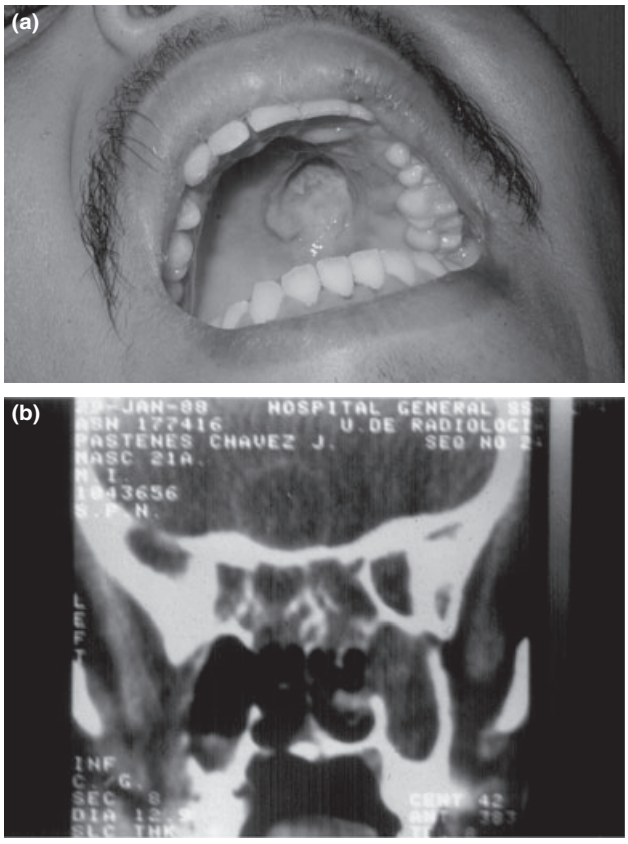

Figure 1 (**a**) Palatal ulcer in adult. (**b**) Palatal perforation and cerebral damage (computed tomography)

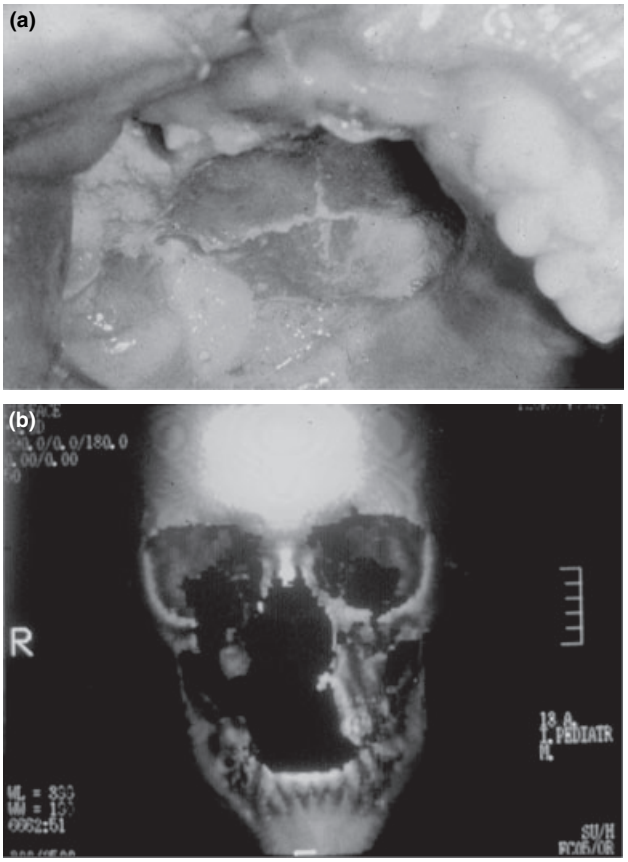

Figure 2 (**a**) Palatal ulcer in a child. (**b**) Maxillar and orbital destruction (3D computed tomography)

Discussion

Zygomycosis consists of a series of conditions that may be divided into two groups: those caused by *Mucorales* fungi (mucormycosis) and those caused by entomophthoral fungi (entomophthoramycosis). Many authors prefer the term mucormycosis, an opportunistic entity that is relatively frequent (Warnock and Richardson, 1982; Rinaldi, 1994; Eucker *et al*, 2001). A recent report of 929 cases by Roden *et al* (2005) states that this disease has truly increased in the past two decades. In our model, we also observed an increment; we even see it more frequently than aspergillosis, probably because we have many patients with decompensated diabetes mellitus.

The oral involvement of *Mucorales* fungi has long been known. However, only isolated reports can be found in the literature, and that is why we believe that this case series adds both experience and knowledge on this disease (Hauman and Raubenheimer, 1989; Van Der Westhuijzen *et al*, 1989; Jones *et al*, 1993; Damante and Fleury, 1998; Kim *et al*, 2001; Kyrmizakis *et al*, 2002; Pandey *et al*, 2004; Tugsel *et al*, 2004; Huang *et al*, 2005; Jayachandran and Krithika, 2006). Oral involvement may occur at different levels. The most frequent manifestations are palatal ulcers, which are almost always necrotic, well-delimited, with well-defined borders, and may be either black or white; they may have a torpid course and at times may form very rapidly, particularly when they are associated with various states of diabetic decompensation (ketoacidosis) or with neutropenia. It is important to stress that clinically these manifestations cannot be distinguished from those of aspergillosis (Karabulut *et al*, 2005); however, the latter occurs mainly in immunocompromised patients and is exceptional among diabetics (Roden *et al*, 2005). Oral zygomycosis may result from rapid lysis of the maxilla and other adjacent structures; it has been reported in the alveolar ridge, lips, cheeks, tongue and mandible (Van Der Westhuijzen *et al*, 1989; Jones *et al*, 1993; Damante and Fleury, 1998; Kyrmizakis *et al*, 2002; Jayachandran and Krithika, 2006). Clinically, most cases in our report were black necrotic ulcers, all of them involving the palate and only in 2/21 cases did they spread to the maxilla and alveolar buccae.

Most cases of oral zygomycosis are related with the RC forms. As was mentioned above, disease progresses rapidly and tends to spread and involve deep structures thus affecting several bones (palate, ethmoid and sphenoid bones, etc.); in most cases, the dissemination converges in the nasal sinuses and cranial nerves, and the disease finally affects the brain (Van Der Westhuijzen *et al*, 1989; Jones *et al*, 1993; Rinaldi, 1994; Damante and Fleury, 1998; Kyrmizakis *et al*, 2002; Jayachandran and Krithika, 2006). It is important to stress that in our study, this occurred in 21/112 cases or 18.75%, a figure that explain us that approximately 20% of the cases in a large series have palatal involvement. Among our cases, only 3/21 began in the mouth and the RC process developed later. This is important because the stomatologist may be the first practitioner to make the diagnosis. There are reports of the disease resulting from tooth extractions in patients with pre-disposing factors (Kim *et al*, 2001). It is important to bear in mind two clinical entities when making the differential diagnosis: 'lethal midline granuloma', which is a variety of lymphoma, and Wegener's

Table 2 Treatment outcomes with various therapies

Treatments	*No. cases*	*Dose*	*No./clinical form*	*Mean treatment period*	*Response*
AmB	12	0.75 mg–1.0 g kg^{-1} day	12RC	21 days	2/cure 10/death
Liposomal AmB	1	0.75 mg kg^{-1} day^{-1}	1/D	12 days	1/death
AmB + itraconazole	4	0.75 mg–1.0 g kg^{-1} day^{-1} 400 mg^{-1}	4/RC	23 days	4/death
AmB + fluconazole	4	0.75 mg–1.0 g kg^{-1} day^{-1} 400 mg^{-1}	4/RC 1/D	25 days	2/cure 2/death

AmB, amphotericin B; RC, rhinocerebral; D, disseminated.

granulomatosis. Both of them may present with a similar clinical picture including palatal perforation, which, in these conditions, is chronic (Califano *et al*, 1998; Damante and Fleury, 1998; Kyrmizakis *et al*, 2002; Tugsel *et al*, 2004) (Figures 1 and 2).

The analysis of the patients' demographics (Table 1) shows that the disease may occur both in adults and in adolescents and children. In the two latter groups, it is mainly associated with type-1 diabetes, which more easily becomes decompensated and produces ketoacidotic states (Warnock and Richardson, 1982; Rinaldi, 1994; Eucker *et al*, 2001; Roden *et al*, 2005). Moreover, there are also reports that associate it with neutropenia, mainly caused by acute leukaemia (Hauman and Raubenheimer, 1989; Tugsel *et al*, 2004; Roden *et al*, 2005; Dogan *et al*, 2007). Recently, the factors that influence the development of the disease have been clearly explained. The cases with palatal involvement are particularly associated with patients with ketoacidotic diabetes and neutropenia. In the former, the disease results from the acidosis that causes the release of iron ions (Fe^{2+}) attached to serum proteins; these ions are fundamental to *Mucorales* enabling them to infect the host's cells. The first factor is the capacity of fungi to incorporate into their energy metabolism the excessive ketone bodies in these patients. Both processes work jointly (Spellberg *et al*, 2005). The second relevant factor is the impairment of cell-mediated immunity, which occurs particularly in neutropenic patients, as the function and migration of neutrophils and macrophages are disrupted or impaired (Weinberg *et al*, 1993; Eucker *et al*, 2001; Roden *et al*, 2005; Spellberg *et al*, 2005; Chayakulkeeree *et al*, 2006; Kontoyiannis and Lewis, 2006). The available AIDS-related reports are exceptional (Moraru and Grossman, 2000; Roden *et al*, 2005). In our study, virtually all patients had ketoacidotic diabetes and only one case was associated with acute leukaemia.

Zygomycosis is usually an acute condition; our data indicate that it develops in a mean of 8.3 days and oral (palatal) ulcers developed at 9.5 days; thus the importance of making an early diagnosis. In cases of clinical suspicion, mycological tests, such as direct examinations, are extremely effective. Usually, clearing substances like KOH (10–20%), chlorazol black or dimethyl sulfoxide (20%) are used. They allow seeing under the microscope thick, dichotomic, branched, cenocytic hyphae; this is a characteristic image that confirms the diagnosis. In our report, these structures were present in all cases (100%). Cultures are useful to confirm the species; growth occurs in approximately 5–7 days. It is important to mention that these fungi are environmental pollutants and may lead to false positive results (out of contamination), thus the importance of observing the fungal parasitic forms (cenocytic hyphae) and correlating them with the clinical features (Warnock and Richardson, 1982; Rinaldi, 1994; Eucker *et al*, 2001; Kontoyiannis and Lewis, 2006) (Figures 3 and 4).

The main aetiological agent is *Rhizopus* sp. and, to a lesser extent, other species may be isolated, like *Mucor, Absidia, Cunninghamella, Rhizomucor and Apophysomyces,* among others (Roden *et al*, 2005). The major causative agent in our report was *R. oryzae*, which coincides with other series (Hauman and Raubenheimer, 1989; Van Der Westhuijzen *et al*, 1989; Jones *et al*, 1993; Damante and Fleury, 1998; Kyrmizakis *et al*, 2002; Pandey *et al*, 2004; Tugsel *et al*, 2004; Huang *et al*, 2005; Roden *et al*, 2005; Jayachandran and Krithika, 2006; Kindo *et al*, 2007). It is important to emphasize that the virulence of strains is difficult to evaluate, but differences have indeed been reported (*in vitro*) in the susceptibility of fungi to various antifungals. However, most authors agree that the most important factor for therapeutic success is the antifungal agent, but the possibility of stabilizing the patient is of the utmost importance; for example, normalizing the hyperglycaemia and ketoacidosis in the case of diabetics and controlling the neutropenia in the case of patients with leukaemia (Eucker *et al*, 2001; Greenberg *et al*, 2004; Kontoyiannis and Lewis, 2006; Mohindra *et al*, 2007) (Figure 5).

Most treatment reports indicate that zygomycosis is a disease with a poor prognosis. In our experience, when patients present during early diabetic decompensation with minor immunocompromise, together with an early diagnosis, therapeutic success is easier to achieve

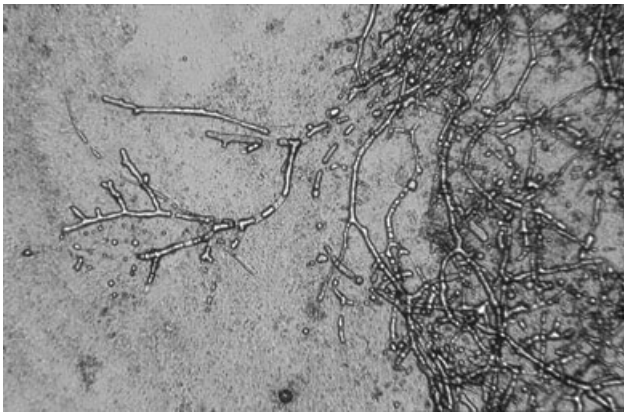

Figure 3 Direct exam, multiple non-septated hyphae (KOH, 20×)

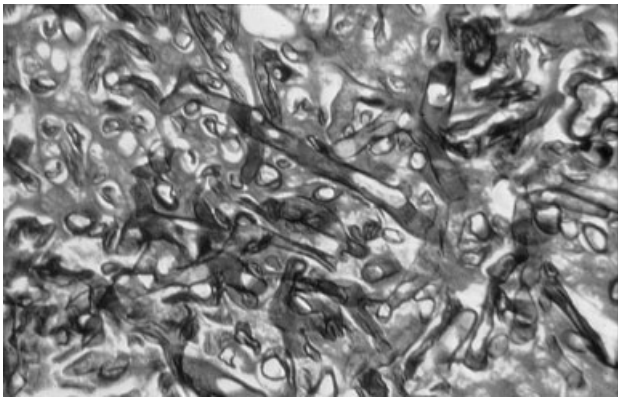

Figure 4 Histopathology, multiple non-septated hyphae (Grocott, 40×)

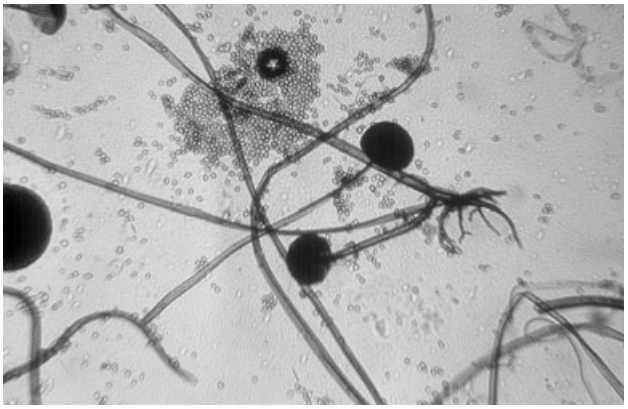

Figure 5 *Rhizopus oryzae*, direct exam (Cotton blue, 10×)

(Greenberg *et al*, 2004; Kontoyiannis and Lewis, 2006; Mohindra *et al*, 2007).

In our case series, 3/21 cases (19.04%), achieved cure, with a cure rate similar to that reported in other communications (Warnock and Richardson, 1982; Rinaldi, 1994; Eucker *et al*, 2001). However, in an analysis of the cases reported in dental literature, Jones *et al* (1993) reported a therapeutic success rate of 42%. Most authors consider that the treatment of choice is still AmB. Nevertheless, its side effects are a drawback, particularly renal ones. Many of the therapeutic failures are even because of the fact that patients develop renal intolerance quite easily. The combination of AmB with other triazoles may produce higher therapeutic response rates, but the control of pre-disposing factors still plays a major role (Greenberg *et al*, 2004; Spellberg *et al*, 2005; Kontoyiannis and Lewis, 2006).

Other therapeutic aids are surgical lavage, which allows removing the necrotic tissue together with a large number of fungal elements. Hyperbaric oxygen has also proven useful, as *Mucorales* are highly susceptible to it (Greenberg *et al*, 2004; John *et al*, 2005).

A new triazole derivative has been tested recently, posaconazole, the compound of this type with the greatest *in vitro* activity against *Mucorales*. It has been used alone or in combination with AmB with good results and reports of a cure rate as high as 80%. We have not tried this drug, but we think it represents a new treatment choice against zygomycosis (De Decker *et al*, 2006; Greenberg *et al*, 2006; Rutar and Cockerham, 2006).

Author contributions

Bonifaz A created and designed the study, Macias B and Paredes F were involved in the stomatology study, Arias P the study of the cases, Ponce R the final review and Araiza J the mycology studies and statistical analysis.

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