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Zygomycete Fungi Infection in Colombia: Literature Review

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Abstract
Purpose of Review This review summarizes the reports of Zygomycete fungi infection in Colombia, as well as include the geographical distribution, species identification, and treatment of those clinical cases.
Recent Findings Zygomycosis is not a new disease. However, the use of molecular tools has allowed the identification of some recently described species as their causal agents.
Summary In Colombia, the prevalence of zygomycosis is unclear because reporting is not mandatory and because in many cases the etiological agent was not identified. It is important to establish the mandatory reporting of cases, to know the circulating fungal species, the treatment used, and the outcome of the patients. Regarding the treatment, amphotericin B remains as the best alternative. To our knowledge, this is the first compilation of the published cases of zygomicosis in the country.

Keywords Fungal infections · Zygomycosis · Mucormycosis · Entomophthoromycosis · Colombia

Introduction

In 2016, Spatafora et al. proposed the phylogenetic classification of zygomycete fungi in two phylum or major clades: Mucoromycota and Zoopagomycota. The phylum Mucoromycota contains the Subphylum Mucoromycotina, which includes the genera *Saksenaea*, *Apophysomyces*, *Mortierella*, *Syncephalastrum*, *Cokeromyces*, *Cunninghamella*, *Rhizopus*, *Rhizomucor*, *Actinomucor*, *Leichtheimia*, and *Mucor*, among others, and the phylum Zoopagomycota includes the genus *Conidiobolus* and *Basidiobolus* in the entomophthoromycotina subphylum [1••, 2–4].

The pathogenic species classified in the Subphylum Mucoromycotina and those classified in Entomophthoromycotina are strongly different in ecologic, epidemiologic, morphologic, and clinicopathologic characteristics. While species of phylum Mucoromycotina are distributed worldwide in the environment, soil, vegetation, and organic matter; those of phylum Entomophthoromycotina are considered tropical and subtropical fungi [5]. In all cases, the most frequent routes of infection include the inhalation of spores disseminated in the air and the direct inoculation by skin trauma and contaminated food materials, such as fermented milk, fermented porridge, and herbal/homeopathic remedies [6, 7].

In 1976, Ajello et al. proposed the name zygomycosis as an inclusive name for two diseases: mucormycosis caused by members of Mucoromycotina and entomophthoramycosis caused by species in the order Entomophthorales; however, the name zygomycosis had more often been used as a synonym only for mucormycosis. Today, the name zygomycosis has been increasingly used instead of name mucormycosis for two reasons: (1) mucormycosis sounds as though the disease is caused by Mucor spp., and (2) some infections caused by the species of Entomophthorales, although rare and restricted in humans to genera Conidiobolus and Basiodobolus, are clinically an epidemiologic distinguishable from mucormycosis [1••, 8, 9].

In histopathological evaluation, the size and the morphology of hyphae of the two phylum grown in host tissues are indistinguishable, but in some cases, we can see the special spores from *Conidiobulus* [9]. Nevertheless, the infections caused by Mucorales are characterized by a progress rapidly

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along with a wide tissue destruction and direct invasion of blood vessels with easy hematogenous spread to another location [8], and the Entomophtoromycosis infections are usually characterized by chronic subcutaneous, progressive, granulomatous, and inflammatory subcutaneous tissue lesions, and mainly occurred in host non-inmunocompromised, and it is related with tropical endemic zones.

Colombia is a country located in the extreme northwest of South America. Its territory presents a variety of reliefs which causes the simultaneous presence of several climatic zones; however, more than 80% of the territory presents a warm climate (temperatures above 24 °C/75.2 °F). The population in the country was estimated for 2018 close to 50 million inhabitants (49.769.115) for the Colombian Department for National Statistics [10].

In Colombia, the Zigomycete fungi have been described in the air [11] and the mud [12]. However, any mycosis including the zygomycosis is not a disease considered as epidemiological surveillance; therefore, its notification is not mandatory, and there are no exact data of its prevalence.

For this review, an exhaustive search was made in Google, MEDLINE, and Google Scholar searching for specific genera, as well as the terms "zygomicosis," "phycomycosis," "mucormicosis," "Mucorales," "Zygomycetes," and "Colombia," including all articles in English or in Spanish. We considered reported cases with any clinical, epidemiological, and laboratory information to identify an organism as the cause of the zygomycosis. We further investigated the search results for single-case reports or case series with compiled data and the individual references listed in each publication, for ascertainment of additional cases.

Collected patient data included gender, age, sex, city of probable infection, year of isolation, clinical sample, immune status, and predisposing factors and diagnosis (pathology or microbiological). Data on antifungal therapy were included in case summaries when available. Furthermore, outcomes included recovery and death caused by Zygomycete infection or other causes.

Results

Thirty-eight articles of Zygomycete fungi infection in Colombia from 1961 to 2017 were identified. Four articles included data referenced in other articles and were not considered so as not to repeat data. The total database thus consisted of 60 cases reported in 34 published reports in 56 years [13–32, 33•, 34•, 35–46]. Making a grouping by age life stages/age groups with children 0–17, adult 18–55, and aged > 56 years, the number of cases was the following 15 (25%), 28 (47%), 6 (10%), respectively, and 11 (18%) no data. In terms of gender, a total of 31 (52%) of the cases of zygomycosis occurred in males, 13 (22%) in females, and no data 16 (27%).

The survival rates attributed to these infections, per the data obtained, were percentage of deaths 48%, life 36%, and undated 16%.

Of the 26 cases where culture was performed, 7 (27%) were due to *Conidiobolus* sp., 12 (46%) to *Rhizopus* sp., *Mucor* sp., *Apophysomyces* sp., *Saksenaea* sp., 2 isolates for each genus and *Lichteimia* sp. 1 (4%). In two cases, molecular confirmation of the agent was made.

No reports were found for infections caused by *Cunninghamella bertholletiae*, *Rhizomucor pusillus*, *Syncephalastrum racemosum*, *Cokeromyces recurvatus*, *Actinomucor elegans*, or *Mortierella wolfii.* No cases of simultaneous infection by more than one fungus were found.

Nine patients did not receive treatment with antifungal agents. Amphotericin B was the most used antifungal agent (19 cases) and the first case in receiving it dates from 1967.

The demographic characteristics and underlying conditions are summarized in Table 1, and the Colombian departments (states) to which the publications cases belong are described in the Figure 1.

Discussion

Zygomycoses are widely distributed entities, although they are infrequent. The first case of zygomycosis as a human disease was reported in 1885, and the first reported case of zygomycosis in Colombia was reported 76 years more later, by Trujillo in 1961 [13, 47].

In Colombia, cases of zygomycosis are widely distributed in the country, without an obvious geographical limitation. Nevertheless, because zygomycosis is not a notifiable disease and there is not national report, these data may be underestimated. In a recent study, Alvarez et al. estimated the annual incidence of mucormycosis in Colombia in 99 cases, with a rate/100,000 inhabitants in 0.2 [48••].

Zygomycete fungi have a great capacity to cause devastating diseases in people without underlying disease, and their cutaneous inoculation can have important consequences [4]. It is important to note that several patients in this review did not have a triggering factor, but they had been exposed to traffic accidents, cosmetic surgery, or natural phenomena (avalanches) that facilitated the traumatic inoculation of the fungus, causing necrotizing fasciitis [20, 34•, 37, 46].

The identification of the fungi can be overlooked: the size and the morphology of the hyphae of the two phylum grown in the tissues of the host are indistinguishable [9], the sporulation of rare fungi (*Saksenaea* and *Apophysomyces*) does not occur in the media of culture routinely used in clinical laboratories [34•, 37], and in some cases, prior training or the use of advanced tools to reach identification at the species level is needed [4]. Thus, to continue recovering those organisms, we strongly recommend the permanent training of microbiology

Table 1 Epidemiological data on reported cases of publicated Zygomycete fungi infection in Colombia

Patient parameter	Apophysomyces	Saksenaea	Conidiobolus	Common Mucoromycotina (Mucor, Rhizopus, Leichtheimia)	No identification
Agent, no. of cases	*A. elegans* (1) *A. variabilis* (1)	*S. vasiformis* (1) *S. erythrospora* (1)	*C. coronatus* (9)	*Lichtheimia* (1) *Mucor* (2) *Rhizopus* (12)	22
Year of publication (range)	2004–2017	1984–2016	1967–2016	1987–2017	1961–2017
Age range (year)	7–35	26–29	9–56	19–63	0–70
No. and % of male patients	2 (100%)	2 (0%)	8 (89%)	9 (60%)	10 6 (Sin data)
Underlying conditions				a.1	a.2
a. Hematological malignancy				b.2	b.1
b. Diabetes				c.3	–
c. Transplantation	d.2	d.2	d.9	d.9	d.5
d. None					e.2
e. Malnutrition					f.1
f. Prematurity					g.7
g. Others					
Predisposing factor:	a.2 (Post traffic	a.1 (Post IM	–	–	a.1 (Wasp sting)
a. Trauma	accident)	injection)	b.9	b.9 (Post avalanche)	–
b. Unknown	–	–	–	–	–
c. Health care	–	c.1 (Post surgery)			
Clinical syndrome reported	Necrotizing fasciitis (2)	Necrotizing fasciitis (2)	Rhino entomophthoromycosis (9)	Necrotizing fasciitis (10) Rhinofacial mucormycosis (1) Rhinocerebral mucormycosis (3) Rhinoorbitocerebral mucormycosis (1)	Rhinocerebral mucormycosis (2) Rhinoorbital mucormycosis (1) Gastrointestinal mucormycosis (3) Invasive mucormycosis (6) Orbit cerebral mucormycosis (1) Subcutaneous mucormycosis (1) Systemic entomophthoromycosis (1) Rhinoenthomophthoromycosis (1) Pulmonary mucormycosis (1) No date (5)
Pathology identification	2 (100%)	2 (100%)	4 (44.4%)	13 (86.66%)	22 (100%)
Culture identification	2 (100%)	2 (100%)	6 (66.6%)	15 (100%)	0
Treatment	Amphotericin B, Posaconazole (2)	Amphotericin B (1) Amphotericin B and caspofungin (1)	Amphotericin B (1) Itraconazole (7) No date (1)	Anphotericin B (7) Amphotericin B, posaconazole (2) None (6)	Amphotericin B (6) Amphotericin B and caspofungin (1) Itraconazole (1) Posaconazole (1) Voriconazole (2) Fluconazole (1) None (3) No date (7)
Outcome	1 Alive 1 Dead	1 Alive 1 Dead	9 Alive	5 Alive 10 Dead	6 Alive 15 Dead 1 No date
References	22, 37	34, 44	17, 18, 20, 32, 36, 42	16, 21, 24, 27, 29, 35, 45, 46,	13, 14, 15, 19, 23, 25, 26, 28, 30, 31, 33, 41,

Guajira	1
Sucre	1
Santander	1
Cesar	1
Cundinamarca	2
Córdoba	3
Antioquia	4
Choco	5
Valle	9
Tolima	9
No data	24
Total	60

Fig. 1 Colombian departments with information about cases of Zygomycete fungal infection

professionals, an update of the epidemiology of these fungi by health personnel, and the use of tools in the laboratory that facilitate the recovery and timely identification.

In this review, all patients had infection documented either histologically or by culture, and only in two cases, the identification of the agent was confirmed by molecular methods [34•, 37].

Rhizopus species were the most commonly recovered organisms. These data are consistent with other publications that cite this agent as the zygomycetes most frequently isolated [4, 48••].

We did not find reports of infections caused by *Cunninghamella* sp., *Rhizomucor* sp., *Syncephalastrum* sp., *Cokeromyces* sp., *Actinomucor* sp., or *Mortierella* sp. These data agree with those published by Gomes et al. (2011), who reported a very low global occurrence (range 0–4%) [4].

Entomophthorales organisms caused 15% of all zygomycoses. Eight of nine patients were male; none of the patients presented some underlying condition. In two patients, the diagnosis was made by pathology; in three cases, it was made by culture, and in other three cases, the diagnosis was made by culture and pathology. Of infections due to Conidiobolus species, all (9/9) were cutaneous, and all the patients survived. No cases of basidiobolomycosis were reported.

Interestingly, all cases of conidiobolomycosis were confined to a geographic area (Córdoba, Antioquia, Chocó), which in our opinion could indicate possible limited common foci of infection or limitations in the diagnosis of these fungal infections in other parts of the country.

About the treatment, of the 60 cases reviewed, 28 (46.66%) were treated with some form of antifungal chemotherapy. Survival in this group was 64% (18 of 28 patients).

Of these 28 patients, 19 (68%) received amphotericin B: *Conidiobolus* sp. (2), *Apophysomyces* sp. (2), *Saksenaea* sp. (2), *Rhizopus* sp. (6), *Mucor* sp. (2), not identified (5). Survival in this group was 58% (11 of 19 patients). Treatment with amphotericin B alone or in combination with another antifungal was the most used.

A total of nine patients (15%) received no treatment for their infection (one case in 1961, two case in 1965, and six cases in 1988). In all those, the outcome was death [13, 46, 49].

Zygomycosis (mucormycosis) caused by environmental molds is usually fatal and only appears in critically ill patients with profound neutropenia and, in many cases, in patients with metabolic acidosis. In general, the predisposing factors for suffering zygomycosis in Colombia are the same as those

described in the literature. In addition, its appearance is sporadic and accidental, with no outbreaks described.

Conclusions

Recent studies have described the role of iron release in metabolic acidosis and the correlation of this in the logarithmic growth of the fungus. Based on these findings, the combined use of iron chelating substances for the treatment of mucormycosis has been proposed. However, the few clinical studies carried out have no conclusive results [50–52]. In Colombia, there are no records of therapeutic approaches that include the use of chelating iron molecules in the treatment of these fungal infections.

Because the time of consolidation of the disease is sudden and confirmation of the etiological agent by the laboratory is usually delayed, it would be important to develop biomarkers for the differential diagnosis with other infectious etiologies, which provide tools to choose a timely and appropriate treatment.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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