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Mucormycosis in immunocompetent patients: a case-series of patients with maxillary sinus involvement and a critical review of the literature

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SUMMARY

Objectives: To review the current literature on mucormycosis in immunocompentent/otherwise healthy individuals, to which five new cases with maxillary sinus involvement have been added.
Methods: We searched in the PudMed database all articles in the English language related to human infections caused by fungi of the order *Mucorales*, in immunocompetent/otherwise healthy patients, starting from January 1978 to June 2009. In addition, we updated the literature by reporting five new cases diagnosed and treated at the oral medicine unit of our institution.
Results: The literature review showed at least 126 articles published from 35 different countries in the world, to a total of 212 patients described. The most affected country was India with 94 (44.3%) patients and the most representative clinical form was the cutaneous/subcutaneous with 90 (42.5%) patients. Our five immunocompetent patients with a diagnosed infection of *Mucorales* localized at the maxillary sinus completely healed with lyposomial amphotericin B.
Conclusions: The literature analysis revealed that even in immunocompetent/otherwise healthy individuals mucormycosis infection has a worldwide distribution. What might be the real predisposing factors involved in its pathogenesis in such patients and the real causes of this peculiar geographic distribution still remains unknown. It is likely that, in our cases, a chronic insult of a well-defined and localized body area might have resulted in a local immunocompromission, thus fostering the development of an invasive fungal infection.

1. Introduction

Mucormycosis is a rare opportunistic infection, which represents the third most common angio-invasive fungal infection after candidiasis and aspergillosis and is considered as one of the most important medical complications in immunocompromised patients.[1,2] Even though it is extremely rare, it has been reported from all corners of the world.[3]

The majority of patients developing mucormycosis reported having history of risk factors. The most common risk factors for mucormycosis are summarized in Table 1.[3–5]

The increase in the number of cases of invasive mucormycosis is attributable to the recent rise of cancer incidence, the resistance to the commonly used antifungal agents and immunosuppressive therapies, including organ transplantations, which result in growing of highly immunocompromised population,[1,2,4] although, in the last 30 years, several cases of mucormycosis in immunocompetent/otherwise healthy individuals have been described.[5–130] Also, some patients with mucormycosis have no identifiable risk factors.[131]

Management of mucormycosis still represents a big challenge and is based on different strategies which envisage a rapid diagnosis, removal or reduction of risk factors (drugs or underlying diseases), rapid and aggressive antifungal infection (polyenes) with or without surgical debridment, and, lastly, with adjuvant therapies in patients refractory or intolerant to polyene-based therapy (posaconazole, deferasirox plus lipid polyenes, recombinant cytokines granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, or interferon-γ, hyperbaric oxygen).[132] The main purpose of this review is to report data over the last 30 years about the percentage of immunocompentent/otherwise healthy individuals suffering from mucormycosis, of the

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Table 1
Main risk factors for the development of mucormycosis in humans[5–130]

Underlying disease	Therapy	Transplantation	Local conditions	General conditions
Leukemia	Antineoplastic agents	Solid organ	Burns	Malnutrition
Lymphoma	Corticosteroids	Bone marrow	Trauma	
Multiple myeloma	Antibiotics	Peripheral blood stem cell		
Neutropenia	Antirejection agents			
Matabolic disorder (Diabetes type I and II) with or without ketoacidosis	Intravenous drug abuse			
Cirrhosis	Radiation			
Acute renal failure	Deferoxamine			

most common form, and the most affected country, as no similar data are currently available in the literature. The secondary outcome was to update the current literature adding five new cases of mucormycosis in immunocompetent patients, referred to and treated by our institution, who developed the disease following a chronic localized inflammation, and discuss the likely underlying pathogenetic mechanism.

2. Patients and Methods

We retrospectively reviewed all human infections caused by fungi of the order *Mucorales*, by searching in the PudMed database each of the following Key words: "*Mucormycosis*; *Zygomycosis*; *Phycomycosis*; *Mucor racemosus*; *Mucor circinelloides*; *Mucor ramosissimus*; *Mucor indicus*; *Mucor hiemalis*; *Rizopus arrhizus*; *Rizopus oryzae*; *Rizopus rhizopodiformis*; *Rizopus azygosporus*; *Rizopus stolonifer*; *Rizopus schiperrae*; *Rizopus microsporus microsporus*; *Rizopus microsporus rizhopodiformis*; *Rizopus microsporus oligosporus*; *Rhizomucor pusillus*; *Absidia corymbifera*; *Mycocladus corymbifer*; *Apophysomyces elegans*; *Cunninghamella bertholletiae*; *Saksenaea vasiformis*; *Cokeromyces recurvatus*" in association with "healthy" and "immunocompetent" alternatively.

The inclusion criteria of this review encompass: 1) articles in the English language published between January 1978 and June 2009, reporting the clinical form of mucormycosis for all patients described; 2) healthy or immunocompetent patients who contracted an infection of the order *Mucorales* between January 1978 and June 2009; 3) absence of any predisposing risk factors in the present or past medical history, except for local conditions (Table 1); 4) absence of any previous underlying diseases to the diagnosis of mucormycosis; 5) documentation of *Mucor* infection either histologically or by culture. We also included cases of pregnant women and drug-addicted or alcoholic patients.

Of the overall reviewed articles we collected, tabulated, and depicted the following information: number of patients reported in each article, clinical manifestations of mucormycosis, place of origin.

Fisher's exact test, Odds Ratio (OR) and 95% confidence interval (CI) were calculated comparing the cutaneous/subcutaneous form with all the other forms, and India with all the other countries in the world. Statistical analysis was performed using GraphPad 5.0 (Prism 5.0, GraphPad Software, Inc., San Diego, CA).

Commonly, clinical manifestations of mucormycosis are classified in: 1) rhino-orbito-cerebral, 2) disseminated/miscellaneous, 3) cutaneous/subcutaneous, 4) gastrointestinal, 5) pulmonary, and 6) uncommon presentations.[133] For the sake of brevity, we grouped the category of either isolated cerebral or isolated rhino-cerebral or isolated sinuso-orbital or isolated maxillary (sinusal) or isolated orbital mucormycosis into rhino-orbito-cerebral mucormycosis.

In order to update the current literature on this topic, we also report five new cases (4 men and 1 woman) with a history of chronic sinusitis were admitted for evaluation of aggravation of a cohort of long-lasting and debilitating related symptoms (Table 2), diagnosed and treated at the Oral Medicine Unit, Federico II University of Naples, Italy, between 2003 and 2008.

All patients, after providing their written informed consent, were hospitalized and examined by a head and neck CT scan, and complete laboratory work-up. For a thorough evaluation, they were also referred to the nearby othorhynoloaringological (ORL) unit, where a biopsy of sinusal mucosa was taken via a rigid nasal endoscopy. A diagnosis of mucormycosis was established, based on the clinical, radiological, and histopathological criteria. Invasion seen on histopathology was needed to confirm a diagnosis.

In order to evaluate the extent of the disease, they underwent a total body computed tomography (CT) scan, an electrocardiogram, and serum tumor markers

All patients received the same treatment protocol that has consisted in an adequate hydration and a premedication with acetaminophen (500 mg qd PO), chlorpheniramine (20 mg daily, intravenous) and methylprednisolone (40 mg daily, intravenous), 30 minutes before each infusion. Liposomal amphotericin B (Ambisome®, Gilead Sciences S.r.l., Milan, Italy) was infused intravenously by an electronic pumping device (Optima MS, Fresenius Vial, France) at a total dose of 3 mg/kg/die given over 5 consecutive days. The therapy was adjusted from 5 to 3 mg/kg/die due to a localized involvement and patients' immunocompetent status. The infusion was administered slowly at 70 – 100 mg per hour. All patients received three cycles of therapy to a total of 15 days of treatment. Vital signs were monitored before, during, and after each infusion.

After treatment, each patient underwent all the laboratory, histological, and radiological investigations, in order to ascertain whether or not a complete healing occurred. Patients were also regularly followed-up every two months for at least 6 months to ensure complete resolution of mucormycosis and to detect any possible relapse.

3. Results

The analysis of literature review revealed at least 126 articles published between 1978 and 2009, from 35 different countries in the world, to a total of 212 patients described. The most affected place was India with 94 (44.3%) patients, followed by USA and Australia with 42 (19.8%) and 12 (5.7%) patients, respectively (Table 3). Just 6 (2.8%) cases have been described from Italy, to which our 5 new cases should be added, reaching a total of 11 cases. The higher prevalence of mucormycosis in India turned out to be statistically significant ($p < 0.0001$) in comparison with all other countries, from USA (OR: 3.22; CI 95%: 2.09 – 4-97) to Argentina, Belgium, and so on (OR: 168.1; CI 95%: 23.12 – 1222) (Table 4).

The most representative clinical form described in immunocompetent/otherwise healthy patients was the cutaneous/subcutaneous form with 90 (42.5%) patients, followed by the rhino-orbito-cerebral with 81 (38.2%) patients and genitor-urinary with 18 (8.5%) patients (Table 3). Even though the cutaneous/subcutaneous form was the most representative, our analysis revealed that no statistical difference exists with the rhino-orbito-cerebral form (OR: 1.19; CI

Table 2
Patients' characteristics

Pts	Age/Sex	Clinical signs and symptoms	Radiology	Involved sites	Underlying or past diseases	Predisposing risk factors	Predisposing local conditions	Treatment	Follow-up (months)
1	67/M	Ill-defined chronic bilateral oro-facial pain, fever	CT scan: Dense and non-homogenous mass involving all nasal cavity and the upper rhinopharynx. Maxillary and sphenoidal sinuses are both opacified by an hyperdense mass	Bilateral maxillary and sphenoidal sinuses	Rhino-pharyngeal cancer 10 years earlier	None	Chronic sinusitis	LAmB	6
2	46/M	Respiratory distress, headache	CT scan: a dense and non-homogeneous mass in the right maxilla	Right maxillary sinus	None	None	Chronic sinusitis	LAmB	24
3	47/M	Acute diploipia, orbital pain	CT scan: a dense and non-homogeneous mass in the left maxilla, occupying nasal fossa up to the ethmoidal cells	Left maxillary sinus and nasal fossa	BPH	None	Chronic sinusitis	LAmB	60
4	54/M	Rhinorrhea, monolateral facial pain	CT scan: well-defined mass in the left maxilla	Left maxillary sinus	None	None	Chronic sinusitis	LAmB	14
5	53/F	Rhinorrhea, headache, orbital pain	CT scan: well-defined mass in the left occupying all maxillary sinus with an initial erosion of the floor of the orbit	Left maxillary sinus	None	None	Chronic sinusitis	LAmB	20

M, male; F, female; CT, Computed tomography; BPH, benign prostatic hypertrophy, LAmB, Liposomal Amphotericin B.

Table 3
Geographic distribution and clinical forms of mucormycosis in 212 immunocompentent/ otherwise healthy individuals described over the last 30 years

		Number of Patients (%)
Country	India	94 (44.3)
	USA	42 (19.8)
	Australia	12 (5.7)
	Italy	6 (2.8)
	Brazil, Pakistan	5 (2.4)
	Venezuela	4 (1.9)
	Canada, China, France, Germany, UK	3 (1.4)
	Arabia, Holland, Japan, Qatar, South Korea, Spain	2 (0.9)
	Argentina, Belgium, Colombia, Denmark, Ecuador, Finland, Greece, Iraq, Ireland, Israel, Kuwait, Oman, Sri-Lanka, South Africa, Swiss, Taiwan, Turkey	1 (0.5)
Forms	Cutaneous/subcutaneous	90 (42.5)
	Rhino-orbito-cerebral	81 (38.2)
	Genitourinary	18 (8.5)
	Disseminated	10 (4.7)
	Pulmonary	7 (3.3)
	Gastrointestinal	5 (2.4)
	Vascular	1 (0.5)
Years	2006–09	61 (28.7)
	2001–05	72 (33.9)
	1996–00	25 (11.7)
	1991–95	21 (9.9)
	1986–90	18 (8.5)
	1981–85	7 (3.3)
	1978–80	8 (3.7)

95%: 0.80 – 1.76; p= 0.42). Conversely, a significant statistical difference was found with all the remaining clinical forms, form genitourinary (OR: 7.95; CI 95%: 4.56 – 13.84; $p < 0.0001$) to vascular form (OR: 155.7; CI 95%: 21.41 – 1132; $p < 0.0001$) (Table 5).

Lastly, the majority of patients with mucormycosis have been reported over the last eight years, with 72 (33.9%) patients described in the five-year 2001-2005, and 61 (28.7%) patients in the three-year 2006-2009 (Table 3).

In our study group, four patients were male and one patient was female. Their age at the time of diagnosis ranged from 46 to 67 years (mean, 54.5 ± 8.6 years) (Table 2). They were seen 2-4 weeks after the onset of the following clinical signs and symptoms: fever, headache, orbital pain, diplopia, rhinorrhea, trigeminal nerve distribution pain (Table 2).

Intra and extra-oral examination did not reveal any ulcerations or necrosis. The examination of nasal mucosa of 2 out of 5 patients showed necrotic tissue with black eschar, whereas nasal endoscopy in all patients demonstrated a variously inflamed sinusal mucosa with or without the presence of purulent exudates.

In all cases routine blood tests, serum tumor markers and electrocardiogram did not reveal any abnormalities that could predispose to invasive fungal infections (IFIs), except for a mild increase of Fibrinogen at the time of admission in 3 out of 5 patients. Similarly, total body CT scan to evaluate the extension of the disease was negative in all patients. So, we concluded that infection was localized at the oro-facial area.

Patients' characteristics including clinical, radiological, and therapeutic parameters are summarized in Table 2. Histologically all cases exhibited numerous broad aseptate fungal hyphae, with a right-angle branching varying from 45 to 90°, consistent with the morphology of the order *Mucorales* (Figure 1). There was no chance in our institution to determine the genus of *Mucorales*.

Patients had no history of travel or physical trauma or burn. All patients reported a history of chronic sinusitis of unknown

Table 4
Comparison between India and all other countries in the world (Fisher's exact test, $p < 0.05$).

Country	OR	CI 95%	*p*-value
USA	3.22	2.09–4.97	< 0.0001
Australia	13.3	6.98–25.25	< 0.0001
Italy	27.35	11.62–64.37	< 0.0001
Brazil, Pakistan	32.98	13.04–83.4	< 0.0001
Venezuela	41.42	14.85–115.6	< 0.0001
Canada, China, France, Germany, UK	55.5	17.16–179.1	< 0.0001
Arabia, Holland, Japan, Qatar, South Korea, Spain	83.64	20.24–345.7	< 0.0001
Argentina, Belgium, Colombia, Denmark, Ecuador, Finland, Greece, Iraq, Ireland, Israel, Kuwait, Oman, Sri-Lanka, South Africa, Swiss, Taiwan, Turkey	168.1	23.12–1222	< 0.0001

OR, Odds Ratio; **CI**, Confidence Interval.

Table 5
Comparison between the cutaneous/subcutaneous clinical and all other forms (Fisher's exact test, $p < 0.05$).

Forms	OR	CI 95%	*p*-value
Rhino-orbito-cerebral	1.19	0.80–1.76	0.42
Genitourinary	7.95	4.56–13.84	< 0.0001
Disseminated	14.9	7.46–29.74	< 0.0001
Pulmonary	21.6	9.69–48.14	< 0.0001
Gastrointestinal	30.54	12.07–77.26	< 0.0001
Vascular	155.7	21.41–1132	< 0.0001

OR, Odds Ratio; **CI**, Confidence Interval.

etiology. Just one patient reported a history of radiotherapy due to a rhino-pharyngeal cancer occurred 10 years earlier, that might have made him more susceptible of developing a chronic sinusitis. No patient presented with any underlying diseases, except one patient with a very mild benign prostatic hypertrophy, for which no medical treatment was required (Table 2).

All patients were considered completely healed after the infusion therapy, based on general criteria for global response to antifungal therapy in invasive mold disease.[134] Indeed, clinical, radiological, histological, and serological examinations performed after treatment were negative. The average duration of the follow-up was 24.8 ± 20.8 months.

4. Discussion

According to the new taxonomic revision of the fungi,[135] the phylum Zygomycota, subphylum Zygomycotina, and class Zygomycetes disappeared in their widely understood sense to be replaced by the phylum Glomeromycota (for arbuscular mycorrhizal fungi). Glomeromycota has a subphylum Mucormycotina, which includes the order *Mucorales*, which in turn are considered as etiologic factor of mucormycosis infection. They are characterized by the production of a coenocytic mycelium and the formation of asexual spores (sporangiospores) in a variety of fungal structures.[136]

These opportunistic pathogens are ubiquitous organisms, existing in the environment, soil, air, food, compost piles, animal excreta, and play a pivotal role in the cycle of decomposition in the natural world. Although the majority of these pathogenic fungi require oxygen, they are capable of growth in anaerobic and microaerophilic conditions.[133,137,138]

For many years the term mucormycosis has been interchangeably used with zygomycosis in the medical literature.[139] Currently, in line with a recent classification,[135] we prefer to use the term mucormycosis rather than zygomycosis.

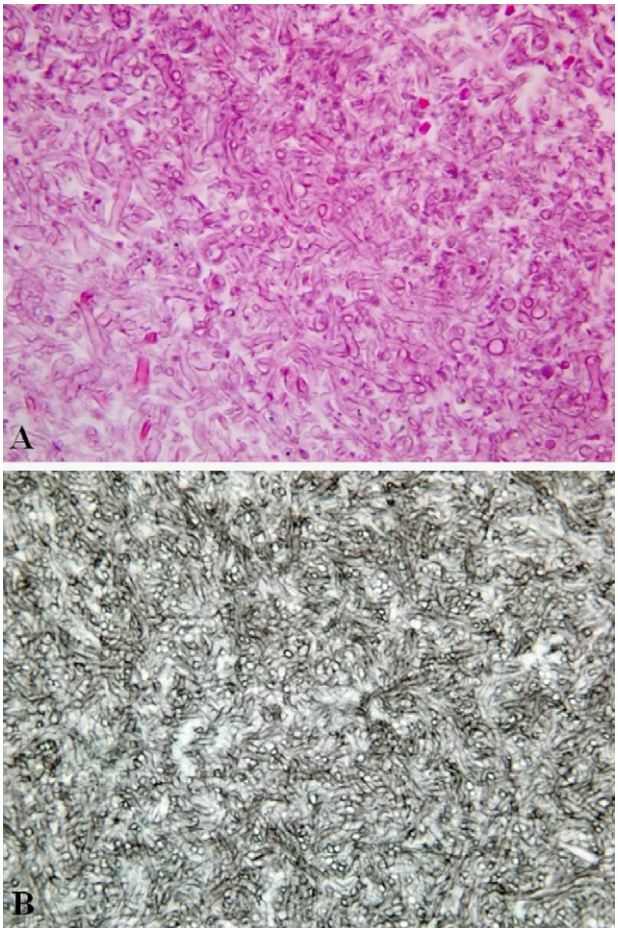

Figure 1. (A) Histological analysis showed the presence of broad aseptate fungal hyphae, with a right–angle branching varying from 45 to 90. (B) Grocott methenamine–silver staining confirmed the presence of a fungal infection of the order *Mucorales*. Specimen isolated from patient 2.

Due to the rarity of this infection, it is difficult to calculate accurately its incidence. In US the annual incidence of mucormycosis has been estimated as 1.7 infections per million populations, i.e, approximately 500 cases per year.[140] More recently, in tertiary care hospital at the University Hospitals Leuven, the overall incidence has been calculated in 0.042 cases per 10,000 patient.[141] In transplanted patients, the incidence of mucormycosis ranged from 0.2 to 1.2% of renal transplants, 0 to 1.6% of liver transplants, 0 to 0.6% of heart transplants, 0 to 1.5% of lung transplants, and 0.9 to 1.9% of allogenic bone marrow transplants.[3]

Commonly, mucormycosis has shown an equal sex distribution, although a recent review of all published cases of pulmonary mucormycosis showed a male-to-female ratio of 3:1.[142]

Mortality rate is higher than 50% with an incidence ranging from 62.5% in rhino-cerebral form[143] to 100% in disseminated form.[140] Its high morbidity and mortality rates are related to its capacity for rapidly vascular invasions, with subsequent tissue necrosis and infarction.[133]

The overall survival rate of patients with mucormycosis ranges approximately from 50% to 85% with a higher survival rate of rhino-cerebral mucormycosis than pulmonary or disseminated form because the rhinocerebral disease can frequently be diagnosed earlier, and the most common underlying cause, diabetic ketoacidosis, can be readily treated.[140] Notably, if the disease has not penetrated beyond the sinus, the prognosis is much better; indeed, in local sinonasal disease, the mortality has been reported to be less than 10%.[140]

Clinically, the most common clinical form of mucormycosis is rhino-orbito-cerebral (44–49%), followed by cutaneous (10–16%), pulmonary (10–11%), disseminated (6–11.6%) and gastrointestinal (2–11%) presentations.[3]

Due to ubiquitous nature of this fungus (excavation, construction, contaminated air ducts),[133] inhalation of sporangiospores from the atmosphere is the most common route for rhino-orbito-cerebral and pulmonary infections, whereas the cutaneous form is usually related to a contamination following physical trauma. The disseminated and gastrointestinal forms are mainly due to cancer, transplantations, metabolic diseases, malnutrition, chemo, radio and/or immunosuppressive therapy.[3]

In immunocompetent patients, the nose and/or maxillary sinuses appear to be the predominant source of infection of the respiratory tract. If sporangiospores are larger than 10 μm, they may remain localized to the upper airways, giving an isolated form, i.e., sinusal or rhino form; otherwise they may colonize the distal alveolar spaces involving the pulmonary tract.[3,133] Once infection has colonized nose and paranasal sinuses, if not promptly diagnosed and treated, it is likely that, in such patients, this infection may invade the base of the skull through blood vessels, disseminating to the central nervous system, giving the rhino-orbito-cerebral form,[3] or everywhere in the body, giving the disseminated form.

As the mucosal/cutaneous epithelium and endothelium represent a fundamental and effective barrier against tissue invasion and angioinvasion, it appears that this IFI in immunocompetent/otherwise healthy patients might be relatively rare. Actually, the possibility of developing a *Mucor* infection in such patients seems to be related to the ability of this fungus of attacking the epithelium previously damaged by prior infection, cytoxic agent or direct trauma.[133] It is likely that *Mucor* sporangiospores are also capable of secreting several toxins or proteases, which may directly destroy endothelial cells in mucosal membranes.[133]

We do not know when and how our patients had contracted it. We may speculate that these fungi might have availed of the damaged epithelium in order to invade the mucosal sinuses, spreading along vascular and neuronal structures and infiltrating the walls of blood vessels. Infection would have eroded bone through walls of the sinus and remained localized, thanks to an early diagnosis and aggressive systemic treatment; otherwise, it is assumable that *Mucor* infection would have spread into the orbit and the retro-orbital area, thereby extending into the brain, and resulting in a more widespread form such as rhino-orbital or rhino-orbito-cerebral form.

So, we have hypothesized that a chronic local insult, such as a chronic sinusitis, might have acted as a predisposing factor for a possible development of *Mucor* infection in immunocompetent/otherwise healthy individuals.

This speculation seems to be supported by the evidence that a chronic sinusitis might be caused by an alteration of first-line barrier defense of upper airway (sinusal mucosa) caused by an impairment of mucociliary clearance. An impairment or loss of immune defense at the sinusal mucosa would render individuals more vulnerable to fungal colonization.[144] In addition, it has been hypothesized that patients with chronic sinusitis have a reduction of several molecules, such as S100 and SPINK5, members of epidermal differentiation complex, which are necessary in maintenance of barrier function in the upper airways and sinuses.[145]

The analysis of literature review has shown that even in immunocompetent/otherwise healthy individuals mucormycosis infection has a worldwide distribution with 35 countries involved[5–130] (Figure 2A). In Italy, it appears very rare with only six cases reported over the last 30 years: two cases of rhino-orbito-cerebral,[5,32,] and four cases of cutaneous/subcutaneous.[66,112,116,127] However, adding our 5 cases to the 6 already described, despite the rarity of this infection, Italy gained the fourth place with 11 cases, after India with 94, USA with 42 and Australia with 12, thus rendering the rhino-orbito-cerebral form as the most represented in Italy.

Moreover, it has been recently published an Italian survey describing 60 cases of mucormycosis, of which 18 turned out to be immunocompetent. This is a relevant paper, because Italy should reach a total number of 30 immunocompetent/otherwise healthy patients with mucormycosis.[146] However, even though this is a remarkable report, we were unable to add it to our review, because it was impossible to determine what kind of clinical form of mucormycosis each single patient had suffered from.

To the best of our knowledge, at least 212 cases of mucormycosis in immunocompetent/otherwise healthy individuals, without underlying risk factors and/or concurrent or past medical illnesses have been descried.[5–130] Of these 212 patients showed a predominance of the cutaneous/subcutaneous forms with 90 patients described as regards to other forms, such as 81 rhino-orbito-cerebral, 18 genito-urinary, 10 disseminated, 7 pulmonary, 5 gastrointestinal, and 1 vascular (Table 3).

It also seems that the clinical form of mucormycosis in such patients would be tightly related to the type of risk factor. Indeed,

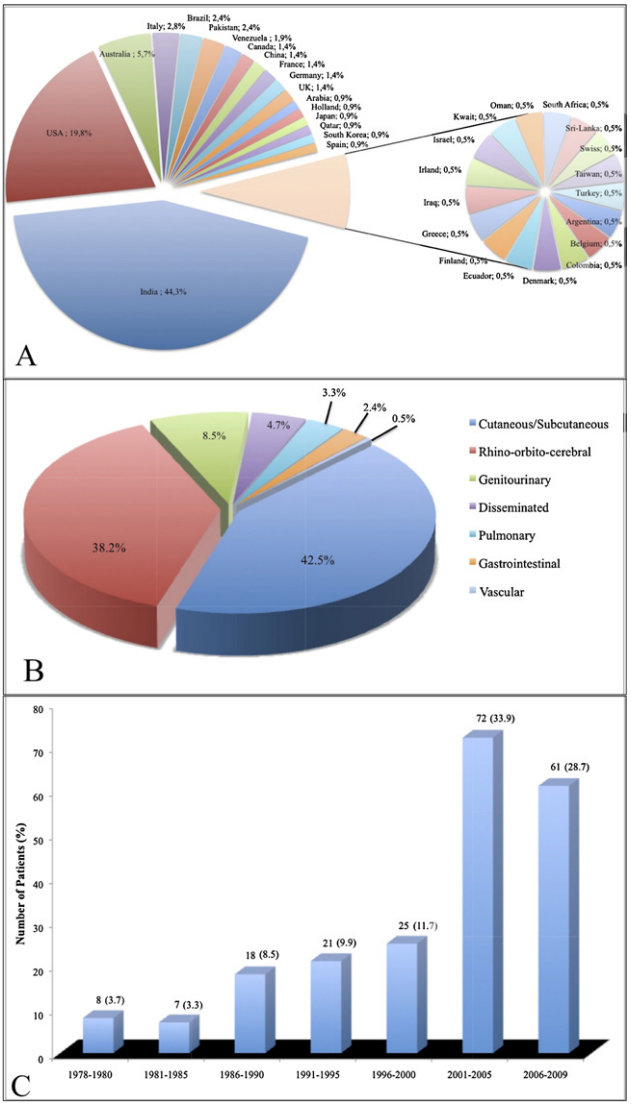

Figure 2. (A) Percentage of patients with mucormycosis in 35 different countries; (B) percentage of patients with each of the seven different clinical forms of mucormycosis and (C) trends in mucormycosis over the last 30 years in 5-year increments. Data calculated from 212 immunocompetent/otherwise healthy patients.

as demonstrated by a previous investigation,[147] the majority of patients (73%) without any underlying risk factors, who developed mucormycosis following burn, trauma, or surgery, presented with the cutaneous form, whereas among patients with mucormycosis due to other causes rather than burn, trauma, or surgery, the cutaneous form was just represented by 28%.

Intriguingly, although inhalation appears to be the most common route of infection with subsequent involvement of respiratory tract, resulting in both rhino-orbito-cerebral and pulmonary forms, the literature review has shown that in immunocompetent/otherwise healthy patients, the most common clinical presentation of mucormycosis turned out to be the cutaneous/subcutaneous form (Figure 2B), following burns or trauma with a contaminated object or soil. Considering the ubiquitous nature of this infective agent, it is likely that in immunocompetent patients the immunological defense of upper airways is more capable of facing IFIs. Conversely, disseminated forms might have been due to undiagnosed underlying risk factors, or a delay of diagnosis or appropriate treatment.

We do not know what might have been the route of infection of genitor-urinary form and it is also surprising to notice from literature review how large is the number of immunocompetent/otherwise healthy patients with this form (8.5%) (Figure 2B), as it usually occurs as a part of disseminated form in patients with predisposing risk factors, such as intravenous drug abuse or corticosteroids therapy.[73] Thus, further investigations are required to better elucidate the epidemiology and pathogenesis of this entity.[73]

The largest review on mucormycosis, published in 2005, gathered 929 cases from 1885 to 2005.[147] This study demonstrated that patients with mucormycosis with no underlying condition at the time of infection were 176 out of 929 (19%) with a mortality rate of 35% (61 out of 176). Also, of the overall 176 patients, 87 developed mucormycosis following trauma, burns or surgery and 89 following other causes, to a total of 88 patients with cutaneous form (50%). These data are quite similar to ours, which showed a rate of 42.2% about the cutaneous/subcutaneous form. Conversely, different results come from the remaining forms: indeed, in the Roden et al.'s review, the rhino-orbito-cerebral form (including cerebral, rhinocerebral, sinus, and sino-orbital) showed a rate of 25%, comparing with a rate of 38.2% from our review, and gastrointestinal and pulmonary showed 9% and 8% respectively, comparing with a rate of 2.4% and 3.3% form our review (Figure 2B). In addition, a rising trend has been noticed, with more than half cases (62.6%) described over last 10 years (Figure 2C). Whether this implies a rise of *Mucor* infection in immunocompetent/healthy individuals in the next decade and whether this trend may reflect a rise in global poverty and difficulty in receiving adequate medical/surgical treatments either in developed or developing countries is unknown.

The fact that India turned out to be the most affected country (Figure 2A) might be probably related to climatic, socio-economic, scarce hygienic conditions, and, last but not least, diagnostic delay. Indeed, a significant proportion of the Indian population lives below the poverty line and hence may be malnourished, which may predispose them to more easily contract an IFI.[148] Also, as diabetes mellitus is extremely common in India, some patients with IFI may have had undiagnosed diabetes mellitus, that is a well-known predisposing factor.[148] Conversely, in USA turned out to be the second most common country (Figure 2A) as it is probably due to its multiethnic background where people travel worldwide to a greater extent, and to difficulty for poor persons to access appropriate medical and/or surgical therapies.

However, we do not know whether this peculiar geographic distribution may even reflect a genetic predisposition of the inhabitants.

Eventually, we have to consider that the analysis of the literature review might present a significant bias, as we do not know if all the immunocompetent/otherwise healthy patients with mucormycosis have ever been reported worldwide: many clinicians in developed countries might have underestimated the importance of reporting such cases rather than other clinicians in developing countries.

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Conflict of interest

The authors have no conflict of interest to declare.

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