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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