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NASAL AND PARANASAL SINUSES MUCORMYCOSIS: A CASE REPORTS AND CASE SERIES LITERATURE REVIEW

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ABSTRACT

Mucormycosis is an opportunistic and progressive mycotic infection with a high risk of mortality. A filamentous fungus of the order mucorales is the pathogen responsible for this infection. We present a review of the literature. The aim of the study was to highlight and compare the cases of mucor mycosis affecting the districts of otolaryngological relevance, evaluating the outcome of patients undergoing surgical and / or medical treatment in the light of the presence of comorbidities. The bibliographic search was conducted on Pubmed by searching for the following keywords: "ENT mucormycosis", "nose and paranasal sinuses mucormycosis", "Rhino-oculo cerebral mucormycosis". Mucormycosis is an infectious disease that requires early diagnosis and rapid therapeutic intervention, including the immediate involvement of a multidisciplinary medical, surgical, radiological and laboratory team. The combination of surgical and pharmacological strategies is essential for successful disease management.

1. Introduction

Mucormycosis is an emerging angioinvasive infection caused by the ubiquitous filamentous fungi belonging to the order of Mucorales[1]. This orderconsists of 4 main species: Mucor, Rhizopus, Rhizomucor and Absidia / Lichtheimia. This pathogen represents the third agent responsible for invasive fungal infection after Candida and Aspergillus in subjects with severe immunodeficiency[2]. While in the mid-twentieth century, diabetes evolved as an important risk factor for mucormycosis, nowadays the increasing number of patients undergoing chemotherapy or immunotherapy for cancer represents the main risk factor of this disease[3]. Transmission is by air with a predominant nasal sinus fungal tropism (about 40%); localizations in the pulmonary, digestive and cutaneous districts are possible but less frequent[4]. The gateway is the colonization of the nasal mucosa, which allows the fungus to spread into the sinuses and other districts. Diagnosis of mucormycosis is often difficult, as cytological and culture tests in tissue samples are only successful in about 50% of cases[5]. Suspicion of such an infection should lead to a surgical procedure to confirm the diagnosis and surgical debridement combined with liposomal amphotericin B drug treatment[6]. The outcome of an advanced stage of the infection remains poor despite treatment; early diagnosis is important for the course of the disease and patient survival[7].

The objective of our study is to identify the most frequent sites of Mucorales infection in the rhino-sinus district; evaluate the dissemination site and the most frequently associated comorbidities; and finally clarify which treatment gives a better outcome and greater survival.

2. Material and methods

An SRL was carried out on Mucorales infection in the rhino-sinus district and its dissemination sites and complications, through a bibliographic search, conducted on Pubmed, using the following search keywords obtained from the National Library of Medicine's Medical Subject Heading (MeSH) terms: "ENT mucormycosis", "nose and paranasal sinuses mucormycosis", "Rhino-oculo cerebral mucormycosis" (Table 1). The Pubmed/MEDLINE online databases were considered, as well as the gray literature, and a manual search was performed based on the references of the articles retrieved. The inclusion criteria in this present literature reviewwere: articles published from 2000 to 2022, articles (full text or abstracts) in English, individual case reports or case series that reported rhino-sinus Mucormycosis in patients with diabetes mellitus and other comorbidities.
The exclusion criteria taken into consideration were: articles published in

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a language different from English and prior to 2000; Mucormycosis case report related to COVID-19; non-human study, review articles, systematic review and guidelines; Mucormycosis of other ENT districts.
The literature search and systematic review were conducted by two independent investigators. In case of any incongruity, the two investigators came to an agreement after further analysis and discussion.
17 articles were selected from case reports and case series for a total of 47 patients affected by mucor mycosis of the nasal cavities or paranasal sinuses, as reported in Table 2.

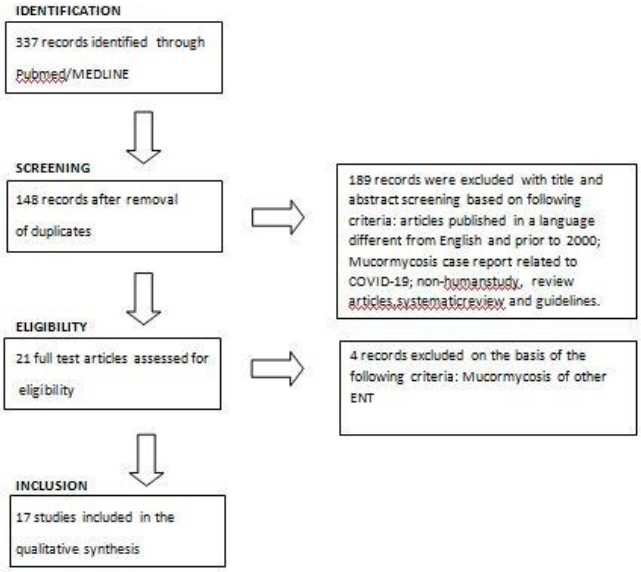

Figure 1. Representation of Systematic Literature review processes of identification, screening, eligibility and inclusion.

3. Results

Overall, from the 17 selected studies, data on 47 patients were extracted, of which 32 males (68.08%) and 15 females (31.92%) with an average age of 48.51 years.
Symptoms most frequently reported by patients were nasal dysfunction, visual changes including diplopia and decreased vision, facial pain and swelling, headache, cranial nerve dysfunction and fever (Table 3).
The nasal cavities were affected by mucor mycosis in 27 patients (57.44%); the maxillary sinus in 12 patients (25.53%), the ethmoid sinus in 10 patients (21.27%); the frontal sinus in 2 patients (4.25%) and the sphenoid sinus in 7 patients (14.89%).The orbital cavity was involved in 26 patients (55.31%), whereas the cranial cavity in 12 patients (25.53%). Only in 2 (4.25%) patients, the infection also involved the pterygopalatine fossa. The most frequently identified fungal species are Rizopus (48.93%), followed by Mucor (8.51%), and in the same percentages Lichthemia and Zygomyces (2.12%). The species responsible for mucor mycosis was not reported in 18 patients (38.32%).The comorbidities found in patients with mucor mycosis are diabetes mellitus (33 patients - 70.21%), immunosuppression (7 patients - 14.89%), oncohematological diseases (5 patients - 10.63%), solid tumors (3 patients - 6.38%), other (5 patients - 10.63%).There are 5 patients in apparent good health who are not affected by other pathologies (10.63%).7 patients (14.89%) underwent medical treatment only, of these 5 patients died (10.63%). Whereas, 40 patients (85.11%) underwent surgical treatment associated with medical treatment, of these 12 patients died (25.53%).20 patients (42.55%) reported complications of which 4 (8.51%) post-surgical treatment (paralysis of the VI and VII c.n.); 1 patient (2.12%) had cerebral ischemic-haemorrhagic complications and 2 (4.26%) cavernous sinus thrombosis due to progression of the underlying disease; 5 (10.63%) developed iatrogenic renal failure from treatment with amphotercin b.
In total 17 patients died (36.17%).

SYMPTOMS	N° CASES	%
FEVER	7	14,89
COUGH	1	2,13
DYSPNEA	1	2,13
HEADACHE	6	12,77
NASAL DISCHARGE	17	36,17
FACIAL PAIN	9	19,15
FACIAL SWELLING	16	34,04
DECREASED VISION	16	34,04
DIPLOPIA	14	29,79
CRANIAL NERVE PALSY	7	14,89
EPISTAXIS	1	2,13
ANOSMIA	1	2,13
NOT REPORTED	12	25,53

Table 3. Frequency of symptoms reported by patients with mucormycosis.

4. Discussion

In literature, most of the mucormycosis infections occur in patients with decompensated diabetes and in the presence of keto acidosis[25]. In our studies we have highlighted 33 patients - 70.21% suffering from diabetes mellitus and of these 39.39% (13 patients) were in diabetic ketoacidosis.
The incidence of mucormycosis seems to increase in the last few decades due to the growing number of immunocompromised patients. This infection is now widespread all over the world, but there are differences between developed and developing countries. In Western countries, cases of mucormycosis remain rare and associated with oncohematological pathologies; in developing countries, they are much more frequent and related to decompensated diabetes mellitus[26]. For optimal growth in humans, mucoral fungi require neutropenia, as neutrophils play a key role in the defense against these pathogens[27]. In patients with leukemia, the bone marrow produces dysfunctional neutrophils and induction-remission cycles of chemotherapy cause severe neutropenia and myelosuppression. This condition in association with the use of broad-spectrum antibiotics increases the risk of opportunistic fungal infections[28].
In the last year there was an increasing in the incidence of mucormycosis, in particular rhino-orbital localization, in severe patients with COVID-19. Immune dysregulation associated with SARS COV 2, the widespread use of corticosteroids and broad-spectrum antibiotics and ventilatory support seem to be the main factors that make these patients more sensitive[29].
As highlighted by Corzo-Leon, in patients with diabetes the rhino-sinusal manifestation of the disease is more frequent, while in patients with neoplastic pathologies there is a similar percentage of presentation between the rhino-sinusal and pulmonary forms[30]. In addition, the same author provides "red flags / warned signs" for early identification of rino-orbital-cerebral mucormycosis in diabetic patients and patients with sinusitis: cranial nerve deficit, orbital apex syndrome and palatine ulcers. In the presence of such signs, the patient should be subjected to blood chemistry and imaging tests[27].
Rhinosinusalmucormycosis originates from the nasal mucosa and turbinates and extends to the paranasal sinuses either by contiguity or

through the angular, lacrimal and ethmoid vessels[13].

Necrosis and ulcerative lesions represent the most important diagnostic sign. The angioinvasive effect of the hyphae, in particular in the arteries' internal elastic lamina, induces thrombosis and reduction of tissue vascularization[31].

Imaging represents a fundamental step in the early diagnostic setting and in the evaluation of the extent of the pathology. CT or MRI or their combination are strongly recommended in all cases, after clinical and endoscopic ENT evaluation, in particular in the presence of symptoms strongly suggestive of sinusitis and / or orbital, ocular and cerebral involvement. In the latter cases, the use of MRI is preferable[25].

Immunocompetent and non-comorbid patients have better prognosis; A better outcome is often observed when the pathology is localized in a paranasal sinus or in the skin, if an early diagnosis is done and if it is possible to perform a surgical debridement. Mortality rates of over 80% have been recorded in patients with disseminated disease, with involvement of the central nervous system[25]. This is also evident in immunocompetent patients belonging to the studies we considered, with the exception of the case reported by A. Dadhich[15] in which the onset of ischemic / hemorrhagic complications of the CNS led the patient to exitus. Liposomal amphotericin B (AmBisome) has been shown to be substantially less toxic than conventional amphotericin B, with reference to nephrotoxicity. The recommended starting dose is 5 to 10 mg / kg to be administered once daily. The duration of therapy must be determined on an individual basis. Cycles of 6-8 weeks are commonly used in clinical practice; longer therapy may be needed for deeper infections or in case of prolonged chemotherapy or neutropenia. This review confirms what is established by the most recent guidelines regarding second-line and / or maintenance drug therapy[25]: in fact, in case of renal insufficiency (to be evaluated by monitoring creatinine levels) caused or aggravated by the administration of Liposomal amphotericin B, there is a strong recommendation for the administration of Isavuconazole or Posaconazole. On the contrary, we can highlight how most of the authors do not comply with the recommended dosage of liposomal amphotericin B, starting or re-adapting therapy with doses often lower than 5 mg / kg / day.

It is essential to associate antifungal therapy with surgical debridement therapy, as the drug has a poor diffusion within the necrotic tissue. This allows for better control of the pathology[16]. As can be seen from the review of the literature, infact, only diabetic patients underwent debridement and the presence of serious comorbidities, such as immunosuppression or keto acidosis, was often associated with an unsuccessful surgery and therefore with the exitus.

5. Conclusions

Early diagnosis and rapid therapeutic intervention are essential to avoid a bad outcome or serious sequelae in a patient with mucormycosis. A multidisciplinary approach[32] with the immediate involvement of a medical, surgical, radiological and laboratory team and the combination of surgical and pharmacological strategies are essential for the successful management of the disease.

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Table 2. Literature Review for ENT mucormycosis (DM: Dabetes Mellitus; DKA: Diabetic Keto Acidosis)

Patient / Age / Gender	Site of disease	Fungi species	Comorbidity	Medical treatment	Surgical treatment	Complications	Outcome	Author/ year of publication
77 y.o. M	left nasal soft tissues left ethmoid sinus	Lichtheimia corymbifera	Acute Myeloid Leukemia	liposomal Amphotericin B 5 mg/kg/day combined with Posaconazole	No	Not reported	Remission	P. Danneels/2018[8]
12 patients:8 M; 4F Average age: 58 years (range, 5-86)	11 rhino-orbital 1 rhino-orbital-cerebellar	Not reported	8 : type II DM 3 : immune suppression 3 solid organ malignancy 4 hematologic malignancy 2 renal transplantation	Liposomal amphotericin B	Yes	5 patients: severe hypotension	3 Patients died	E. Karaaslan/2018[9]
24 y.o. F	Necrotic aspect in the right inferior turbinate and right peritonsillar phlegmon complicated by ipsilateral lateral cervical cellulitis	Rhizopus arrhizus	Type I DM	Amphotericin B 1 mg/kg/d	Yes: Right inferior turbinectomy, ipsilateral ethmoidectomy and right maxillary sinus debridement	Not reported	Remission	W. Kermani/2016[10]
13 patients: 8 M; 5 F; Average age: 46 y.o. (range 39 to 70 years)	Sino-nasaldisease; Rhino-orbitaldisease; Rhino-orbital-cerebraldisease	Rhizopus	13: Uncontrolled DM: diabetic ketoacidosis. 1: renal failure.	Amphotericin B 1 to 1.5 mg/kg/d	Yes: **Group A** (9pt): amphotericin B + sinonasal debridement only **Group B** (1pt) amphotericin B + sinonasal debridement with orbital exenteration and /or palatal excision.**Group C** (3 pt) amphotericin B	2 patients: renal failure	10 patients died	R. S. Mane (2007)[11]
21 y.o.M	Sino-nasal disease with orbital complication	Not reported	Type 1 DM with DKA	Amphotericin- B 1 to 1.5 mg/kg/day	Yes: Nasal debridement	Not reported	Remission	R. K. Mundra (2008)[12]
6 patients: 5 M; 1 F Average age: 52 y.o (range 42 to 65 years)	Rhino-oculo cerebral disease with multiple cranial nerve palsy	Rhizopus oryzae	6: DM 2: diabetic ketoacidosis.	Amphotericin B	Yes: 4 Pt: Cald Well Luc surgery and debridment	4 pt: persisting 6 and 7 nerve palsy 1 pt: recurrence after 6 months	2 patients died.	K. Sachdeva (2013)[13]
29 y.o.M	Rhino-cerebraldisease	Mucor	Type 1 DM	Amphotericin B (1.5 mg/kg of bw/day) with wide spectrum antibiotics parentally; Amphotericin B lipid complex 3 mg/bw kg/day	Yes: Right Winkler–Jansen transmaxillary–ethmoidectomy. Second surgery: Right total maxillectomy, sphenoidectomy and orbital exenteration	Renal failure	The patient died	G. Szalai (2006)[14]
35 y.o.M	Anterior wall of the left maxillary sinus and left orbital floor.	Not reported	Immunocompetent. history of trauma over left midface region 4 years ago	Amphotericin B 0.7mg/kg/day; Itraconazole 200mg x2/day.	Yes: Weber Ferguson incision and excision.	Acute non hemorragic infart in the left thalamo capsular region. Intracerebrali, intraventricolar and subarachnoid hemorragy	The patient died	A. Dadhich (2021)[15]
39 y.o.M	Pansinusitis with a subperiosteal collection of 7 mm at the posterior wall of the right maxillary sinus extending to the retropterygoid space	Rhizopus arrhizus	Untreated DM and gout	Cefotaxim 6000 mg/day; Metronidazole 1500 mg/day; Fosfoycin 1200 mg/day; Amphotericin B 1mg/kg/day; Dexamethasone 4 mg/day; Cetirizine 10 mg/day; Hyperbaric oxygen therapy (HBOT)	Yes: meatotomy with exeresis of necrotic tissue. Trepanation of the anterior wall of the maxillary sinus	Not reported	Remission	L. Mtibaa (2020)[16]
12 y.o.F	Sinusitis involving right ethmoid and maxillary sinus extending into the inferior wall of right orbit. Osteolysis of the lateral and medial walls of maxillary sinus and orbital floor	Not reported	Type 1 DM and Ketoacidosis	Cefoperazone; Sulbactam; Metronidazole ; Amphotericin B.	Yes: Right maxillary sinus drainage with middle meatotomy	Right temporale intracranial collection, right cavernous sinus thrombosis	Remission	M. Masmoudi (2021)[17]
85 y.o.M	Nasal septum; right maxillary sinus; hard palate; sphenoid sinus; ethmoid.	Mucor	Type 2 DM; coronary artery disease and two previous cerebrovascular incidents.	Liposomal amphotericin B therapy 5 mg/kg/day	No	Not reported	Remission	K. Dimaka (2014)[18]
22 y.o.F	Right nasal cavity.	Zygomyces	Diabetic ketoacidosis	Amphotericin 10 mg/kg Micafungin 100 mg/day Isavuconazonium sulfate.	Nasal septum and hard palate removal, radical maxillectomy and right orbital exenteration, suboccipital craniectomy and shunting for hydrocephalus	Right internal carotid artery occlusion and cavernous sinus thrombosis, right-sided cerebral watershed infarctions and large abscesses in right cerebellum, temporal lobe and pons	Remission	S. Zafar (2017)[19]
38 y.o.M	Osteolytic infiltrating infectious process (bilateral ethmoid opacity and lysis of the right papyraceous lamina and lachrymal bone and osteitis of the nasal bone)	Not reported	acidoketotic coma	Liposomal amphotericin B 3 mg/kg/day Oral Posaconazole 400 mg twice daily	Right ethmoidectomy and right medial meatotomy, and left anterior ethmoidectomy	Not reported	Remission	O. Mimouni (2010)[20]
61 y.o.F	Right maxillary sinusitis and right orbit.	Rhizopus arrhizus	Chronic obstructive pulmonary disease; Type 2 DM	Ceftriaxone 2gx2/day; Metronidazole 500mgx3/day; Topical chloramphenicol 0.5% drops x2/day; Liposomal amphotericin B 5mg/kg daily; Amphotericin B 0.06mg/L; Posaconazole 0.25mg/L; Isavuconazole 1mg/ L; Voriconazole 8mg/L; Itraconazole 0.5mg/L	Medial maxillectomy, anterior and posterior ethmoidectomy, right sphenopalatine artery ligation and medial orbital wall decompression	Intra and extra conal right orbital abscess, abscess formation in the right masticator space, erosion of the right lateral maxillary wall. Renal impairment	Remission	R. Miller (2021)[21]
1. 23-y.o. M 2. 40-y.o. M	1. Left maxillary sinus. Left orbit 2. middle and posterior ethmoid air cells and in sphenoid sinuses. Bilateral maxillary sinuses. Left orbit.	Not reported	1.Immunocompeten 2.Immunocompetent	1.Amphotericin B 1.0 mg/kg/day 2.Amphotericin B 1.0 mg/kg/day	1.endoscopic clearance of the maxillary, ethmoid and sphenoid sinuses; eye's enucleation 2.Uncinectomy ethmoidectomy and sphenoidectomy	1.and 2. chronic inflammatory tissue with necrosis of the eyeball	1.and 2.: Remission	H. Chopra (2008)[22]
1. 32-y.o. F 2. 77-y.o. M	1.L and R coanae, right orbit, sphenoid sinus, sella turcica 2.sphenoid sinus	Mucor	1. and 2. Immunocompetent	1.and 2. amphotericin B	1.and 2. Endoscopic sphenoidotomy	1. and 2. Not reported	1. and 2.: Remission	H. Chopra (2006)[23]
59 y.o.M	Left orbit, left ethmoid, maxillary and sphenoid sinuses, extension into the pterygopalatine and infratemporal fossae	Rhizopus arrhizus	DM	Amphotericin B 5 mg/kg/day; Oral posaconazole 400 mg tw	Left lateral rhinotomy, maxillectomy ethmoidectomysphenoidectomy and orbital exenteration	Renal failure	Remission	K. Kulendra (2010)[24]