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Review

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The importance of mucormycosis infections on example of Rhino Orbital Cerebral Mucormycosis

Znaczenie zakażeń mukormykozą na przykładzie mukormykozy nosowo-oczodołowo-mózgowej

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Summary

Mucormycosis is an angioinvasive fungal infection, characterized by high morbidity and mortality and is strongly dependent on the patient's general health condition, initial site of infection, and the time from diagnosis to treatment commencement. It has been reported that the occurrence of mucormycosis has increased rapidly, also among immunocompetent patients. Moreover, the rise in number is expected to continue. Among all clinical manifestations of mucormycosis, the rhino-orbital-cerebral type (ROCM) is the most common. The aim of this article is to increase the awareness of mucoral infections, especially ROCM, and to describe its first symptoms, as proper treatment requires immediate surgical and medical intervention.

Keywords: **mucormycosis, rhino-orbital-cerebral mucormycosis, fungal infection**

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Abbreviations: **ROCM**- rhino-orbital-cerebral mucormycosis

INTRODUCTION

The Mucorales belong to the group of fungi responsible for opportunist fungal infections (OFI) together with Candida and Aspergillus [30, 31]. Currently, mucormycosis is the second or third most common invasive fungal infection characterized by high mortality, affecting not only immunocompromised patients, but also immunocompetent patients with burn, accident, or combat injuries [19, 55]. Additionally, Jeong et al. have reported cases of fungal infections related to minor iatrogenic penetrating traumas, pointing to intravenous, intramuscular, insulin injections, or catheter insertions as possible factors responsible for infection [32].

Mucormycosis, first described by Paultauf in 1885, is a disease caused by filamentous fungi (Mucorales) [45]. Eleven genera and ~36 species under Mucorales are associated with human infections [56]. They are the largest order of zygomycete fungus among which Rhizopus arrhizus, Mucor spp., Lichtheimia spp., Apophysomyces variabilis, Rhizopus homothallicus are predominant contributors.

The first three may be responsible even for 70% of the reported mucormycosis cases, probably because they contain more copies (3-7) of the fungal ligand from the CotH protein family [19].

Mucormycosis is a life-threatening fungal infection that mostly occurs in immunocompromised patients with hematological malignancies, neutropenia, undergoing chemotherapy, steroid treatment, dialysis, or after an organ transplant [4]. It may also affect patients suffering from diabetes mellitus, with a history of pulmonary tuberculosis or chronic kidney diseases [4]. The typical ways of becoming infected with Mucorales sporangiospores are through inhalation, ingestion of contaminated food, and through skin wounds, and the course of infection strongly depends on the innate host defenses. From there, the spores may spread through the bloodstream or by direct penetration, e.g., in the case of the paranasal sinuses infection affecting the orbits or central nervous system [19].

Based on the clinical presentation and the involvement of a particular anatomic site, mucormycosis can be divided into eight clinical categories: rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, central nervous system, nasal cavities, disseminated, and miscellaneous [5, 14, 19]. A change in the epidemiology of mucormycosis has been noted in developing countries in recent years, especially in patients with chronic renal failure and prolonged hospital intensive care. Also, patients who have had tuberculosis are at risk. Atypical different locations of mucormycosis like bones, heart, ear, parotid gland, uterus, urinary bladder, and lymph nodes have been recently reported as well [32].

It seems that four factors are critical for eradicating mucormycosis: rapidity of the diagnosis, the reversal of the underlying predisposing factors (if possible, e.g., diabetes mellitus), appropriate surgical debridement of the infected tissue, and appropriate antifungal therapy.

Even with the rapid development of novel drugs, rhino-orbital-cerebral mucormycosis is difficult to control and, in many cases, leads to death, and those who did survive have to face postsurgical disabilities. The aim of this article is to increase the awareness of mucoral infections, especially ROCM, and to describe its first symptoms, as proper treatment requires immediate surgical and medical intervention.

EPIDEMIOLOGY

Patient population

According to the Leading International Fungal Education (LIFE) organization, the annual prevalence of mucormycosis reaches around 10,000 cases worldwide. Inbarajan et al. and Jeong et al. have suggested that this number is not complete, as it does not include incidents from India and China, which can change the statistics dramatically, reaching even 91,000 cases globally [31, 32].

In France, the incidence of mucormycosis infections rose from 0.7/million in 1997 to 1.2/million in 2006, mostly because of the number of immunocompromised patients and increased survival of patients with hematological malignancies [12]. A single-center study from Spain documented tripled mucormycosis cases between 1988-2006 and 2007-2015 [27]. Ambrosioni et al. analyzed mucormycosis cases in Switzerland from before 2003 and after and observed that the prevalence rose from 0.57 to 6.3 cases per 100,000 patients per year. Interestingly, this rise coincided with the increased use of voriconazole and caspofungin [3]. Saegeman et al. reported a sevenfold increase between 2000 and 2009 in Belgium [49].

Increased incidence of mucormycosis in India and China has been attributed to a continued increase in patients with uncontrolled diabetes. The environmental factors such as humid climate and high temperatures provide optimum conditions for these fungi to survive [16, 18]. According to Prakash et al., the incidence of mucormycosis reaches 89 cases per year, and Chakrabarti et al. estimated it at 24% of all invasive fungal infections in India [17, 47].

Different countries consider different risk factors most significant; in the United States, Iran, and Mexico, diabetes is a risk factor in 52%-74% cases of mucormycosis. In Europe, the most common underlying disease is hematological malignancy occurring in even 62% of cases [40].

Routes of infection

The hallmark of mucormycosis infections is extensive angioinvasion, resulting in vascular thrombosis and subsequent hard and soft tissue necrosis. It penetrates and damages the endothelial cells lining the blood vessels by fungal ligand from spore coating (CotH) protein family binding to the endothelial cell receptor GRP-78. First, the spores specifically adhere to laminin and type IV collagen and, after recognition of host receptor (GRP-78), invade endothelial cells leading to their death by endocytosis. Recent studies also indicate that this is not the only mechanism responsible for endothelial cell death and suggest the presence of mycotoxins in mucormycosis pathogenesis [8].

The angioinvasion is associated with the ability of the fungi to hematogenously disseminate from the original site to other target organs [8]. It depends on the interaction between Mucorales CotH and endothelium GRP78, which invades the host cell and leads to the dissemination of the fungus [8]. From the immunological perspective, phagocytes the a primary host defense mechanism against mucormycosis. Neutropenia, hyperglycemia, and acidosis are known to impair the ability of phagocytes to move and kill the organisms by both oxidative and non-oxidative mechanisms [52]. Also, iron plays a vital role in the growth of mucormycosis. It seems that GRP78 is overexpressed on endothelial cells in order to decrease cell toxicity in case of excess iron availability. Fungal hyphae produce "rhizoferrin," which binds iron fervently. This

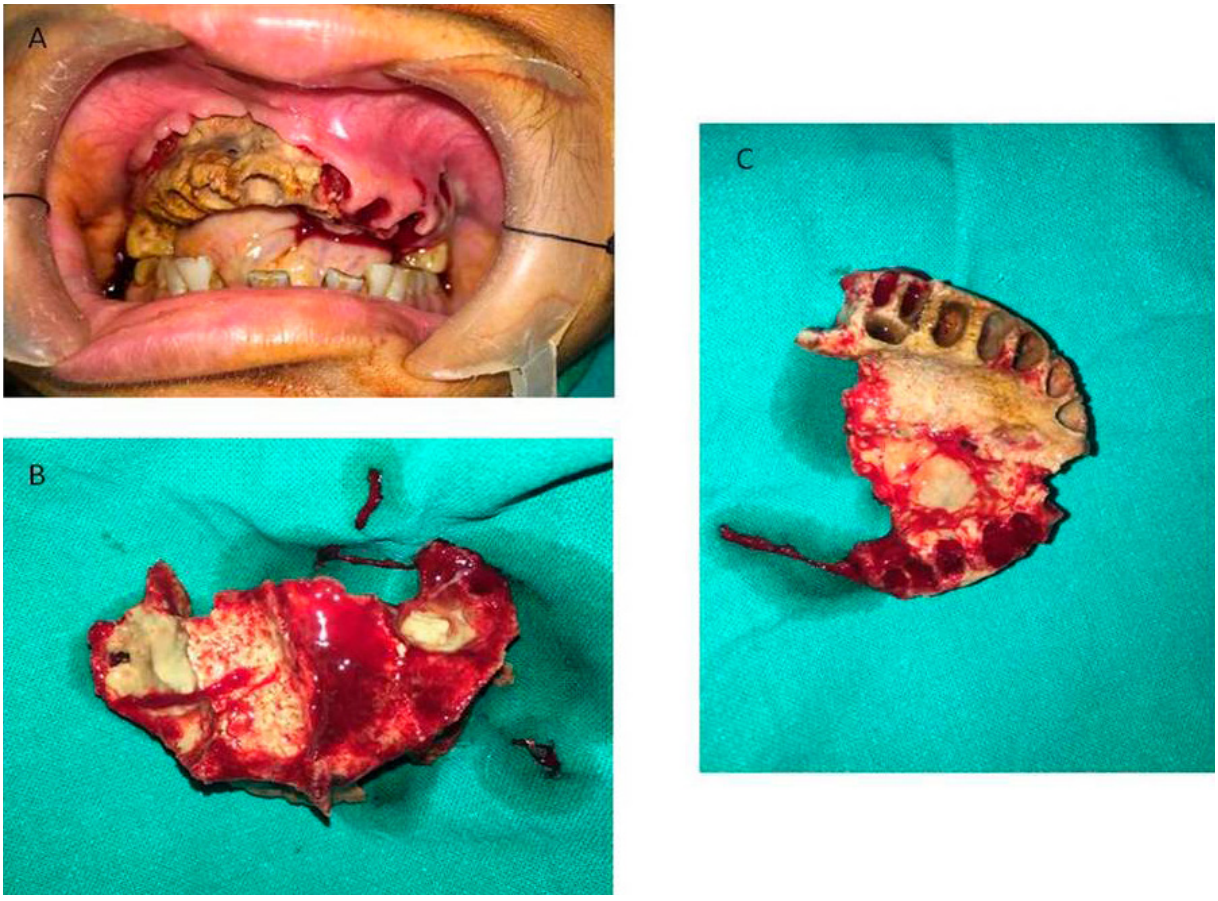

Fig. 1. A - the level of the bone necrosis in the maxilla; B - exenterated maxilla (nasal view); C - exenterated maxilla (palatal view)

iron-rhizoferrin complex is taken up by the fungus and becomes available for its vital functions [39]. Artis et al. have reported that acidosis may interfere with the iron biding of transfferin and leads to an increased amount of unbound iron [13]. Thus, the patients with diabetic ketoacidosis are at high risk due to the elevation in the available serum iron [22]. Since the infection involves blood vessels and causes subsequent destruction, poor penetration of antifungal agents to the infected area is observed.

Clinical manifestations

Rhino-orbital-cerebral mucormycosis is the most common type under the zygomycosis classification, with morbidity reaching even 85% despite rapidly implemented treatment [19]. Most cases of ROCM result from the inhalation of fungal sporangiospores that have been released in the air. The fungal infections may also develop at the secondary location in the mouth, nasal area, and paranasal sinuses. From there, invasion of the sphenopalatine and internal maxillary arteries occurs, leading to thrombosis, resulting in palatal and alveolar necrosis [22], as shown in Figure 1. Common oral manifestations are tissue destruction with progressive non-healing necrotic ulcers. When the maxillary antrum is the site of origin of the infection, osseous destruction with oroantral fistula formation is a typical result of erosive behavior of the infection [23]. In patients with ROCM, sinus surgery is the first choice of treatment, but the extent of surgical debridement varies from limited to radical resection [11, 42, 48]. Even though over the years, our epidemiological awareness of fungal infections as well as diagnostic techniques have increased considerably [39, 40, 50], there are still no established treatment protocols [9, 10, 15, 37]. The studies across the world show that 17-88% of patients with ROCM have uncontrolled diabetes mellitus and ketoacidosis. Moreover, the diagnosis of diabetes was a risk factor in 51% to 64% of the ROCM cases [45, 47].

In the beginning, the infection involves the turbinates and paranasal sinuses. At this point, symptoms can simulate common sinusitis, including sinus pain, congestion, mouth or facial pain, toothache, facial numbness, and nasal discharge. With the developing infection and invasion of the blood vessels, characteristic symptoms appear, such as epistaxis or erythema of the nasal mucosa. Subsequently, nasal mucosa turns purple and black as the hard palate also undergoes rapid necrosis [51]. Already at this stage, even in around 20% of the patients altered mental status together with bone destruction is observed [51].

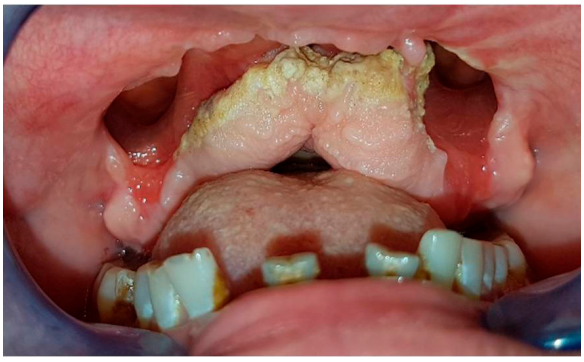

Fig. 2. Intra-oral view of the post-resection condition

Further disease progression leads to ophthalmic signs and development of symptoms, such as eye pain, blurred vision, ophthalmoplegia, proptosis, chemosis, orbital cellulitis, periorbital discoloration, and necrosis. The infection may extend further to the brain where the disease may manifest itself as cranial nerve palsy, cognitive disturbances, intracranial abscess, or bone erosion of the skull base [45]. In severe cases, surgical excision of the infected sinus tissue, appropriate debridement of retro-orbital space along with the involved palate, is needed to restrict the spread of the disease [26]. Extensive en bloc resection often leads to communication between oro-antral and oro-nasal compartments, resulting in masticatory, speech, deglutition, articulation, and breathing difficulties (Fig. 2). Treatment of such severe conditions needs to be addressed by complex reconstruction with a vascularized free flap or osteotomized myocutaneous flap. When it is not technically possible, the defect needs to be closed by maxillofacial obturator and prosthesis [31, 38].

TREATMENT

Surgical debridement

Surgical intervention is vital to keep the infection under control. Limited or radical surgical debridement of the sinus with the removal of the infected tissue is recommended in the case of rhino-orbital-cerebral mucormycosis, whereas for localized fungal sinusitis, endoscopic surgery is advised [20, 25, 33]. Orbital exenteration and craniofacial resection have been related to high morbidity and deformations [21, 54, 57]. Even though surgical debridement is considered a life-saving procedure, it has to be carefully discussed among all the medical professionals involved in the treatment, as well as the family and the patient.

Pharmacological treatment

Pharmacological treatment may be hindered as a result of the angioinvasive nature of the disease. Abu El-Najj et al. described successful post-operation treatment with liposomal amphotericin B combined with posaconazole or voriconazole, and locally with Sofra-Tulle gauze immersed in amphotericin B diluted in 5% dextrose solution [1]. In other studies, also fluconazole and isavuconazole [30] or micafungin in combination with amphotericin B [43] were prescribed, although, in the literature, the duration of treatment and dosage are not consistent [32, 36]. In contrast, Trifilio et al. reported a link between the widespread use of voriconazole prophylaxis and the breakthrough of mucormycosis [53]. Also, antifungal prophylaxis has been reported in immunocompromised patients with the use of itraconazole, posaconazole,and caspofungin as predisposing to the mucoral infection [46].

The increased ability of Mucorales to invade host tissues is directly connected with the increased expression of GRP78 (heat shock protein) receptor and its ligands from the CotH family (CotH1, CotH2, and CotH3). Treatment strategies targeting GRP78 with the use of suppressors or inhibitors (lignan honokiol, questiomycin A, thiazole benzenesulfonamide HA15, etc.) can also prove beneficial in the treatment of mucormycosis [7, 24, 29].

CONCLUSIONS

Mucormycosis is a disease with high morbidity and mortality, whose treatment effect is strongly time-dependent, placing an additional burden on the physicians treating immunocompromised patients. Among different types of this fungal infection, ROCM is the most common and causes the most physical and psychological damage, as it requires extensive surgical debridement, including maxillectomy or enucleation of the eye socket, which can drastically decrease the quality of life [3, 39]. Curreently, there are no effective standard treatment protocols [39]. Moreover, antifungal prophylaxis therapy can trigger mucormycosis infection. That is why new drugs and treatment strategies should focus on CotH/GRP78 interaction. The number of infections is very likely to increase dramatically, together with an increase of organ transplants, diabetic incidences, and environmental disasters, forcing us to draw more attention to the fungus infection in order to win the war despite losing a fight.

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