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Mucormycosis in head and neck area — the emerging health problem in COVID-19 pandemic. The perspective of a dental practitioner

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Abstract: Mucormycosis is an invasive fungal disease caused by saprophytic molds and is characterized by a fulminant course and high mortality. Reported increase of disease cases and more frequent mucormycosis superinfections in COVID-19 patients are of a serious concern. Head and neck area is the most typical location of mucormycosis and often the first symptoms are eminent in oral cavity, therefore a dentist may be the first healthcare practitioner to recognize signs of this dangerous and potentially fatal disease. Urgent diagnosis and implementation of appropriate treatment are essential for the patient's survival. The dentist's participation in postoperative care is necessary and due to the destructive nature of radical surgical treatment, prosthetic rehabilitation is required to improve the patient's function and quality of life. Furthermore the vigilance of dentists will also allow early recognition of frequent recurrences of this insidious infection.

Keywords: mucormycosis, rhino-orbito-cerebral mucormycosis, dental care, COVID-19.

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Introduction

Mucormycosis is a rare disease caused by fungi of *Mucorales* order. The disease is characterized by a high mortality rate and a rapid course [1]. The first case of mucormycosis was described in 1885 by Paultauf, in the patient with diabetic ketoacidosis [2]. The terms 'mucormycosis' and 'zygomycosis' are often used interchangeably in literature, however, after phylogenetic reanalysis of the Fungi kingdom the first one is correct [3]. Due to the rapid progression and high mortality rate, quick diagnosis and

immediate implementation of appropriate treatment are essential for the patient's survival. As the most common form of disease affects tissues of the head, neck and mouth, a dentist may be the first practitioner to diagnose mucormycosis. In this article, we briefly summarize the most important data about the mucormycosis, with particular emphasis on information crucial for dentists who may be more likely to encounter patients showing signs and symptoms of disease, especially now, during the COVID-19 pandemic.

Etiopathology

Mucormycosis accounts for 9% of all invasive fungal infections in immunocompromised patients and 4% of all mycoses in immunocompetent patients, respectively, being the third commonest fungal infection after aspergillosis and candidiasis [4]. The incidence of mucormycosis in recent years and during COVID-19 pandemic has increased gradually, because of higher number of susceptible population, longer life span of immunocompromised patients, better diagnostic tools, immunological changes induced by SARS-CoV-2 infection as well as pharmacotherapy used in severe

Table 1. Factors predisposing to mucormycosis.

General conditions	Local factors	Other
• uncontrolled diabetes mellitus, • neutropenia, • immunosuppression, • hematological malignancies, • bone marrow or solid organ transplantation, • chronic kidney disease, • COVID-19, • high serum iron concentrations, • high serum ferritin and transferrin levels, • intravenous drug use, • malnutrition, • general steroid therapy, • antineoplastic chemotherapy, • deferoxamine use, • broad-spectrum antimicrobial therapy, • voriconazole use	• chronic sinusitis, • burns, • tissue injuries — including surgery	• hot and humid climate zone • use of non-humified oxygen • improper sanitization of disposable humidifiers for oxygen administration • reusing the same face mask (especially in damp environment)

COVID-19 cases [5–7]. Noteworthy, the real incidence rate of mucormycosis may be higher, as sample collection poses some difficulties especially from the deep tissues and sensitivity of diagnostic tests is low [8]. The 11 genera and 27 species under

Mucorales order are pathogenic to humans [8]. The most common causative agents in mucormycosis are: *Rhizopus spp*., *Mucor spp*., *Lichteimia spp*., *Rhizomucor spp*., *Cunninghamella spp*., *Apophysomyces spp*. and *Saksenaea spp*. [3] The *Rhizopus arrhizus* plays the most important role in pathogenesis of mucormycosis, being responsible for majority of infections [8]. Geographical differences in incidence (often reflecting local epidemiological situation) are visible in the case of other fungi — in general *Lichteimia spp*. is more frequently identified among patients in Europe, while *Apophysomyces variabilis* in Asia [3, 8].

All *Mucorales* are saprophytes found in soil and rotting organic matter, they play a crucial role in decomposition processes in nature [9]. It has been shown, that humid and hot climate zone is important risk factor for spreading the infection [4]. The spores are ubiquitous in air, therefore *Mucorales* can be isolated from mucosa of upper respiratory tract, mouth, nose, and throat of healthy individuals presenting no symptoms of the disease [9, 10]. On the contrary, in susceptible patients with reduced phagocytic activity of granulocytes spores germs sprout into a hyphae form that invades blood vessels, causing thrombosis and progressive necrosis leading to soft tissue and bone destruction [10].

Depending on the localization, mucormycosis can be classified as: rhino-orbito-cerebral (ROCM, the most common type) and located in other organs and tissues i.e. pulmonary, cutaneous, gastrointestinal — collectively named as extra-rhino-orbito-cerebral types of mucormycosis. Another two types have been also described: disseminated and uncommon types. ROCM also referred to as rhino-cerebral is the most common presentation [6]. ROCM can be subdivided into rhino-maxillary and rhino-oculo-cerebral [11]. The mortality rate in ROCM, even despite adequate treatment is as high as 40–63% and prognosis becomes poor at the moment when through blood transmission or tissue continuity the fungus reaches central nervous system [11, 12]. *Rhizopus spp*. being the major pathogen in mucormycosis is responsible for 90% of ROCM cases [1]. Next ROCM, rarely extra-rhino-orbito-cerebral mucormycosis can be encountered in head and neck area. Based on source of infection extra-rhino-orbito-cerebral mucormycosis can be divided into primary or secondary disease. Based on tissue involvement three forms of extra-rhino-orbito-cerebral mucormycosis could be distinguished: localized — limited to the skin or mucosa, deep — besides involving underlying structures like muscle and bone, and disseminated — when infection spreads via hematogenous dissemination to other anatomical areas [13]. Due to early angioinvasion the spread of infection is rapid [10]. Factors promoting the development of this life-threatening, angio-invasive fungal infection are presented in Table 1.

In majority of cases, the infection is opportunistic, affecting patients with primary or secondary immunodeficiencies [14]. In recent years, in developed countries, the disease was most often favored by hematological malignancies, and immunosuppres-

sive therapy. In developing countries, the uncontrolled/poorly controlled diabetes mellitus is the most common predisposing factor [5]. With the proper immune system function, *Mucorales* are eliminated by mononuclear phagocytes and multinucleated cells, which release oxidative metabolites and cationic peptides [12]. Neutrophiles are of paramount importance in fungi elimination — it was observed that mucormycosis is more frequent in patients with neutropenia than with AIDS [5].

Importantly, in half of cases of mucormycosis the infection is preceded by uncontrolled diabetes mellitus [15]. Hyperglycemia, low tissue pH, decreased oxidative capacity, as well as impaired chemotaxis and phagocytosis of neutrophiles and monocytes favor the growth of fungi [16].

It was demonstrated, that high serum concentrations of iron, ferritin, transferrin play an important role in mucormycosis development. Hyphae of *Rhizopus spp*. produce rhizoferrin, which binds serum ion. The rhizoferrin-iron complexes are necessary for further fungi growth [17]. Paradoxically, the use of deferoxamine, a chelating agent that binds to serum iron and aluminium is another mucormycosis predisposing factor [18]. Deferoxamine is used to lower iron levels in patients with diabetic ketoacidosis, hemodialyzed with renal failure or after multiple blood transfusions — conditions that already promote mucormycosis. Iron removed by this medication are recaptured by siderophore — rhizoferrin and rhizoferrin-iron complexes are then transported to fungal cells. Modern chelating drugs — deferasirox and deferiprone bind iron permanently, preventing its binding to rhizoferrin, and therefore they do not predispose to the mucormycosis [8]. In recent years the incidence of mucormycosis in immunocompetent patients has been also increasing [19]. Local factors — mainly burns, injuries and iatrogeny — play a key role in the development of infection in this group [20, 21]. Importantly, oral surgery procedures may be also predisposing factors: extraction socket could be a portal of entry of the fungi, the more that the invariably the most common causes of tooth extraction — periapical inflammation or periodontal disease — impair the host immune mechanisms [1, 9]. Cases of mucormycosis in patients with oroantral communication after upper molars extraction have been described in Poland and other countries recently [1, 4, 9].

Mucormycosis in COVID-19 patients

In comparison with general population, in hospitalized COVID-19 patients secondary fungal infections are 10 times more common [22]. Both the pathophysiology of COVID-19 and the treatment used may predispose to the mucormycosis infection. According to current reports, almost 14% of COVID-19 cases develop severe condition associated with the increase of C-Reactive Protein (CRP), interleukin-6 (IL-6) and ferritin levels [23]. Furthermore, SARS-CoV-2 may invade pancreatic β cells binding to angiotensin converting enzyme — 2 receptors (ACE-2) and destroy them causing

'acute diabetes'-like state [23]. Due to hemolysis, which occurs frequently in severe COVID-19 serum concentration of iron increases [24]. What is more, recommended therapeutic strategy in severe SARS-CoV-2 pneumonia is based on general use of corticosteroids which exert immunosuppressive effects and predispose to secondary bacterial and fungal infections, including increasingly often mucormycosis [7]. Finally, the hydroxychloroquine administration, which despite withdrawal of recommendation is still in use in several countries can also impair phagocytic activity of macrophages and neutrophiles [25].

Increasing incidence of ROCM during COVID-19 pandemic, first reported in India then increasingly in other countries is of serious concern [14]. Among possible reasons for this secondary to COVID-19 health crisis several factors, broadly related to the general condition of healthcare are described [26]. Lack of oxygen supply chain for medical use forced the use of 'industrial oxygen' — often inadequately sanitized. Furthermore both non-humified oxygen and steam-inhalation can lead to mucosal damage, facilitating *Mucorales* infection. Due to the scarcity of disposable oxygen humidifiers reusable ones have been used posing a likely risk of nosocomial infections, especially when maintenance is inappropriate and water undistilled. Wearing facemask should minimize the risk of spores inhalation, but reusing the same mask for weeks may increase the risk of mucormycosis [26]. To other implicated factors for increased ROCM incidence in COVID-19 pandemic in one has to include difficulties in appropriate care of patients with chronic medical conditions predisposing to mucormycosis at time of lockdowns [25].

Diagnosis and treatment — dental considerations

Diagnosis

Indefinable clinical appearance and recurrent, occult distribution pose the major problem in the diagnosis of mucormycosis [20, 21]. This condition should gain a special interest of dental practitioners [27], as the disease most often develops within the head and neck tissues, both ulceration of the oral mucosa and post-extraction wounds are a potential portal of entry for infection [28]. Symptoms are mostly non-specific and often lead patients to seek dental care at first [7]. Clinical manifestations are misleading and often delay accurate diagnosis and treatment implementation significantly worsening prognosis [28]. Unfortunately, the clinical signs and symptoms of the early stages of the ROCM are not specific — patients suffer from unilateral headaches and face pain, fever, numbness, and nasal discharge. As the infection progresses and the further anatomical structures and areas are rapidly involved and paresthesias of the facial and trigeminal nerves, paralysis of other cranial nerves, ophthalmic symptoms and meningitis arise [10, 29]. Complaints such as toothache

and unilateral facial swelling often encourage patients to seek dental care [7]. Ophthalmic symptoms caused by involvement of the orbital tissues include pain in the orbital area, ophthalmoplegia, unilateral exophthalmos, conjunctivitis, diplopia, visual impairment up to blindness [1, 11, 29]. Central nervous system involvement in course of mucormycosis implicates a poor prognosis, and presents with altered sensorium, focal seizures and paralysis [14].

Besides ROCM other mucormycosis entities can occur. The presentation of extra-rhino-orbito-cerebral mucormycosis in head and neck area included involvement of submandibular region (mimicking abscess), persistent cutaneous nodular lesions on the face, and otitis media accompanied with facial palsy [13].

An ambiguous clinical picture requires careful differential diagnosis. Among infections other invasive fungal infections — especially aspergillosis, as well as the necrotizing ulcerative gingivitis and stomatitis, chronic granulomatous infections like tuberculosis and syphilis should be considered. Benign and malign lesions that may result in similar signs and symptoms to mucormycosis include: melanoma, squamous-cell carcinoma, multiple myeloma, salivary gland adenocarcinomas, peripheral giant-cell granuloma and other granulomatous diseases [4, 30].

The primary form of ROCM occurs by inhalation of spores and most often affects the maxillary sinuses [31], but it may also originate in oral cavity [15]. The isolated sinus mucormycosis in immunocompetent patients, characterized by a relatively mild course has been recently described [8, 28]. The involvement of nasal cavity and sinuses presents with symptoms similar to bacterial infection. The obstruction and a foul-smelling discharge from nose, sometimes dark in color, are observed [16]. The disease is rarely limited to the paranasal sinuses and in a majority of cases mucormycosis is spreading further to the palate [30]. Most often, the rhino-cerebral form manifests itself in this anatomical area [5]. During a routine examination dental practitioners can notice: ulceration, ischemic necrosis and palatine bone denudation [27, 32]. The occurrence of black or grey necrotic eschars on the palate, especially in patients from groups at risk, should arouse suspicion of mucormycosis [6, 18]. In retrospective Mexican studies, the main symptom observed during oral cavity examination were ulcerations of the palate and mandible mucosa, and to a lesser extent necrosis of gingiva and tongue [33]. Gingival involvement is accompanied with bone destruction and increased teeth mobility [16]. Mucormycosis in the mandible is less common than in the maxilla, but importantly, the anatomy of the lower jaw favors the infection progression into osteitis [34, 35]. Other symptoms of ROCM include painful ulceration of buccal mucosa [26] and non-healing extraction sockets [9]. Notably, the disease is particularly common after upper molars extractions due to teeth proximity to the maxillary sinus [1].

Unlike aspergillosis diagnosis of mucormycosis with the use of serological or imaging techniques is difficult [10]. The sensitivity of radiological examination in

early stages of the disease is low [10] and histopathological examination of paraffin-embedded tissue samples is still a golden standard in diagnosis of disease (hematoxylin-eosin — HE, periodic acid-Schiff stain — PAS or Grocott-Gomori's methenamine-silver staining — GMS) [19]. Characteristic features of infection on biopsy are: presence of broad, ribbon-like, aseptate hyphae branching at right angle, submucosal infiltration, angioinvasion, perineural invasion, tissue infarction [13]. For intraoperative histology examination frozen sections are used. The detection of fungal DNA in plasma and secretions appears to be a promising method, although it still needs to be standardized [3]. If such examination is planned fresh tissue material is preferred — specimens fixed in paraffin are previously treated with formalin, which damages DNA. The tissue handling should be gently and material cannot be homogenized as *Mucorales* hyphae are extremely fragile. In about half of the cases where the presence of the fungus is confirmed by microscopic examination, the culture shows negative results, which is associated with damage of biopsy specimen during collection. The culture is also time-consuming, and therefore is not of a first choice as disease progression is often fulminant [22]. Among the new, promising methods of diagnosis assessment of T-lymphocytes populations associated with fungal infection (Fungus-specific T-cells CD4 + CD154 +) may provide some information [4].

Treatment

Due to the rapid progression of the infection and its highly devastating nature suspicion of mucormycosis requires immediate action. Any delay in the start of therapy is associated with higher mortality [3]. Even a 12-hour delay in the implementation of appropriate therapeutic treatment has been reported to result in the patient's death [4].

Treatment must be decisive and quick and requires treatment of chronic comorbidities (diabetes!), thorough surgical debridement of tissues and the implementation of proper antifungal pharmacotherapy [10]. It should be emphasized that the surgery is essential for successful treatment. In the rhino-orbital-cerebral form of disease it is associated to significantly better treatment outcome than the pharmacotherapy alone [36]. Importantly, at 36°C, the hyphae of *Rhizopus arrhizus* — the most common etiological agent of mucormycosis — can grow as much as 3 mm/hour, therefore the surgery must be performed under microscopic scrutiny [24, 28]. Surgical treatment of ROCM is often extensive and requires resection or exenteration procedures resulting in disfigurement and functional morbidity [11]. It has been reported that the implementation of pharmacotherapy without surgery may result in the passage of invasive mucormycosis into chronic form [4].

Pharmacotherapy must be quickly established and long-lasting (usually weeks or even months) [3, 36]. Hyphae-induced thrombosis with subsequent ischemic necrosis

promote fungal growth and impede drug penetration [37]. Only few drugs present with significant anti-*Mucorales* activity [36]. Amphotericin B is a polyene macrolide, it combines with ergosterol in fungal membranes, creating pores in them, but in the case of *Mucorales* it has a more fungistatic than fungicidal effect, which is often responsible for extending the duration of treatment [11, 31]. Due to the strong nephrotoxicity of the colloidal sodium deoxycholate form, the liposomal formulations and the lipid complexes are of prime importance as they have a better safety profile [5, 36]. New azole drugs, especially posaconazole and isavuconazole, play an important role in the pharmacotherapy of mucormycosis. The mechanism of their action is based on the inhibition of the synthesis of ergosterol in fungal cells, however, they may exhibit hepatotoxicity and, by affecting cytochrome P450 enzymes, they can cause numerous pharmacological interactions [3]. Posaconazole is a broad-spectrum triazole derivative and it can also be used to prevent mucormycosis and other invasive mycoses in patients with bone marrow and solid organ transplantation or neutropenia [32]. Isavuconazole is a new triazole drug that is effective against *Mucorales*. In Europe, it is a second-line drug, especially in patients with low tolerance of amphotericin B therapy [3, 5]. In contrast to posaconazole and itraconazole, isavuconazole penetrates well into the central nervous system. Itraconazole may be valuable drug in the treatment of infections caused by susceptible *Mucorales*, especially *Lichteimia spp*. [28].

It should be emphasized, that voriconazole and echinocandins (caspofungin, micafungin and anidulafungin) are ineffective. Voriconazole is often used for the therapy and prevention of aspergillosis, but it has been reported that it may even foster *Mucorales* infection [36].

Drugs should be administered immediately after diagnosis and in high doses. According to the recommended scheme, at the beginning, amphotericin B is administered intravenously for approx. 3 weeks, after that time being replaced by oral posaconazole or isavuconazole, usually in the form of delayed-release tablets [11, 36].

Despite single reports on the promising results of the simultaneous administration of amphotericin B and posaconazole, the combined use of drugs remains controversial and is not recommended in the first-line therapy of mucormycosis due to the increase in toxic reactions with an unclear cost-benefit balance [32, 36]. Moreover, azole drugs inhibit the synthesis of ergosterol, which constitutes the target for amphotericin B and combined use of these drugs is generally not recommended.

There are several additional therapeutic strategies in the treatment of mucormycosis i.e. administration of granulocyte colony growth factors — filgrastim or pegfilgrastim, use of recombinant cytokines, transfusion of granulocytes and hyperbaric oxygen therapy [20, 21, 37]. Special attention should be given to the avoidance of the use of 'immunity boosters' containing iron and zinc, due to associated risk of iron overload — well-known mucormycosis predisposing factor [25].

Mucormycosis is characterized by a high recurrence rate [37]. Even after successful treatment, the disease may go dormant and reappear in neutropenic states or during chemical antineoplastic treatment [35], thus regular follow up is as important as radical surgical treatment, long-term pharmacotherapy and auxiliary strategies to improve immunity [37].

A significant loss of hard and soft tissue implicates the need of prosthetic rehabilitation. Frequent difficulties in opening the mouth exclude the use of removable obturator prosthesis, which, due to the high recurrence rate of mucormycosis, is the recommended solution. On the other hand, dentures should be as small as possible in size and weight with the greatest possible retention. In the case of post-resection cavities, remote implant-bone anchorage is more effective than conventional implants. Solutions using pterygoid, zygomatic and nazalus implants, which can be a retention for prosthesis are advisable [38].

Summary

Mucormycosis becomes a serious health problem, emerging significantly in COVID-19 pandemic. Due to the most frequent occurrence of mucormycosis symptoms in the tissues of the head, neck and mouth, a dentist may be the first healthcare practitioner to recognize this dangerous disease. Rapid diagnosis and implementation of appropriate treatment are essential for the patient's survival. Extensive nature of radical surgical treatment results in disfigurement and prosthetic rehabilitation is necessary in order to improve the function and quality of life of the patient. The vigilance of dentists will also allow early recognition of frequent recurrences of this insidious infection.

Authors' contribution

Marcin Pasternak, D.D.S. — conception of the work, drafting the article.
Rafał Olszanecki, M.D., Ph.D. — critical revision of the article, final approval of the version to be published.

Conflict of interest

None declared.

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