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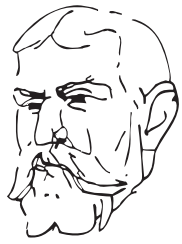

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## Editorial Team

## CASE STUDIES

CASE STUDY

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# Rhinocerebral form of mucormycosis in a patient with post-COVID-19 syndrome and type 1 diabetes mellitus: clinical and morphological analysis of the case from practice

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## ABSTRACT

Mucormycosis is a serious life-threatening opportunistic infection which is characterized by various clinical and morphological manifestations, rapid progression, unpredictable course and high mortality. The development of mycormycosis depends on the metabolic and immune status of the human body. The authors conducted a clinical and morphological analysis of the case of rhinocerebral mucormycosis in a patient who was diagnosed lifetime, but despite a set of therapeutic and surgical measures led to death, which was due to the severity of the pathology, late hospitalization of the patient and the presence of comorbidities (type 1 diabetes mellitus and post-COVID-19 syndrome). The clinical case presented by the authors raises the issue of the need to increase physicians' awareness about the rhinocerebral form of mucormycosis, improve early diagnostic methods and find effective approaches to therapeutic and surgical treatment of this pathology.

**KEY WORDS:** mucormycosis, rhinocerebral form, comorbidity, clinical and morphological analysis, case from practice

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## INTRODUCTION

Mucormycosis is a serious life-threatening opportunistic infection caused by ubiquitous molds belonging to the order Mucorales [1]. Today mucormycosis is the third most frequent invasive mycosis, following candidiasis and aspergillosis [2]. The most frequently reported pathogens in mucormycosis are Rhizopus spp, Mucor spp, and Lichtheimia spp, followed by Rhizomucor spp, Cunninghamella spp, Apophysomyces spp, and Saksenaea spp [3]. Rhizopus oryzae being the most common species. It is responsible for approximately 60% of mucormycosis cases and 90% of rhinocerebral form in humans.

The incidence of mucormycosis in developed countries is lower than that in developing countries [4]. Mucormycosis pathogens are widespread in the environment in different climatic zones. They enter the human body through inhalation of infected dust, ingestion of food, and traumatic damage to the eyes and skin. There are cases of mucormycosis infection in case of skin damage as a result of tattoos, drug addicts, and the use of medical instruments contaminated with fungal spores [5]. Nosocomial infections caused by Mucorales commonly develop as complications in healthcare settings, particularly intubation and mechanical ventilation, in surgical wounds or at intravenous catheter insertion sites. [6].

Mucormycosis is characterized by various clinical and morphological manifestations, rapid progression, unpredictable course and high mortality [7]. There are five main clinical and morphologic forms of mucormycosis: rhinocerebral, cutaneous, pulmonary, gastrointestinal and disseminated. Some scientists also identify rare forms characterized by damage to the kidneys, heart, joints, etc. The most common clinical presentation of mucormycosis is the rhinocerebral and pulmonary forms [8]. The mortality rate of mucormycosis has been reported as 96% for disseminated form, 85% for gastrointestinal form, 76% for pulmonary form, 69% for rhinocerebral form [9].

The development of mycormycosis depends on the metabolic and immune status of the human body. Nu-

merous studies have proven that a predisposing factor for the development of mucormycosis in a patient is the presence of an immunodeficiency state. The reasons for the latter may be the use of glucocorticosteroid drugs, immunosuppressive therapy after organ transplantation, irrational use of antibiotics, oncohematological diseases, HIV/AIDS, severe diabetes mellitus [10]. Diabetic ketoacidosis is a major predisposing comorbid condition that can help Mucorale [11]. During ketoacidosis, iron disengages from transferrin, and the released free iron impairs the function of neutrophils and undermines their ability to damage and kill Mucorales hyphae [12]. In recent times, tuberculosis and chronic renal failure have also become more prominent as risk factors [13]. Malnourishment and neonatal prematurity are also referred to as risk factors for the development of mucormycosis [4].

COVID-19 infection increases the incidence of COVID-19-associated mucormycosis and post-COVID-19 mucormycosis. It's remarkable that before the pandemic, mucormycosis was reported at a rate of 0.5 to 1.5 cases per million, but with the advent of COVID-19, this rate has surged to 26.7% [14]. Research indicates that mucormycosis typically develops around 10 to 15 days after a COVID-19 diagnosis [15].

The ability of SARS-CoV-2 to damage not only lung tissue but also vascular endothelium, activate nonspecific cellular response and production of proinflammatory cytokines, causing, on the one hand, a cytokine storm, and on the other hand, enhancing immunosuppression by reducing the levels of $CD4^+$-, $CD8^+$-lymphocytes, creates favorable conditions for the development of mucormycosis [11, 16, 17]. Our previous study identified the bacterial and fungal genesis of rhinosinusitis in patients in post-COVID-19 period. Among the bacteria, it was noted Staphylococcus aureus, Staphylococcus epidermidis, Klebsiella pneumonia, Streptococcus pneumonia and Enterococcus faecalis. Among fungi, there were Aspergillus, Candida, Mucor and Coccidioides [18].

The diagnosis of mucormycosis, especially in the setting of unfavorable comorbidity, is extremely difficult, requires an interdisciplinary approach and occurs during morphological examination of the material. The purpose of this work was to conduct a detailed clinical and morphological analysis of a fatal case of rhinocerebral mucormycosis in a patient with post-COVID-19 syndrome and type 1 diabetes mellitus.

## CASE STUDY

Patient M., female, 42 years old, was hospitalized on September 3, 2023. The anamnesis revealed that the patient had a long history of type 1 diabetes mellitus, and in August 2023 she was hospitalized for severe coronavirus infection (COVID-19). From August 28 to September 2, 2023, the patient was treated for a cavernous sinus thrombosis, but the treatment did not give the desired result, the patient's condition deteriorated, and she was transferred to another hospital.

At the time of the last hospitalization, the patient was in an extremely serious condition. During the examination, the skin of the face on the left side in the infraorbital region, in the lower eyelid, and nose was necrotic, black in color. The nasal mucosa was black, with fragments of necrotic tissue and bloody clots in the nasal passages. Cytological examination of nasal discharge revealed abundant mixed flora and inflammatory cells. On September 6, 2023, the patient underwent enucleation of the left eye and necrectomy of the soft tissues of the left face. On September 8, 2023, a computed tomography scan diagnosed multiple foci of infarction in the left temporal, parietal and frontal lobes, left cerebellar hemisphere, and brainstem. Over time, the patient's condition progressively deteriorated. On September 12, 2023, the patient died.

During the autopsy, the woman's left eye was absent. The skin of the face on the left side in the infraorbital region, in the lower eyelid, nose, as well as the mucous membrane of the nose and the soft and hard palate on the left were necrotic and black in color. The dura mater was tense and full of blood. The soft meninges looked swollen, dull and sharply hemorrhagic. The brain was edematous and moist, the furrows were smoothed, and the gyri were flattened. Multiple small abscesses and ischemic infarcts were recorded in the left temporal, parietal and frontal lobes, left cerebellar hemisphere, and brainstem. In areas of infarcts the brain acquired a mushy consistency and was whitish-gray in color. Macroscopic examination of other organs and systems did not reveal any pathology.

Histologic examination of the surgical material in the eyeball revealed purulent panophthalmitis, acute thrombosis of dilated choroid and iris vessels. In the removed skin fragments with underlying soft tissues, severe necrotic and hemodynamic changes, moderate inflammatory changes, and a proliferation of plexiform fungal hyphae growing through the walls of blood vessels and filling their lumens, and in some places growing into nerve trunks were detected (Fig. 1).

Histologic investigation of the autopsy material revealed hemodynamic disorders in the soft meninges, severe diffuse infiltration of neutrophilic leukocytes and lymphocytes, which in some visual fields extended to the brain tissue (Fig. 2). Alternative and hemodynamic disorders were noted in the brain tissue, diffuse leuko-

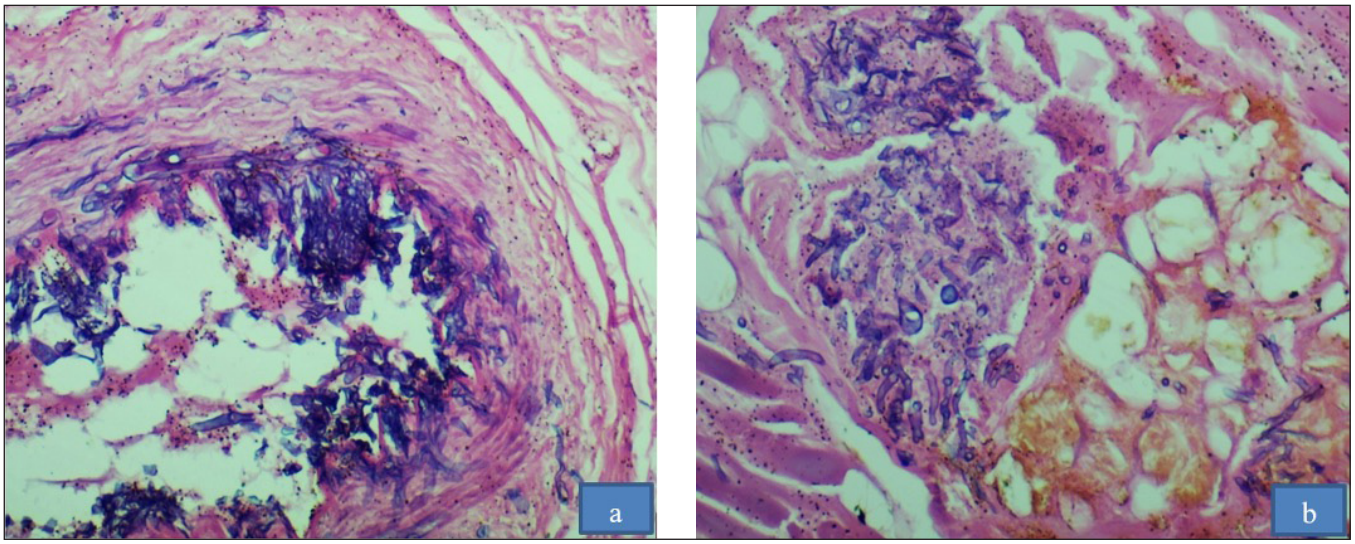


**Fig. 1.** Disseminated fungal hyphal plexuses in the skin with underlying soft tissue. Hematoxylin and eosin staining, a) ×200, b) ×200.

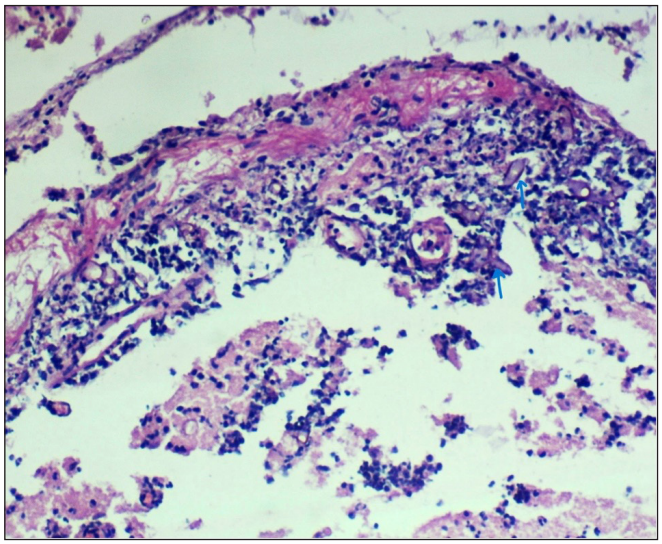

**Fig. 2.** Fungal hyphae (marked with a blue arrow), diffuse infiltration with neutrophilic leukocytes, lymphocytes of the dura mater and brain tissue. Hematoxylin and eosin staining, ×200.

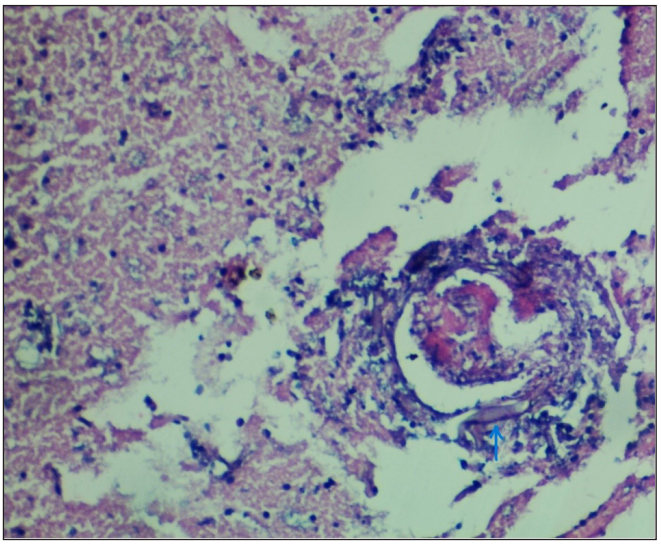

**Fig. 3.** Alternative, hemodynamic and inflammatory changes in the brain tissue. Accumulation of fungal hyphae in the brain tissue, in thrombotic masses that obstruct the lumen of the vessel. Fungal hyphae (marked with a blue arrow) sprouting through the vessel wall. Hematoxylin and eosin staining, ×400.

cyte infiltration in some visual fields, and multiple acute abscesses with the presence of coenocytic (aseptate) hyphae in some visual fields (Fig. 3). The cerebral vessels were characterized by plethoricity and the presence of acute thrombi with coenocytic hyphae in the lumen (Fig. 3). In some of the fields of view, fungal hyphae sprouted through the vessel wall (Fig. 3). The mucous membrane of the paranasal sinuses on the left showed severe necrotic changes.

Thus, the results of the autopsy, histological examination of the surgical and autopsy material indicated that the patient died as a result of intoxication and brainstem dislocation caused by the rhinocerebral form of mucormycosis.

## DISCUSSION

Rhinocerebral mucormycosis used to be a rare fungal infection, which, taking into account the literature and the results of our previous studies, is now quite common in patients of different ages, especially against the background of comorbid pathology, manifested by weakened immunity [18, 19]. In rhinocerebral form of mucormycosis the fungus penetrates the nasal cavity through the skin-mucosa junction, spreads to the palate, sinuses, and orbit, and finally causes intracranial infection [20, 21].

Major insights in mucormycosis pathogenesis have brought into focus the host receptors (glucose-regulated protein 78 (GRP78)) and signaling pathways (epidermal growth factor receptor activation cascade)

as well as the adhesins used by Mucorales for invasion [4, 22]. Notably, GRP78 also serves as a shared entry route for both the SARS-CoV-2 virus and Mucor fungi into the nasal and paranasal sinus mucosa [23].

In the article, the authors conducted an analysis of the clinical and morphological features of the rhinocerebral form of mucormycosis in a patient with type 1 diabetes mellitus and post-COVID-19 syndrome. The observed case of rhinocerebral mucormycosis was characterized by typical clinical manifestations and diagnosed during life, but despite the complex of therapeutic and surgical measures, this pathology led to death, which, in our opinion, was due to the severity of the pathology, late hospitalization of the patient and the presence of unfavorable comorbidity (type 1 diabetes mellitus and post-COVID-19 syndrome).

Early diagnosis of mucormycosis is extremely important, which is possible during morphological examination of biological material from the lesion. During the examination of the material, fungal hyphae are characterized by uneven thickness. The mycelial filaments branch at different angles, are unseptate, with a double-circular membrane and coarse-grained cytoplasm. Clusters of mycelium form disorderly plexuses [22].

The pathognomonic morphological feature of mucormycosis is the lesion of blood vessels, which is important in the manifestation and generalization of the pathological process. Some scientists characterize mucormycosis as an angioinvasive disease [24]. The lesions of blood vessels, as shown by our morphological examination of the surgical and autopsy material, were characterized by the fact that fungal hyphae germinated the vessel wall, formed clusters of threads and thrombi in their lumen. Changes in the vessel walls caused trophic disorders and, accordingly, the development of severe necrotic changes in the patient's skin of the face on the left side in the infraorbital region, in the lower eyelid, nose, as well as the mucous membrane of the nose and the soft and hard palate on the left. The literature describes cases of rhinocerebral mucormycosis manifested by necrosis of the bone tissue of the facial skull [25].

Multiple ischemic infarctions in the left temporal, parietal, and frontal lobes, left cerebellar hemisphere, and brainstem, which were found during the autopsy, are most likely caused by cerebral vascular thrombosis. According to the literature, as a result of angioinvasion in mucormycosis, not only ischemic infarctions occur in the brain, but also intracerebral hemorrhages [24].

## CONCLUSIONS

Mucormycosis is a life-threatening pathology characterized by various manifestations, severe course and high mortality. This disease, which was previously considered rare, shows a significant increase in the incidence, especially among patients with comorbid conditions, manifested by weakened immunity. The authors conducted a clinical and morphological analysis of a case of rhinocerebral mucormycosis in a patient who was diagnosed lifetime, but despite a set of therapeutic and surgical measures led to death, which was due to the severity of the pathology, late hospitalization of the patient and the presence of comorbidities (type 1 diabetes mellitus and post-COVID-19 syndrome). The clinical case presented by the authors raises the issue of the need to increase physicians' awareness about the rhinocerebral form of mucormycosis, improve early diagnostic methods and find effective approaches to therapeutic and surgical treatment of this pathology.

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**CONFLICT OF INTEREST**

The Authors declare no conflict of interest

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