

A Rare Presentation of a Case of Cerebral Mucormycosis as a Solitary Intraparenchymal Lesion

Anna Balaji Karthikeyan^{1,*}, Rakesh Gupta², Zafar Sheikh²

¹Department of General Surgery, Mahatma Gandhi Memorial Medical College, Indore, India

²Department of Neurosurgery, Mahatma Gandhi Memorial Medical College, Indore, India

Email address:

karthikeyan.94.ab@gmail.com (A. B. Karthikeyan), drrakeshgupta@yahoo.com (R. Gupta), zafar18@gmail.com (Z. Sheikh)

*Corresponding author

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Abstract: Rhinocerebral mucormycosis is an opportunistic infection of the sinuses, nasal passages, oral cavity, and brain caused by saprophytic fungi and is known to be rare in occurrence. This infection can result in a rapid death. Rhinocerebral mucormycosis is known to commonly affect individuals who are in an immunocompromised state. Isolated cerebral mucormycosis, in the absence of rhino-orbital focus, is an extremely rare but life-threatening infection of central nervous system that is most commonly found in intravenous drug abuser. We present a case of isolated cerebral mucormycosis that presented as a case of malignant glioma and was later diagnosed as a case of cerebral mucormycosis by open biopsy and treated with antifungals. A 45-year-old male patient presented to the casualty with complaints of altered behaviour and speech with right hemiparesis for 1 week. He also lost continence of micturition and defecation. Though the patient was conscious, his presenting GCS was E4V1M6. He had suffered from COVID-19 infection 2 months back and recovered without any steroid medications. An MRI (tumour protocol) of the brain and a CECT brain revealed a high grade multicentric glial neoplasm involving left thalamocapsular region and extending into adjacent cortical/subcortical left high parietal and posterior temporal lobe and a midline shift of 6-8mm to the right. A left parietal craniotomy was done which revealed a pus-filled cavity which was drained, and marsupialization of cavity wall was done. Biopsy revealed the final diagnosis of Isolated cerebral Mucormycosis. Isolated Cerebral mucormycosis is a rare occurrence and a confusing presentation and thus, an intracranial SOL should be approached with caution to minimize patient morbidity.

Keywords: Cerebral Mucormycosis, Solitary Intraparenchymal Lesion, COVID-19, Mucor, Malignant Glioma, Glioblastoma

1. Introduction

Mucormycosis, which was previously known as zygomycosis, is a serious and rare fungal infection caused by a group of molds called mucormycetes. These molds are found throughout the environment. Spores of these ubiquitous fungi (commonly found in soil, fallen leaves, compost, animal dung and air) is often inhaled and this leads to an infection in the lungs, sinuses and extend into the brain and eyes. Rarely, there have been instances when infection develops when the spores enter the body through a cut or an open wound.

Rhinocerebral mucormycosis is a rare opportunistic infection of the sinuses, nasal passages, oral cavity, and brain

that is caused by saprophytic fungi. The infection can rapidly result in mortality. Rhinocerebral mucormycosis commonly affects individuals in an immunocompromised state. Most mucormycosis cases are of rhinocerebral nature in which the infection ascends from the nasal passage to sinuses or orbit and then sometimes to the brain. [1-3] Open head injury can also result in implantation of the fungus directly into the brain. [4] Early intervention is a must to save lives and prevent permanent neurological complications. It is an acute fungal infection in most cases, but chronic presentations have also been described, which is indolent and slowly progressive, occurring over several weeks.

Diseases commonly associated with mucormycosis include diabetic ketoacidosis, severe burns, steroid therapy, solid organ transplantation, prolonged corticosteroid therapy,

hemochromatosis, patients with HIV, neutropenia, malnutrition, hematologic malignancies, etc. But the absence of predisposing factors is not an exclusion criterion for the presence of mucormycosis. Some research has demonstrated that about 9% of Rhinocerebral mucormycosis was found in patients without any predisposing factors.

In spite of the second wave of COVID-19 coming under control in India after a tough and prolonged battle, the healthcare system had to play catch up in order to manage the complications of COVID. New and Emerging complications associated with COVID-19 were reported, with mucormycosis becoming a serious issue in India due to its unprecedented surge and high morbidity. [8] Mucormycosis, in India, was given the colloquial term 'black fungus'. The angioinvasive nature of mucormycosis that is characterised by thrombosing vasculitis, and its role in host invasion have been attributed to increased expression of platelet-derived growth factor (PDGFRB) signalling. [9] The fatality rate for a serious bout of mucormycosis can be close to 100% in spite of active intervention. When there is a suspicion of mucormycosis, then adequate imaging should be done to confirm the diagnosis, followed by prompt surgical debridement. Following a sharp rise in the number of mucormycosis cases in India after the second wave of COVID-19, the Indian Health Ministry had advised that all the states should declare mucormycosis as an epidemic. Several risk factors, such as the long-term use of steroids, antibiotics, multivitamins, and zinc, have been associated to its incidence. In addition, mucosal erosion secondary to the aggressive use of steam inhalation or the use of high-flow oxygen have also been viewed as factors promoting fungus colonisation. Contamination from the use of industrial oxygen, low-quality oxygen cylinders, low-quality oxygen piping systems, and ordinary tap water in ventilators, are also being cited as causative factors. Additionally, COVID-19 is known to cause hyperglycaemia in some patients, which could predispose to fungal infection. [10]

Isolated cerebral mucormycosis, without rhino-orbital focus and without PNS involvement, is an extremely rare (16% among mucormycosis cases) but life-threatening infection of central nervous system that is most commonly found in intravenous drug abuser. [5] Most mucormycosis cases are rhinocerebral in which the infection ascends from the nasal passage to sinuses or orbit and then sometimes to the brain.

We present a case of isolated cerebral mucormycosis that presented as a case of malignant glioma and was later diagnosed as a case of cerebral mucormycosis by open biopsy and treated with antifungals.

2. Case Report

Generally, the symptoms which a patient of rhinocerebral mucormycosis typically presents with are low-grade fever, cephalgia, sinusitis, facial swelling, orbital apex syndrome with blurred vision, and cranial palsies from cavernous sinus involvement in an immunocompromised patient. [13-16] It has been observed that more commonly the first complaint

that brings such a patient to the hospital is sinusitis.

2.1. History

A 45-year-old male was brought to the casualty with complaints of altered behaviour and speech for 1 week and associated right hemiparesis. He also lost continence of micturition and defecation for 1 week. The patient had no complaints before 1 week. Patient had an episode of COVID-19 infection 2 months back and recovered fully (without steroid administration). There were no h/o seizures. There was no past surgical history that compromised his immunity. He was not a known diabetic or hypertensive. He was not on any medications known to cause immunosuppression. There was no significant family history. There was no history of contact with patients of mucormycosis.

2.2. Examination

On examination, general condition of the patient was average. The patient was vitally stable and conscious with a GCS score of 11 (E4V1M6). Pupils were bilateral reacting to light. Right side hemiparesis present. Power in the left upper limb and left lower limb was 5/5. Power in right upper and right lower limb was 1/5. Babinski response was negative on both sides. Other systems examination was normal.

2.2.1. Emergency Investigations

After emergency resuscitation of the patient with IV fluids, emergency ultrasound (abdomen and pelvis) and Digital X-ray chest and abdomen was done, all of which were suggestive of no remarkable abnormality. An emergency opinion from oral and maxillofacial surgery, ophthalmology and otorhinolaryngology was taken, and they ruled out rhinocerebral mucor as the cause of the symptoms. The patient was then admitted and a full routine blood investigations were sent, followed by CECT brain and MRI brain (tumour protocol).

2.2.2. Contrast Enhanced CT Brain

Imaging plays a key role in the diagnosis of primary tumors of the brain as well as metastasis. The most reliable initial investigation that most patients presenting with symptoms of a space-occupying lesion are subjected to is a contrast enhanced computed tomography study of the brain. In difficult cases, such as newly diagnosed solitary enhancing brain lesions in patients without known malignancy, advanced imaging techniques including MRI brain, proton magnetic resonance spectroscopy (MRS), contrast enhanced magnetic resonance perfusion (MRP), diffusion weighted imaging (DWI), and diffusion tensor imaging (DTI) are useful in arriving at the correct diagnosis.

The patient was subjected to a contrast enhanced computed tomography of the brain which revealed an approximately 5.5cm x 3.8cm hypodense mass in the left peritrigonal and posterior parietal lobe with thin hyperdense margin, with moderate mass effect and mild right midline shift suggestive of High-grade Astrocytoma versus metastatic disease.

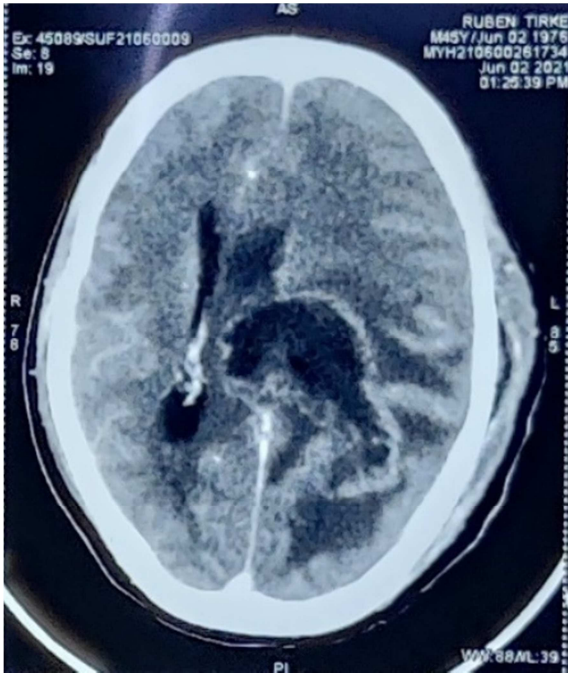


Figure 1. CECT brain axial section.

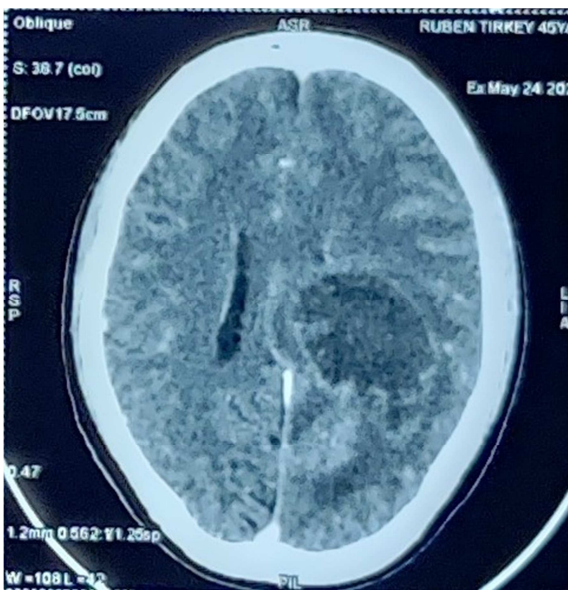


Figure 2. Contrast enhanced image of CT brain axial section.

2.2.3. MRI brain (Tumor Protocol)

Contrast enhanced computed tomography of the brain was then followed by a magnetic resonance study of the brain on the lines of tumor protocol to expand further on the nature of tumor. The report was suggestive of a large, ill-defined, lobulated, infiltrative, irregular peripheral enhancing mass lesion along left thalamocortical region extending to left high parietal and posterior temporal lobe features suggestive of a high grade glial neoplasm (glioblastoma) versus metastasis. Magnetic resonance perfusion study was suggestive of significant hypoperfusion. Magnetic resonance spectroscopy was suggestive of large lipid/lactate peakson short TE, significant decrease in n-acetylaspartate (NAA), mild elevation of choline peak on intermediate TE.



Figure 3. MRI brain axial section.

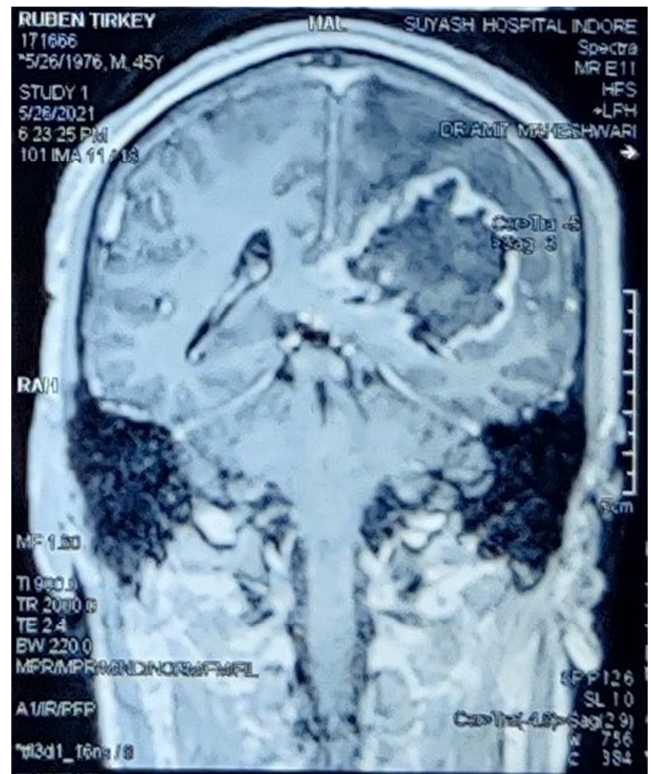


Figure 4. MRI brain coronal section.



Figure 5. MRI brain Sagittal section.

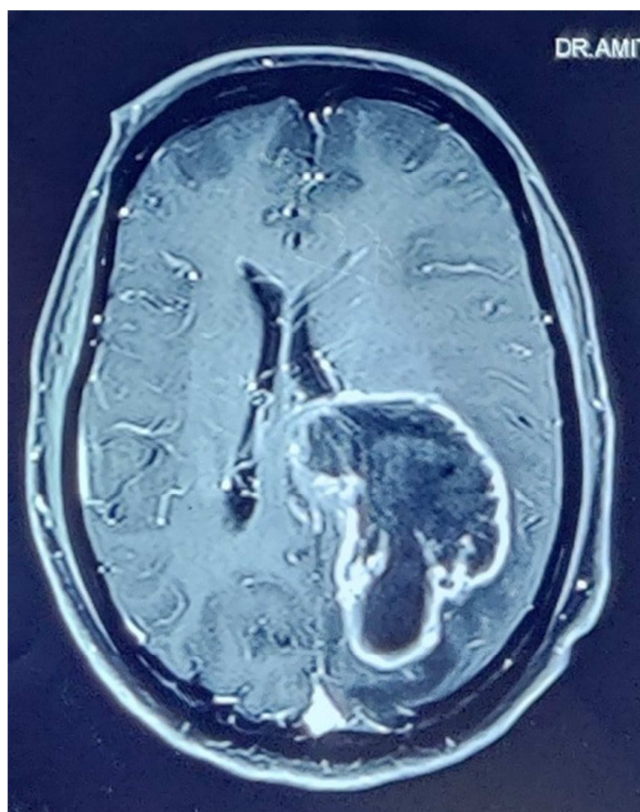


Figure 6. MR spectroscopy axial section.

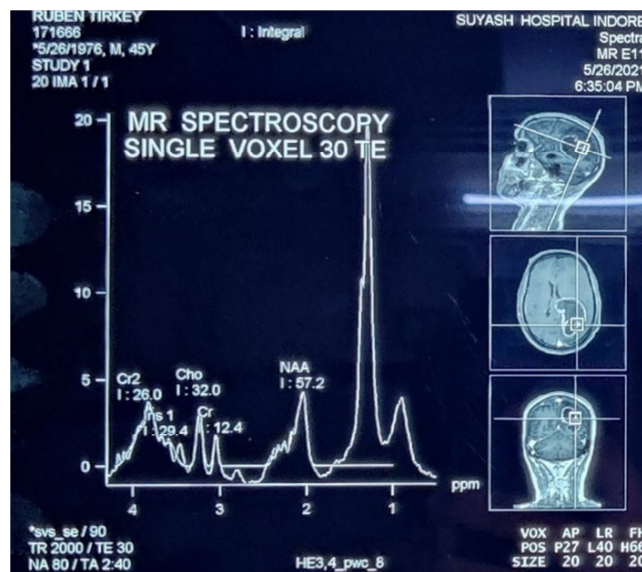


Figure 7. MR spectroscopy single voxel.

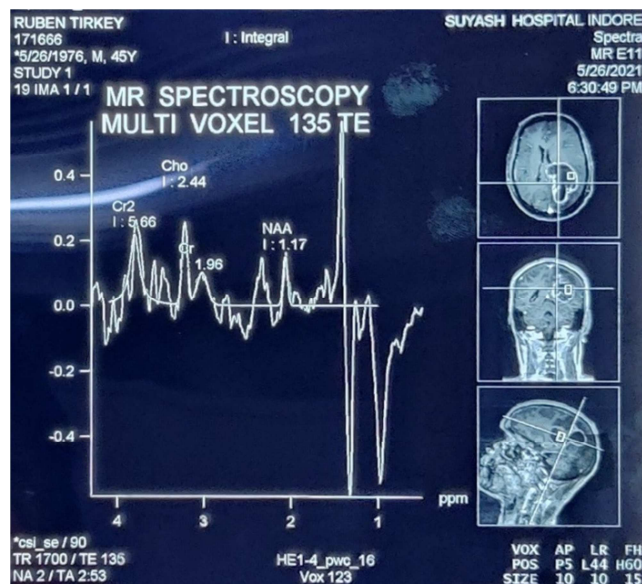


Figure 8. MR spectroscopy multi voxel.

3. Management

3.1. Surgical Management

Based on the findings of CT brain and MRI brain, the patient was taken up for emergency surgery for excision of tumor. A left parietal craniotomy was done, revealing a pus-filled cavity; drainage of pus with marsupialisation of cavity wall was done. Specimen was sent for biopsy, which revealed a final histopathological diagnosis of Mucormycosis.

3.2. Postoperative Management

In the immediate postoperative period, the patient was kept nil by mouth, and required oxygen by mask which was gradually tapered down. He was given intravenous fluids (normal saline) at a rate of 120 ml/ hour. The patient was

started on higher antibiotics (intravenous meropenam and vancomycin). Intravenous phenytoin along with leviratracetam was also started to prevent seizures. Intravenous mannitol was started to reduce cerebral edema. Patient was taken off oxygen support on first postoperative day and Ryle's tube feeding was started. The biopsy report arrived on the third postoperative day, giving the confirmative diagnosis of mucormycosis. The patient was subsequently started on intravenous liposomal amphotericin B and intravenous posaconazole. He should gradual response to the medication and GCS was improving. Unfortunately, the patient succumbed on 29th postoperative day to aspiration pneumonitis.

4. Discussion

Mucormycosis is a fungal infection that is often seen to develop in individuals with immunologically compromising conditions and it most commonly occurs in the context of acute myeloid leukemia (and other hematological malignancies), severe neutropenia, graft-vs-host disease, diabetes, or end-stage renal disease patients who are dependent on dialysis and the use of iron chelators. The various forms of mucormycosis (disseminated, rhinocerebral, pulmonary, cutaneous, gastrointestinal, and isolated cerebral disease) are seen to differ in predisposing conditions and prognosis.

The COVID-19 outbreak in India has emphasized the need to understand the complex pathogenesis of diabetes and its relation to other diseases. Pathological changes in the pancreas were seen in patients with severe form of COVID-19, indicating that SARS-CoV-2 can cause pancreatic injury, and this could be one of the reasons behind why COVID-19 patients with no history of diabetes have high blood glucose levels. The most common cause of drug-induced hyperglycaemia is steroids, [11] which aggravate hyperglycaemia in patients with known diabetes mellitus (DM). Diabetes-related hyperglycaemia is thought to be the cause of immune response dysfunction, resulting in an inability to control the spread of invading pathogens. [12]

Diabetes mellitus, when occurring in combination with the SARS-CoV-2 virus and steroid therapy, is known to lead to a vicious cycle of hyperglycaemia and immunosuppression, which can lead to severe fungal colonisation such as mucormycosis in the present epidemic.

Typically, the disease was seen in patients during the COVID-19 recovery period, suggesting that multiple factors facilitate fungal colonisation. In most of the cases, it was observed that the time period between recovery from COVID-19 infection and onset of mucormycosis was around 10 to 15 days, unlike our case in which the time interval was observed to be for about 2 months. There are many instances when patients have overlooked symptoms of mucormycosis mistaking it for residual symptoms of COVID-19, thus leading to a delay in diagnosis or under-diagnosis of mucormycosis due to late presentation to the hospital.

In individuals with diabetes, especially in the setting of ketoacidosis, the most common form of mucormycosis seen

is the rhinocerebral form, due to the direct invasion of central nervous system (CNS) through the air sinuses [5]. Those who have no underlying comorbidities are most likely to present with cutaneous mucormycosis which often follows trauma, but other forms of mucormycosis involving the sinuses and brain should not be ruled out. [5] Isolated cerebral mucormycosis is commonly seen to occur due to hematogenous seeding following intravenous inoculation and among immunocompetent individuals, this is an important presentation. Most of the published cases of isolated cerebral mucormycosis are associated with a past history of injection drug use, thus making this a critical component of history, particularly in the current setting of COVID-19 and rampant drug addiction.

Isolated cerebral mucormycosis in immunocompetent adults, defined as an infection with the Mucorales species, isolated from the brain only, in an immunocompetent host without diabetes, is an extremely rare entity. The strongest association in previously reported cases is seen in injection drug use as it facilitates hematogenous introduction of the mold. It has been observed from previous studies that cerebral mucormycosis has a predilection for the basal ganglia, probably due to its high iron content, and germination of *Rhizopus* spp. Spores require free iron. [6, 7]

Diagnosis of mucormycosis requires tissue, which should be sent for culture and pathology to look for characteristic broad-based aseptate hyphae. Even when visible clearly on histopathology, the organisms do not grow in culture at all times, because at times they might be nonviable. This is particularly likely if antifungals have been administered before sample collection, thus highlighting the utility of PCR-based testing. The imaging modality of choice is MRI study of the brain with special sequences, including gradient echo and susceptibility weighting, to assess for microhemorrhage, which is suggestive of a potentially invasive process.

There are several important treatment considerations for mucormycosis. Amphotericin is essential to treatment, as no patients have survived without amphotericin B (AmB). It has been observed from previous studies that early diagnosis and early initiation of amphotericin B improve survival in immunocompetent patients with mucormycosis. Whether to add additional agents for combination therapy is controversial. Some providers may prefer adding a triazole with anti-Mucorales activity, such as posaconazole or isavuconazole, to initial treatment, as observed in our case.

5. Conclusion

The second wave of COVID-19 was devastating in India as it was associated with more COVID related deaths than the first wave. However, the twist in the storyline was the associated overwhelming mucormycosis cases that followed up after the decline of the COVID-19 wave. The sudden breakout of mucormycosis proved to be immensely challenging to tackle because it was the first time that Indian doctors were bombarded with such a rare case in huge

numbers. It was equally challenging for the pharmaceutical companies to satisfy the sudden increase in demand for liposomal amphotericin B, which was a scarcely used drug prior to the mucor crisis.

Isolated cerebral mucormycosis in immunocompetent adults is a rare and underrecognized syndrome that requires a high index of suspicion for diagnosis and prompt treatment. Patients often present with headaches and cranial nerve deficits, and some of them might present with fevers or altered mental status further confusing the clinician. Tissue from biopsy is important for establishing the diagnosis. Treatment should include amphotericin B. Given the current COVID-19 crisis and rampant use of injectable steroids, the frequency of cases might increase.

References

- [1] Multiple brain abscesses from isolated cerebral mucormycosis. Escobar A, Del Brutto OH, *J Neurol Neurosurg Psychiatry*. 1990 May; 53 (5): 431-3.
- [2] Paranasal sinus mucormycosis: a report of two cases. Ruoppi P, Dietz A, Nikanne E, Seppa J, Markkanen H, Nuutinen J, *Acta Otolaryngol*. 2001 Dec; 121 (8): 948-52.
- [3] Long-term survival in rhinocerebral mucormycosis. Case report. Weprin BE, Hall WA, Goodman J, Adams GL, *J Neurosurg*. 1998 Mar; 88 (3): 570-5.
- [4] Isolated cerebral mucormycosis: report of a case and review of the literature. Verma A, Brozman B, Petito CK, *J Neurol Sci*. 2006 Jan 15; 240 (1-2): 65-9.
- [5] Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2005; 41: 634–653.
- [6] Malik AN, Bi WL, McCray B, et al. Isolated cerebral mucormycosis of the basal ganglia. *Clin Neurol Neurosurg* 2014; 124: 102–5.
- [7] Kousser C, Clark C, Sherrington S, et al. *Pseudomonas aeruginosa* inhibits *Rhizopus microsporus* germination through sequestration of free environmental iron. *Sci Rep* 2019; 9: 5714.
- [8] Szarpak L., Chirico F., Pruc M., et al. Mucormycosis — a serious threat in the COVID-19 pandemic? *J Infect*. 2021; 83: 237–239.
- [9] Park Y. L., Cho S., Kim J. W. Mucormycosis originated total maxillary and cranial base osteonecrosis: a possible misdiagnosis to malignancy. *BMC Oral Health*. 2021; 21: 65.
- [10] Montefusco L., Ben Nasr M., D'Addio F., et al. Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. *Nat Metab*. 2021; 3: 774–785.
- [11] Coutinho A. E., Chapman K. E. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Mol Cell Endocrinol*. 2011; 335: 2–13.
- [12] Berbudi A., Rahmadika N., Tjahjadi A. I., et al. Type 2 diabetes and its impact on the immune system. *Curr Diabetes Rev*. 2020; 16: 442–449.
- [13] Imaging of mucormycosis skull base osteomyelitis. Chan LL, Singh S, Jones D, Diaz EM Jr, Ginsberg LE *AJNR Am J Neuroradiol*. 2000 May; 21 (5): 828-31.
- [14] Craniofacial mucormycosis: assessment with CT. Gamba JL, Woodruff WW, Djang WT, Yeates AE *Radiology*. 1986 Jul; 160 (1): 207-12.
- [15] MR imaging in rhinocerebral and intracranial mucormycosis with CT and pathologic correlation. Terk MR, Underwood DJ, Zee CS, Colletti PM *Magn Reson Imaging*. 1992; 10 (1): 81-7.
- [16] Chronic rhinocerebral mucormycosis. Harrill WC, Stewart MG, Lee AG, Cernoch P *Laryngoscope*. 1996 Oct; 106 (10): 1292-7.