# 81050_Auto_Edited.docx

WORD COUNT 2188
TIME SUBMITTED 13-JAN-2023 12:16PM
PAPER ID 95489411

**Name of Journal:** *World Journal of Clinical Cases*
**Manuscript NO:** 81050
**Manuscript Type:** CASE REPORT

**Stroke? Brain abscess? A case report of isolated cerebral mucormycosisand literature review**

none

Caihong Chen, Jingnan Chen, Hanggen Du, Dongliang Guo

**:**

**Abstract**

BACKGROUND

Cerebral mucormycosis is an infectious disease of the brain caused by fungi of the order Mucorales. These infections are rarely encountered in clinical practice and are often misdiagnosed as cerebral infarction or brain abscess. Increased mortality due to cerebral mucormycosis is closely related to delayed diagnosis and treatment, both of which present unique challenges for clinicians.

CASE SUMMARY

Cerebral mucormycosis is generally secondary to sinus disease or other disseminated disease. However, in this retrospective study, we report and analyze a case of isolated cerebral mucormycosis.

CONCLUSION

The constellation of symptoms including headaches, fever, hemiplegia, and changes in mental status taken together with clinical findings of cerebral infarction and brain abscess should raise the possibility of a fungal brain infection. Early diagnosis and prompt initiation of antifungal therapy along with surgery can improve patient survival.

**Key Words:** cerebral mucormycosis; stroke; brain abscess; diagnosis; treatment

Chen C, Chen J, Du H, Guo D. Stroke? Brain abscess? A case report of isolated cerebral mucormycosisand literature review. *World J Clin Cases* 2023; In press

**Core Tip:** Cerebral mucormycosis is an infectious disease of the brain caused by fungi of the order Mucorales. These infections are rarely encountered in clinical practice and often misdiagnosed as cerebral infarction or brain abscess. Diagnosis and treatment are challenging, and as such this disease is often associated with a high mortality rate.

Through this case study, we aim to further understand the pathophysiology of cerebral mucormycosis and suggest strategies for the improvement of clinical diagnosis and treatment thereof.

## INTRODUCTION

Cerebral mucormycosis is a life-threatening fungal infection[1]. Although modern technology advances and various imaging techniques are available to aid its diagnosis and treatment, this disease still carries a mortality rate as high as 62%[2-4]. Mucormycosis can affect various areas of the body, including rhino-cerebral tissue, lung, skin, and gastrointestinal tract, and can even present as a disseminated infection. Cerebral mucormycosis is the most common presentation of infection caused by Mucorales fungi and can occur *via*direct invasion of rhino-orbital structures or by hematogenous spread to the brain[5].

Cerebral mucormycosis cases can be found across the globe, with 47 countries reporting this infection. North America accounts for the majority of reported cases (130/345, 37.68%), followed by Asia (87/345, 25.22%). The incidence of cerebral mucormycosis is higher in males (60%) and the age distribution of affected patients is wide (2 mo to 89 years)[6]. Cerebral mucormycosis is generally diagnosed in patients with underlying medical conditions, with diabetes being the most common[7]. Amphotericin B deoxycholate (AmB) antifungal therapy and surgical debridement are the most commonly utilized methods for the treatment of cerebral mucormycosis.

Isolated cerebral mucormycosis is very rare. Due to the lack of specific clinical manifestations, the misdiagnosis rate is high in the early stages of the disease. Up to 90% of cases are reported to go undiagnosed and untreated[8-10]. The most common symptoms are orbital and neurological, followed by headache. Neurological symptoms are often associated with other extracerebral symptoms, with fever reported in greater than 1 in 5 cases[11-12]. Therefore, the presence of any of these symptoms in immunocompromised patients requires a high degree of suspicion for fungal brain

infection. Here, we present a case of isolated cerebral mucormycosis followed by discussion and review of the current literature.

## CASE PRESENTATION

### *Chief complaints*

A 49-year-old femalepresented to the outpatient clinic with 11 d of headache and 1 wk of left upper and lower extremity weakness accompanied by fever.

### *History of present illness*

The patient endorsed persistent pain mainly due to right frontal and parietal headache not relieved after rest. The patient was hospitalized at the Department of Neurology with a body temperature of 39.2 ◦C.

### *History of past illness*

The patient had type 2 diabetes. A diagnostic consultation did not identify any foci of infection. She had no past history of otitis media, sinusitis, or head trauma.

### *Personal and family history*

The patient denied having any other relevant personal history and her familial history was unremarkable.

### *Physical examination*

The physical examination revealed intact consciousness with a Glasgow coma scale (GCS) score of 15, a soft neck, left upper and lower extremity muscular strength (1 out of 5), a shallow left nasolabial fold, and intact deep and superficial sensation.

### *Laboratory examinations*

A complete blood count and differential revealed a white blood cell count of 13.4 × $10^9$/L (normal reference range: 4.0–10.0 × $10^9$/L), 80.0% neutrophils (normal reference

range: 50%–70%), 12.1% lymphocytes (normal reference range: 20%–40%), and C-reactive protein (CRP) level of 50.1 mg/L (normal reference range: 0–10 mg/L). Urinalysis revealed a white blood cell count of 229/μg (normal reference range: 0-26/μg). Urine culture grew *Enterococcus faecalis*. Blood and sputum cultures were negative.

***Imaging examinations***

No obvious abnormalities were observed in a computed tomography (CT) scan of the chest. A cardiac Doppler ultrasound revealed mild mitral regurgitation. Magnetic resonance imaging (MRI) of the head with and without contrast demonstrated the following: (1)large-scale abnormal signal lesions in the right frontal lobe and right basal ganglia with low signal onT1-weigted imaging (T1WI), slightly higher signal on T2-weigted imaging (T2WI), and high signal on diffusion-weighted imaging (DWI); (2) enhancement of the gyrus around the lesion without significant space-occupying effect; and (3) multiple long T2 signals and enhanced DWI signals in the left cerebral hemisphere (Figure 1A–J). CT angiography (CTA) of cervical arteries demonstrated occlusion of the right internal carotid artery (Figure 2A–D).Further examination of the arteries with magnetic resonance angiography (MRA) showed that there was no development of the right internal carotid artery skull base and intracranial segments, and the anterior and posterior cerebral arteries were supplied by the traffic branch (Figure 2E–F).

## FINAL DIAGNOSIS

A final diagnosis of cerebral mucormycosis was made following histopathological examination of the resected brain lesion.

## TREATMENT

Following surgical resection of the right cerebral lesion, the patient received therapy with intravenous amphotericin B.

## OUTCOME AND FOLLOW-UP

There were signs of improvement in the first 3 d following resection of the lesion. However, the patient gradually deteriorated and brain death was pronounced 1 mo later.

## DISCUSSION

Cerebral mucormycosis is a life-threatening acute or chronic central nervous system disease caused by Mucorales fungi. In most cases, cerebral mucormycosis is caused by the spread of infection from the sinuses, and isolated cerebral mucormycosis is extremely rare. In a meta-analysis of 929 cases of mucormycosis, 30% described central nervous system disease, of which only 16% were confined to the central nervous system[2]. In other studies, isolated cerebral mucormycosis was found to account for up to 8% of all cases of mucormycosis[13-15]. Several risk factors are described in the literature, including intravenous drug use, diabetes mellitus, malignancy, solid and bone marrow transplantation, and iron overload status. Intravenous drug use is the most important risk factor for the development of isolated cerebral mucormycosis[16-17]. Verma *et al*[18]reported 30 cases of isolated cerebral mucormycosis, of which 17 cases were notable for history of intravenous drug abuse. Diabetes mellitus is the strongest risk factor for development of other mucormycosis infections, and in the meta-analysis of 929 cases mentioned above, 36% of patients with mucormycosis had a history of diabetes. It is believed that diabetic patients are susceptible to mucormycosis due to the fungal ketoreductase system allowing the organisms to metabolize ketone bodies. In addition, the hyperglycemia and acidosis often found in the setting of diabetes reduce neutrophil chemotaxis and adhesion to fungal hyphae as well as impair the inhibition of Mucorales spores and mycelia by alveolar macrophages[19]. In the present case, the patient had a history of poorly controlled diabetes mellitus, and as such carried an increased susceptibility to mucormycosis infection due to these immunosuppressive mechanisms.

As mentioned previously, the most common symptoms of cerebral mucormycosis are orbital and neurological, followed by headache. Neurological symptoms are often related to other extracerebral symptoms such as fever. In our case, the symptoms demonstrated in the patient were headache, hemiplegia, and fever. In a review of 13 cases of isolated cerebral mucormycosis, altered mental status (54%) and headache (51%) were common[20]. Considering the presenting symptoms of our patient and those of patients discussed in the literature, it is apparent that these nonspecific signs and symptoms are largely responsible for the challenges faced by clinicians in diagnosing cerebral mucormycosis, as many other conditions must be considered in the differential. To further add to these challenges, imaging findings can also vary widely. For example, Kursun *et al*[11]report cavernous sinus involvement as the most common brain imaging sign in 27 patients with cerebral mucormycosis, whereas in our case, abscess-like enhancing lesions were prominent.

In addition to the nonspecific presenting symptoms and imaging findings discussed above, many reported cerebrospinal fluid cultures are essentially negative, and culture conditions necessary for the growth of Mucorales fungi are inconsistently reported[21]. Histopathological examination of involved tissue can confirm the diagnosis; however, this requires invasive surgery. Taken together, these difficulties underscore the importance of a high clinical suspicion of cerebral mucormycosis and careful differential diagnosis.

Histopathological visualizationof broad, ribbon-like, pauciseptate hyphae with wide-angle branching supports the diagnosis of mucormycosis. Acute inflammation with predominant neutrophilia is usually present, but may be difficult to identify in patients with underlying neutropenia. In addition, histopathological identification of mucormycosis does not provide genus and species information nor antifungal susceptibility data, and has limited ability to detect mixed fungal infections[22-23]. New diagnostic methods, including matrix-assisted laser desorption/ionization-time of flight (commonly known as MALDI-TOF) testing of serum and cryosections, can be used to aid diagnosis[24]. Unfortunately, molecular techniques may not be available at all

institutions, and histopathological examination remains the gold standard for the diagnosis of isolated cerebral mucormycosis[25-26]. In our case, the histologic diagnosis was confirmed by hematoxylin-eosin staining and periodic acid-silver methenamine staining of resected brain tissue.

Mucorales fungi are extremely invasive,and their hyphae can invade blood vessels. The growth of hyphae in the lumen of the blood vessels with associated damage to the endothelium can cause vascular occlusion, and formed fungal emboli can easily cause cerebral infarction. The blood vessels usually involved are the basilar artery and carotid artery, and the extravasation of fungal elements can lead to brain abscess formation[27-28]. In our case, the right internal carotid artery was completely occluded, and the MRI of the head demonstrated infarction in the right frontal lobeand right basal ganglia, likely due to impediment of blood flow by fungal emboli. However, infarction may also be a consequence of abscess formation.

The treatment of patients with mucormycosis is challenging, and even in adequately treated patients the associated mortality rate is still high. Standard treatments include AmB and its lipid formulation and surgical debridement[29-30]. In most retrospective studies, AmB and its lipid formulation are the preferred treatment and are part of any potential combination therapy. Posaconazole in combination with AmB is reported to offer treatment benefits when compared to antifungal monotherapy[32-34]. In some reports, posaconazole may be a more advantageous treatment strategy when used as the first line treatment for cerebral mucormycosis in diabetic patients with antifungal-resistant infections[31-33]. Moreover, vascular invasion by Mucorales fungi leads to vascular occlusion and necrosis, in turn significantly reducing drug distribution to target tissue. This emphasizes the importance of surgical debridement in the treatment of cerebral mucormycosis, especially in the setting of vascular occlusion[34-36]. Debridement can aid in treatment by reducing the microbiological load and altering anaerobic and microaerobic conditions conducive to fungal reproduction. However, in many case studies, death occurred despite surgical debridement and adequate antifungal treatment. These deaths are largely attributed to the rapid invasion of the

brain by Mucorales fungi, delayed surgical treatment, and progressive infections[37-38]. The combination of surgery and medication is superior to either treatment alone. Roden *et al*[2] reported in a review of 929 cases that the survival rate was 61% (324 of 532) in the AmB alone treatment group, 57% (51 of 90) in the surgery alone treatment group, and 70% (328 of 470) in the antifungal and surgical combined treatment group.

A literature review suggests that the risk factors for death of patients with cerebral mucormycosis can be categorized as follows: (1) susceptibility to infection (*e.g.*, history of diabetes, long-term use of broad-spectrum antibiotics); (2) site of infection (*e.g.*, Kerezoudis *et al*[39] found in a retrospective analysis of 68 cases that basal ganglia lesions carried increased mortality due to higher iron availability in that region); and (3) delay in diagnosis and treatment (*e.g.*, studies finding that a treatment delay of longer than 6 d[40] or 1 wk[41] was associated with increased mortality).

## CONCLUSION

Isolated cerebral mucormycosis is rare and diagnosis is challenging and requires a high degree of clinical suspicion. When a patient presents with headache, fever, hemiplegia, and altered mental status, his or her history and physical examination results should be closely followed by an investigation of the possibility of fungal infection. Histopathology can reveal the pathological characteristics of Mucorales fungi, and molecular methods (MALDI-TOF testing of serum and cryosections) may help to confirm the diagnosis and identification of pathogenic species. Early diagnosis and initiation of antifungal therapy and surgery can improve patient survival.

# 81050_Auto_Edited.docx

ORIGINALITY REPORT

9%
SIMILARITY INDEX

PRIMARY SOURCES

| | | |
|---|---|---|
| 1 | Fatehi Elzein, Kiran Kalam, Nazik Mohammed, Ahmed Elzein, Fadhel Zaben Alotaibi, Mujtaba Khan, Abeer Albadani. "Treatment of cerebral mucormycosis with drug therapy alone: A case report", Medical Mycology Case Reports, 2018<br>Crossref | 39 words — 2% |
| 2 | Saira Farid, Omar AbuSaleh, Rachael Liesman, Muhammad Rizwan Sohail. " Isolated cerebral mucormycosis caused by ", BMJ Case Reports, 2017<br>Crossref | 34 words — 1% |
| 3 | www.frontiersin.org<br>Internet | 34 words — 1% |
| 4 | Wei Zhou, Xuefei Shao, Xiaochun Jiang. "A Clinical Report of Two Cases of Cryptogenic Brain Abscess and a Relevant Literature Review", Frontiers in Neuroscience, 2019<br>Crossref | 26 words — 1% |
| 5 | Nan Dong, Ashly E. Jordan, Xiaozhu Shen, Xuan Wu, Xianghong Guo, Hongru Zhao, Yajuan Wang, Dapeng Wang, Qi Fang. "Rhino-Orbital Cerebral Mucormycosis in a Patient With Diabetic Ketoacidosis: A Case Report and Literature Review", Frontiers in Neurology, 2022<br>Crossref | 14 words — 1% |

| | | |
|---|---|---|
| 6 | www.jetir.org<br>Internet | 14 words — 1% |
| 7 | autopsyandcasereports.org<br>Internet | 13 words — 1% |
| 8 | umbalk.org<br>Internet | 12 words — 1% |
| 9 | www.wjgnet.com<br>Internet | 12 words — 1% |

| | | | |
|---|---|---|---|
| EXCLUDE QUOTES | ON | EXCLUDE SOURCES | < 12 WORDS |
| EXCLUDE BIBLIOGRAPHY | ON | EXCLUDE MATCHES | < 12 WORDS |