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Isolated cerebral mucormycosis in post-COVID-19 pneumonia

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ABSTRACT

Background: Rhino-orbital-cerebral and isolated cerebral involvement of basal ganglia by mucormycosis are two different manifestations of CNS mucormycosis. The former variant caused by inhaled fungal spores and is common with immunosuppressive conditions. The latter form is caused by intravascular inoculation of spores as seen in intravenous drug abusers.
Case report: Here we describe a case of young, non-addict patient with a history of recent mild COVID-19 pneumonia who presented with isolated cerebral mucormycosis involving bilateral basal ganglia.
Discussion: The pulmonary vasculitis associated with COVID-19 is probably the cause of direct intravascular entry of inhaled fungal spores leading to direct isolated cerebral involvement. Such condition may rapidly turn fatal.
Conclusion: This is the first reported case of isolated cerebral mucormycosis following post-COVID-19 infection. Early tissue diagnosis and intravenous amphotericin B is the key management.

1. Introduction

The central nervous system (CNS) invasion of mucormycosis differs in its presentation based on fungal spores' route of entry into the body (Kerezoudis et al., 2019). The commoner type called rhino-orbital-cerebral mucormycosis (ROCM) usually presents after nasal inoculation of these ubiquitous saprophytic fungi. In such cases, the CNS involvement was via cavernous sinus, cribriform plate, orbit, or pterygopalatine fossa (Sen et al., 2021). The CNS manifestations included cavernous sinus thrombosis, frontal/temporal lobe abscess, skull base osteomyelitis, and internal cerebral artery stenosis. The direct intravascular inoculation (especially intravenous drug addicts) of the mucor may present as an isolated cerebral mucormycosis of basal ganglia (Kerezoudis et al., 2019). In the former situation, the hosts usually have diabetes mellitus, steroid or deferoxamine use, recent COVID-19 pneumonia, etc. as contributing factors (Singh et al., 2021). In the latter situation, hosts are usually young (< 35 years) and immunocompetent and are usually recreational intravenous drug abusers (approximately 92%) (Meyerowitz et al., 2020). Here, we present a rare scenario of isolated cerebral mucormycosis of bilateral basal ganglia in a non-addict, young patient with a recent history of mild COVID-19 infection.

2. Case description

A 34-years old man, a farmer by occupation, presented with a bifrontal headache especially in the morning for 4–5 days. He had developed progressive left side weakness over last 2 days. On admission in an emergency, he was unconscious with an extensor response with laboured breathing. His-both pupils were dilated and the right pupil was not reacting to light.

In the recent past (2 weeks ago) he had a low-grade fever with a cough. He was diagnosed with a COVID-19 infection based on nasal/oropharyngeal swab reverse transcriptase polymerase chain reaction (RTPCR) test. High-resolution computed tomography (HRCT) of the chest showed the findings of multiple small ill-defined predominantly subpleural ground-glass densities in both lungs with a CT severity index of 7. His-saturation remained normal and he did not require any oxygen support. He had no history of diabetes mellitus, intravenous drug abuse or immunosuppressant drugs or conditions. He was treated symptomatically without any oral or intravenous steroids in an isolation facility.

On present admission, he underwent MRI brain (Fig. 1 A) which showed a non-enhancing mass lesion involving the right basal ganglia and insular cortex with petechial hemorrhages and small patches of restricted diffusion. It was causing severe mass effect with subfalcine herniation. The lesion was thought to be due to focal cerebritis due to fungal or viral source versus a glial-origin tumor. As the patient was deteriorating rapidly neurologically, probably due to mass effect, he was taken up for emergency decompressive craniectomy and excision biopsy of the lesion. Intraoperatively, the brain was diffusely swollen. The lesion was seen as a friable, suckable mass with the poor plane of cleavage with surrounding parenchyma. It also showed thrombosed vessels along with the

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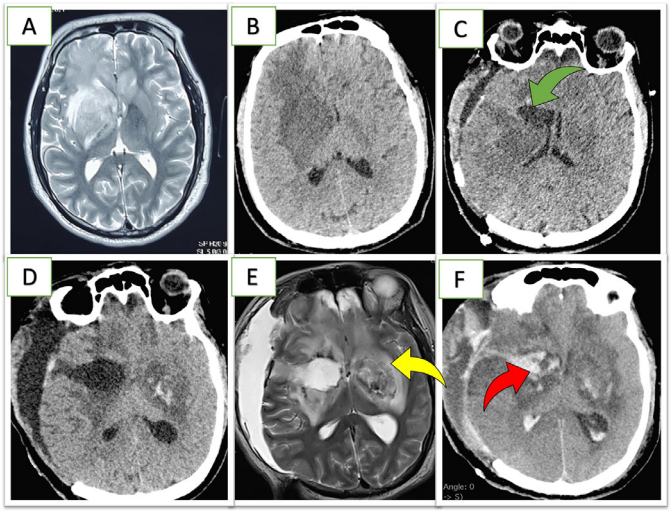

Fig. 1. A) Day one, MRI (T2W) showing signal intensity changes in right basal ganglia, insula with extension to right frontal white matter, B) CT brain (plain) showing similar findings (as A) with mass effect, C) Postoperative day one CT brain (plain) showing excision cavity (green arrow), D) & E) Postoperative day five CT and MRI (Plain) showing mucor involvement of left basal ganglia with early bleed (yellow arrow) F) Postoperative day eight, CT scan showing extensive hemorrhage involving left basal ganglia, operative site, and lateral ventricles.

necrosis. The potassium hydroxide (KOH) mount of the tissue (Fig. 2A) showed fungal forms with broad non-septate hyphae branching at wide angles, confirming the diagnosis of mucormycosis-associated cerebritis. Subsequent histopathological examination (Fig. 2D-G) showed angioinvasion, fibrinoid necrosis of vessel wall, and a prominent neutrophilic, lymphocytic infiltration. Fungal culture on Sabouroud's dextrose agar (SDA) (Fig. 2B) showed a cottony growth. He was started immediately on intravenous amphotericin B (AmpB).

The postoperative CT scan and subsequent MRI showed adequate decompression of the edematous brain(Fig.1B-E). However, the lesion had grown to involve the basal ganglia on the left side as well in another couple of days. The CT of paranasal sinuses (PNS), lungs, and abdomen did not reveal any other focus of fungal involvement. The blood and urine examination and culture did not grow any fungal elements. On day 8, he showed further neurological deterioration with completely dilated non-reacting pupils and no motor response. The CT scan of the brain (Fig.1F) showed an extensive bleed in the bilateral basal ganglia lesion along with the intraventricular and the operative site. Fungal cerebral vasculitis was thought to be the cause of the hemorrhage. The patient continued to deteriorate further and expired on hospital day 9 after the admission.

3. Discussion

Isolated cerebral mucormycosis is a rare manifestation of fungal invasion with nearly 60% mortality (Malik et al., 2014). Intravascular fungal inoculation is thought to result from an unhygienic injection practice seen in intravenous drug abusers. The increased expression of divalent metal transporter (type 1) in basal ganglia creates an iron-rich environment (Pandian et al., 2007). Such a conducive milieu could explain the preferential involvement of mucormycosis in basal ganglia after intravascular inoculation.

In general, mucormycosis is closely associated with DM, diabetic ketoacidosis, deferoxime / steroid use, organ transplantation, chemotherapy, chronic kidney disease, chronic alcoholism, HIV infection, solid organ transplant, low birth weight, malnutrition, hematologic malignancy, etc. (Prakash and Chakrabarti, 2019). India recently saw a steep rise in mucormycosis following the second wave of COVID-19 infection (Sen et al., 2021). The observational study of 2826 such mucormycosis cases revealed rhino-orbital-cerebral (ROCM) variant as the commonest type (Sen et al., 2021). The contiguous spread from paranasal sinuses to the CNS was the most common mechanism (Sen et al., 2021). Most of these patients present with nasal discharge and ocular symptoms (loss of vision and restricted eye movement) (Sen et al., 2021). COVID-19 produces a hypoxic environment with high glucose levels, high levels of ferritin, and attenuated phagocytic activity of leukocytes due to immunosuppression by the virus itself and the corticosteroids used in the management. This setting is highly conducive for the fungal spores to germinate and proliferate (Sen et al., 2021). Unhygienic practices, a prolonged hospital stay with the possibility of nosocomial infection, use of immunosuppressants like tocilizumab might be the additive factors (Sen et al., 2021).

In the present case, the patient had the classic presentation and course of the isolated cerebral mucormycosis involving the basal gan-

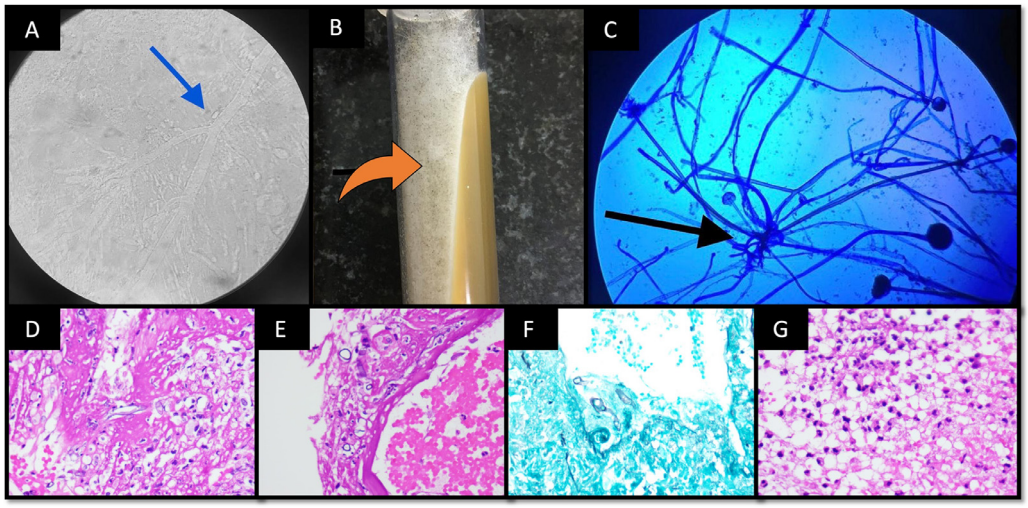

Fig. 2. A) KOH direct tissue showing aseptate branched fungal hyphae (blue arrow) B)Sabouroud's dextrose agar showing cottony growth (orange arrow) C) Lactophenol cotton blue mount showing sporangiospores, fungal hyphae with rhizoids (black arrow) D) (H&E, 40x) Photomicrograph showing broad aseptate fungal hyphae against necrotic background, E) (H&E, 40x) Transversely cut fungal hyphae within the vessel wall, which shows fibrinoid necrosis, F) (GMS, 40x) Fungal hyphae highlighted by the GMS stain, G) (H&E, 40x) Aggregates of polymorphs against necrotic background, forming micro-abscesses.

glia. He was neither an intravenous drug abuser nor had any comorbidities. The only probable contributing factor was recent mild COVID-19 pneumonia. However, he had not received any steroids or immunosuppressants and his glycemic records were normal. The endothelial damage (along with thrombosis, lymphopenia, reduction in CD4/8 levels) caused by COVID-19 might have led to leaky pulmonary capillaries and some ubiquitous fungal microspores could have escaped the filtering (Singh et al., 2021; Dhakar et al., 2015). Thereby gaining access to the arterial circulation and ultimately to intracranial structures (Dhakar et al., 2015). Despite receiving the standard treatment of surgical debridement and intravenous AmpB, the patient could not be survived. To the best of our knowledge this is the first case description of post COVID-19 isolated cerebral mucormycosis.

This particular case scenario highlights three important points 1) COVID-19 infection associated vasculitis as probable source of intravascular fungal inoculation 2) Rapid involvement of contralateral basal ganglia by mucor as demonstrated by subsequent radiological imaging. 3) Fungal vasculitis associated bleed is the probable cause of ultimate fatality. The contralateral involvement could be due to persistent fungemia or direct invasion by surgical violation of tissue planes. The mucorale inoculum volume and host immune response ultimately decide the fatality of the disease (Meyerowitz et al., 2020). Amphotericin B (AmpB) is a drug of choice (Meyerowitz et al., 2020).

4. Conclusion

Rhino-orbital-cerebral mucormycosis is a common variant after the recent COVID-19 infection. However, though rare, isolated cerebral mucormycosis also needs to be considered.

The clinical symptoms usually helps to differentiate between these two conditions. Rapidly appearing neurological symptoms in a young patient with a recent history of COVID-19 infection warrants early neuro-imaging. The doubtful involvement of basal ganglia (even in the absence of PNS involvement) mandates an early surgical intervention (either stereotactic biopsy or surgical decompression). The tissue diagnosis can be rapidly obtained by intraoperative KOH mount and frozen section studies. It will also help to expedite the treatment with intravenous AmB. In the advanced course of the disease, the case fatality remains high.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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