CASE REPORT

COVID-19 associated mucormycosis: A case report in Pakistan and a review of 144 cases

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Abstract

Mucormycosis is the third most common mycosis in order of its importance as a human pathogen, occurrence of which has become more frequent around the world. Although not proven as a causal association, the increased number of cases has been attributed to Covid-19, the rampant use of corticosteroids, and diabetes. We report the case of a 53-year-old male with mucormycosis related to a Covid-19 infection as the novel case from Pakistan and discuss its epidemiology, diagnostic principles, and management. In our literature review, this is the 145th case being reported with most cases occurring in India, mostly in males, of rhino-orbital form and about a third of them leading to the death of the patient.

Keywords: Black Fungus, Phycomycosis, Zygomycosis, Diabetes Mellitus, Corticosteroids

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Introduction

Mucormycosis, Zygomycosis and Phycomycosis are all terms used to describe an infection by mould fungi of the genus *Rhizopus, Mucor, Rhizomucor, Cunninghamella* and *Absidia* of the Order Mucorales, Class *Zygomycetes,* with *Rhizopus Oryzae* being the most common human pathogen.[1] It is a thermo-tolerant fungi with a ubiquitous distribution found on organic substrates within indoor and outdoor environments and occurring as an opportunistic infection seen in patients with uncontrolled diabetes or having immunosuppressive conditions such as patients receiving corticosteroid treatment, cancer chemotherapy or immunotherapy, haematological stem cell transplants, prolonged neutropenia or solid organ transplants, with HIV.[2] However, new studies have emerged that report mucormycosis in the description of a triad of risk factors, along with diabetes mellitus, and use of corticosteroids in the management of Covid-19.[1,2]

Here we report a case of mucormycosis in a 53-year-old male with history of Covid-19 as the first report from Pakistan.

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Case Report

A 53-year-old male, known diabetic on oral hypoglycaemics (Sitagliptin & Metformin), tested positive for coronavirus (SARS-CoV-2) and was put on symptomatic treatment with Paracetamol, Aspirin, Clopedogrel, Famotidine, and multivitamin supplements and home quarantine. Twelve days later, he tested negative for Covid-19 in June 2021 but two days later presented to the medical department of Pak-Emirates Military Hospital, Rawalpindi with complaints of right-sided facial asymmetry and inability to open his right eyelid. The symptoms had developed gradually within the past few days and were progressively worsening. He assumed his current symptoms to be part of his recovery from Covid-19. At presentation, he was tachycardic (113 bpm) but otherwise vitally stable. On examination, he had mild right-sided periorbital swelling and examination of cranial nerves showed anosmia (Olfactory nerve), reduced visual acuity of the right eye (Ocular Nerve), right-sided ptosis with pupillary sparing and ophthalmoplegia (Occulomotor, Trochlear, and Abducent nerve), numbness along the right side of his face (Trigeminal nerve) and ptosis of right angle of the mouth with weakness of right facial muscles (facial nerve). The rest of his neurological examination was unremarkable. He was referred to the neurology department for further management.

On admission, his blood counts, liver function tests, renal function tests, coagulation profile and serum electrolytes were all within normal limits. He was incidentally discovered to be positive for Hepatitis C. Contrast-Enhanced Computed Tomography (CECT) and Contrast-Enhanced Magnetic Resonance Image (CE-MRI) of the head and peripheral nasal sinuses were marked as normal studies with no organic lesions and he was started on Dexamethasone 4 mg/day and Meropenem.

In the meanwhile, an ENT consultation was requested due to raised CRP (143 mg/L) and raised plasma Lactate levels (2.6 mmol/L) for a suspected skull-base infection. His Otorhinolaryngological examination showed a small amount of purulent discharge on the nasal floor and the presence of a 9x11 mm ulcer at the right side of the palate with black-brown discoloration over and around it, which visually seemed to be extending deep into the bone. (Figure) A naso-endoscopic examination of the right nasal

Figure: Palatal ulcer in our case diagnosed Covid-19 associated Mucormycosis.

cavity showed the presence of black necrotic material over the middle meatus, inferior turbinate, and nasal floor. Samples of the necrotic material were sent for microscopy and culture & sensitivity. Microscopy revealed the presence of non-septate fungal hyphae and a preliminary diagnosis of fungal skull-base infection was made. Dexamethasone was stopped six days after his admission and he was started on Voriconazole. The patient was shifted to the ENT department and an endoscopic debridement was done. The debridement involved removal of the infected necrotic material over the nasal floor, inferior turbinate, middle meatus, posterior part of the nasal septum, sphenoidal sinus, anterior, and posterior ethmoids. His recovery from the surgery was unremarkable. Culture showed the presence of Rhizopus spp. The final diagnosis was Covid-19 complicated by rhinosinus mucormycosis.

An infectious disease consultation was requested and, based on their recommendation, Liposomal Amphotericin B was initiated at 5mg/kg/day. After a total of 34 days, the patient was discharged on Posaconazole and with outpatient follow-up every two weeks. He is planned to undergo a plastic surgery review, once the infection resolves, for reconstruction and nerve injuries.

Discussion

In 1950, Smith and Krichner developed the gold standard clinical diagnostic criterion for mucormycosis[3] which includes black, necrotic turbinates easily mistaken for dried, crusted blood, blood-tinged nasal discharge and facial pain, both on the same side, soft periorbital/perinasal swelling with discolouration/induration, ptosis of the eyelid, proptosis of the eyeball and complete ophthalmoplegia, multiple cranial nerve palsies unrelated to documented lesions.

Our case also fulfils the parameters of this criterion and were used initially for suspecting the diagnosis of mucormycosis. This is the first case report of Covid-associated-mucormycosis (CAM) from Pakistan and serves as a guideline for the diagnosis and management of Covid-19 and its complications.

Mucormycosis is the third invasive mycosis after candidiasis and aspergillosis in order of their importance. The most common clinical presentation of mucormycosis is rhino-orbito-cerebral, rhinosinus, pulmonary and disseminated. Nonetheless, it does have the ability to involve any organ or body part.[1,4] New data shows that pathogenetically, mucormycosis utilises a ricin-like protein, namely 'mucoricin', that has the ability to inhibit protein synthesis and provides an important therapeutic target. Typically, in an immunocompromised subject, the body's natural humoral immunity produces antibodies against mucoricin, hence, making the condition prevalent in immunocompromised hosts.[5]

We reviewed a total of 144 cases of CAM from inception till February 2022,[6-44] the breakdown of which is given in table. Our literature review is in line with those done previously[1,45] including most reports from India (60.4%),

Table: Analysis of cases of Covid-19 associated Mucormycosis reported till June 2021 (n=144).

	Parameter	n (%)
Country of Reporting		
1	India [6-19]	87 (60.4)
2	Iran[20-23]	18 (12.5)
3	Turkey[24,25]	13 (9)
4	USA[26-35]	12 (8.3)
5	Egypt[36]	6 (4.17)
6	UK[37,38]	2 (1.39)
7	Austria[39]	1 (0.69)
8	Brazil[40]	1 (0.69)
9	France[41]	1 (0.69)
10	Iraq[42]	1 (0.69)
11	Italy[43]	1 (0.69)
12	Mexico[44]	1 (0.69)
Gender		
1	Male[6-13,16,18,19,21-24,26-30,32-34,36-43]	102 (70.8)
2	Female[6, 11,12,14-16,19,20, 22-25, 31,35,36,44]	31 (21.5%)
3	Undetermined[17]	11 (7.64)
Spread of Disease		
1	Rhino-Sinus[6,11,19,20,27]	30 (20.8)
2	Rhino-Orbital/ Rhino-orbital-Cerebral[6,8-19,21-25, 28,33,35,36,42,44]	102 (70.8)
3	Pulmonary[7,29-31,34,37,39,41,43]	9 (6.25)
4	Disseminated[38]	1 (0.69)
5	Cutaneous[32]	1 (0.69)
6	Gastrointestinal[40]	1 (0.69)
7	Musculoskeletal[27]	1 (0.69)
Outcome		
1	Death[6,9-12,16,17,22,23,25,28,30-34,36-44]	47 (32.6)
2	Improved, Improving or Recovered	97 (67.4)

most patients were male (70.8%) and rhino-orbital mucormycosis was the most common form (70.8%).

A high index of suspicion is required to suspect mucormycosis in a patient. Nonetheless, there are always certain red-flags to look for, including cranial nerve palsies, diplopia, sinus pain, proptosis, periorbital swelling, orbital apex syndrome, and palatal ulcers. Such findings warrant the need for tissue microscopy and imaging via either CT scan or MRI to assess for the spread of disease.[46] On confirmation of fungal hyphae, specifying the microbe requires the need for culture, immunoblots molecular assays and/or tissue histopathology.[46,47]

The treatment involves using a multimodal approach with systemic antifungals at optimal doses, correcting risk factors, surgical debridements and corrective reconstructive surgeries.[26,46] Posaconazole, Isavuconazole, and Amphotericin are commonly noted to be active against most strains of mucormycosis.[26] Liposomal amphotericin B is the drug of choice, strongly recommended at a dose of 5 mg/kg per day in 200 ml of 5% dextrose over 2–3 h for 3–6 weeks.[26,48]

Keeping in view this emerging threat, it is strongly recommended to reduce the use of corticosteroids in mild or moderate Covid-19 and only allow its use in patients with severe Covid-19. Secondly, limiting the commutative dose of corticosteroids given per day at Dexamethasone 6mg/day, Hydrocortisone 150 mg/day, Methylprednisolone 32 mg/day and Prednisolone 40 mg/day, respectively, is also recommended.[48]

Conclusion

Conclusively, mucormycosis is increasingly being reported globally in patients with or after Covid-19 and should be suspected in any patient with the triad of Covid-19, corticosteroid use and diabetes, especially if the relevant clinical symptoms develop.

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Conflict of Interest: None.

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