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Case Report

Internal Medicine Section

Primary Cutaneous Mucormycosis in a Patient with Severe COVID-19 Infection

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ABSTRACT

A 47-year-old male was brought to the hospital with the chief complaints of fever, breathlessness and cough since one week. He was a known case of Type 2 Diabetes Mellitus (T2DM) for five years and was on oral hypoglycaemic drugs. On presentation, he was hypoxemic with a SpO_2 of 91% at 13 LO_2 and his sugar level was 286 mg/dL. Further, chest imaging and Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) was suggestive of severe COVID-19 pneumonia and his hypoxemic respiratory failure required Intensive Care Unit (ICU) stay. He was started on high flow oxygen therapy and due to further worsening of his condition, he required endotracheal intubation and mechanical ventilation. On 18th day after admission, he developed blackish blister lesion, insidious on onset and gradually spreading over right forearm over a week. Skin lesions have grown *Mucor* spp. in microbiological culture. It was diagnosed as primary cutaneous mucormycosis with no involvement of rhinocerebral region and pulmonary region. Immediately antifungal therapy was started and the lesion started resolving. The patient developed secondary bacterial infection, multiorgan dysfunction, the patient could not be revived. This case report demonstrates cutaneous mucormycosis as a rare possible complication of Coronavirus Disease 2019 (COVID-19) infection and emphasises the risk factors and diagnostic measures which helped to arrive at the diagnosis.

Keywords: Diabetes mellitus, Sepsis, Severe pneumonia

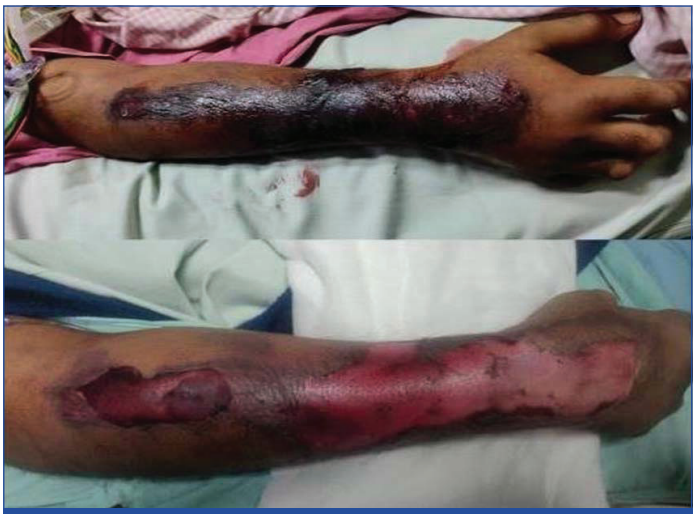
CASE REPORT

A 47-year-old male with history of fever for six days, dry cough and breathlessness for three days, was tested positive for COVID-19 RT-PCR test, five days before coming to the hospital. He was known to have uncontrolled T2DM.

On presentation, he was hypoxemic, with oxygen saturation of 91% at 13 LO_2 on non-rebreather mask. His sugar level was 286 mg/dL. He was treated with antipyretic medications before coming to the hospital. After coming to the hospital, he was treated with antiviral and antibiotic drugs along with Injection Remdesivir and Injection Dexamethasone (6mg once daily) for 10 days. On the third day, heated humidified high flow therapy was started and the saturation was 98% at 60% FiO_2 with 50 LO_2 flow. The P/F ratio being 206 but as his condition further worsened, he was given non-invasive ventilation on 12th day with SpO_2 82% and $Fi0_2$ 100%, P/F being 47 and hence, he was intubated on the same day maintaining 91% SpO_2 on volume control mode with 100% FiO_2 and P/F ratio was 79. He was advised for proning five cycles for 16 hours each. There was Right Ventricular (RV) dysfunction on the 18th day secondary to severe COVID-19 pneumonia and Computed Tomography (CT) pulmonary angio showed minimal thromboembolism in the left lower lobe pulmonary artery not explaining the severe RV dysfunction.

Eighteen days after admission, multiple pricks were made in the right forearm to place peripheral cannula which was unsuccessful. On 19th day, there was blackish discolouration resembling necrotic lesion over the dorsum of the right forearm extending from the wrist to elbow and was associated with swelling. On the 20th day the patch got converted into blisters which were multiple in number, irregular in shape with surrounding blackish discolouration [Table/Fig-1]. On 21st day blisters burst open with red serous discharge. Wound dressing and limb elevation was started as there was significant local edema. The patient was advised non surgical and medical management as the skin lesions were very superficial.

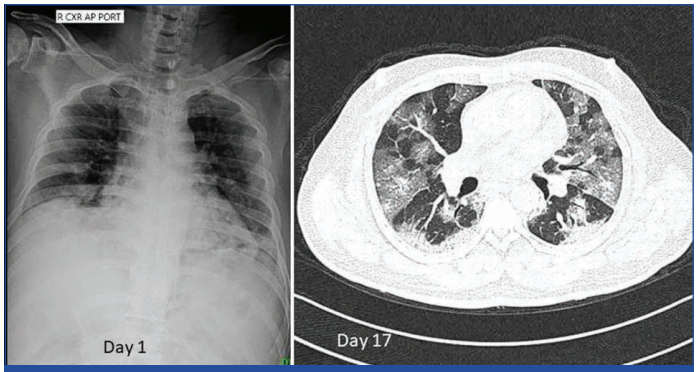
But, it progressed into an ulcer which was irregular in shape measuring 10x5 cm, with punched out edge, subcutaneous tissue as the floor and base being muscle. Blister fluid and tissue specimens were sent for microbiological investigations and tissue cultures from these specimens showed the growth of fungus, which was identified as *Mucor* spp. Blood culture done from 16th day, showed growth of *Candida krusei*, and Multidrug Resistant (MDR) *Pseudomonas aeruginosa*. On 19th day, thrombocytopenic purpura was suspected as the platelet counts were low (75,000/mL) and bullous haemorrhagic dermatitis secondary to heparin. Skin biopsy was taken from the edge of the ulcer and sent for culture and it showed the presence of *Mucor* spp. and was treated with amphotericin B.



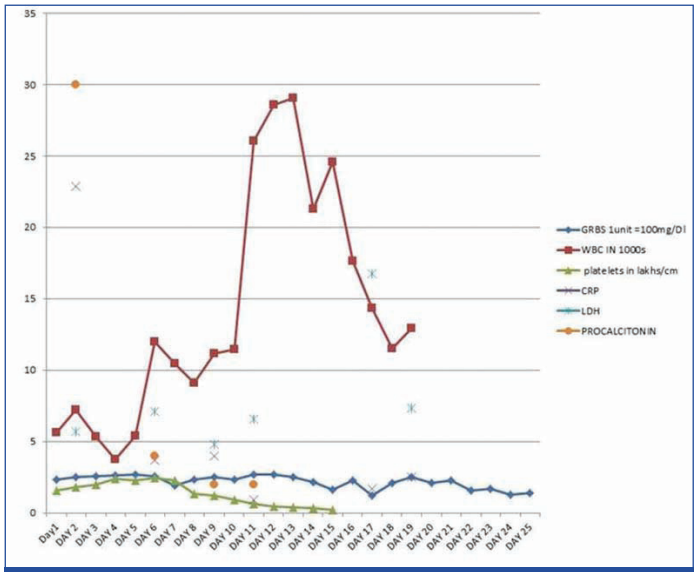
[Table/Fig-1]: Cutaneous lesion-Primary mucormycosis in severe COVID-19 pneumonia Day 2 (above) Day 4 (below).

The chest radiography on day one and chest CT imaging on day 17 [Table/Fig-2] showed worsening pulmonary infiltration as the day progressed. There was raised procalcitonin, C-Reactive Protein (CRP), Interleukin-6 (IL-6), Ferritin and Lactate Dehydrogenase (LDH) when the patient got admitted. This symbolises the severity of COVID-19 infection and [Table/Fig-3] explains trend in investigations during 25 hospital days.

Skin biopsy showed fungal colonies of broad aseptate hyphae at an obtuse angle with Periodic Acid-Schiff (PAS) stain, which was consistent with Mucormycosis [Table/Fig-4]. The patient was



[Table/Fig-2]: Chest radiography on D1 and chest CT imaging on D17 confirms worsening pulmonary infiltration.



[Table/Fig-3]: Blood/Serum Investigations trend during 25 hospital days.
GRBS: General random blood sugar

hospitalised for 25 days and his average General Random Blood Sugar (GRBS) level during hospital stay was 217 mg/dL (target <180 mg/dL). There was acute rise in Serum Glutamic Oxaloacetic Transaminase (SGOT)/Serum Glutamic Pyruvic Transaminase (SGPT) on day 18 which was supported by 2D echo and severe RV failure. Uncontrolled T2DM with high means random blood sugar.

[Table/Fig-4]: Culture on Sabourauds Dextrose Agar (SDA) showing typical tube filling, white cotton colony (left side) Lactophenol Cotton Blue (LPCB) mount (40X) showing growth of *Mucor* species (right side).

He was treated with antiviral therapy remdesivir, steroids and oxygen support. As mentioned earlier due to gradual worsening respiratory failure required escalating oxygen support, endotracheal intubation and prone ventilation for severe Acute Respiratory Distress Syndrome (ARDS). He developed secondary bacterial and fungal infection (*Pseudomonas* and *Candida* in blood) which was treated appropriately with antibiotics and antifungals (voriconazole). For skin lesions (initially thought to be thrombophlebitis) regular dressing with bactrigrass, limb elevation and continued systemic antibiotics were prescribed. Later skin lesions were identified as *Mucor* (with KOH, cultures) with insidious spreading nature and target lesions. The patient was started on amphotericin B 50 mg bid (3rd day from the day of development of skin lesions). Regular wound dressing was done. The spread of the new target lesions were controlled after amphotericin B therapy.

To summarise, his hypoxic state was improved on day six of mechanical ventilation (FiO_2 45, PO_2 111, P/F ratio 246) subsequently on day 15 to day 20 he required vasopressors support and later it was switched to dobutamine in view of RV failure. But on day 20, the patient had multi-organ dysfunction, there was refractory hypoxemia, septic shock, secondary bacterial infection and worsening renal failure (required two cycles of haemodialysis). The patient could not be revived and he died on the 25th day after admission.

DISCUSSION

The COVID-19 pandemic caused by novel Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), has affected more than 188 million people worldwide, accounting for over four million deaths. Secondary fungal infections are predominantly associated with COVID-19. Cases of COVID-19 associated invasive pulmonary aspergillosis and COVID-19 associated mucormycosis have been reported worldwide [1-9]. Studies from Europe reported variable frequencies (3-33%) of COVID-19 associated pulmonary invasive aspergillosis, but these studies have been limited to anecdotal reports or small case studies [1-8].

Even though mucormycosis is considered as community acquired, there has been increasing reports of healthcare associated mucormycosis, among this the common site is skin followed by gastrointestinal tract, pulmonary, rhinocerebral respectively. The cutaneous mucoemycosis is often noted after trauma or breach in skin and can be observed in immunocompetent host [9-11].

In a prospective, observational, multicentre study from India of 2,567 COVID-19 patients, 47 (1.8%) were diagnosed with mucormycosis [12]. The global incidence of mucormycosis ranges from 0.005 to 1.7 per million population [12,13]. However in India, the reported prevalence was 0.14 per 1000, which is around 80 times higher than that in developed countries, and country with the highest burden of mucormycosis [12,13]. Further, the major risk factors for mucormycosis, among COVID-19 patients, are poorly controlled diabetes mellitus and use of corticosteroids [12]. Mucor mainly occurs between age group of 46-61 years, ICU admission is also one of the predisposing factors [12,14].

COVID-19 induces damage of pancreatic islets resulting in acute diabetes and diabetic ketoacidosis. COVID-19 also results in alteration of iron metabolism (hyperferritinemic syndrome). IL-6 and cytokines are the stimulating factors for ferritin; pulmonary vascular endothelial injury could also lead to mucormycosis [15].

Primary cutaneous mucormycosis may be very invasive locally, involving cutaneous tissue also the fat, muscle and fascial layers beneath. Primary cutaneous mucormycosis usually presents as nodular subcutaneous lesion which may ulcerate. The development of cutaneous necrotic lesion resembles pyoderma gangrenosum in critically ill patients. A case study on primary cutaneous mucormycosis reported that the histological examination of a necrotic region in the skin showed presence of rhizomucor [16]. Other differential diagnosis for the ulcerative skin lesions are drug reactions, infiltrative diseases, aspergillosis, autoimmune disorders, neoplastic disorders, which can be differentiated by angio-invasive property of fungus, on histopathological examination [16].

The index patient had superficial bullous cutaneous lesion and was diagnosed with Mucormycosis along with severe COVID-19 pneumonia. In a systematic review of cases reported worldwide and in India among 101 cases, one patient was detected with cutaneous mucormycosis which accounts to less than 1% which makes this case unique [14].

The present patient had prolonged ICU stay with slow recovering COVID-19 pneumonia complicated with severe RV failure and in

the later phase of ICU stay, he had secondary bacterial infection with multi-organ failure and could not be revived. Skin lesions were initially considered as thrombotic event, later incidentally detected to have significant growth of mucormycosis. On further work-up, he did not have evidence of mucormycosis lesion or growth in ear, nose, throat region and in respiratory secretions. So, primary cutaneous mucormycosis was considered due to severe immunosuppression with critical illness and poorly controlled sugars. Even though the patient was kept on insulin infusion, due to unpredictable fluctuations in the blood sugar levels, it was difficult to bring target level less than 180 mg/dL in the initial days, this could be partly due to steroids and intermittent nasogastric feeding. The present patient was on dexamethasone (6 mg) for 10 days and injection Tocilizumab 400 mg one dose along with antibiotics and antifungal.

Cutaneous mucormycosis can be treated using a multi-disciplinary approach which includes antifungal therapy, correction of the underlying metabolic or impaired immunological status, surgical debridement and control of other contaminant infections. Mainstay of the therapy is surgical debridement and early antifungal therapy. The drug of choice is deoxylate amphotericin B, but considering nephrotoxicity as a risk factor lyophilised, amphotericin B is a better alternative kept aside due its high cost.

The recommended dose of amphotericin B is 1-1.5 mg/kg/day, for liposomal amphotericin B, 5-10 mg/kg/day. It is ideal to start the treatment within five days of onset of the infection [14]. This has shown to increase the survival rate. The duration of the therapy remains a question. Azole derivatives have shown variable activity against mucorales. If the patient is intolerant to amphotericin B, the preferred second line of medical management is posaconazole followed by isavuconazole with suggested dose of 400 mg bid [17-19].

Amphotericin B has played a major role in bringing down the mucormycosis related mortality rate from 84% in 1950s to 47% in 1990s [14,17,18,20]. According to Global guideline for the diagnosis and management of mucormycosis [14], suspected and confirmed mucormycosis are considered to be emergencies and this require rapid action, surgical debridement is strongly recommended for mainly disease control, microbiological diagnostics and histopathology, followed by anti-fungal therapy. This case further highlights the difficulties faced by clinicians amidst the current pandemic. With patients, presenting with necrotic skin lesions presumed to have caused by thrombosis, thorough examination and clinical acumen is at risk of being replaced by protocol driven treatment strategies. Hence, thorough history taking and clinical examination is very vital in diagnosis and management of the disease.

CONCLUSION(S)

Even during tough times like the COVID-19 pandemic, it is vital that an open diagnostic is maintained when approaching critically unwell patients. In patients with suspected COVID-19, cutaneous mucormycosis should be considered as one of the complications. While protocols play an important role in the management of acutely unwell patients, these do not replace thorough clinical examination.

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