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Case Report

Post coronavirus disease- 19 invasive renal and gastrointestinal mucormycosis

Sonali Vadi *, Abhijit Raut, Sweta Shah, Attar Mohammad Ismail

Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, India

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ABSTRACT

A 68-year-old female patient who was treated with anti-viral, steroids and biologics for coronavirus disease- 19 (COVID- 19) infection presented to our facility following right abdominal and flank pain since a week. Initially attributed to pancreatitis and right sided pyelonephritis, it was diagnosed as mucormycosis on KOH mount following CT-guided renal biopsy. She underwent right total nephrectomy and Whipple's surgery followed by Isavuconazole and liposomal Amphotericin B. This is a rare presentation of renal and gastrointestinal mucormycosis in a patient without diabetes mellitus following COVID- 19 infection. High suspicion and early diagnosis help in timely treatment of this life-threatening infection.

1. Introduction

An angioinvasive disease, mucormycosis is commonly seen in immunocompromised individuals. The trinity of lack of glycaemic control, immune-suppression and coronavirus disease- 19 (COVID- 19) infection increase virulence of fungi, predisposing these patients to mucormycosis. We discuss a rare presentation of renal and gastrointestinal mucormycosis in the context of COVID- 19 infection. Biological therapeutic antibodies have come to the forefront following an enthusiastic trend in prescription following COVID- 19 infection. The significance of this fungal infection has increased due to active clinical usage of these biological agents. Fungal infections in patients who have received these biologics have been associated with devastating consequences. Fungal spores evade innate immune system, germinate, angio-invade, leading to tissue destruction.

2. Case scenario

This 68-year-old obese patient was managed for COVID- 19 infection in second week of April 2021 with Remdesivir, intravenous immunoglobulin, intravenous methylprednisolone, and Bevacizumab, at a peripheral hospital. A week later she developed right upper abdominal and flank pain. Computerized tomography (CT) scan of abdomen and pelvis (non-enhanced) were suggestive of pancreatitis and right pyelonephritis for which she was administered Meropenem, Metronidazole, and Ceftazidime-Avibactam. She was transferred to our facility for further management.

On presentation to the emergency room, she was afebrile. Her pulse was 80/minute, blood pressure 130/80 mmHg, and oxygen saturation of 99% on room air. Clinical examination revealed tenderness in right flank region. Abdomen was soft with normal bowel sounds. Physical examination of head, sinuses and rest of systemic examination was unremarkable. CT scan with contrast was performed on arrival. This revealed sharply demarcated area of hypo attenuation involving lower pole of right kidney, while the main and lobar branches of right kidney and renal vein were patent. Significant perinephric inflammation was seen with thickening of anterior and posterior renal fascia. Also noted was diffuse duodenal wall thickening and patchy non enhancing areas involving second and third parts of duodenum. Patchy para duodenal non-enhancing area with entrapped fat within was seen mainly along its posterior wall. Pseudo wall thickening of gall bladder and hepatic flexure were noted. This was suggestive of acute pancreatitis, necrotic tissue near pancreas, and suspicion of thrombosis vs. vasculitis vs. fungal infection of right kidney [Fig. 1].

Vasculitic work-up was sent. Right renal biopsy was done on hospital day 1. Potassium hydroxide mount of the biopsy showed aseptate ribbon-like branching (at 90°) fungal hyphae resembling Mucorales which later grew Mucor sp. and with a positive polymerase chain reaction (MucorGenius®, PathoNostics. The Netherlands) of the biopsy. This was confirmed by slide culture on potato dextrose agar. The rhizoids were absent. Sporaniospore were round like mucor. Colony were black wooly filling up the tube. Urine routine microscopy was unremarkable. Glycosylated haemoglobin was 5.6%. She underwent right

* Corresponding author.
E-mail addresses: sonali.vadi@kokilabenhospitals.com (S. Vadi), abhijitaraut@gmail.com (A. Raut), sweta.shah@kokilabenhospitals.com (S. Shah), attarmohammad@rediffmail.com (A.M. Ismail).

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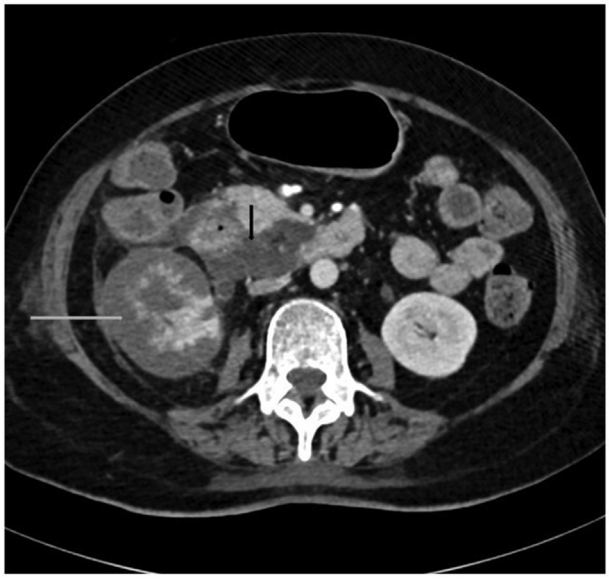

Fig. 1. CT scan of abdomen (Axial, post-contrast) The vertical black arrow shows non-enhancing D3 segment of duodenum. Note normal enhancement of uncinate process pancreas. The horizontal gray colored arrow demonstrates bulky right kidney showing non enhancing renal cortex and striated and delayed nephrogram. Seen is surrounding posterior renal fascia thickening.

total nephrectomy with Whipples surgery and cholecystectomy for gangrenous gall bladder on hospital day 2. Histopathology examination revealed mucormycosis of renal tissue. This was managed with Isavuconazole (200 mg intravenously 8 hourly for six doses, followed by 200 mg intravenously once daily) due to shortage of amphotericin B in the city. A week later as per the availability, liposomal Amphotericin B (300 mg intravenously once daily) was administered for 14 days. Vasculitis work-up returned negative. Antibiotics (Ceftriaxone-Sulbactam-EDTA 3 g intravenously stat, followed by 1.5 g intravenously twice daily and Minocycline 200 mg intravenously stat followed by 100 mg intravenously twice daily) were administered as per the abdominal tissue culture and sensitivity results for *Acinetobacter baumanii* and *Klebsiella pneumoniae* in abdominal tissue culture collected at surgery. Nutrition was administered in form of total parenteral nutrition that was later switched to naso-jejunal feeds. She was discharged 3 weeks later. On post-discharge follow-up she is stable.

3. Discussion

This enigmatic combination of benign clinical findings with disturbing radiologic findings acute pancreatitis with localized pyelonephritis was invasive fungal infection or vasculitis on biopsy in the setting of COVID- 19 infection. It is unclear as to how she developed renal and GI mucor. *Cunninghamella bertholletiae, Rhizomucor pusillus* and *Rhizopus microsporus* have been stated to set off mucorycosis infection in the immunocompetent [1] raising a possibility in the immunocompromised too. Possible mechanism for acquisition of infection in this patient include likely blood borne following colonization of lungs that had been injured by COVID- 19 pneumonia leading to renal as well as GI involvement, or an ascending infection from bladder [2] leading to renal seeding. Duodenum and pancreas are located in anterior pararenal space. Retroperitoneal location of the kidneys, duodenum, and pancreas may be a plausible reason for contiguous spread of infection.

Renal and gastrointestinal mucormycosis affliction would present with high grade fever associated with systemic toxicity. This patient was relatively stable with abdominal and flank pain since a week prior to presentation. She was off steroids. Findings of contrast-enhanced CT scan led to a suspicion for an infective pathology that was proven by tissue diagnosis. Her blood glucose levels were fairly under control.

Aggressive nature of Mucorales is influenced by their innate thermotolerance, quick progression, ability to bind to endothelial surfaces, and obtain iron, downregulation of host-defence genes, evolutionary duplication of systems involved in virulence, and their inherent resistance to most available antifungals [3]. Fungal infections, both endemic and opportunistic are common following biological therapies [4]. The chance of acquiring mucormycosis is higher following immunosuppression, COVID- 19 infection and monoclonal antibody [4,5] as in this patient. SARS CoV2 affects $CD4^+$ and $CD8^+$ T-cells, Mucorales-specific T-cells. These produce IL-4, IL- 10, IL- 17, and interferon-gamma that destroy fungal hyphae. Immune dysfunction occurs following COVID- 19 infection. There is an absolute reduction of lymphocytes and T-cells. Alteration in cell-mediated immunity occurs in patients with diabetes mellitus. Natural killer cell activity is reduced. Pro-inflammatory macrophages increase. Delayed interferon gamma response with a prolonged hyperinflammatory state ensues. At the vascular level, endothelial inflammation, and vasoconstriction predispose towards endothelitis in various organs. Bevacizumab binds to circulating vascular endothelial growth factor (VEGF) preventing its binding to cell surface receptors and inhibits angiogenesis. Viral infection [6] as well as individual host response influence disease severity. Additionally, corticosteroids interfere with host's ability to block germination of spores.

Traditional risk factors have been diabetes mellitus with or without ketosis, steroids, poor glycemic control, malignancies, transplantation, prolonged neutropenia, antifungal prophylaxis against *Aspergillus* i.e. voriconazole and echinocandins, iron overload, intravenous drug use, acquired immuno deficiency syndrome, and malnutrition [7]. Direct inoculation of spores into skin may be a predisposing cause of mucormycosis in the immunocompetent [7]. Typical sites for mucormycosis have been sinuses and nose. Reported incidence of renal mucormycosis stands at 0.5–9%, and of gastrointestinal involvement at 2–8% [8]. Early diagnosis is associated with increased survival. A high index of suspicion is important. A clinical approach to diagnosis has low sensitivity and specificity. Recognition of risk factors in the presence of a highly suspicious clinical scenario, early use of imaging, tissue diagnosis, and a coordinated team work are the hallmarks of managing a patient with mucormycosis.

Treatment consists of surgical and medical management. Excision of devitalized tissue in association with amphotericin B (AmB) is the treatment of choice. Major surgery has its risk in the setting of malnutrition. Hypoalbuminemia and catabolic state placed this patient at a high risk for surgery, a definitive treatment. Posoconazole and Isavuconazole have been used as rescue therapy. Isavuconazole is a relatively new anti-Mucorale medication available in India with its efficacy yet to be assessed in the country. In view of shortage in availability of AmB in India following the second wave of COVID- 19 infection, Isavuconazole was used as first line of pharmacological therapy in our patient.

Mortality stands at 50–61% in cases treated by AmB monotherapy as compared to 19–44% following combination of AmB and surgical debridement.[8] Mortality rate following gastrointestinal mucormycosis is at 67–94%, following renal mucor at 50–60%, and disseminated mucor at 62–79%.[8]

4. Conclusion

COVID- 19 infection plus its immunosuppressive therapy were contributory to mucormycosis in the patient discussed. In the wake of this causative association, we recommend a high index of clinical suspicion, early contact with concerned specialists, and early recognition with early start of appropriate anti-fungal. Use of Isavuconazole as first line of therapy needs to be investigated.

Credit author statement

Conceptualization- Sonali Vadi.
Investigation- Sonali Vadi, Abhijit Raut, Sweta Shah, Attar Ismail.

Writing- Original draft- Sonali Vadi.
Writing- Review and Editing- Abhijit Raut, Sweta Shah, Attar Ismail.

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Conflict of interest

None.

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