

COVID-19 and fatal renal mucormycosis: Contributory or coincidental?

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ABSTRACT

Association of mucormycosis with COVID-19 disease is emerging as a matter of concern, with multiple reports of rhino-cerebral-orbital and pulmonary involvement. The association of isolated renal mucormycosis in a patient with a history of COVID-19 infection is unknown. The immune dysregulation associated with COVID, along with the use of steroids, mechanical ventilation, and interleukin-6-directed therapies, predisposes to the development of mucormycosis. We report a rare case of primary renal mucormycosis in a young male following recovery from COVID-19. The unusual mode of presentation, rapidly progressive disease course, and the ensuing dilemmas in diagnosis and treatment merit critical analysis.


INTRODUCTION

Isolated renal mucormycosis is a rare occurrence.^[1] The association of mucormycosis in patients with a history of COVID-19 disease is emerging as a matter of concern with multiple reports of craniofacial, rhinocerebral, and pulmonary mucormycosis.^[2] We report a rare case of primary renal mucormycosis in a young male following recovery from COVID-19.

CASE REPORT

A 32-year-old male, with a history of moderate COVID-19 pneumonia 45 days ago, for which he had required hospital admission, high-flow oxygen, and intravenous (IV) steroids for 7 days along with IV remdesivir, presented to us with the complaints of low-grade fever (up to 100°F) and dull-aching flank pain of 7 days' duration. He was documented COVID negative by reverse transcription-polymerase chain reaction at admission. He also had a history of having taken intramuscular analgesics for his flank pain 5 days ago along with oral steroid use. The patient's general condition was good with normal vital signs and

measurements. A vague, nontender lump was palpable in the left flank and hypochondrium. Rest of the examination including that of the chest and oral cavity was normal. At admission, the chest X-ray did not show any abnormalities in bilateral lung fields. The patient was not a known diabetic and his blood sugar monitoring showed normal range on daily charting. His total leukocyte count (TLC) was 19,000/mm³. Serum creatinine was 1.9 mg/dL and blood urea nitrogen was 32 mg/dL. Urine routine and microscopy showed plenty of red blood cells and pus cells per high-power field. Ultrasound abdomen showed an enlarged left kidney with features suggestive of pyelonephritis. Doppler showed absent flow in the left renal vein. IV broad-spectrum antibiotics were started along with IV hydration, with a plan to do contrast-enhanced cross-sectional imaging of the abdomen after repeating renal function tests. In view of absent flow in the renal vein on Doppler, unfractionated heparin was also started in therapeutic dose. Over the next 48 h, the patient developed progressive tachypnea and hypotension. Examination revealed left flank pitting edema with bluish discoloration and erythema. Laboratory evaluation revealed TLC of 50,000/mm³ and serum creatinine of 2.2 mg/dL. A noncontrast computed tomography (CT)

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/iju.iju_197_21

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Received: 18.05.2021, **Revised:** 04.06.2021

Accepted: 22.06.2021, **Published:** 01.07.2021

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

showed pyelonephritis of the left kidney with extensive perinephric and paranephric fat stranding with some inflammation of the overlying mesenteric fat [Figure 1a]. Emergency DJ stenting of the left kidney was done with a diagnosis of severe pyelonephritis with a possibility of papillary necrosis. About 12 h post-DJ stenting, the patient developed hematochezia, bilious vomiting, and abdominal distension. Urine output decreased to 10–15 mL/h. Evaluation revealed TLC of 70,000/mm³, serum creatinine of 2.7 mg/dL, and metabolic acidosis on blood gas analysis. Urine culture sent at the time of admission came out to be sterile. Urine examination for fungus was negative. A repeat CT scan of the abdomen showed that the inflammation in the paranephric area had increased along with extensive inflammation of the mesenteric and pericolic fat, extending superiorly up to the spleen and also toward the pancreas and lesser sac [Figure 1b]. In view of unstable vitals requiring vasopressor support along with worsening laboratory parameters, a multidisciplinary decision was taken to start the patient empirically on liposomal amphotericin and take the patient for nephrectomy. The patient was explored through a left flank incision. The abdominal wall incision did not bleed, and there was extensive subcutaneous and muscular edema. The kidney was enlarged with thickened, hard, and saponified perinephric fat. Hilar structures were thrombosed. The left colon was gangrenous up to the distal third of the transverse colon, with gangrene of the 2nd part of the duodenum up to 80 cm distal to the duodenojejunal flexure. The flank incision was closed, and the abdomen was opened in the midline. There were also ischemic changes on the posterior wall of the stomach, which reversed with 100% oxygen and warm sponge application. Left-sided nephrectomy was done. The gangrenous segment of the bowel was resected, and tube gastrostomy, feeding jejunostomy, and end ileostomy were done. Cut section of the kidney showed wedge-shaped infarction of the cortex [Figure 2]. Area of necrosis with blackish discoloration was noted in the substance of the kidney and the perinephric fat. The hilar structures of the kidney showed similar changes on gross inspection. Microscopy of the renal tissue from the affected areas on potassium hydroxide (KOH) mount showed broad, septate fungal hyphae, with branching at right angles suggestive of mucor [Figure 3]. Fungal culture from the tissue grew *Rhizopus oryzae*, thus confirming the diagnosis of mucormycosis. In the postoperative period, the patient continued to deteriorate and succumbed to multiorgan failure due to severe sepsis. The subsequent histopathology report showed extensive areas of necrosis in the renal parenchyma with thrombosed blood vessels and aggregates of fungal hyphae within the vessel lumens.

DISCUSSION

Mucormycosis is caused by filamentous fungi called *Zygomycetes*. Most patients with mucormycosis have at least one predisposing cause, of which the most common is poorly

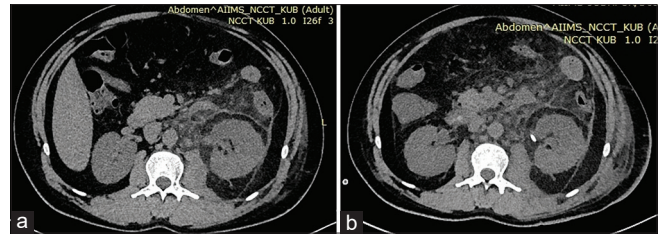


Figure 1: (a) Noncontrast computed tomography scan showing pyelonephritis left kidney with extensive perinephric and paranephric fat stranding with involvement of the left colonic mesentery by the inflammatory process. (b) Noncontrast computed tomography scan showing progression of the inflammatory process compared to Figure 1a. There is extensive inflammation of the colonic mesentery with thickening and stranding of the colonic wall. There is extension of inflammation into the lesser sac also

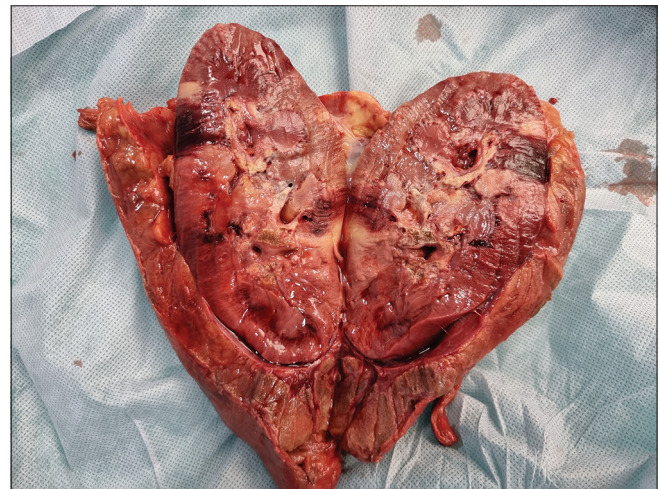


Figure 2: Cut surface of the left kidney showing wedge-shaped area of infarction with areas of necrosis and areas of blackish discoloration. The perinephric fat is thickened and appears saponified



Figure 3: Broad, sparsely septate, right angle branched fungal hyphae seen, suggestive of mucormycosis, in potassium hydroxide smears from the resected tissue

controlled diabetes. Rhino-cerebral-orbital mucormycosis is the most common type of involvement followed by pulmonary, with mortality rates ranging from 33% to 80%.^[3] Patients with isolated renal mucormycosis usually

have predisposing conditions such as immunosuppression, history of renal transplant, or intravenous drug abuse. Renal mucormycosis in apparently healthy individuals is a very rare occurrence, with most of these cases being reported from India.^[1,4] COVID-19 infection has emerged as an important predisposing factor for post-COVID systemic mycoses. COVID leads to innate immune dysregulation, ciliary dysfunction, cytokine storm, thromboinflammation, microvascular hypercoagulability, and eventual immune exhaustion. COVID patients are subjected to corticosteroid treatment and anti-IL-6-directed therapies in addition to invasive procedures, mechanical ventilation, administration of industrial-grade oxygen, extracorporeal membrane oxygenation, prolonged hospital stays along with poor nursing ratios, and breaches in asepsis. These factors, along with the inherently high fungal spore counts in patients of these geographical areas, provide the perfect setting for secondary fungal infections. In India, the epidemiology reveals a significant burden of invasive mucormycosis.^[5] The strongest predisposing factor appears to be hyperglycemia, resulting in polymorphonuclear dysfunction, impaired chemotaxis, and defective intracellular killing. An increased availability of free iron during hyperglycemia is also conducive to the growth of the fungus.^[6] These effects are greatly amplified by the use of corticosteroids and immunosuppressants in susceptible hosts.^[7] The landmark RECOVERY trial paved the way for use steroids in patients with COVID-19.^[8]

The most commonly reported sites of COVID-associated invasive mucormycosis till now have been rhino-cerebral-orbital followed by pulmonary. This is a rare instance where an apparently healthy male, who had recovered completely from COVID-19, presented with fulminant isolated renal mucormycosis. A few points of this case merit critical analysis. First, the site of primary mucormycosis in COVID-associated setting is usually the respiratory tract, which has already been damaged by the coronavirus infection and associated inflammation and is susceptible to colonization. Therefore, in this case, we can hypothesize that the primary site was the kidney and the infection was blood borne, probably from the original site of colonization of the respiratory tract. However, the examination of the oral and nasal cavity and chest X-ray at admission were normal. The other possibility is that the mucor spores could have been inoculated into his blood stream during the intramuscular analgesic injections he had taken prior to presentation to us. However, there were no local findings at the site of the previous intramuscular injection. Second, the use of steroids in this patient for treatment of COVID-19 along with the immune dysregulation caused by COVID itself changed his mode of presentation. Normally, patients with renal mucormycosis have high-grade fever and unrelenting flank pain, and this progresses rapidly to a picture of systemic toxicity.^[1] In our patient, fever was of low grade and the flank pain was

dull aching in nature, and both these symptoms had been present for 7 days before the patient came to us. Though the patient went on to develop edema and discoloration of the abdominal wall subsequently, there was an absence of flank tenderness and other signs and symptoms of systemic fungal sepsis. Usually, patients with this particular type of systemic mycoses are more sick at presentation. Third, we possibly erred by not obtaining a contrast-enhanced scan early on. The typical features of renal mucormycosis on contrast-enhanced CT scan (CECT) such as patchy or diffuse areas of hypoenhancement of the kidney, if present, along with the findings of bowel and mesenteric involvement would have probably alerted us toward the etiology in this case. However, avoiding CECT in a patient who already had compromised renal function coupled with the unusual presentation probably led to loss of precious time. Lastly, even in those patients that present with evidence of systemic mucormycosis in association with COVID-19, a history of diabetes or deranged blood sugars following steroid therapy is a very common association.^[9] Our patient did not have any deranged sugars on his blood sugar charts. While we were well aware of the association between COVID-19 and rhino-cerebral-orbital and pulmonary mucormycosis, the absence of fungal hyphae on urine examination in this apparently healthy nondiabetic male, and also the absence of any previously reported association between isolated renal mucormycosis and COVID-19, led us to place this quite low on our list of differentials.

The treatment of diagnosed renal mucormycosis is prompt institution of IV amphotericin B along with emergency nephrectomy, with emphasis on radical debridement of the retroperitoneum and excision of whole or part of the surrounding involved organs in order to achieve uninvolved margins. Despite such aggressive measures, mortality rates vary from 40% to 100% in most series. In our patient, the extensive bowel gangrene that had already set in was an extra cause of the systemic sepsis and the radical excision of bowel also contributed to the morbidity and eventual mortality. Isolated renal mucormycosis in apparently healthy, immunocompetent patients is known to occur. Furthermore, the diagnosis of mucormycosis in our patient was a retrospective one, confirmed only after surgical exploration and examination and culture of the resected tissue. Therefore, it is quite possible that the association of renal mucormycosis and history of COVID-19 in this patient was coincidental rather than contributory.

CONCLUSION

There is an increased predisposition for systemic mucormycosis in association with COVID-19 disease. While most such cases involve the respiratory system, we report a rare case of isolated renal involvement in a patient without other predisposing factors such as diabetes mellitus. The use of systemic steroids and the immune dysregulation brought

on by COVID infection, may lead to atypical presentation of such cases and therefore a high index of suspicion along with a low threshold for investigation must be present to achieve timely diagnosis and appropriate treatment in such patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgments

The authors would like to thank Prateek Gupta, Sand Nikita Shrivastava, Senior Residents, Department of Urology, All India Institute of Medical Sciences, Jodhpur.

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How to cite this article: Choudhary GR, Aggarwal A, Jain V, Jena R. COVID-19 and fatal renal mucormycosis: Contributory or coincidental? *Indian J Urol* 2021;37:270-3.