Original Article

Outcome of post-COVID-19 fungal pyelonephritis: A single Indian tertiary center experience

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ABSTRACT

Introduction: COVID-19 pandemic is associated with secondary opportunistic fungal infections. These have an aggressive course with a high mortality rate. We present our experience of seven cases of post-COVID-19 fungal pyelonephritis.

Methods: An observational study over a period of 8 months of May to December 2021 was carried out at our tertiary care hospital, including all patients with features of fungal pyelonephritis in post-COVID-19 setting. The patient demographics, details of previous COVID-19 infection, details of present admission and management were collected. The endpoints were either discharge from the hospital or death.

Results: Seven patients were included. Mean age of presentation was 42 years (range: 20–63 years, standard deviation ± 14.2). Male-to-female ratio was 6:1. One patient was diabetic. Two patients were asymptomatic, one had mild infection, and four patients had severe COVID-19 infection as per National Institute of Health criteria. In the present admission, all patients had symptomatic pyelonephritis with laboratory parameters showing elevated D dimer, C reactive protein, and total leukocyte counts. In all seven patients, ultrasound of kidney ureter bladder region showed bulky kidney, color Doppler showed main renal arterial thrombosis in two patients, segmental arterial thrombosis in another patient. Computed tomography scan was suggestive of changes of pyelonephritis in all patients with multiple renal hypodense areas. All patients required nephrectomy with biopsy suggestive of changes of necrotizing fungal inflammation. Three patients expired.

Conclusion: Management of post-COVID-19 fungal pyelonephritis should be aggressive and suspicious laboratory and imaging findings should be treated by early nephrectomy.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which has caused the coronavirus disease 2019 (COVID-19) pandemic is associated with a variety of opportunistic fungal and bacterial infections.[1] Among fungal infections, *Candida* and *Aspergillus* have been the main pathogens causing co-infection in COVID-19-infected individuals.[2] In the recent times, multiple cases of mucormycosis in people with COVID-19 infection were reported throughout the world and especially from India during the second wave of the pandemic.[3] The proposed reasons for fungal infection in COVID-19-infected patients appears to be an ideal environment for their growth due to low oxygen, high blood glucose levels seen in diabetics, steroid induced hyperglycemia, acidic medium due to metabolic acidosis, high iron levels, decreased white blood cells phagocytic activity due to immunosuppression which may be steroid mediated or COVID-19 infection mediated, prolonged hospitalization, and mechanical ventilation.[4]

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Post-COVID-19 fungal infections are of high public health importance, especially due to the high mortality and aggressive presentation with a documented in hospital mortality rate of 49% for post-COVID-19 mucormycosis.[5] We evaluated our experience of fungal pyelonephritis cases leading to nephrectomy with the objectives being to evaluate the outcome of these cases and to study the factors predicting the outcome.

MATERIALS AND METHODS

This was an observational prospective study conducted from May 1, 2021, to December 31, 2021, at a tertiary care hospital. All patients with clinical features suggestive of pyelonephritis with sepsis and prior history of COVID infection were included. The basic demographic data of these patients were collected. On admission, clinical assessments were done. The severity of prior COVID infection was categorized as per the National Institute of Health (NIH) guidelines.[6]

During COVID-19 infection, investigations and management details regarding use of steroids, tocilizumab, anticoagulants, supplemental oxygen were noted. On admission, specific investigations such as serum creatinine, complete blood counts, C reactive protein (CRP), D Dimer, Platelet count, Urine for fungus, and blood and urine cultures were done. Ultrasonography (USG) of abdomen and pelvis, color Doppler and computed tomography (CT) kidney ureter bladder (KUB) were obtained in all patients.

All patients received intensive care unit care and management of sepsis was done as in the surviving sepsis campaign 2021 guidelines as mentioned by the Society of Critical Care Medicine. Antifungals were started according to urine for fungus sensitivity report. Specific treatment consisted of double J (DJ) stenting for hydronephrosis and nephrectomy. Endpoints were either discharge from the hospital or death.

Institutional ethics committee approval was taken with written informed consent taken from the patients, and the procedures were done adhering to the ethical guidelines of Declaration of Helsinki and its amendments. The authors confirm the availability of, and access to, all original data reported in this study.

RESULTS

During study period, seven patients were referred for post-COVID-19 fungal pyelonephritis. Mean age at presentation was 42 years (range was 20–63 years). The male-to-female ratio was 6:1. Only one patient included in our study was a known diabetic, remaining patients had no comorbidities. As per NIH criteria, two patients had asymptomatic COVID-19 infection, one had mild illness and four had severe COVID-19 requiring oxygen support, systemic steroids, and anticoagulants.

All patients had elevated d dimer, CRP, and total leukocyte counts on presentation [Table 1]. In all seven patients, USG KUB showed bulky kidney on the symptomatic side. Color Doppler revealed main renal arterial thrombosis in two and segmental arterial thrombosis in one patient. In all seven patients, CT scan was suggestive of changes of pyelonephritis with perinephric fat stranding. The imaging findings are as shown in Figure 1. The three patients with arterial thrombosis underwent nephrectomy after stabilization of general condition. Rest of the four patients were managed conservatively with systemic antifungals as per the fungal sensitivity reports and broad spectrum antibiotics and DJ stent placement for hydronephrosis but did not respond and subsequently underwent nephrectomy. All the patients had unilateral fungal pyelonephritis on the left side.

Meantime between admission and nephrectomy was 6 days, mean time between admission and death was 14 days, meantime from COVID-19 infection to onset of pyelonephritis was 34 days. Final histopathology report was suggestive of necrotizing fungal inflammation in all the patients. The gross images of the nephrectomy specimen are as shown in Figure 2 and the histopathological findings are as shown in Figure 3. Two patients had local wound discharge post nephrectomy which required local debridement and drain placement. Two patients required re-exploration due to reactive hemorrhage from the necrotic tissues in renal fossa. One of these patients improved and the other patient succumbed due to multiorgan failure secondary to sepsis. Four out of seven patients were discharged and three patients died.

DISCUSSION

Post-COVID-19 fungal infection is due to multiple factors.[7,8] The use of steroids leads to hyperglycemia, which may precipitate diabetic ketoacidosis, especially in patients with diabetes mellitus which acts as a fertile ground for the growth of fungi. There is acidosis resulting in low pH which provides the right environment for the fungal spores to germinate. Steroid use reduces the phagocytic activity of white blood cells causing impairment of bronchoalveolar macrophage function. COVID-19 infection itself causes endotheliitis, endothelial damage, thrombosis, lymphopenia, and reduction in CD4 and CD8 T-cell level and predisposing to opportunistic infection. The glycosylation of transferrin and ferritin reduces the iron-binding allowing increased levels of free iron which is required for the growth of fungi. Cytokines like interleukin-6 which are increased in COVID-19 infection also increase free iron by increasing ferritin levels due to increased synthesis and decreased iron transport. Acidosis increases free iron by reducing the ability of transferrin to chelate iron. All these factors also enhance the expression of glucose-regulator protein 78 of endothelium cells and fungal ligand spore containing homolog protein, enabling angioinvasion, hematogenous dissemination, and tissue necrosis.

Table 1: Details of patients with post COVID-19 fungal pyelonephritis

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age (years)	59	35	63	35	20	34	48
Gender	Male	Male	Male	Male	Female	Male	Male
Comorbidities	DM, HTN	None	None	None	None	None	None
COVID 19 severity as per NIH criteria	Severe	Mild	Severe	Severe	Asymptomatic	Severe	Asymptomatic
COVID 19 treatment with corticosteroids	Yes, methylprednisolone	No	Yes, prednisolone	Yes, prednisolone	No	Yes	No
Administration of anticoagulant	Yes	No	Yes	Yes	No	Yes	No
Administration of anti IL6 monoclonal antibodies	No	No	Yes, tocilizumab	No	No	No	No
Administration of supplemental oxygen	Yes	No	Yes	Yes	No	Yes	No
Duration between COVID 19 and pyelonephritis (days)	30	60	55	20	-	5	-
Presentation of pyelonephritis	Flank pain and fever	Flank pain and fever	Flank pain and fever	Flank pain and fever	Flank pain and vomiting	Flank pain and pyuria	Flank pain and fever
D-dimer (mcg/ml)	2.1	3.3	5.5	4.9	5.4	8.3	5.8
C reactive protein (mg/L)	56	296	141	74.9	166.4	99	10.2
Total leukocyte counts	30300	35500	15500	41600	22600	14800	15900
Creatinine (mg/dl)	1.9	2.04	1.87	1.07	1.26	0.76	1.32
Urine/fungal culture	Sterile	Aspergillus	Candida Tropicalis	Saccharomyces, Pseudomonas	Sterile	Mucor-mycosis	Sterile
USG KUB with Color Doppler	Left bulky kidney with Decreased peripheral vascularity	Left bulky kidney with Decreased peripheral vascularity	Left bulky kidney with Decreased peripheral vascularity	No vascularity	No vascularity to mid and lower pole	Left kidney bulky, hypo-echoic areas, peri-nephric abscess	Left kidney no vascularity
CT KUB	Multiple hypodense areas and perinephric fat stranding	Multiple hypodense areas and perinephric fat stranding	Multiple hypodense areas and perinephric fat stranding	Main renal arterial thrombosis	Anterior segmental artery thrombosis	Multiple hypodense areas and renal and peri-nephric abscess	Main arterial thrombosis
Laterality	Left	Left	Left	Left	Left	Left	Left
Presence of hydronephrosis	Yes	No	Yes	No	No	No	Yes
Double J stent/Percutaneous nephrostomy	Yes	No	Yes	No	No	No	Yes
Duration between hospitalization and nephrectomy (days)	10	4	11	7	3	4	2
Nephrectomy approach	Open	Open	Laparoscopic	Open	Open	Open	Lap
Final HPE	Necrotizing Fungal inflammation	Necrotizing Fungal inflammation	Necrotizing Fungal inflammation	Necrotizing Fungal inflammation	Necrotizing Fungal inflammation	Necrotizing fungal inflammation	Necrotizing fungal inflammation
Fungal tissue culture	Aspergillus	Aspergillus	No growth	Mucormycosis	Mucormycosis	Mucormycosis	Mucormycosis
Antifungal type and route	Fluconazole – IV	Amphotericin B – IV, Posaconazole - Oral	Fluconazole - IV	Amphotericin B – IV, Posaconazole - Oral	Voriconazole - Oral	Amphotericin – IV, Posaconazole - Oral	Amphotericin – IV, Posaconazole - Oral
Postoperative complications	-	-	Reexploration for reactive bleeding	Reexploration for reactive bleeding	-	Local wound discharge needing debridement and drain placement	Local wound discharge needing debridement and drain placement
Duration of hospitalization	4	10	30	40	7	44	42
Duration from admission to death (days)	4	-	30	-	7	-	-
Outcome	Died	Improved	Died	Improved	Died	Improved	Improved

DM=Diabetes Mellitus, HTN=Hypertension, COVID 19=Coronavirus disease 2019. COVID 19=Coronavirus disease 2019, CT=Computed tomography, USG=Ultrasonography, KUB=Kidney, Ureter and Bladder, HPE=Histopathological Examination

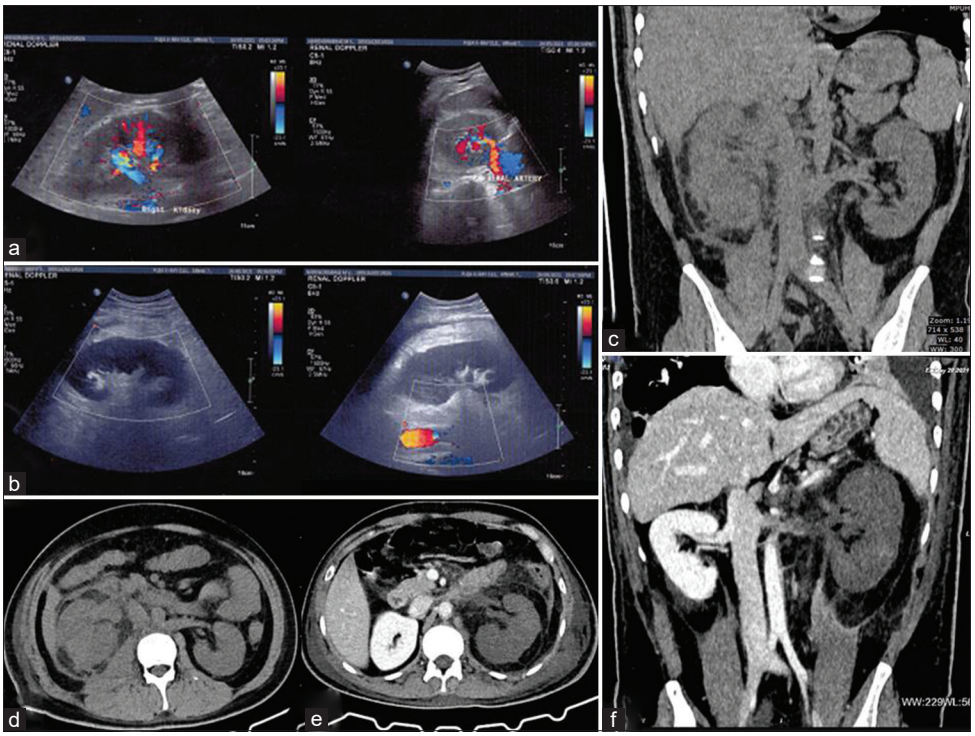

Figure 1: (a) Color Doppler ultrasonography image of normal right kidney. (b) Color Doppler ultrasonography image of hypoechoic, enlarged left kidney with absent flow in left renal artery suggestive of thrombosis. (c and d) Coronal and axial views on plain computed tomography kidney ureter bladder showing enlarged right kidney with extensive perinephric fat stranding with thickening of Gerota's fascia suggestive of right pyelonephritis. (e and f) Axial and coronal views on computed tomography angiography showing enlarged left kidney, marked perinephric fat stranding, and no contrast filling seen in mid and distal segment of left renal artery with no contrast enhancement suggestive of left renal artery thrombosis with renal infarct

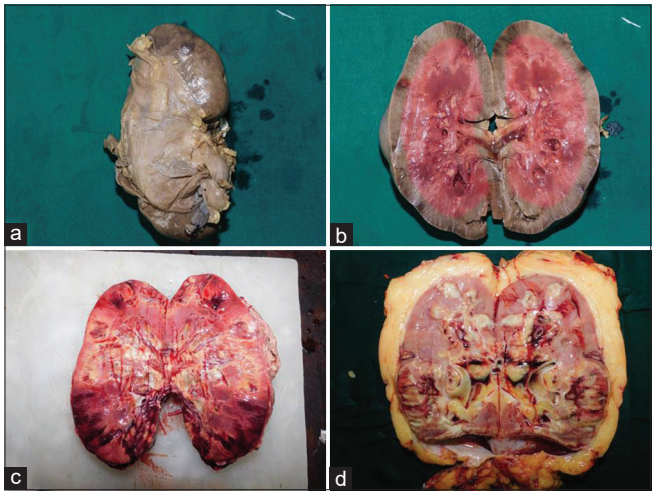

Figure 2: (a) Gross external image of left kidney specimen with segment of ureter weighing 287 g and measuring 13 cm × 6.5 cm × 6 cm. Capsule could not be stripped off. Dark and dusky external appearance of kidney noted. (b) Bisected specimen of kidney mentioned in image A, showing mildly dilated pelvicalyceal system and necrotic areas in kidney. (c) Bisected specimen of kidney of another patient showing mildly dilated pelvicalyceal system areas of necrosis and hemorrhage and loss of corticomedullary differentiation. (d) Bisected specimen of kidney of another patient showing mildly dilated pelvicalyceal system with multiple necrotic foci in mid and lower pole of left kidney with loss of corticomedullary differentiation

Fungal infection can involve lungs, skin, jawbones, heart, joints, kidney, mediastinum, orbit, nose, sinus, central nervous system.[9] Renal involvement as a part of multiorgan disease is seen in immunocompromised hosts but isolated renal mucormycosis in immunocompetent individuals is rare and reported mostly from China and India.[10] A total of 33 cases are published till now with more cases being reported in recent times probably due to increased detection or increasing incidence.[9] In another large Indian case series, renal involvement was found in 14% of the 129 cases of mucormycosis.[11] In our study, seven patients presented in 8-month time which is a significantly high incidence.

Age group of patients included in our study ranged from 20 to 63 years (±14.2 standard deviation) with a mean of 42 years, proving that there is no age-related predisposition for the condition. The patients included in our study, developed fungal pyelonephritis 5–60 days after COVID-19 infection with a mean interval of 34 days. This is similar to the case reported by Choudhary *et al.*[12] Primary mucormycosis of kidney was recorded in a 32-year-old male 45 days after treatment for COVID-19.

Although diabetes is a significant risk factor for fungal infection, in our study among seven patients only one patient was diabetic. Similar to our study, the case reported by Choudhary *et al.*,[12] was nondiabetic. The observation of our study and the study performed by Choudhary *et al.*[12] suggests that immune dysregulation associated with COVID-19, along with the use of steroids, mechanical ventilation, and interleukin-6-directed therapies, predisposes

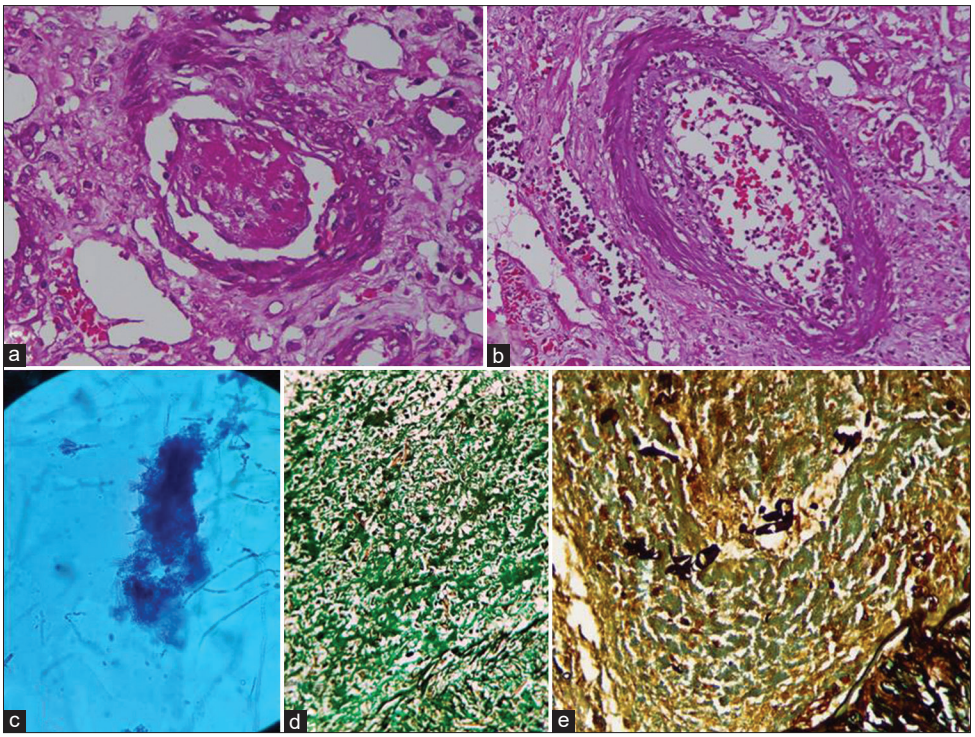

Figure 3: (a) HPE image showing fibrin platelet thrombi in arteriole- ×400. (b) HPE image showing changes of endotheliitis- ×400. (c) Lactophenol blue stain for fungi from nephrectomy specimen showing Aspergillus Species- ×400. (d) Grocott-Gomori Methenamine Silver (GMS) stain for fungi from nephrectomy specimen showing fungal septate hyphae- ×400. (e) GMS stain from nephrectomy specimen of another patient showing fungal septate hyphae- ×400

to the development of mycotic infections rather than the hyperglycemic state associated with diabetes.

Renal mycosis presents with varied manifestation from asymptomatic involvement to fever, chills, and flank pain. Urine may reveal pyuria or fungal material. Imaging studies such as renal sonography may demonstrate filling defects compatible with fungal infection, CT scan or radionuclide scan may demonstrate altered renal perfusion and function.[13,14] All patients included in our study also presented with flank pain and fever. One patient presented with hematuria. High index of suspicion is required to diagnose mycotic co-infection in patients previously treated for COVID-19 infection.

There are various mechanisms proposed for renal injury by SARS-COV2, namely direct injury due to highly expressed angiotensin converting enzyme 2 in renal tissue, or through systemic effects such as host immune clearance and immune tolerance disorders, endothelial cell injury, thrombus formation, glucose and lipid metabolism disorder and hypoxia which aggravates renal injury.[15] Literature reveals multiple case reports of post-COVID-19 infection renal arterial thrombosis.[13] All patients included in our study had elevated D-Dimer levels. Tang *et al.*[16] in their study described that at late stages of COVID-19 infection, levels of fibrin-related markers (D-dimer and fibrin degradation products) are moderately or markedly elevated in all mortalities, which suggested a common coagulation activation and secondary hyperfibrinolysis condition in these patients. Post-COVID-19 thrombotic disease incidence has been reported to be as high as 31% and in a case series, prevalence rate of renal arterial thrombosis was found to be 0.02/1000 and in an autopsy series, it was 14/1000.[17] A case of bilateral renal arterial thrombosis in COVID-19 infection patient is also reported.[17] Similar to the above findings in the present study, three patients had unilateral renal arterial thrombosis and all the patients had elevated D dimers.

In our study, all seven patients had fungal pyelonephritis, three patients were managed conservatively initially with antibiotics and antifungals. In addition, DJ stent placement was done in two patients with hydronephrosis. However, these patients general condition worsened with persistent symptoms and hence eventually required nephrectomy. All the patients were having bulky kidney on USG and color Doppler suggestive of diminished vascularity especially on periphery and CT scan showed multiple hypodense areas suggestive of abscess. It is likely that these hypodense areas were actually patchy renal infarcts. Hence, antibiotics and antifungals did not reach the areas where the fungi were lodged. On histology of specimen, fungal septate hyphae with vascular microthrombi were seen in all the cases. Choudhary *et al.*[12] described a young male presenting with primary renal mucormycosis during recovery from COVID-19 with an unusual presentation, rapidly progressive disease course, failed trial of conservative management,

requiring nephrectomy and tissue fungal culture growing Rhizopus oryzae, succumbing to multiorgan failure due to severe sepsis with histopathology showing extensive areas of necrosis in renal parenchyma with thrombosed blood vessels and aggregates of fungal hyphae within the vessel lumen.

Fungal pyelonephritis presents a medical challenge in terms of accurate speciation of the invasive fungus infection, use of biomarkers to confirm diagnosis and progress of disease, and role of antifungal therapy directed against specific invasive fungi. If mucormycosis or invasive aspergillosis is suspected, empirical treatment with amphotericin B is warranted. It has known nephrotoxicity.[18] It is claimed that liposomal amphotericin B is less nephrotoxic than the deoxycholate salt but efficacy remains similar.[19] Prehydrating with 1 liter bolus of 0.9% normal saline may mitigate renal damage. Although it appears challenging to administer a potentially nephrotoxic drug to patient with single kidney status post nephrectomy for fungal pyelonephritis, it provides rapid and effective source control and should be drug of the first choice in such circumstances. In the present study, in spite of antifungal therapy postnephrectomy, two patients required re-exploration due to bleeding from renal fossa and additional two patients required local wound debridement and drain placement. This suggests that aggressive and long-term use of antifungals is required even after nephrectomy with long-term postoperative drain placement till there is negligible output.

In all seven patients, final histopathology showed necrotizing fungal inflammation with the presence of microthrombi. We hypothesize that due to necrotizing inflammation and microthrombi, antifungal and antimicrobial agents fail to achieve tissue concentration of the drugs. Hence, patients who worsen despite conservative treatment with systemic antifungals and DJ stenting may benefit from early open simple nephrectomy. In our study, factors leading to nephrectomy were poor response to conservative treatment and decreased blood flow to the kidney on color Doppler. We advise emergent open simple nephrectomy with wide excision of all necrotic tissue which is in accordance of latest Centers for Disease Control and Prevention guidelines for post-COVID-19 fungal infection which advocates aggressive surgical intervention.[20] In our patients, two patients underwent laparoscopic simple nephrectomy but there were significant difficulties experienced in tissue dissection and kidney mobilization due to intense adhesions. In open approach, we remain retroperitoneal and we can do wide debridement of surrounding tissue with ease and operative time is also less for these patients of whom some had hemodynamic instability. Hence, we advocate open approach in all the suspected cases of post-COVID fungal pyelonephritis planned for nephrectomy.

Fungal infection in post-COVID-19 setting reported in literature has a high mortality rate which was also seen in our study with 43% mortality rate, making it an important public health concern. Our case series attempts to bring to the attention of the urologist/nephrologist this important entity in the present times so that with timely intervention the mortality can be prevented.

Limitation of the present study is small patient numbers and all cases are reported from a single tertiary referral center hence generalization to population as a whole and to all the centers may not be possible. However, given the severity of the condition and sparse literature available, this number is also significant.

CONCLUSION

Pyelonephritis in a patient with a history of COVID-19 infection requires aggressive work up for fungal pyelonephritis as it has a high mortality rate. Investigations in the form of elevated D-dimer levels and imaging findings suggestive of perfusion defects in the kidney can guide us to the existence of this uncommon entity and should be further evaluated and if the diagnosis is confirmed, then can be aggressively treated in the form of early nephrectomy.

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