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CASE REPORT

Rare Case of *Aspergillus fumigatus* Isolated from Renal Stone in an Immunocompetent Patient

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Background: Aspergillus species are relatively rare and typically occur in immune compromised individuals such as those undergoing organ transplantation, chemotherapy, or long-term corticosteroid therapy. Renal Aspergillosis is an uncommon manifestation that generally occurs as part of a disseminated infection in immunocompromised patients.

Case: A 22 yrs male patient came to emergency department of Manipal Teaching Hospital with the chief complaints of right flank pain, 3–4 episodes of vomiting for last 4 days, had acute onset, gradually progressive non-radiating aggravated pain and no history of any other medical conditions. His urine sample showed plenty of red blood cell in routine microscopy and other blood laboratory tests were within normal limit. Computed tomography of the kidneys, ureter and bladder showed multiple bilateral stones in both kidneys. Kidney stones were surgically removed by bilateral retrograde intrarenal surgery with total lithotripsy. After surgery, the renal calculi were received in microbiology laboratory for microbial analysis. The crushed material of renal stone was used for microbial culture and direct microscopy using 10% KOH wet mount which showed hyphae. Both bacterial culture media and Sabouraud's Dextrose Agar showed growth of molds which was identified as Aspergillus fumigatius. The patient was treated with voriconazole intravenously with the loading dose of 6mg/Kg IV 12 hourly for 2 days followed by 4mg/Kg 12 hourly for 7 days. After 7 days of treatment, patient recovered well. Post-operative follow-up and post-operative radiography did not show evidence of any recurrence.

Conclusion: This rare case of fungal etiology in patient having renal stones reveals the importance of closely monitoring post-operative patients, even when typical infection risk factors are absent.

Keywords: Aspergillus, renal stone, immunocompetent

Introduction

Aspergilli are ubiquitous fungi in the environment and can be found in soil, water and air. Clinical infections due to Aspergillus species are relatively rare and typically occur in individuals with compromised immune system, such as those undergoing organ transplantation, chemotherapy, or long-term corticosteroid therapy.[1,2] Renal Aspergillosis is an uncommon manifestation that generally occurs as part of a disseminated infection in immunocompromised patients.[1] Association of fungal pathogens such as Aspergilli with renal stones is even rarer though such association of bacteria with renal stones have been reported earlier.[3,4] The rarity of renal Aspergillosis, especially in patients with renal calculi and without immunosuppressive conditions, highlights the need for awareness of this possibility in cases where standard therapies for bacterial infections fail to yield results. This case reveals the importance of recognizing atypical post-operative complications in patients having renal stones and exploring fungal etiologies in such cases.

Case Report

Twenty-two years of Padam Chettri resident of Pokhara-13 came to emergency department of Manipal Teaching Hospital on 28-11-2024 with the chief complaints of right flank pain and 3–4 episodes of vomiting for the last 4 days. According

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to the patient, he had acute onset, gradually progressive non-radiating aggravated pain and non-projectile mixed with food particles, non-bile, non-blood stained vomiting. The patient was referred to the urology department for the flank pain and vomiting. On examination, the general condition of the patient was fair, there was no pallor, no icterus, no lymphadenopathy or koilonychia. His vital functions were within normal limits. However, he revealed that he was allergic to certain drugs such as antibiotics namely piperacillin and ceftriaxone.

His urine sample was subjected to routine microscopy, which showed plenty of red blood cells and 18–20 pus cells per high power field. Computed tomography of the kidneys, ureter and bladder (CT-CUB) showed the presence of multiple bilateral stones. Right kidney showed one stone of 9.6*8.1*6.4 mm in lower pole calyx. Left kidney showed three stones, 3*2.8 mm in the mid pole; 2.6 mm and 5.5*5.3*4.5 mm in lower pole calyces. Additionally, there was another stone of 5.7*5.4*4.5 mm in the left vesicoureteral causing mild upstream dilatation of ureter and polyvicalyceal system (Figure 1A and B).

His complete blood cell revealed, total white blood cell 8003 cells/cu mm, platelets 257000 cells/cu mm and hemoglobin 14.3% with other serum analysis reports showing urea 24.8mg/dl, creatinine 1.2 mg/dl. The patient's serum sample was negative for Hepatitis B surface Antigen, Hepatitis C Virus and Human Immunodeficiency Virus antibodies. His urine culture was sterile. Thus, removal of stones by bilateral retrograde intrarenal surgery with total Lithotripsy was planned. The procedure was done on both kidneys and was conducted under general anesthesia. A laser was utilized to break stones into smaller fragments after a flexible scope was inserted through the bladder during the

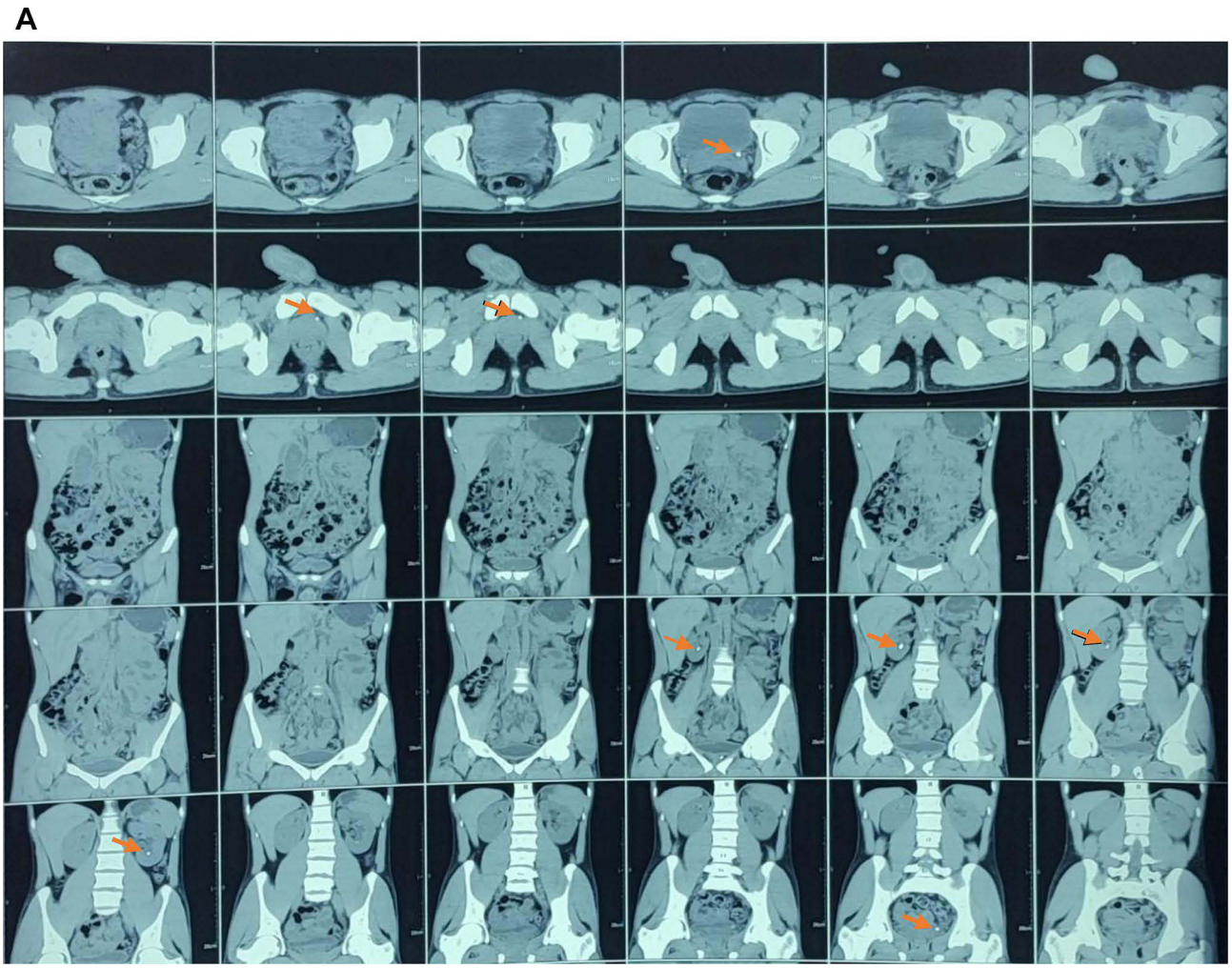

Figure 1 Continued.

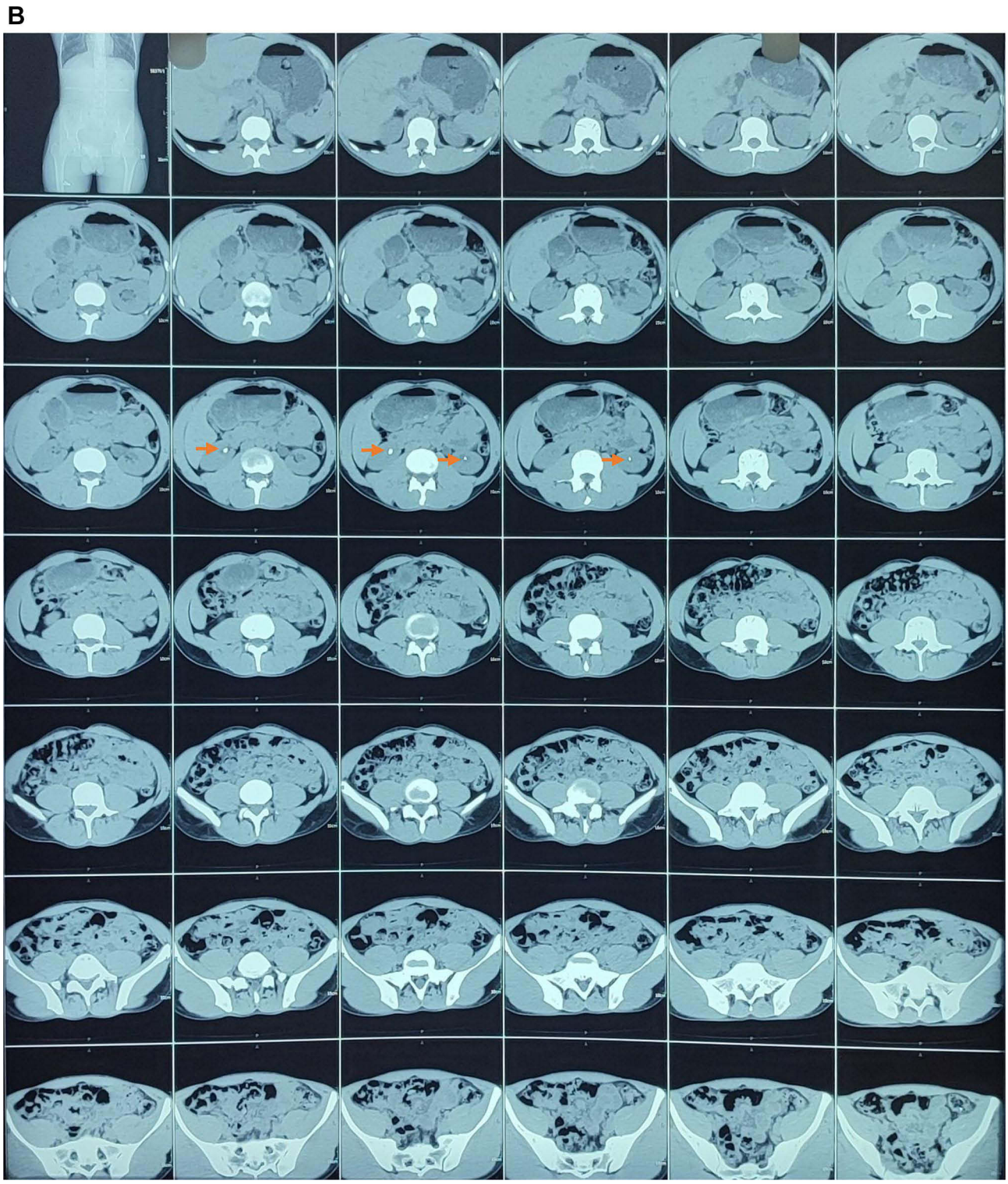

Figure 1 (**A** and **B**) CT-CUB scan showing bilateral multiple stones highlighted by Orange arrows.

procedure. The patient was then moved to the surgical intensive care unit for observation and post-surgery care. He was managed with IV antibiotics, Proton Pump Inhibitors and analgesics.

Renal calculi were collected during surgery in a sterile container on 28-12-2024. Calculi were washed with sterile normal saline 4–5 times and then crushed in mortar and pestle with 5mL sterile saline. The crushed out material (calculus core) was

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Figure 2 10% KOH wet mount of the crushed out stone material showing septate hyphae.

subjected to 10% KOH wet mount cultured in 5 mL thioglycolate broth which was incubated at 37°C for 18–24 hours, and then subcultures were done on blood agar and MacConkey's agar plates and Sabouraud's dextrose agar (SDA) for isolation of microbial agents. KOH wet mount revealed the presence of septate hyphae (Figure 2) Blood agar showed growth of molds after overnight incubation at 37°C. Sabouraud Dextrose Agar (SDA) too yielded greenish confluent growth after three days of incubation at 25°C which was nonvelvety, powdery (Figure 3). A Lacto Phenol Cotton Blue (LPCB) wet mount was performed from the same colony on SDA, which showed septate dichotomous hyphae with conidiophores having vesicle and sterigmata. Based upon such microscopic morphology, the fungus was identified as *Aspergillus fumigatus* (Figure 4). Repeat culture from the remaining parts of the stone from the original collection tube also revealed the growth of *Aspergillus fumigatus*. The isolated *Aspergillus fumigatus* from the stone material is unlikely to be a contaminant because a direct microscopic potassium hydroxide (KOH) wet mount preparation of the stone material demonstrated septate hyphae (Figure 2).

The patient was treated with voriconazole intravenously with the loading dose of 6mg/Kg IV 12 hourly for 2 days followed by 4mg/Kg 12 hourly for 7 days. After 7 days of treatment, patient recovered well. Post-operative follow-up and post-operative radiography did not show any recurrence.

Discussion

Aspergillus, a fungus that is globally distributed filamentous mold grows ubiquitously in nature.[5] Several genera of Aspergilli develop various clinical symptoms including primarily pulmonary manifestations and invasive extra-pulmonary Aspergillosis.[6,7] Invasive aspergillosis, a severe fungal infection, usually affects patients with immunocompromised conditions such as diabetes mellitus, hematological malignancy and neutropenia or prolonged use of immunosuppressive drugs.[5] No such risk factor was present in our case and so it was a rare case of invasive Aspergillosis in an immunocompetent individual. Our case revealed Aspergillus isolated from kidney stones without having any risk factors for an invasive renal Aspergillosis. This patient did not have any clinical or radiological evidence of pulmonary involvement. Jandaghi et al also reported unexpected renal Aspergillosis after percutaneous nephrolithotomy in a patient without predisposing condition.[8] This raises important questions as to how patients can acquire renal Aspergillosis without possible risk factors. One probable mechanism could be that the patient was exposed to Aspergillus spores during surgical procedure, as this fungus is commonly found in hospital environments and it could be as well due to catheter placement.[1,9] On the other hand, use of broad-spectrum antibiotics also could have contributed to an increased risk of Aspergillosis.[4]

Aspergillus fumigatus is a primary causative agent of aspergillosis, accounting for approximately 70–80% of reported cases.[10] Present study also reported *Aspergillus fumigatus* being isolated from the patient having kidney stone evidenced by microbiological culture and identification, supported by direct microscopy (10% KOH wet mount showing hyphae; Figure 2).

Figure 3 Sabouraud's Dextrose Agar (SDA) showing greenish nonvelvety powdery colonies of *Aspergillus fumigatus* after 3 days of incubation at 25 °C.

Inadvertently, histopathological examination of the stone material and galactomanan detection by ELISA are other alternatives to establish invasive disease, and to rule out mere extraneous contamination as reported earlier.[11,12]

The formation of renal calculi, is a complex process influenced by various factors, including urine composition, genetic factors, lifestyle, and medical conditions such as diabetes, hypertension, gout and metabolic syndrome, etc.[13] The most common minerals associated with the formation of kidney stones include calcium, oxalate, uric acid, and cysteine.[14–16] Scanty information is available on the pathogenesis of fungi in the formation or renal calculi. It was reported recently that fungi excreted a number of organic acids (eg, citric, oxalic, and formic acids, etc) due to which there could be microbe-urine-mineral interaction causing stone formation.[17,18] Aspergillus sp. can synthesize oxalic acid, which reacts with blood and tissue calcium to precipitate as oxalate crystals, at the physiologic pH.[19] It was also shown that the amount of oxalate excreted in urine is a critical factor in calcium oxalate stone growth due to fungi.[20,21] Renal fungal ball was shown to be a rare complication that might eventually lead to fungemia, obstructive uropathy, renal failure and bladder rupture.[22] Some studies even showed that renal involvement by fungi was associated with increased morbidity and mortality particularly in cases of infections by angioinvasive fungi such as Aspergillus and Mucor.[23–25]

Exploring further on the pathophysiology of renal stones, recent studies recognized that fungal mycelium, under certain in vivo conditions shared characteristics with biofilm forming bacteria.[26–28] Specifically, fungal mycelium formed a dense,

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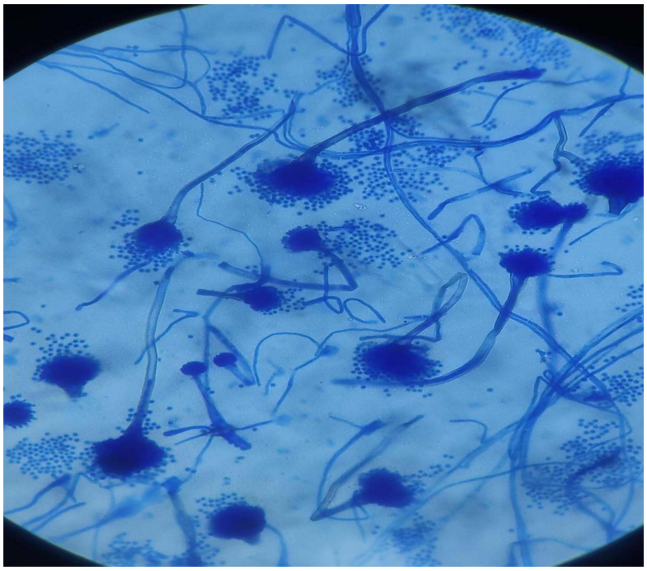

Figure 4 Lactophenol cotton blue wet mount preparation showing microscopic morphology of *Aspergillus fumigatus* with conidiophores bearing vesicles having uniseriate microconidia.

multicellular network that adhered to surfaces, was embedded in an extracellular matrix, and displayed emergent properties similar to bacterial biofilms, including resistance to antimicrobial agents.[29] In vivo formation of fungal biofilms in general and *Aspergillus fumigatus* biofilms in particular are clinically relevant in the context of recent reports of drug resistance among Aspergilli. Thus managing renal and genitourinary Aspergillosis presents significant challenges. In the above context, previous reports suggested that fungal biofilms could in a clinical setting be responsible for recalcitrance to treatment by antifungal drugs. However, antifungal agents like voriconazole and echnocandins would still be effective.

The Infectious Diseases Society of America guidelines for the treatment of Aspergillosis proposed a comprehensive approach, advocating both medical and urologic strategies for renal Aspergillosis.[9] Voriconazole and echinocandins (caspofungin) are new antifungal agents with broad spectrum of activity against a wide variety of fungi including Aspergillus sp.[30,31] Oral voriconazole can be effectively given in patients with renal insufficiency on domiciliary basis.[30] In our case, too, patient responded well to oral voriconazole treatment. Resistance to antifungal drugs, such as that towards fluconazole among clinical isolates of Candida was reported in the recent past.[32] It was also documented that high number of biofilm producing Candida isolates were multidrug resistant as compared to non-biofilm producing organisms.[33,34] Reports on filamentous fungi forming biofilms, though sparse, were reported from various centers from Nepal and other countries.[35–38]

Even though we could not look for biofilm forming ability of the Aspergillus isolate in our study, we convincingly showed that this fungus was isolated from the stone matrix. Ripa et al while analyzing this relationship between bacterial infection and kidney stones postulated that lodgment of organism in the kidney might have etiopathogenic role in the formation of infectious stone.[39] Similarly, it was also observed earlier that individuals with gall stones were likely to become typhoid carriers because *Salmonell typhi* was able to survive in this matrix of the gall stones.[40,41] Recently, our center reported a close association between urinary carriage of *S. typhi*, and kidney stone formation.[42] Whether renal calculus was a nidus for *S. typhi* colonization or repeated urinary tract infection due to *S. typhi* predisposed to renal stone was a conjecture. Notwithstanding the above, the aforementioned view regarding bacterial colonization and gall stone formation being applicable to Aspergillus induced stone in the present case, is a difficult proposition at this stage. Studies involving a number of isolates of Aspergilli from similar cases of urolithiasis will probably have some insight on the fungal etiology of urinary stones.

Conclusion

This rare case emphasizes the importance of closely monitoring postoperative patients, even when typical infection risk factors are absent. While bacterial infections are more frequent after urological procedures, rare fungal infections like Aspergillosis should not be overlooked. In the present case, clinical observations radiological findings and concordant

direct microscopy and culture correlation reiterate the importance of association of Aspergillus with kidney stones. The report highlights that maintaining a high index suspicious and timely intervention can lead to positive outcomes, even in uncommon and complex cases such as renal Aspergillosis in immunocompetent patients.

Abbreviations

CT-CUB, Computed tomography of the kidneys, ureter and bladder; SDA, Sabouraud Dextrose Agar; LPCB, Lacto Phenol Cotton Blue.

Ethical/Copyright Corrections

Publication of this case report was approved by the Institutional Review Committee (IRC) of Manipal College of Medical Sciences (MCOMS/IRC/647/GA).

Consent for Publication

The patient consented to publication of images and other clinical information reported in this article. A written informed consent form was signed by him. We made efforts to ensure information about his identity did not appear in this article.

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Disclosure

The author(s) report no conflicts of interest in this work.

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