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CASE REPORT

Urinary tract aspergillosis in a patient with chronic kidney disease

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SUMMARY

Invasive aspergillosis is a life-threatening fungal infection, especially in immunocompromised patients. Pulmonary aspergillosis is the most common type of the infection, while urinary tract infection is relatively rare. Here, we describe a case of a 46-year-old man with chronic renal disease presenting with intermittent abdominal pain. The diagnosis of aspergillosis was established by pathological findings of the fungal ball in the bladder. The patient underwent multiple antimicrobial treatments and surgical interventions and was finally cured by posaconazole.

BACKGROUND

Invasive aspergillosis, a severe fungal infection, usually affects patients with immunocompromising conditions such as diabetes mellitus, haematological malignancy and neutropenia.¹ Aspergillosis limited to the urinary tract is an uncommon type of invasive aspergillosis, which has been reported to more frequently involve the lung. A combined approach of medical and urological management for renal aspergillosis is recommended. However, no anti-fungal drug has been advised for urinary tract aspergillosis due to the low urine concentration.²

Posaconazole, an extended-spectrum triazole antifungal agent, has great activity against the *Aspergillus* and *Mucorales*.³ Guidelines recommend posaconazole as salvage therapy for invasive pulmonary aspergillosis, but whether it could be used in invasive urinary tract aspergillosis remains uncertain. Here, we report a case of invasive urinary tract aspergillosis with chronic kidney disease that was successfully treated with posaconazole, which suggests that it may be a suitable alternative anti-fungal agent for urinary tract infections.

CASE PRESENTATION

A 46-year-old man presenting with intermittent fever, abdominal pain and flocculi in urine for 1 year was admitted in a local hospital.

He provided a history of well-controlled hypertension for 10 months, type 2 insulin-dependent diabetes for 10 years, HBeAg-negative chronic hepatitis B for 20 years and liver cirrhosis for 12 years.

On physical examination, the patient was febrile (T=39°C) with a heart rate of 78 beats/min, blood pressure 111/77 mm Hg and epigastric pain radiating to the lower back, without abdominal mass. Urinalysis showed urine protein (+), red blood cell

(RBC) count $\times 10^6$ /LL and white cell (WBC) count 0.3774×10^9 /L. Liver and renal function tests were normal. Serological testing was positive for hepatitis B surface antigen. Renal ultrasonography and CT were normal. Repeated urine cultures were negative for bacterium and fungus. On the basis of clinical presentations and investigations, clinical diagnosis of urinary tract infection was suggested, and empirical antibiotics treatment was initiated with ceftriaxone sodium and levofloxacin for 2 weeks but failed. The patient developed anuria and bilateral double J stents were inserted immediately to relieve obstructions. The repeated urinalysis showed RBC count 39.4×10^6 /L and WBC count 0.4506×10^9 /L, and microscopic examination of floccule in urine revealed fungal hyphae and spores. Imipenem/cilastatin (0.5 g every 8 hours) and caspofungin (50 mg daily) were commenced for 10 days, and imipenem/cilastatin was then switched to cefoperazone sulbactam sodium (2g every 12 hours) for 3 weeks.

However, the patient still complained of flocculi in the urine and laboratory investigation showed that 3–4 g protein was excreted over 24 hours. A renal biopsy revealed mesangioproliferative glomerulonephritis which indicated chronic kidney disease. Intravenous methylprednisolone (0.2 g daily) was used for 3 days and fluconazole (0.4 g daily) was later added. The patient then developed confusion, sensory disturbances, speech disorder and high blood ammonia level up to 118.5 μ g/dL, which indicated hepatic encephalopathy and improved after symptomatic treatments.

Two months later, after the patient experienced sudden difficulty in urination, a cystoscopy was performed showing an intraurethral obstruction by a fungal ball, which was found to consist of fungal hyphae. Indwelling catheters were used to address this. But the patient experienced hypouricemia, bilateral renal pain, nausea and vomiting; and subsequent ultrasonography revealed mild bilateral hydronephrosis with ureterectasis, which was attributed to fungal obstruction. Bilateral pelvisotomy and drainage were performed and antifungal therapy was initiated with intravenous itraconazole (0.2 g daily) for 16 days, after which the patient was switched to caspofungin (50 mg daily) for 21 days. During this time, left ureteral patency and obstruction of the right ureter were observed again.

Three months later, the patient was admitted to our hospital complaining of intermittent flocculi in his urine. Pathological examination of the bladder fungal ball was reviewed and demonstrated that



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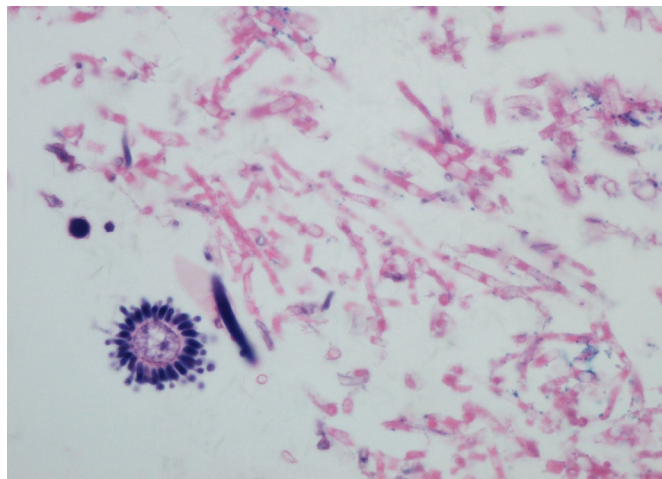


Figure 1 The conidial head (bottom left) consists of a vesicle with sterigmata and chains of conidia, with hyphae (right) beside it (H&E, 20×).

the hyphae are parallel, uniform and septate at regular intervals. Branching is at 45° angle suggestive of invasive aspergillosis (figures 1 and 2). Posaconazole oral suspension was administered (0.4g every 12 hours) for 6 months. The efficacy was excellent, and the patient tolerated well during the treatment. He was asymptomatic at 13-month follow-up.

INVESTIGATIONS

Laboratory investigation revealed a WBC count of $3.21 \times 10^9/L$. Urinalysis showed urine protein (+), nitrite (2+), leucocyte esterase (4+), RBC count $16.6 \times 10^6/L$ and WBC count $1.472 \times 10^9/L$. The liver function tests showed the glutamic-oxaloacetic transaminase level 41U/L, total bile acid 31 $\mu\text{mol/L}$, alkaline phosphatase 194U/L, gamma-glutamyltransferase 194U/L, total protein 59g/L, albumin 32g/L and prealbumin 137mg/L. The renal function tests showed the serum creatinine level 73 $\mu\text{mol/L}$. The carbon dioxide combining power was 14.30mmol/L. The serum CA125 was 46.46U/mL, CA72-4 26.17U/mL, cytokeratin 19 fragment 4.02ng/mL and 1-3-beta-D-glucan measurement was 191.20 pg/mL. Renal ultrasonography showed mild pyelic separation and rigid bladder, without renal abscess. Pathological examination of fungal ball

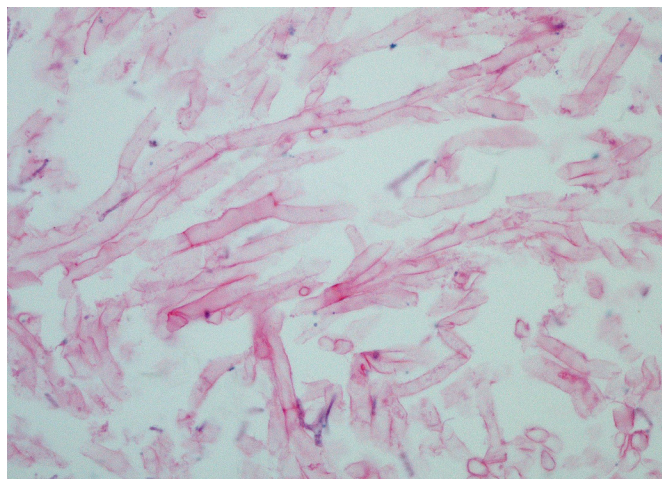


Figure 2 The hyphae are parallel, uniform and septate at regular intervals. Branching is at 45° angle (H&E, 40×).

specimens revealed parallel, uniform hyphae suggestive of invasive aspergillosis.

TREATMENT

On the basis of this evidence, the patient was administered posaconazole 400mg two times per day for 6 months.

OUTCOME AND FOLLOW-UP

The patient was discharged on day 14 with a prescription for posaconazole at a dosage of 400mg two times per day for 6 months. After a follow-up of 13 months, clinical symptoms including dysuria, urination frequency and urgency were relieved. The efficacy was excellent and the patient tolerated the treatment well. Urine cultures were negative and positron emission tomography/ CT showed no abnormalities.

DISCUSSION

Invasive fungal infection of urinary tract, commonly found in immunocompromised patients, remains a great challenge in both the diagnosis and the treatment. There are three main transmission routes, including ascending infections (usually from indwelling bladder catheters), trauma or surgical interventions and haematogenous spread (common in immunocompromised patients). *Candida* is the most common pathogen, followed by *Aspergillus*.¹ Clinical symptoms vary based on whether the underlying pathology is an *Aspergillus* abscess or if there is formation of fungal ball. A fungal ball can originate from agglutination of a necrotic tissue nucleus, mucous debris and foreign or lithiasic debris.⁴ Typically, if the fungal ball blocks the ureters, the infection manifests as acute onset fever, flank pain, nausea, vomiting, dysuria and haematuria.⁵ Further diagnosis of the disease is extremely difficult in the early stage, and direct microscopy or culture of floccules in urine could be helpful. This patient's diagnosis was finally confirmed by pathological examination.

Management of urinary tract aspergillosis remains a therapeutic challenge in clinical settings. Current Infectious Diseases Society of America guidelines recommend a combined therapy of medical and urological management for renal aspergillosis, and voriconazole has been recommended for parenchymal disease.¹ However, it is uncertain whether voriconazole, posaconazole, itraconazole, amphotericin B (AmB) formulations and the echinocandins could be used in the treatment of urinary tract aspergillosis as all exhibit poor urinary concentrations.²

Nevertheless, these antifungal regimens have been used successfully in the treatment of urinary tract fungal infection in a few case reports.^{2 6-10} In our patient, AmB formulations and voriconazole were limited due to its nephrotoxicity and hepatotoxicity, and itraconazole and caspofungin did not show favourable efficacy. Though cystoscopy was performed to remove the fungal ball, the patient still complained of flocculi in the urine, and the obstruction of ureter was revealed by ultrasonography. Posaconazole was then commenced. The patient recovered gradually with no relapse at 13-month follow-up. There are two possible reasons for our successful antifungal treatment. First, recent studies revealed that posaconazole provides a high concentration in renal tissue, and the levels of which could be 40-fold higher than serum levels.^{11 12} Though it is generally assumed that posaconazole penetration in the urine is low, since the elimination occurs primarily through faecal excretion (77%) and to a lesser extent through urinary excretion (14%), only 0.28% of active drug is eliminated in the urine.¹³⁻¹⁵ However, owing to the several surgeries our patient underwent, including cystoscopy, bilateral pelviostomy and drainage, which may lead

to the physiological barrier of renal parenchyma and renal pelvis broken, the patient might achieve high concentration of posaconazole in urine. The second possible reason was that the source of infection of our patient was both in renal tissue and bladder, since the flocculi were still found in urine after the fungal ball removed. According to a recent study, while fungal balls are found in the ureters, the disease originates in or involves the renal parenchyma, and our successful treatment of posaconazole support it.⁵

In conclusion, the diagnosis and treatment of invasive urinary tract aspergillosis is still a great challenge. Patients with iterative flocculi in urine were suspected of infection with a non-*Candida* fungus such as *Aspergillus* or Mucorales. Further diagnosis depends more on pathological examination and culture. Regarding management, surgical interventions in addition to effective antifungal therapy are strongly recommended. For patients with immunocompromised states, posaconazole may be a suitable alternative antifungal option for urinary tract fungal infections.

Learning points

- ▶ Invasive urinary tract aspergillosis is a rare disease and it poses considerable difficulty to diagnosis and treatments.
- ▶ Physicians should remain on high alert for patients presenting with flocculi in urine.
- ▶ Posaconazole may be a suitable alternative agent for chronic kidney disease patients with invasive urinary tract aspergillosis.

Contributors LpZ designed this case. LhZ and HzZ collected the data from medical records and wrote the manuscript. ZqC analysed the pathological findings and revised the discussion. All authors read and approved the final manuscript.

Competing interests None declared.

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