

# CASE REPORT

ONLINE EXCLUSIVE

## > THE PATIENT

39-year-old man

## > SIGNS & SYMPTOMS

- Five-day fever
- Elevated creatinine levels
- Kidney transplant 10 months prior

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*The authors reported no potential conflict of interest relevant to this article.*

## > THE CASE

A 39-year-old man who had received a living non-related donor kidney transplant 10 months earlier presented with a 5-day history of fever, chills, myalgias, dysuria, and urinary urgency. His medications included mycophenolate mofetil 1 g PO bid, tacrolimus 2 mg PO bid, prednisone 5 mg/d PO, and nifedipine extended release 60 mg/d. He also took acyclovir 400 mg PO tid for a history of herpes simplex virus seropositivity in a kidney transplant patient, and trimethoprim/sulfamethoxazole double strength (800 mg/160 mg) PO daily for prophylaxis of urinary tract infections (UTIs). He reported sexual activity with his wife only and denied any new sexual partners. He also denied any missed medication doses.

On examination, the patient appeared to be in mild distress. His vital signs included: temperature 38.5°C, blood pressure 136/94 mm Hg, pulse 89 beats/min, and respiratory rate 18 breaths/min. Cardiopulmonary, abdominal, and genitourinary examinations were unremarkable. A well-healed scar was seen in the right lower quadrant at the site of the renal allograft and was nontender to palpation.

Laboratory values showed a white blood cell (WBC) count of  $4.3 \times 10^9/L$  and an elevated creatinine of 1.16 mg/dL. Six months prior to presentation, his creatinine was 0.98 mg/dL. Blood cultures were obtained, and ceftriaxone (1 g) was given prior to obtaining a urine specimen. A urine dipstick revealed moderate leukocyte esterase, small blood, and 30 mg/dL of protein. Urine microscopy showed >50 WBCs per high power field (hpf), 6-10 red blood cells (RBCs), 30 mg/dL of protein, and an absence of bacteria.

## THE DIAGNOSIS

Fever and urinary symptoms in a renal transplant patient may be due to acute graft pyelonephritis (AGP) or acute renal allograft rejection. Initial assessment should be focused on empiric treatment for infection while also evaluating for the possibility of rejection.

Patients with AGP present with lower urinary tract symptoms suggestive of cystitis (frequency, urgency, dysuria, hematuria, suprapubic pain) along with upper urinary tract symptoms (fever, chills, pain at graft site). However, since the kidney graft is denervated, lack of tenderness over graft site does not rule out pyelonephritis.<sup>1</sup>

This patient was hospitalized and continued on ceftriaxone. Renal ultrasound showed an 11-cm transplanted kidney without hydronephrosis and normal Doppler flow at the anastomotic sites of the renal artery and vein. On hospital Day 2, his urine and blood cultures were negative, but ceftriaxone was continued since it had been given prior to obtaining urine culture. The patient's tacrolimus level was slightly elevated at 15.6 mcg/L (therapeutic range: 5-15 mcg/L). He also tested negative for chlamydia and gonorrhea; a urine Wright stain was negative for eosinophils.

On hospital Day 4, the patient remained febrile, urinary symptoms persisted, and creat-

inine increased to 1.5 mg/dL. Tacrolimus was stopped and mycophenolate mofetil dosing was decreased to 500 mg PO bid, then 250 mg PO bid, and then stopped on hospital Day 5. Tacrolimus was reinitiated on hospital Day 6 at 1 mg PO bid.

Computed tomography (CT) of the abdomen and pelvis without contrast evaluating for a perinephric or renal abscess was negative. Antibiotic coverage was broadened to meropenem 1 g every 8 hours and vancomycin 1500 mg once, with levels to follow. Repeat urinalysis showed persistent pyuria and worsened hematuria and proteinuria. Urine protein to creatinine ratio was elevated at 1.3 mg/mg. Cystoscopy showed a normal urethra and multiple areas of erythema and edema in the bladder, which was consistent with cystitis.

Due to the lack of clinical improvement on broad-spectrum antibiotic coverage, other urinary pathogens, including BK virus, cytomegalovirus (CMV), fungi, and *Mycobacterium tuberculosis* (MTB), were considered. Serum qualitative polymerase chain reaction (PCR) for BK virus and CMV were negative. Quantitative PCR for BK virus revealed presence of <500 copies/mL of BK virus. Quantiferon gold, urine MTB PCR, and urine fungal culture were negative.

The presence of worsening hematuria raised suspicion for hemorrhagic cystitis due to adenovirus. Urine adenovirus PCR confirmed the diagnosis of AGP due to adenovirus.

## DISCUSSION

Acute graft pyelonephritis, also known as pyelonephritis of the renal allograft, can be categorized as early-onset (<6 months after transplant) or late onset (>6 months after transplant). Early-onset AGP is associated with bacteremia, pyelonephritis, and high rate of relapse,<sup>1-3</sup> whereas late-onset AGP is associated with increased risk of graft loss.<sup>4</sup>

In a renal transplant patient, UTIs are usually caused by the same gram-negative bacteria that cause UTIs in patients without a transplant.<sup>5</sup> Additionally, *Pseudomonas aeruginosa* and gram-positive bacteria such

as those within the *Enterococcus* species should be considered. *Candida albicans* is the most common fungal cause and is associated with urinary obstruction.<sup>6</sup>

Fungal culture, CMV PCR, and BK virus PCR should be considered in a patient who does not improve despite appropriate antibiotic coverage. Hematuria should raise concern for BK virus<sup>7</sup> and adenovirus. BK virus should be considered when treating patients on high doses of immune suppression, as there is an association between this infection and graft failure.<sup>7</sup> Rarely, MTB can cause AGP.<sup>8</sup>

■ **Empiric antibiotic coverage** includes broad-spectrum antibiotics against gram-negative enteric organisms, including *Pseudomonas aeruginosa*, and gram-positive organisms, including *Enterococcus* species. Although optimal duration of antibiotics for AGP is unknown, most nephrologists treat graft pyelonephritis due to a bacterial etiology for 10 to 14 days.<sup>1</sup> Complications include poor graft outcome and decreased long-term survival.

■ **Adenovirus infection** in a renal transplant patient is uncommon and typically presents with hemorrhagic cystitis. In rare cases, this infection can cause disseminated infection. Management is mostly supportive. Reduction of immunosuppression may be associated with viral clearance.<sup>9</sup> Cidofovir and intravenous immune globulin may be considered for patients with life-threatening adenovirus infection<sup>10</sup>; however, there are no large trials that show a clear benefit for patients with AGP due to adenovirus.

■ **Our patient's** urinary symptoms and fever resolved after 1 week of hospitalization with supportive measures and a reduction in immunosuppression, namely a reduction of the dosing of mycophenolate mofetil and tacrolimus. (Optimal changes in the dosing of immunosuppressive agents should be carried out under consultation with a transplant nephrologist.) However, our patient's creatinine remained elevated at 1.5 mg/dL. Given the low suspicion for graft rejection, biopsy of the kidney transplant was not performed. He returned to the nephrology clinic 3 months later with an improved creatinine of 1.1 mg/dL.

CONTINUED



**Fever and urinary symptoms in a renal transplant patient suggest either graft pyelonephritis or graft rejection.**

## THE TAKEAWAY

Fever and urinary symptoms in a renal transplant patient suggest either graft pyelonephritis or graft rejection. In addition to the usual gram-negative enteric organisms associated with pyelonephritis in a patient with native kidneys, clinicians should consider low-virulence gram-positive organisms, viruses, fungi, and mycobacteria as potential etiologies. The risks and benefits of reducing or discontinuing immunosuppressive medications in the setting of AGP should be discussed with a nephrologist.

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