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***Ureaplasma urealyticum* pyelonephritis presenting with progressive dysuria, renal failure, and neurologic symptoms in an immunocompromised patient**

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Abstract

Ureaplasma urealyticum is a bacterial species correlated with urethritis in healthy individuals and invasive infections in immunocompromised patients. We describe a 20-year-old female with a history of remote heart transplant on everolimus, mycophenolate, and rituximab presenting with progressive urinary tract symptoms, renal failure, and neurologic symptoms. An extensive workup ultimately identified *U. urealyticum* infection, and the patient successfully recovered after a course of azithromycin and doxycycline.

1 | CASE REPORT

A 20-year-old female with a history of a heart transplant 18 years prior presented to the emergency room with suprapubic pain, flank pain, and dysuria. She had undergone orthotopic heart transplantation at the age of 2 for familial dilated cardiomyopathy secondary to a titin mutation. Immunosuppression included tacrolimus and mycophenolate mofetil, and she had completed six doses of rituximab therapy for early post-transplant lymphoproliferative disease (PTLD) 7 months prior to presentation. On initial presentation, she complained of left flank and suprapubic pain, dysuria, and urgency for 3 days. Review of symptoms was significant for nausea, but the patient denied fever, vomiting, or respiratory symptoms. Initial clean-catch urinalysis demonstrated 1 + leukocyte esterase (LE), negative nitrites, and >20 WBCs/hpf, and she was discharged with empiric trimethoprim/sulfamethoxazole for presumptive urinary tract infection (UTI). A urine culture performed at that time showed <100 000 CFU/mL Group B *Streptococcus*. She returned the following day with worsening flank pain and new-onset vomiting and was found to have an acute increase in creatinine to 4.2 mg/dL from a recent baseline of 3.0. She had no unusual exposures, nor travel, and lived at home with her family while taking local college courses and working at a retail store. She reported being sexually active with consistent condom use. Her most recent intercourse was 2 weeks prior to presentation.

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AUTHORS' CONTRIBUTIONS

DJS, AE, and GAS were infectious disease consultants for the patient. DJS and DAR wrote the manuscript. AE and GAS reviewed the manuscript.

On physical examination, she was afebrile with heart rate 100–110 bpm, blood pressure 140/90 mm hg, and respiratory rate 36 breaths/min, and was generally uncomfortable. She had a 3/6 systolic ejection murmur in the left upper sternal border unchanged from previous examinations. Her abdominal exam was notable for tenderness to light palpation in the left flank and suprapubic region. Repeat urinalysis demonstrated 3 + LE and >50 WBCs/hpf (See Table 1). Renal ultrasonography demonstrated new left hydronephrosis. She was admitted on once daily intravenous ceftriaxone with presumptive diagnoses of pyelonephritis or nephrolithiasis, however, her repeat urine culture was finalized as no growth.

Despite broad spectrum antibiotics for 2 weeks with ceftriaxone and then cefepime, she had progressively worsening renal failure with creatinine peaking at 11.2 mg/dL necessitating hemodialysis. Concomitantly, she had increasing leukocytosis with a WBC peaking at 20 000 cells/mm³ with 81% neutrophils and C-reactive protein (CRP) peaking at 296 mg/L. Repeat urinalyses revealed ongoing pyuria but no growth of organisms (Table 1). Given her persistent flank pain and lack of response to beta-lactam antibiotics, we performed mycobacterial and fungal cultures, adenovirus and BK virus testing of urine, all of which were negative. Multiple abdominal ultra sounds and a computed tomography scan without contrast demonstrated bilateral increased renal echogenicity and pelviectasis. Two weeks into admission, she became febrile for the first time to 39.2°C and experienced altered mental status and seizure requiring transfer to the intensive care unit. Cerebrospinal fluid (CSF), blood, and urine cultures obtained at the time of fever were negative. Brain MRI was unrevealing and CSF analysis revealed 13 total cells, seven nucleated cells (76% lymphocytes, 23% monocytes, 1% neutrophils), glucose 95 mg/dL, and protein 64 mg/dL. Tests for HIV, gonorrhea, and chlamydia were negative. She was placed on continuous hemodialysis and kidney and bladder biopsies were obtained secondary to increasing peripheral uremia and creatinine (Table 1). The kidney biopsy revealed acute pyelonephritis, nonspecific focal segmental glomerulosclerosis, and severe interstitial fibrosis (Figure 1). Bladder biopsy demonstrated diffuse edema and mucosal inflammation, but histopathology and immunohistochemistry were negative for adenovirus, PTLN markers (CD20 and EBER), cytomegalovirus, and Epstein-Barr virus.

Antibiotic coverage was broadened to cefepime and vancomycin, and azithromycin (500 mg on day 1 and 250 mg on days 2–5) was added out of concern for potential *Mycoplasma* or *Ureaplasma* infection. PCRs for *Ureaplasma urealyticum*, *Ureaplasma parvum*, and *Mycoplasma hominis* were sent from urine to the Mayo clinic on day 25; *U urealyticum* was found to be positive (Table 1). When the *Ureaplasma* resulted, the patient was still critically ill with a leukocytosis, so an extended antibiotic course with 100 mg doxycycline BID was administered to continue *Ureaplasma* treatment. At the conclusion of this therapy, she had a negative urine PCR test for *U urealyticum*, return of her baseline renal function, and complete resolution of her symptoms and inflammatory markers. To date, she has not had recurrent symptoms of urogenital infection.

2| DISCUSSION

Ureaplasma urealyticum is a small urease-hydrolyzing member of the order Mycoplasmatales which includes *mycoplasmas* and *ureaplasmas* as the medically-relevant

organisms. *Ureaplasma* species commonly colonize the urogenital tract of women after the onset of sexual activity.¹ Generally, among otherwise healthy individuals, these organisms are asymptomatic colonizers. A recent meta-analysis of 2700 patients concluded that urogenital colonization with *U urealyticum* specifically correlated with nongonococcal urethritis in otherwise healthy patients.² Colonization with a closely-related species, *U parvum*, did not share this association. The treatment recommendations for *Ureaplasma* species are similar to those for the related genera *Mycoplasma*. As these Mycoplasmatales lack a cell wall, they are intrinsically resistant to all beta-lactam antibiotics and vancomycin. They are also resistant to sulfonamides based on in vitro susceptibility testing. Macrolides, doxycycline, and fluoroquinolones are the treatments of choice. Azithromycin has the added benefit of treating potentially concomitant chlamydial infections when the specific etiologic diagnosis is not yet established. Among isolates from a 5-month period from the Mayo clinic, the majority of *Ureaplasma* isolates had low minimum inhibitory concentrations (MICs) to azithromycin and doxycycline.³ Based on the Clinical and Laboratory Standards Institute (CLSI) breakpoints for these antibiotic-organism combinations and low MICs, azithromycin (1–2 µg/mL), ciprofloxacin (4 µg/mL), levofloxacin (1 µg/mL), and doxycycline (<0.125 µg/mL) are presumed to be effective.³ Thus, laboratory data support treating *Ureaplasma* with azithromycin, fluoroquinolones, or doxycycline.

In contrast to otherwise healthy individuals, immunocompromised patients often present with atypical or more invasive infections. One such population of immunocompromised individuals is solid organ transplant recipients. Ekiel et al⁴ found increased *Ureaplasma* and *Mycoplasma* urogenital colonization of kidney transplant and dialysis patients compared with age-matched controls. They found a fourfold increase in *U urealyticum* colonization among transplanted and dialysis patients as well as a 50% increase in any Mycoplasmatale. They did not investigate whether these individuals experienced more urogenital symptoms than the control group, but this research suggests that immunocompromised states may predispose for increased Mycoplasmatale colonization. Furthering this research, Gerber et al⁵ isolated Mycoplasmatale in urine culture from asymptomatic and symptomatic renal transplant patients. Renal transplantation compounded by combined variable immune deficiency resulted in a disseminated *U urealyticum* infection including intra-abdominal abscess.⁶ Eilers et al⁷ reported a 19-year-old female with a kidney transplant who developed renal abscesses with 16S sequencing revealing *U urealyticum* within the transplanted kidney. That patient had repeated positive tests for *Ureaplasma*, whereas our patient had a single positive test, which may reflect an increased burden of organism in a renal abscess vs uncomplicated pyelonephritis. Similar to our case, that patient was treated initially with cephalosporins and had an increase in CRP. Interestingly, both patients were recently treated with rituximab for PTLN.

Rituximab may increase the risk of *Ureaplasma* infection by an unknown mechanism, given the five other reports of severe *Ureaplasma* infection in the context of recent or ongoing rituximab therapy.^{7–11} One hypothesis for the rituximab effect is by reducing immune globulins peripherally. Indeed, many of these patients with severe *U urealyticum* infections were hypogammaglobulinemic from rituximab^{7–11} or congenital absence of gammaglobulins.^{6,12} Our patient had normal immune globulins measured 3 months prior to her current presentation as did the patient identified in Gerber et al.⁵ Therefore, further

research is necessary to determine the mechanism by which rituximab increases susceptibility to *Ureaplasma* infection. While individual treatment regimens differed in these case studies of immunocompromised patients, most clinicians prescribed doxycycline or a macrolide. Thus, *U. urealyticum* can cause invasive disease in the context of solid organ transplantation or from general immunosuppression and may be more serious following rituximab therapy.

We have presented a 20-year-old immunosuppressed female with progressive urinary tract symptoms, physical findings, and laboratory abnormalities not responsive to typical antibiotic therapy. This case highlights the necessity of considering atypical organisms in the immunosuppressed patient who presents with urinary tract symptoms and negative culture results. Based on our experience, we recommend evaluating *U. urealyticum* in immunosuppressed patients presenting with signs and symptoms of a UTI in whom no bacteria grow via conventional culture methods and beta-lactam therapy is unsuccessful. PCR based methods or metagenomic sequencing of clinical samples can often yield a diagnosis in puzzling clinical presentations.

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Neutrophilic tubulitis and
white blood cell cast

Focal segmental glomerulosclerosis

Severe interstitial fibrosis

Normal arteriole

FIGURE 1.

Kidney biopsy demonstrating acute pyelonephritis, focal glomerulosclerosis, interstitial fibrosis as well as a normal renal arteriole

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TABLE 1

Laboratory trend

	Day 0	Day 1	Day 5	Day 13	Day 21	Day 23	Day 29	Day 34	Day 96
Urine LE	1+	3+	2+	3+	3+	ND	ND	ND	Negative
Urine WBC/hpf	>50	>50	>50	>50	>50	ND	ND	ND	ND
Urine testing	Cx: insig. growth	Cx: no growth	ND	Cx: no growth	Cx: no growth	ND	<i>Ureaplasma</i> PCR: positive	<i>Ureaplasma</i> PCR: negative	Cx: no growth
Blood urea nitrogen	41	38	34	38	61	38	11	33	39
Creatinine (mg/dL)	3.9	4.2	6.2	5.8	11.2	8.0	2.7	7.9	4.7
Peripheral WBC	14.0	12.3	11.6	17.3	16.9	20.0	18.6	13	8
CRP(mg/L)	ND	ND	ND	244	296	184	ND	11	ND
Current antibiotic	None	TMP/SMX	Ceftriaxone	Cefepime	None	Cefepime	Cefepime	Vancomycin	Doxycycline

hpf, high power field; LE, leukocyte esterase; ND, not done; TMP/SMX, trimethoprim/sulfamethoxazole.