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RESEARCH LETTER

Pyelonephritis is an Underrecognized Cause of CKD in Patients With Orthotopic Ileal Neobladder Substitution

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INTRODUCTION

Radical cystectomy with urinary diversion, with or without cisplatin-based neoadjuvant chemotherapy, is the current standard of care for nonmetastatic muscle invasive bladder cancer.[1] Orthotopic ileal neobladder is a type of continent urinary diversion that utilizes an intestinal segment as the anatomical and functional substitution of the urinary bladder (Supplementary Figure S1). Compared to ileal conduit, ileal neobladder has the advantage of achieving spontaneous voiding and urinary continence. However, it can be associated with multiple short-term and long-term postoperative complications, including recurrent urinary tract infection (UTI), ileo-ureteral anastomotic strictures, bladder neck or urethral strictures, ureteral reflux, and incontinence.[2] Chronic kidney disease (CKD) has been increasingly recognized as an important long-term complication in patients with ileal neobladder substitution.[3,4] Urinary obstruction and UTI have been identified as risk factors for long-term kidney function decline; however, the spectrum of CKD etiology and the associated clinical phenotypes in this population have not been previously reported.[4,5] To better understand the incidence, clinical, and pathological characteristics of CKD after ileal neobladder substitution, we performed a cohort study including all patients with high grade bladder cancer who underwent radical cystectomy with orthotopic ileal neobladder substitution between August 2001 and March 2022 at Mass General Brigham.

RESULTS

Among the 169 patients who underwent radical cystectomy and ileal neobladder substitution and had at least 1-year of follow-up (Supplementary Methods, Supplementary Figure S2), mean age was 58 years (SD 9.7), 150 (89%) were male, 159 (94%) were White, non-Hispanic. The mean baseline estimated glomerular filtration rate (eGFR) was 75 ml/min per 1.73 m^2 (SD 20) and 47 patients (28%) had stage 3 CKD preoperatively (Supplementary Table S1). During a median follow-up of 44 months (interquartile range 26–78 months), 26 patients (15%) developed progressive CKD, including 2 patients who were started on hemodialysis (1%); median time-to-progressive CKD was 27 months (interquartile range 12–39). Estimated annual eGFR decline of the entire cohort was 3.5 mL/min per 1.73 m^2 (95% confidence interval, 2.3–4.6) using a mixed effect linear model. A graph of the annual average eGFR of the entire cohort is shown in Supplementary Figure S3.

The most common nephrologist-adjudicated cause of CKD was urinary obstruction (13 cases, 50% of patients with progressive CKD): 6 patients had anastomotic

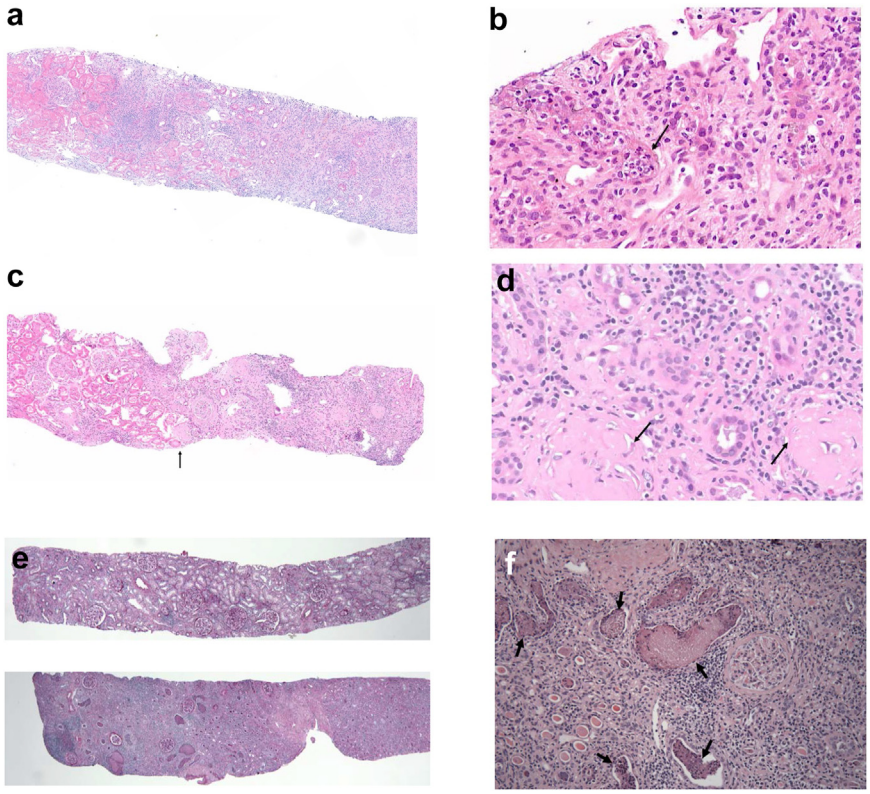

Figure 1. Kidney pathology in patients with biopsy-proven pyelonephritis. Kidney pathology of patient 1 is shown in in Figure 1a and 1b whose clinical course is described in Figure 2a. 1a shows diffuse interstitial inflammation (low power, H&E) and 1b shows neutrophil cast characteristic of acute pyelonephritis (high power, H&E). Patient 2 is shown in in Figure 1c and 1d whose clinical course is described in Figure 2b: 1c shows abrupt transition of preserved renal parenchyma to tubular atrophy and interstitial fibrosis from left side of the core to the right (low power, H&E), and 1d shows global sclerosis of the glomeruli (arrows) with predominantly lymphocytic infiltrate (high power, H&E). Patient 3 is shown in Figure 1e and 1f whose clinical course is described in 2c: 1e shows renal cortex with preserved parenchyma and minimal nonspecific focal tubular atrophy (top core, low power, PAS), whereas the bottom core reveals a chronic active inflammatory infiltrate that has resulted in extensive tubular atrophy and early interstitial fibrosis (bottom core, low power, PAS). 1f shows cortical tissue with several distended tubules that contain necrotic debris and degenerated neutrophils (neutrophil casts, black arrows); the interstitium is occupied predominantly by mononuclear cells (lymphocytes and plasma cells) with isolated neutrophils (high power, H&E). The focal nature of the processes (indicated by 1c and 1e) was highly suggestive of bacterial infection due to urinary reflux. H&E, hematoxylin and eosin; PAS, periodic acid-schiff.

strictures (ileo-ureteral stricture ± bladder outlet obstruction), 5 had malignant obstruction due to cancer recurrence, and 2 had both benign ileo-ureteral stricture and malignant obstruction (Supplementary Table S2). There were 2 patients who experienced CKD attributed to chemotherapy nephrotoxicity, and 1 case had progressive CKD attributed to advanced heart failure. There were 10 cases of unexplained CKD, 4 of which lacked sufficient electronic medical record documentation to allow adjudication of the CKD etiology. Among the 6 unexplained CKD cases with adequate medical record documentation, 3 underwent kidney biopsy, and each showed interstitial nephritis, with pathological features consistent with ascending bacterial pyelonephritis, including neutrophil casts, focal inflammation alternating with normal interstitium. Biopsy findings are shown in Figure 1, and each patient's corresponding clinical course is shown in Figure 2 and Supplementary Table S2. All 3 patients with biopsy-proven pyelonephritis presented with subacute rise in serum creatinine in the setting of chronic bacteriuria and each lacked imaging evidence of urinary obstruction. None were suspected to have pyelonephritis at the time of biopsy (each lacked typical symptoms including fever, flank pain, dysuria, and absence of leukocytosis); rather, fatigue was the predominant symptom. All had elevated inflammatory markers including erythrocyte sedimentation rate and/or C-reactive protein. In patient 1 and patient 2, prolonged antibiotic therapy led to partial improvement and stabilization of serum creatinine; and in patient 3, serum creatinine stabilized after cessation of atezolizumab, corticosteroids, and antibiotic treatment.

Furthermore, extended follow-up for patient 1 demonstrated a correlation between rise in erythrocyte

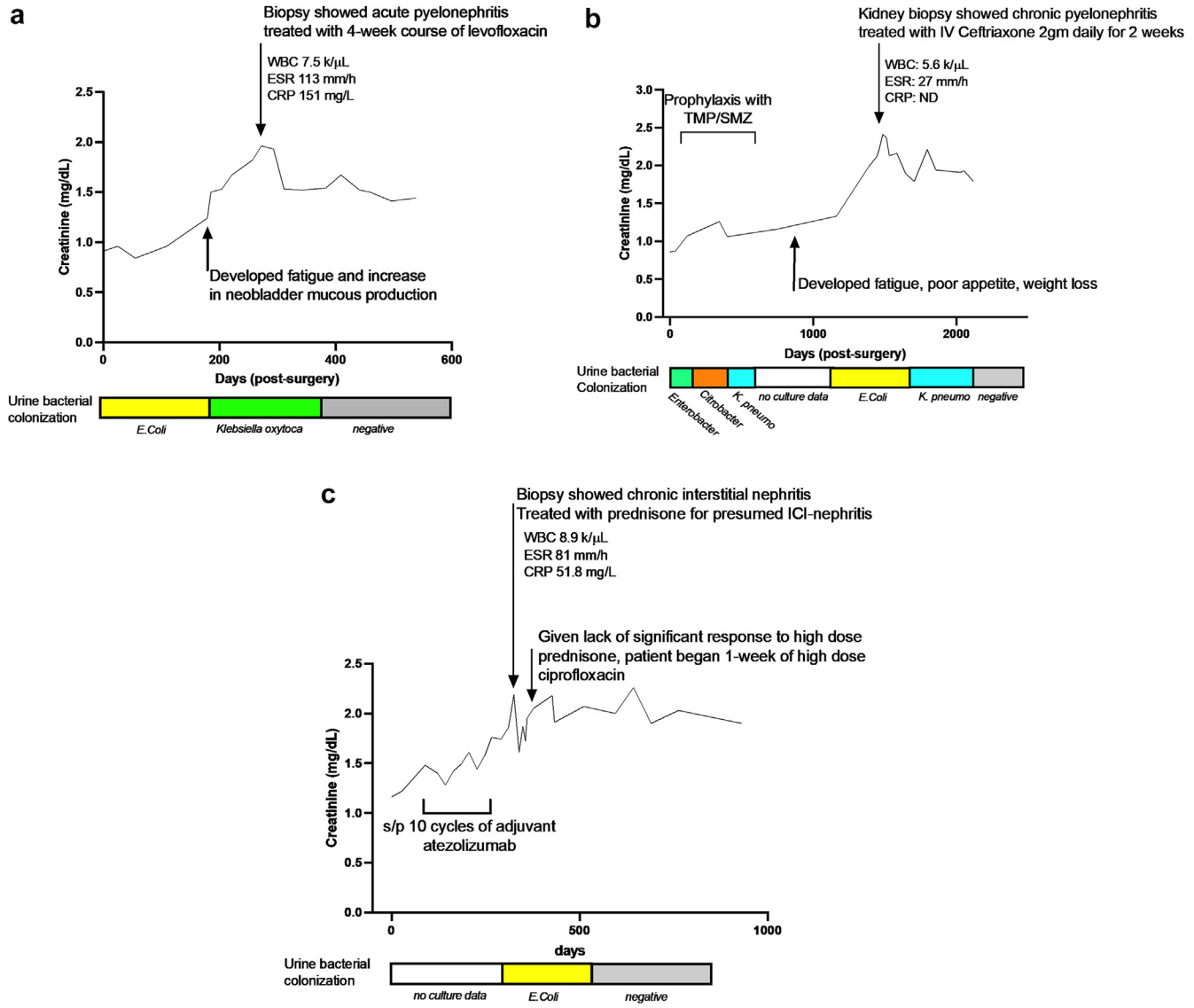

Figure 2. Clinical course in patients with biopsy-proven pyelonephritis. Creatinine trend, clinical course, and urine culture results in patients with biopsy-proven pyelonephritis. Color scheme at the bottom of each graph represents urine bacterial colonization at different time-periods. ESR/CRP trend during extended follow-up of patient 1 was shown in Supplementary Figure S4. ESR/CRP was not trended in patient 2 and patient 3. In patient 3, immune checkpoint inhibitor-associated interstitial nephritis was initially diagnosed in the context of atezolizumab (anti-PDL1) use, and steroid treatment was started; however, given the lack of sustained improvement in kidney function after approximately 4 weeks of high dose steroids, and careful reexamination of the biopsy demonstrating neutrophil casts (Figure 1e), focal inflammation alternating with normal interstitium (Figure 1f), and positive urine culture for *E. Coli*, the diagnosis of pyelonephritis was favored and treatment with high dose ciprofloxacin (500 mg twice daily) began. The patient's kidney function stabilized with cessation of atezolizumab, corticosteroids, and antibiotic treatment, though did not show a significant improvement. ESR, erythrocyte sediment rate; CRP, C-reactive protein; TMP/SMZ, trimethoprim/sulfamethoxazole; *K. pneumo*, *Klebsiella pneumonia*; *E. Coli*, *Escherichia coli,* WBC, white blood cell count, ND, not done.

sedimentation rate and C-reactive protein concurrent with a positive urine culture and increase in serum creatinine, suggesting these inflammatory markers may be useful for monitoring of recurrent active pyelonephritis when typical clinical symptoms are absent (Supplementary Figure S4). Of the 3 remaining cases with unexplained CKD that did not undergo biopsy, all had persistent urinary bacterial colonization and recurrent UTI episodes. Case summaries of patients who developed progressive CKD are shown in Supplementary Table S2.

DISCUSSION

CKD is an important long-term complication following radical cystectomy and ileal neobladder substitution.[6,7,S1] In our study, we found that 15% of patients developed progressive CKD during a median follow-up of 44 months,

with an estimated average annual eGFR decline of 3.5 mL/min per 1.73 m^2. Consistent with previous literature, we found that urinary obstruction was the most common cause of progressive CKD in this population.[4] In addition, we identified a subset of patients with "unexplained progressive CKD" (23%, 6/26 cases), and somewhat surprisingly, acute and chronic pyelonephritis was found on all 3 patients who underwent kidney biopsy. The fact that all 3 biopsy-proven cases lacked typical symptoms of pyelonephritis and prolonged antibiotic treatment led to improvement and stabilization of kidney function highlights that pyelonephritis may be an underrecognized cause of progressive CKD in patients with ileal neobladder substitution. For the 3 other cases of "unexplained CKD" that did not undergo kidney biopsy, we hypothesize that their progressive CKD could also be due to pyelonephritis with subsequent renal parenchymal scarring in the setting of recurrent overt/indolent upper tract UTI.

Although urinary obstruction and recurrent UTIs are both common complications following ileal neobladder substitution that are associated with long-term kidney function decline,[2,3] it is difficult to isolate the independent effects that each may have on kidney function. Urinary obstruction promotes the development of UTIs, and recurrent UTIs may increase the risk of developing anastomotic strictures.[S2] In our study, we identified a subset of patients without evidence of obstruction who developed progressive CKD in the setting of chronic bacteriuria, with pyelonephritis demonstrated in all who underwent kidney biopsy. One potential explanation for this observed association between chronic bacteriuria and CKD is the high prevalence of urinary reflux (affecting >50%) in patients with ileal neobladder substitution; and chronic reflux of the bacteriuric urine could be a predisposing factor for recurrent low-grade upper tract infections that eventually lead to renal parenchymal scarring.[S3–S8]

Bacterial colonization is extremely common following ileal neobladder substitution: more than half of patients have at least 1 positive urine culture within 30 months after surgery,[8] and between 20% and 40% of patients develop symptomatic UTI requiring antibiotic treatment within the first 2 years.[2,8,S9–S11] Differentiating UTI versus asymptomatic bacteriuria can be challenging in patients with ileal neobladder substitution: symptoms of UTI are often atypical and dysuria is less common due to altered nerve innervation; instead, fatigue, malaise, back pain, and increased mucus production are among the most commonly reported UTI symptoms.[9] The high prevalence of bacterial colonization and nonspecific clinical symptoms of infection pose diagnostic challenges which may lead to undertreatment of UTI.[S12] When this is combined with the inherent high risk of urinary reflux after ileal neobladder substitution, the risk of upper tract infection could be substantial.[S3]

Our study has several limitations. First, there is variability among providers in clinical diagnosis of UTI and the threshold for performing urine cultures, and there may be a selection bias in identifying patients with persistent/chronic bacteriuria. Second, we did not perform detailed chart review in patients with stable kidney function, and there could be a subset of patients who did not meet our definition of progressive CKD and had smaller degrees of eGFR decline in the setting of chronic bacteriuria. Third, even among patients with CKD attributed to chronic urinary obstruction, subclinical pyelonephritis may have contributed to the kidney function decline given urinary stasis and the high rates of urinary bacterial colonization. Given that these patients are unlikely to undergo kidney biopsy, we may have underestimated the incidence of this complication.

In conclusion, our study suggests that pyelonephritis may be an underrecognized cause of CKD in patients with ileal neobladder substitution. Clinical diagnosis of pyelonephritis in patients with ileal neobladder could pose a significant challenge given the high prevalence of bacteria colonization and its subclinical presentation. Clinical consequence and threshold for antibiotic treatment of "asymptomatic" bacteriuria, especially in those who experience subacute kidney function decline, may need to be reevaluated.

DISCLOSURE

MES is funded by NIH R01DK130839, and participated in a scientific advisory boards for Mallinckrodt, Travere, and Novartis; and had research funding from Angion, EMD-Serono/Merck, Gilead, and AbbVie. SG reports research support from BTG International, and GE Healthcare; and serves as the consultant for GlaxoSmithKline and Secretome. All the other authors have declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Figure S1. Illustration of orthotopic ileal neobladder and common locations of mechanical obstruction.

Figure S2. Patient flow.

Figure S3. Average annual eGFR trend in patients with ileal neobladder substitution.

Figure S4. Monitoring of recurrent pyelonephritis using inflammatory markers (ESR, CRP) in patient 1.

Table S1. Baseline characteristics.

Table S2. Case summaries of patients with progressive CKD.

Supplementary References.

STROBE Checklist.

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