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Alkaline-Encrusted Pyelitis in a Renal Allograft

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INTRODUCTION

Alkaline-encrusted pyelitis is an infectious disease of the renal pelvicalyceal system characterized by calcific encrustation of the urothelium. *Corynebacterium urealyticum* (*C urealyticum*) has been identified as the causative organism. This slow-growing, gram-positive bacillus is a skin commensal with a tropism for uroepithelial cells.[1] As a urease-producing organism, *C urealyticum* converts urea to ammonia within the urinary tract. The resultant alkalinization of urine causes precipitation of struvite and calcium phosphate along the mucosal surface of the renal pelvis.[2]

The initial presentation is often nonspecific, but commonly reported clinical features include hematuria, fever, and declining renal function.[3–5] Diagnosis is based on the triad of an alkaline urine, positive cultures for *C urealyticum,* and urothelial calcification on noncontrast computed tomography (CT).[6] However, diagnosis is often delayed. *C urealyticum* is a fastidious organism that will not grow using routine culture methods.[7] Unless there is a specific request for prolonged culture using enriched media, the urine will be reported as sterile.[1] A high index of clinical suspicion is therefore vital. Both renal allograft loss and patient mortality have been reported due to a delay in diagnosis.[3,4,8]

Treatment is aimed at eradicating *C urealyticum* with antibiotic therapy and dissolving the encrusted material by urinary acidification.[2] The duration of treatment is ill defined, but prolonged hospital admission with i.v. antibiotic administration for 4 weeks has been reported.[2,9]

We present a case of alkaline-encrusted pyelitis in a kidney transplant recipient successfully managed with a predominantly home-based treatment regimen.

CASE PRESENTATION

A 55-year-old woman was admitted with malaise and visible hematuria 18 months after a living donor kidney transplantation. These symptoms had been present for several weeks and had failed to resolve with oral antibiotic therapy. The patient had a history of spina bifida and neurogenic bladder, with ileal conduit formation in childhood. Refractory urolithiasis and subsequent nephrectomies had rendered her hemodialysis dependent 3 years prior to transplantation. *Escherichia coli* (*E coli*) bacteriuria had been demonstrated consistently on cultures at routine transplantation follow-up, and antibiotics were prescribed on 4 occasions when there were symptoms of infection.

Several complications developed in the post-transplantation period. At month 4, new-onset diabetes mellitus necessitated the introduction of an oral hypoglycemic agent. Prednisolone (which had been rapidly tapered and subsequently withdrawn by week 5) was reintroduced in preference to mycophenolate following the development of leukopenia 8 weeks postoperatively. This leukopenia was persistent despite maintenance immunosuppression with prednisolone 7 mg once daily and tacrolimus 4 mg twice daily. A combination vitamin D−calcium preparation had been commenced for osteoporosis prevention 6 months prior to admission.

On physical examination, there was no fever, the graft was nontender, and the ileal conduit appeared healthy. There was visible hematuria. Laboratory test results revealed acute graft dysfunction with an elevation in serum creatinine from a baseline of 0.9 mg/dl to 3.61 mg/dl. Additional results, which are summarized in Table 1, demonstrated a C-reactive protein level of 72.7 mg/l, hemoglobin of 9.3 g/dl, and white cell count of 2.0 × 10^3/μl. An ultrasound of the allograft showed a large amount of calcification within the mid and lower pole calyces suggestive of a staghorn calculus. There was associated dilatation of the upper pole calyces.

The working diagnosis was of a calculus within the graft, causing urinary obstruction and pyelonephritis. A nephrostomy tube was inserted. Urine cultures were

Table 1. Summary of laboratory results

Laboratory variable	On admission	5-mo Follow-up	Reference range
Hemoglobin	9.3 g/dl	11.7 g/dl	11.5–16.5 g/dl
White blood cells	2.0 × 10^3/μl	10.2 × 10^3/μl	4–11 × 10^3/μl
Neutrophils	1.24 × 10^3/μl	9.27 × 10^3/μl	1.5–8 × 10^3/μl
Lymphocytes	0.39 × 10^3/μl	0.63 × 10^3/μl	1–4.8 × 10^3/μl
Platelets	267 × 10^3/μl	236 × 10^3/μl	150–450 × 10^3/μl
Sodium	140 mmol/l	144 mmol/l	133–146 mmol/l
Potassium	6.6 mmol/l	5.1 mmol/l	3.5–5.3 mmol/l
Chloride	111 mmol/l	108 mmol/l	95–108 mmol/l
Bicarbonate	12 mmol/l	20 mmol/l	22–29 mmol/l
Creatinine	3.61 mg/dl	1.18 mg/dl	0.51–0.95 mg/dl
Calcium	2.31 mmol/l	2.46 mmol/l	2.2–26 mmol/l
Phosphate	1.7 mmol/l	1.09 mmol/l	0.8–1.5 mmol/l
C-reactive protein	72.7 mg/l	23.3 mg/l	0.1–5 mg/l
Urine albumin/creatinine ratio	378 mg/g	120 mg/g	<30 mg/g
Urine pH	>9.0	5.0	5.0–8.0

sent prior to empirical treatment with piperacillin/tazobactam. Vitamin D−calcium supplementation was discontinued. The noncontrast computed tomographic scan images were consistent with widespread calcific material (Figure 1). Initially, this was reported as a staghorn calculus, although there was caution with the interpretation, as nephrostomy tube insertion with contrast injection had occurred 24 hours earlier.

In the following days, the patient became oliguric with rising creatinine and C-reactive protein. A nephrostogram demonstrated free passage of contrast from the renal pelvis into the ileal conduit without entering the calyces. Repeated flushing and aspiration of the nephrostomy tube with saline removed a substantial amount of debris from the calyces, with subsequent improvement in radiological appearances. Urine output improved and creatinine began to fall after this intervention, but there was no improvement in C-reactive protein despite broad-spectrum antibiotic treatment. Urine cultures demonstrated no growth.

At this point, a comprehensive review of imaging raised the possibility of alkaline-encrusted pyelitis as a unifying diagnosis. The plausibility of this was supported by a urinary pH >9.0. Repeat culture of the initial urine sample identified the presence of *C ureolyticum* and confirmed the diagnosis. Vancomycin was substituted for piperacillin/tazobactam, and acidification

Table 2. Teaching Points

- Alkaline-encrusted pyelitis is a rare infectious disease characterized by deposition of struvite within the renal pelvis
- Renal transplant recipients are at particular risk due to immunosuppression use and an increased prevalence of urological abnormalities
- The diagnosis must be considered in any recipient displaying urinary symptoms associated with culture-negative, alkaline urine and calcification of the urothelium on unenhanced computed tomography
- Home-based therapy is an option for suitable patients to avoid prolonged hospitalization

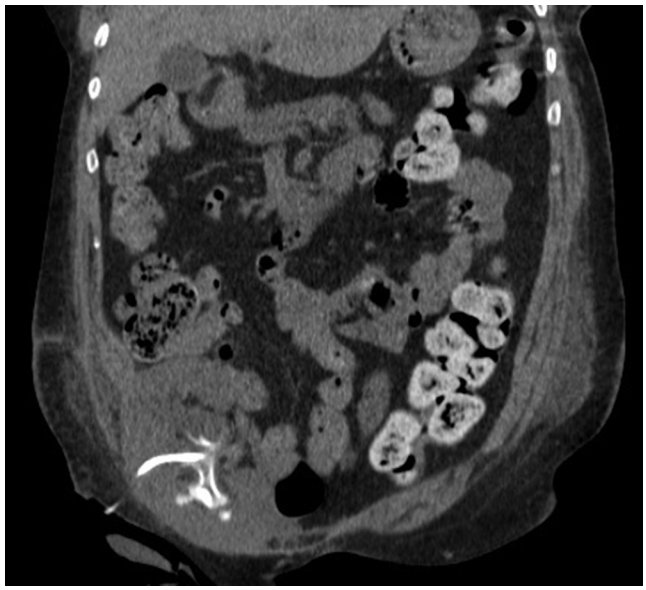

Figure 1. Computed tomographic scan prior to treatment demonstrating a nephrostomy tube *in situ,* with a thin layer of calcification involving the calyces, renal pelvis, and proximal ureter in the transplant kidney.

of urine was undertaken. It was hypothesized that direct acidification of urine within the renal pelvis was more likely to be effective than use of oral agents. Therefore, 200 ml of Suby G solution (citric acid, magnesium oxide, sodium bicarbonate, and sterile water) was administered via the nephrostomy tube 4 times daily. To achieve this, a solution-containing bag was attached to the nephrostomy tube via a connector and stop-cock, before being elevated so that administration occurred by gravity.

Resolution of the hematuria and improvement in inflammatory markers followed the instigation of appropriate treatment for encrusted pyelitis. To facilitate hospital discharge, the patient was trained to self-administer Suby G solution, and antibiotic therapy was switched to oral with doxycycline, based on organism sensitivities. At the time of discharge, the serum creatinine had fallen to 1.73 mg/dl and C-reactive protein to 12.3 mg/l. A follow-up nephrostogram 6 weeks later confirmed that much of the calcification had resolved. The nephrostomy tube was removed and Suby G administration discontinued.

Five months later, the patient was clinically well and free of urinary symptoms. Her serum creatinine was 1.18 mg/dl and urinary pH was 5.0, obviating the need for an oral acidification agent. Prophylactic doxycycline was continued. A computed tomographic scan demonstrated only a small area of residual calcification at the lower pole calyx (Figure 2). Notably, the leukopenia has resolved and mycophenolate has been reintroduced without concern, allowing withdrawal of prednisolone.

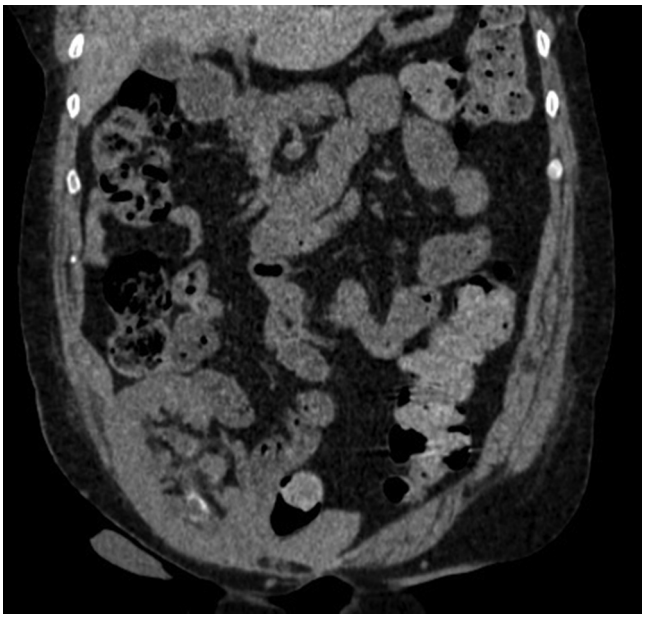

Figure 2. Computed tomographic scan following treatment, showing almost complete radiological resolution, with a small area of residual calcification in the lower pole of the transplant kidney.

DISCUSSION

Although it can occur in native kidneys, encrusted pyelitis was first described as a complication of renal transplantation.[10,11] Even amongst renal transplant recipients, who are at increased risk, it is rare, with a reported incidence of 0.2%.[12]

Risk factors for its development include immunosuppression, prior urological procedures, broad-spectrum antibiotic use, and a history of urinary tract infections.[12–14] In the present case, all of these predisposing factors were evident, and the patient was further immunocompromised by the presence of post-transplantation diabetes mellitus and leukopenia. However, there was a delay before the diagnosis was suspected and then subsequently confirmed.

Reaching a diagnosis of alkaline-encrusted pyelitis is challenging, despite the clearly defined diagnostic triad of alkaline urine, *C urealyticum* on culture, and urothelial calcification on imaging. The clinical features are nonspecific, and, in many cases, as in this report, the urine will be reported as sterile due to the fastidious nature of *C urealyticum*.[9] Indeed, as a skin commensal, *C urealyticum* may be cultured but reported as a contaminant.[3] To avoid a delayed or even missed diagnosis, the clinician must be aware of this condition and the factors that predispose to its development (Table 2). Prolonged cultures for the causative organism must specifically be requested.[7]

It is notable in this case that leukopenia, which had persisted for 12 months prior to admission, resolved with appropriate treatment. This has not previously been reported in relation to infection with *C urealyticum*. However, bacterial infection is an uncommon but recognized cause of leukopenia. It is vital that leukopenia acts as an additional alert to the transplant physician to consider the possibility of occult infections, such as alkaline-encrusted pyelitis, at an earlier stage.

The treatment of alkaline-encrusted pyelitis, in the first report by Morales *et al*. in 1992, involved surgical removal of the encrustations alongside other approaches.[11] Conservative management is now advocated.[9] Chemolysis of encrusted struvite is undertaken by administration of an acid solution directly into the renal pelvis via a nephrostomy tube, ensuring that adequate drainage is present. This can be supplemented with the use of oral agents.[2] *C urealyticum* must be targeted simultaneously with an antimicrobial agent. It is known to be multidrug resistant but universally sensitive to glycopeptides.[15] Use of vancomycin is frequently reported.[3,8,11,16] The duration of treatment is adjusted according to disease severity and response but is often up to 4 weeks.[2,9]

In this case, both the patient and staff were keen to avoid prolonged hospitalization, so alternative strategies were considered to facilitate ongoing treatment at home. Due to the position of renal allografts anteriorly in the pelvis, the attached nephrostomy tube is easily accessible. It was therefore possible for the patient to self-administer Suby G solution once shown how to do so. The patient had independently performed home hemodialysis via a central venous catheter for 3 years prior to transplantation, with no recorded episodes of catheter-related infection. Fortunately, this background allowed her to become rapidly reaccustomed to attaching devices under aseptic technique.

Although *C urealyticum* is usually sensitive to doxycycline,[7] there is a concern that tetracycline activity *in vivo* is lowered by an alkaline pH.[17] However, the concurrent acidification of urine negated this issue. By tailoring the established treatment for alkaline-encrusted pyelitis to the patient, her wish for home-based therapy was respected and associated health care costs reduced.

CONCLUSION

To our knowledge, this is the first report of successful treatment of alkaline-encrusted pyelitis using a home-based regimen of oral antibiotics and patient self-administration of Suby G solution. Despite an extensive review of existing literature, we were unable to locate any previous reports of a patient being trained to self-administer therapy via a nephrostomy tube for this, or any other, condition.

DISCLOSURE

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