Multifocal bacterial osteomyelitis in a renal allograft recipient following urosepsis

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ABSTRACT

Non-tubercular bacterial osteomyelitis is a rare infection. We report on a renal allograft recipient with osteomyelitis complicating urosepsis, manifesting as a multifocal infection poorly responsive to appropriate antibiotics and surgical intervention and culminating in graft loss.

Key words: *Escherichia coli*, osteomyelitis, renal transplant, urinary tract infection

Introduction

Urinary tract infections (UTIs) are the most common post-transplant infections[1] and the portal for upto 40% of post-transplant sepsis.[2] Previously thought to be benign, late post-transplant UTIs adversely impact patient survival,[3] reduce graft survival,[4] cause residual scarring and compensatory hyper-filtration and reactivate latent cytomegalovirus (CMV) infection.[1] A renal allograft recipient with multifocal osteomyelitis secondary to *Escherichia coli* urosepsis is discussed here.

Case Report

P, a 25-year-old male with unknown native kidney disease, underwent renal transplantation from his haplomatched mother in June 1990. His initial immunosuppression was prednisolone and azathioprine, to which cyclosporine was added as rescue therapy following a steroid resistant acute vascular rejection in the 5th month post-transplant, at which time serum creatinine was 2.6 mg/dl. Chronic rejection was confirmed on graft biopsy done in 1997, and by 1999, he had reached end stage kidney disease, was initiated on haemodialysis, and underwent a second renal transplant 8 months later, from his single antigen matched aunt at another center. Immunosuppression consisted of prednisolone, azathioprine and cyclosporine and his post-transplant period was uneventful until January 2005 when evaluation for nephrotic range proteinuria revealed mild graft hydronephrosis, which was not investigated further. There was no prior history of UTI or opportunistic infections.

In April 2005, he was treated with ofloxacin for 2 weeks, intravenous (IV) cefaperazone 1 g twice daily for 10 days and nitrofurantoin 100 mg thrice daily for 15 days for a relapsing *E. coli* UTI. In June 2005, when fever recurred, he came to our center. Blood and urine grew *E. coli* susceptible to carbapenems, nitrofurantoin and aminoglycosides, and he received imipenem for 2 weeks, resulting in sterile urine. A micturating cystourethrogram showed grade 4 vesico-ureteric reflux into the graft with mild hydronephrosis. He received antibiotic prophylaxis with nitrofurantoin and was planned for ureteric re-implantation if UTI recurred. Immunosuppression consisted of prednisolone 10 mg/D, azathioprine 125 mg/D and cyclosporine 50 mg twice daily (trough of 85 ng/ml). He discontinued prophylaxis after 6 months, but it was re-instated in May 2006, for asymptomatic bacteruria with *E. coli* susceptible to cefuroxime and nitrofurantoin.

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Access this article online	
Quick Response Code:	Website: www.indianjnephrol.org
	DOI: 10.4103/0971-4065.132022

In November 2006, he developed high grade fever lasting a month, which was empirically treated with cefepime, ampicillin and cloxacillin for 10 days without benefit and returned to our center with fever and pain over the right upper tibia. X-ray showed multiple lytic lesions in the tibial tuberosity consistent with acute osteomyelitis [Figure 1] and pus grew *E. coli* susceptible to imipenem and amikacin. As fungal, mycobacterial and anaerobic cultures of pus and blood and urine cultures were sterile, a diagnosis of primary osteomyelitis was made, surgical drainage was carried out and IV imipenem 1 g twice daily commenced. Although on imipenem, he developed left tibial osteomyelitis requiring surgical drainage. Bone scan showed no lesions elsewhere with no evidence of infective endocarditis on transthoracic and transesophageal echocardiography. He received a 2-month course of valgancyclovir for CMV viremia (7961 copies/ml of blood) and azathioprine reduced to 50 mg/D.

As both legs continued to suppurate, he underwent bilateral surgical decompression and insertion of gentamicin beads into the right tibia in February 2007. By June 2007, despite 7 months of IV imipenem, osteomyelitis had progressed to involve the ankles, humeri, iliac bones, scapula, sternum, clavicles and both femurs [Figure 2]. Radical limb amputation was not considered due to the multifocal nature of the disease. Azathioprine was withdrawn and Imipenem continued. In October 2007, he underwent sequestrectomy, curettage and gentamicin bead insertion for persistent left tibial discharge. A second course of valganciclovir was given for CMV retinitis without CMV viremia, following which the lesions healed.

Graft function steadily declined due to a combination of recurrent UTI, graft reflux, secondary glomerulosclerosis, compensatory hyperfiltration and chronic rejection secondary to suboptimal immunosuppression, and by January 2008, serum creatinine having increased to 4.5 mg/dl, immunosuppression was further reduced to prednisolone 5 mg daily and IV carbapenems discontinued after a graft biopsy revealed diffuse global glomerulosclerosis. Three months later, afebrile and asymptomatic for his bone lesions, he was initiated on maintenance hemodialysis, switched to continuous ambulatory peritoneal dialysis in October 2008 and had no recurrence of osteomyelitis after 5 years.

All *E. coli* isolates had similar disk diffusion readings and minimum inhibitory concentration breakpoints and were positive for extended-spectrum beta-lactamase production. The modified Hodge test for production of carbapenamase and *bla*KCP polymerase chain reaction for *Klebsiella pneumoniae* carbapenamase (courtesy Dr. Jean Patel, Antimicrobial Resistance Team, Centers for Disease Control and Prevention, Atlanta) were both negative.

Discussion

The known risk factors for late post-transplant UTI include an abnormal urinary tract, diabetes mellitus, female gender and antirejection therapy.[5] *E. coli* is the most common uropathogen in the post-transplant setting;[5] uropathogenic strains have virulence factors such as adhesins and pili, which mediate binding and entry into urothelium, and fimbriae, which promote renal tropism and impair ureteric motility.[6,7]

Recurrent and relapsing UTIs are a complement of both microbial virulence and defective host defense mechanisms and mandate evaluation of the urinary tract for prostatic

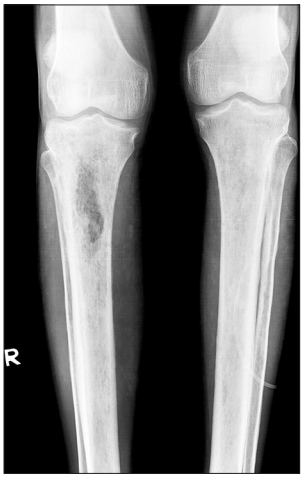

Figure 1: X-ray taken at the time of initial presentation in November 2006, showing lytic areas in the right upper tibia, consistent with acute osteomyelitis

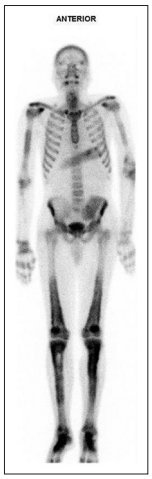

Figure 2: Technetium-99 methylene diphosphonate bone scan image of the patient, showing increased tracer uptake in both tibiae, shaft of humerii, femorii, ankle joints, iliac bones, sternoclavicular joint, lateral end of clavicle and corocoid process of scapulae (June 2007)

enlargement or prostatitis, nephrolithiasis, voiding dysfunction and vesicoureteric strictures or reflux.[8] This patient had high grade reflux which, by causing distal tubular atrophy and impaired Tamm Horsfall protein secretion, promoted binding of bacterial adhesins to urothelium. The cumulative immunosuppression associated with a second transplant impaired local inflammatory responses and pro-apoptotic pathways that normally promote exfoliation and clearance of infected cells, thus creating a reservoir for recurrent infection.[7] Infection and inflammation promote CMV activation and replication through tumor necrosis factor-α release and in turn, CMV suppresses host defenses, predisposing to bacterial and fungal infections.[9] CMV infection, along with long standing nephrotic range proteinuria leading to loss of protective immunoglobulins, may have perpetuated both UTI and the osteomyelitic process in this patient.

Although osteomyelitis as a metastatic complication of *E. coli* infection has been reported in the general population,[10] non-tubercular osteomyelitis in renal allograft recipients is rare, having only been described with *Rhodococcus equi*,[11] *Staphylococcus aureus*[12] and *Yersinia pseudotuberculosis*.[13]

It is likely that *E. coli* metastasized to the bones during the first episode of urosepsis in April 2005, which was inadequately treated. Although the subsequent 2 week course of imipenem was sufficient to clear the urine of the organism, it was inadequate to eradicate bone foci. The discontinuation of suppressive therapy, which had hitherto delayed the overt clinical manifestation of osteomyelitis, favored infection recrudescence.

Osteomyelitis is characterized by intense inflammatory destruction of bony trabeculae as a result of the host immune response to seeded bacteria. A three phase technetium-99m methylene diphosphonate bone scan is both sensitive and specific (94% and 95% respectively) for the diagnosis of osteomyelitis in the absence of recent trauma or surgery.[14] Multifocal uptake on a bone scan is also seen with multifocal bone tumors (osteochondromas, osteosarcomas, histiocytosis X, fibrous dysplasia), bone lymphomas and bone metastasis;[15] however the history, examination findings and isolation of *E. coli* from repeated pus cultures, confirmed the diagnosis of multifocal osteomyelitis in this patient.

The release of cytokines and proteolytic enzymes by infiltrating leucocytes in osteomyelitis raises intra-osseous pressure leading to destruction of vascular channels and ischemic necrosis of bone and when chronic, separation of necrotic bone to form sequestrae, which continue to harbor bacteria.[16]

The avascularity of sequestrae limits antibiotic delivery and healing.[17] Positively charged antibiotics like gentamicin have better penetration into the glycosaminoglycan rich bone matrix compared to negatively charged beta lactams and neutral fluoroquinolones.[16] Therefore, local instillation of gentamicin impregnated beads is an effective therapeutic option for chronic osteomyelitis in renal allograft recipients, in whom systemic aminoglycosides may compromise graft function.

Finally, to preserve life, overwhelming or refractory infection requires reduction in immunosuppression, but may result in permanent graft dysfunction or worse, graft loss. This is a painful trade-off in developing countries with scarce financial resources, where few have access to transplantation as a mode of renal replacement therapy.

To conclude, UTI beyond 6 months of transplant is not a benign entity and requires prompt treatment with adequate and appropriate antibiotics, documentation of clearance after completing the antibiotic course and a diligent search for possible risk factors. Wherever indicated, a urological abnormality should be surgically corrected. Post-transplant urosepsis, if inadequately treated, can result in complications such as osteomyelitis, which requires prompt and adequate surgical drainage coupled with prolonged IV and if necessary, local antibiotic therapy. Immunosuppression reduction for refractory infection may result in permanent graft dysfunction.

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How to cite this article: Valson AT, David VG, Balaji V, John GT. Multifocal bacterial osteomyelitis in a renal allograft recipient following urosepsis. Indian J Nephrol 2014;24:189-92.

Source of Support: Nil, **Conflict of Interest:** None declared.