A case of an acute kidney injury secondary to an implanted aminoglycoside

Ian M. Wu[1], Ethan P. Marin[1], Michael Kashgarian[2] and Ursula C. Brewster[1]

[1]Section of Nephrology, Yale University School of Medicine, New Haven, Connecticut, USA; [2]Department of Pathology, Yale University School of Medicine, New Haven, Connecticut, USA

CASE PRESENTATION

An 80-year-old African American woman with a past medical history of type II diabetes mellitus, hypertension, bilateral knee replacements and peripheral vascular disease presented to the nephrology clinic for evaluation of an elevated serum creatinine. Six weeks earlier she underwent removal of a total knee prosthesis due to septic arthritis with coagulase-negative staphylococci. A vancomycin and tobramycin-impregnated cement spacer block was mixed in the operating room and implanted. Her serum creatinine concentration (sCr) was 0.9 mg/dl upon hospital discharge. Periodic laboratory studies performed at the nursing facility showed a steady increase in sCr to 1.6 mg/dl at 2 weeks and then to 3.7 mg/dl by 6 weeks (Figure 1). One week before to presentation at the nephrology clinic, she began to develop uremic symptoms including nausea, vomiting, a metallic taste, and muscle cramps. Her furosemide and lisinopril had been held for 3 weeks due to her rising serum creatinine with no improvement. Her medications on presentation were insulin, omeprazole, synthroid, metoprolol, multivitamin, clopidogrel, atorvastatin, amlodipine, warfarin and minocycline. The minocycline had been initiated after she completed a 2-week course of intravenous vancomycin. Other than the warfarin, minocycline and intravenous vancomycin, she was on no new medications. There was no documented history of hypotension and she took no non-steroidal, herbal or over-the-counter medications.

Physical examination revealed that she was afebrile, her blood pressure was 124/73 mmHg and pulse was 73 beats/min. She was alert and conversant. There was pitting edema of the lower extremities to the knee, but the lungs were clear to auscultation. No rashes or joint abnormalities were noted. She did not have asterixis. She had no auditory or vestibular symptoms although these were not formally tested. Laboratory studies are shown in Table 1. Her urinalysis revealed a specific gravity of 1.013, pH of 5.0, no protein or blood, and a positive spot leukocyte esterase with 2–5 white blood count per high powered field. Urine microscopic analysis by the nephrology consult team revealed few renal tubular epithelial cells and scant granular casts without red blood cells. She remained non-oliguric during her first few days of her admission. Based upon her clinical presentation, tobramycin toxicity from her knee cement spacer was suspected. Since this diagnosis would entail surgical treatment, a transjugular renal biopsy was performed for confirmation (Figures 2, 3).

RENAL BIOPSY FINDINGS

The biopsy consisted of 2 fragments with 20 glomeruli present for examination of which 5 were sclerotic (Figure 2). The architecture of the kidney was preserved with focal interstitial scarring. The tubules were vacuolated with blebbing. There was arterial and arteriolar nephrosclerosis. The glomeruli showed focal global sclerosis. Immunofluorescence staining for immunoglobulin A, immunoglobulin G, immunoglobulin M, C3, C4, fibrinogen, κ, or λ light chains was negative. Electron microscopy (Figure 3) demonstrated that the glomerular architecture was well preserved with normal basement membranes, epithelial cell foot processes, and endothelial fenestrations. There were no electron-dense deposits. Within the cytoplasm of the proximal tubule cells, lysosomal swelling is observed with myeloid bodies present.

DIAGNOSIS

Acute tubular necrosis secondary to aminoglycoside exposure superimposed on hypertensive nephrosclerosis.

CLINICAL FOLLOW UP

She was admitted to the hospital where hemodialysis was initiated. Despite hemodialysis treatments, her serum tobramycin level continued to rebound (Figure 1). Surgeons removed her antibiotic-impregnated cement spacer and her serum tobramycin became undetectable. Unfortunately, she remains dependent on hemodialysis 5 months later.

Correspondence: *Ursula C. Brewster, Section of Nephrology, Yale University School of Medicine, FMP 107, 330 Cedar Street, PO Box 208029, New Haven, Connecticut 06520-8029, USA. E-mail: ursula.brewster@yale.edu*
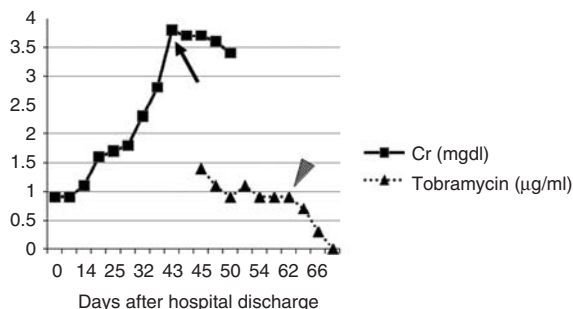
Figure 1 | A graph showing the patient's gradual rise in creatinine after her hospitalization when she had the tobramycin-impregnated cement implanted into her knee. Hemodialysis was initiated after she was readmitted, on day 45 (arrow). Tobramycin levels were notably persistently elevated until she underwent a second surgery on day 63 (arrowhead) to extract her tobramycin-impregnated knee implant.

Table 1 | Serum laboratory values at the time of presentation to renal clinic

| Serum laboratory test	Conventional units	SI units
Sodium	144 mequiv./l	144 mmol/l
Potassium	4.7 mequiv./l	4.7 mmol/l
Bicarbonate	14 mequiv./l	14 mmol/l
Blood urea nitrogen	74 mg/100 ml	26.4 mmol/l
Creatinine	3.7 mg/100 ml	282 µmol/l
Calcium	8.4 mg/100 ml	2.1 mmol/l
Albumin	2.9 g/100 ml	29 g/l
Magnesium	2.0 mg/100 ml	0.82 mmol/l
Phosphorus	5.4 mg/100 ml	1.74 mmol/l
White blood count	10.5×10^3 per µl	10.5×10^9 per l
Hemoglobin	10.7 g/100 ml	107 g/l
Tobramycin	1.4 µg/ml	—
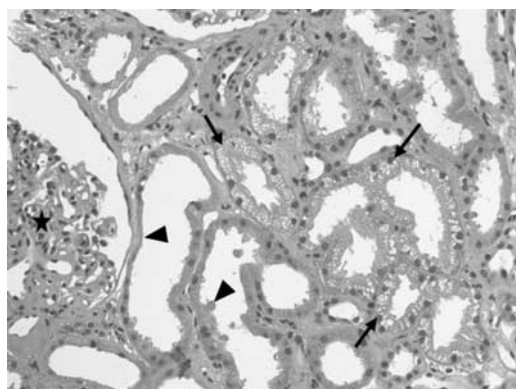
Figure 2 | Light microscopy showing diffuse vacuolization in the proximal tubular cells (arrows). There is tubular cell dropout with blebbing (arrowheads) suggestive of acute tubular necrosis. Glomeruli (star) show global sclerosis (hematoxylin and eosin Original magnification $\times$ 40).

DISCUSSION

Aminoglycosides are well known to induce nephrotoxicity. The incidence varies from 7 to 36% and increases with the
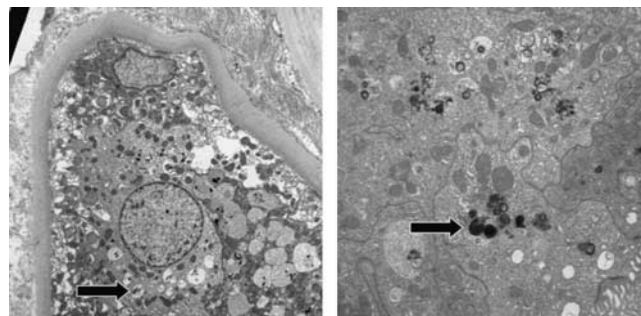

Figure 3 | Electron microscopy of kidney biopsy showing myeloid bodies (arrows) consistent with a diagnosis of aminoglycoside-induced nephrotoxicity.

duration of therapy.[1] Clinically, aminoglycoside nephrotoxicity frequently presents as nonoliguric acute tubular necrosis.[2] It can also present in a variety of electrolyte abnormalities (Table 2).[3–6] Risk factors for aminoglycoside nephrotoxicity include a baseline-elevated serum creatinine (sCr), increased duration of therapy, and an elderly age.[7] Other potential risk factors include shock, liver disease, hypotension, elevated levels of the aminoglycoside, female sex, and low serum albumin concentration.[8,9] Coadministration of vancomycin and a more frequent dosing regimen have been shown to be associated with the development of nephrotoxicity.[10]

Renal excretion of aminoglycosides is the sole method of elimination of the drug from the plasma and aminoglycosides are known to be freely filtered by the glomeruli and excreted by the kidney unchanged.[1] However, aminoglycosides are reabsorbed by proximal tubular epithelial cells and accumulate locally to levels beyond what is observed in the plasma. This high local concentration of drug in the proximal tubule leads to nephrotoxicity.[11,12] Vancomycin may enhance binding of aminoglycosides to the brush border membranes and enhance absorption into the proximal tubule cells.[10]

Reabsorption of aminoglycosides, and hence its nephrotoxicity, is mediated by binding to acidic phospholipids and uptake is facilitated by the endocentric receptor megalin, also known as gp330.[12,13] Megalin belongs to the superfamily of low-density lipoprotein receptors and is responsible for the uptake of many proteins.[14] Megalin was established to have a crucial role in the uptake of aminoglycosides into proximal tubular epithelial cells by the usage of animal models. Knockout animals in which megalin expression was disrupted were noted to have reduced accumulation of aminoglycosides into proximal tubular epithelial cells relative to wild-type animals.[15] Maleate, a substance that impairs uptake of megalin-mediated ligands by inducing megalin shedding, has also been shown to prevent uptake of aminoglycosides into proximal tubule epithelial cells.[11] As uptake is mediated by an endocytic process rather than diffusion, aminoglycoside uptake appears to be saturable at clinically relevant levels. This is important as once-daily dosing leads to less renal accumulation of aminoglycosides than a continuous infusion of the drug at the same concentration.[16]

Table 2 | Possible clinical presentations of aminoglycoside nephrotoxicity

Acute tubular necrosis
Nonoliguric acute kidney injury

Proximal tubular dysfunction
   Tubular proteinuria
   Glucosuria
Hypomagnesemia
Hypokalemia
Hypocalcemia
Barter's-like syndrome
   Metabolic acidosis
   Hypokalemia
   Hypomagesemia
   Hypocalcemia

Once-daily aminoglycoside therapy or consolidated therapy has been clinically validated in many studies as being associated with less nephrotoxicity than the standard multiple-daily dosing regimens.[17] It has been well described that the area under the curve is an important determinant of nephrotoxicity, with once-daily dosing having a lower probability of inducing nephrotoxicity with similar area under the curve's as three times a day dosing.[18] This is because the constant exposure of the kidney to the aminoglycoside saturates uptake through limited transporters as previously described. A continuous low level can be more nephrotoxic than a high level that is associated trough and peak variability. Delivering a higher dosage of aminoglycosides at an extended dosing interval may induce less nephrotoxicity as uptake is saturated and the excess of aminoglycosides that is filtered by the glomeruli is freely excreted.[11,19]

After renal tubular epithelial cells take up aminoglycosides, the mechanism of nephrotoxicity is not fully understood. It is likely partially mediated by accumulation of drug in lysosomes. This accumulation induces lysosomal swelling, which leads to phospholipidosis and eventual apoptosis of the renal tubular epithelial cells. This process can be visualized by electron microscopy where myelin-like structures or myeloid bodies form, as seen in our patient (Figure 3). The presence of myeloid bodies visualized by electron microscopy is thought to be specific for a toxic etiology of acute tubular necrosis rather than an ischemic etiology.[20]

Total joint replacement is a routine operation in orthopedics with an infection rate of 0.5–3% of cases.[21] Using antibiotic-impregnated cement to treat these artificial joint infections is associated with a higher success rate than nonimpregnated cement and has become the standard of care for patients with an infection at the site of a joint replacement.[21] The theory behind using an aminoglycoside-impregnated cement is that it delivers high levels of antibiotics at the site of joint infection while avoiding systemic side effects.[22] This method of drug delivery takes advantage of the known concentration-dependent bactericidal effect of aminoglycosides. Patients avoid systemic exposure by having high local aminoglycoside concentrations with low systemic concentrations.

Drug elution from an impregnated spacer is known to be greatest within the first 24 h, and then rapidly tapers.[23] One case series reported no nephrotoxicity, but it was only 36 patients.[23] Another series reported on the pharmacokinetics of one commercially available tobramycin bone cement in 10 patients. The mean serum tobramycin concentration with this compound peaked at 0.94 mg/l and declined to 0.2 mg/l by 48 h.[24] In 10 patients with gentamicin-impregnated spacers, the peak blood concentration was 0.12 mg/l.[25] Our patient had higher levels of tobramycin than reported in the above series. This was also true in other case reports.[26–28] The variability in serum levels may be related to manufacturing differences between brands, variability in those compounds mixed by hand in the operating room (as was true in our patient) or to patient-specific factors. Despite the relatively low serum concentrations of tobramycin, these patients have a high area under the curve given the continuous excretion of tobramycin from the cement spacer.

In our patient, measurable serum levels persisted, despite the initiation of hemodialysis treatments, until the spacer was removed. She may also have been at increased risk because of advanced age, medical comorbidities, and concurrent use of vancomycin. The observation of myeloid bodies in our patient's renal biopsy confirmed our suspicion of aminoglycoside-induced nephrotoxicity.

CONCLUSION

We report the first case of biopsy-proven aminoglycoside nephrotoxicity from an antibiotic-impregnated cement spacer. Clinicians should be aware that aminoglycoside-induced acute tubular necrosis might occur and follow sCr measurements in high-risk patients. If patients develop kidney injury after surgery, aminoglycoside levels should be monitored and the cement may need to be removed.

REFERENCES
1. Nagai J, Takano M. Molecular aspects of renal handling of aminoglycosides and strategies for preventing the nephrotoxicity. *Drug Metab Pharmacokinet* 2004; **19**: 159–170.
2. Gary NE, Buzzeo L, Salaki J et al. Gentamicin-associated acute renal failure. *Arch Intern Med* 1976; **136**: 1101–1104.
3. Ghiculescu RA, Kubler PA. Aminoglycoside-associated Fanconi syndrome. *Am J Kidney Dis* 2006; **48**: e89–e93.
4. Nanji AA, Denegri JF. Hypomagnesemia associated with gentamicin therapy. *Drug Intell Clin Pharm* 1984; **18**: 596–598.
5. Chou CL, Chen YH, Chau T et al. Acquired bartter-like syndrome associated with gentamicin administration. *Am J Med Sci* 2005; **329**: 144–149.
6. Houghton DC, Hartnett M, Campbell-Boswell M et al. A light and electron microscopic analysis of gentamicin nephrotoxicity in rats. *Am J Pathol* 1976; **82**: 589–612.
7. Paterson DL, Robson JM, Wagener MM. Risk factors for toxicity in elderly patients given aminoglycosides once daily. *J Gen Intern Med* 1998; **13**: 735–739.
8. Moore RD, Smith CR, Lipsky JJ et al. Risk factors for nephrotoxicity in patients treated with aminoglycosides. *Ann Intern Med* 1984; **100**: 352–357.
9. Contreras AM, Ramirez M, Cueva L et al. Low serum albumin and the increased risk of amikacin nephrotoxicity. *Rev Invest Clin* 1994; **46**: 37–43.

10. Yano Y, Hiraoka A, Oguma T. Enhancement of tobramycin binding to rat renal brush border membrane by vancomycin. *J Pharmacol Exp Ther* 1995; **274**: 695–699.
11. Silverblatt FJ, Kuehn C. Autoradiography of gentamicin uptake by the rat proximal tubule cell. *Kidney Int* 1979; **15**: 335–345.
12. Nagai J, Tanaka H, Nakanishi N et al. Role of megalin in renal handling of aminoglycosides. *Am J Physiol Renal Physiol* 2001; **281**: F337–F344.
13. Toner M, Vaio G, McLaughlin A et al. Adsorption of cations to phosphatidylinositol 4,5-bisphosphate. *Biochemistry* 1988; **27**: 7435–7443.
14. Christensen EI, Birn H. Megalin and cubilin: multifunctional endocytic receptors. *Nat Rev Mol Cell Biol* 2002; **3**: 256–266.
15. Schmitz C, Hilpert J, Jacobsen C et al. Megalin deficiency offers protection from renal aminoglycoside accumulation. *J Biol Chem* 2002; **277**: 618–622.
16. Verpooten GA, Giuliano RA, Verbist L et al. Once-daily dosing decreases renal accumulation of gentamicin and netilmicin. *Clin Pharmacol Ther* 1989; **45**: 22–27.
17. Freeman CD, Strayer AH. Mega-analysis of meta-analysis: an examination of meta-analysis with an emphasis on once-daily aminoglycoside comparative trials. *Pharmacotherapy* 1996; **16**: 1093–1102.
18. Murry KR, McKinnon PS, Mitrzyk B et al. Pharmacodynamic characterization of nephrotoxicity associated with once-daily aminoglycoside. *Pharmacotherapy* 1999; **19**: 1252–1260.
19. Olsen KM, Rudis MI, Rebuck JA et al. Effect of once-daily dosing vs. multiple daily dosing of tobramycin on enzyme markers of nephrotoxicity. *Crit Care Med* 2004; **32**: 1678–1682.
20. Jao W, Manaligod JR, Gerardo LT et al. Myeloid bodies in drug-induced acute tubular necrosis. *J Pathol* 1983; **139**: 33–40.
21. Cui Q, Mihalko WM, Shields JS et al. Antibiotic-impregnated cement spacers for the treatment of infection associated with total hip or knee arthroplasty. *J Bone Joint Surg Am* 2007; **89**: 871–882.
22. Bertazzoni Minelli E, Benini A, Magnan B et al. Release of gentamicin and vancomycin from temporary human hip spacers in two-stage revision of infected arthroplasty. *J Antimicrob Chemother* 2004; **53**: 329–334.
23. Springer BD, Lee GC, Osmon D et al. Systemic safety of high-dose antibiotic-loaded cement spacers after resection of an infected total knee arthroplasty. *Clin Orthop Relat Res* 2004; **427**: 47–51.
24. Sterling GJ, Crawford S, Potter JH et al. The pharmacokinetics of Simplex-tobramycin bone cement. *J Bone Joint Surg Br* 2003; **85**: 646–649.
25. Bunetel L, Segui A, Cormier M et al. Release of gentamicin from acrylic bone cement. *Clin Pharmacokinet* 1989; **17**: 291–297.
26. Curtis JM, Sternhagen V, Batts D. Acute renal failure after placement of tobramycin-impregnated bone cement in an infected total knee arthroplasty. *Pharmacotherapy* 2005; **25**: 876–880.
27. Patrick BN, Rivey MP, Allington DR. Acute renal failure associated with vancomycin- and tobramycin-laden cement in total hip arthroplasty. *Ann Pharmacother* 2006; **40**: 2037–2042.
28. van Raaij TM, Visser LE, Vulto AG et al. Acute renal failure after local gentamicin treatment in an infected total knee arthroplasty. *J Arthroplasty* 2002; **17**: 948–950.