CLINICAL VIGNETTE

Minimizing Vancomycin-Associated Acute Interstitial Nephritis

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Introduction

Acute kidney injury (AKI) is one of the most important adverse reactions associated with antimicrobial therapy.[1] Vancomycin, a commonly used antibiotic for the intended treatment of methicillin-resistant Staphylococcus aureus (MRSA), has been known to contribute to AKI for decades.[2-4] Incidence of vancomycin-associated AKI is variable but previous meta-analysis estimates prevalence ranging from 5-43%. Risk factors that enhance the likelihood of renal toxicity revolve around dose of drug, obesity, baseline chronic kidney disease (CKD), critical illness and coadministration of nephrotoxic agents.[5,6] Vancomycin causes renal injury through induced apoptosis from accumulation in proximal tubular epithelial cells.[7,8] The most common patterns of AKI based on previous case reports appear to be acute interstitial nephritis (AIN) and/or acute tubular necrosis (ATN) that occur about 4-17 days after initiation of therapy.[9-14]

To reduce AKI risk from vancomycin, plasma drug levels are commonly monitored during therapy, because of a linear relationship between higher AKI events with higher plasma trough concentration.[14,15] One study showed that the incidence of AKI for those with trough levels of 10–15, 15–20, 20–35 and greater than 35 mg/l, was 3.1%, 10.6%, 23.6% and 81.8%.[15] Thus, if levels are not carefully monitored during therapy and drug levels increase, rapid renal injury can occur, especially when other risk factors are present.

We present a biopsy-proven case of severe acute interstitial nephritis with acute tubular injury in a woman with supra-therapeutic vancomycin levels and ceftriaxone exposure that was successfully treated with corticosteroids and without need for kidney replacement therapy.

Case Description

Clinical History and Initial Laboratory Data

A 44-year-old woman with a history of obesity was diagnosed with severe mastoiditis after one month of debilitating right-sided ear pain. She was subsequently taken to the operating room for tympanoplasty and mastoidectomy, where intraoperative bacterial culture was found to be polymicrobial. Infectious disease consultation recommended a 6-week course of IV ceftriaxone and vancomycin with goal trough level 15-20 mcg/mL to be continued on discharge with monitoring by an outpatient parenteral antibiotic therapy (OPAT) program. Her serum creatinine (SCr) at the time of discharge was at her baseline of 0.92 mg/dL.

Two weeks later, the patient returned for evaluation after developing a pruritic morbilliform rash that started on her abdomen and spread diffusely across her entire body. There was no desquamation of the skin or mucosa. Labs from the OPAT program 3 days prior revealed her SCr level had increased to 3.8 mg/dL, and that her vancomycin trough level was >80 mcg/mL. The levels were repeated at presentation and found to be 5.27 mg/dL and 74.3 mcg/mL. Her last dose of IV vancomycin was 1 day prior.

Physical exam was notable for erythematous macules and papules across the trunk, proximal extremities and upper neck. There was no edema, and she was non-oliguric. Urine microscopy showed 1+ protein, 104 white cells and 36 non-dysmorphic red cells. Fractional excretion of sodium was calculated to be 1.3%. Urine eosinophils were negative; however, peripheral eosinophilia was present. Tests for hepatitis B and C were negative, and kidney ultrasonography was unremarkable. Her SCr initially improved with intravenous hydration to 3.93 mg/dL, but remained stable at that level.

Renal Biopsy Findings

To assess the cause of the patient's persistent kidney injury, a kidney biopsy was performed. The biopsy (Figure 1) was an adequate sample composed of cortex and contained 34 glomeruli that were largely unremarkable. However, there was diffuse acute tubular injury represented by epithelial cell simplification and marked cell sloughing. In addition, there was diffuse tubulointerstitial inflammation associated with moderate interstitial edema. The inflammation was composed of lymphocytes, prominent histiocytes, plasma cells, and conspicuous eosinophils. Rare interstitial neutrophils were also present. There was minimal cortical scarring, and there was no evidence of vasculitis or vascular thromboses. Special stains were negative for microorganisms. After immunofluorescence and electron microscopy studies were found to be insignificant, the final diagnoses were severe acute interstitial nephritis with eosinophils and acute tubular injury with etiology favoring an allergic/drug related interstitial nephritis.

Treatment and Resolution

Due to the initial high suspicion of vancomycin-associated AIN, vancomycin was stopped and changed to ciprofloxacin and daptomycin upon infectious disease recommendation. On the day of kidney biopsy, she was started on prednisone 1 mg/kg, which she continued for 6 weeks on a gradual taper that she tolerated well. Her SCr at follow-up 6 weeks after her presentation had improved to 0.85 mg/dL (baseline). She did not require kidney replacement therapy at any time during her kidney injury.

Discussion

AIN classically presents after the use of known offending drugs (in this case favored to be vancomycin) and is coupled with the typical urinary findings of pyuria, microscopic hematuria, and white cell casts. Systemic symptoms comprising of a maculopapular rash, peripheral eosinophilia, and eosinophiluria, are present in less than one-third of patients.[16-18] Gross hematuria and red blood cell casts are unusual. Our patient exhibited most of these classical findings other than white blood cell casts and eosinophiluria.

Although not required in all cases of AIN, kidney biopsy was pursued because of AKI severity that did not improve with conservative management. Additional diagnostic confirmation and prognostic information help clarify the role of corticosteroids as a therapeutic option in addition to cessation of vancomycin. Treatment of AIN with corticosteroids is controversial because there are no randomized, controlled trials or large observational studies. Evidence for the use of corticosteroids is described only from retrospective studies. Nevertheless, review of available evidence seems to lean more toward a benefit of corticosteroids on renal recovery and possible prevention of long-term dialysis, particularly if kidney biopsy only shows low-to-moderate findings of interstitial fibrosis and tubular atrophy.[18] A reasonable regimen for corticosteroid therapy is 1 mg/kg per day of oral prednisone with or without initial 250-500 mg IV methylprednisolone therapy loading dose ideally within 1-2 weeks of presentation.[19] Therapy is generally continued for 8 weeks in total if a response noted by monitoring of serum creatinine, with a taper of 10 mg ever 3-5 days after the first 2 weeks.

The supratherapeutic dose of vancomycin was the leading suspicion for etiology of AIN. She also exhibited other risk factors such as obesity and critical illness which may have lowered her threshold of AKI. In terms of other possible etiologies, she did not report taking nonsteroidal anti-inflammatory agents (NSAIDs), proton pump inhibitors, diuretics, allopurinol, H2 blockers or antibiotics other than those mentioned. While coadministration of vancomycin and piperacillin/-tazobactam is associated with increased incidence of nephrotoxicity,[20] it is unclear whether coadministration of vancomycin and the cephalosporin ceftriaxone could have a comparable increased risk. Interestingly, only 3 cases of acute interstitial nephritis associated with coadministration of vancomycin and ceftriaxone have previously been reported, however, these cases were not biopsied.[18,21] Although our suspicion is low for ceftriaxone contributing, it is theoretically possible.

Early recognition of AIN is important in treating medication associated kidney injury to prevent subsequent fibrosis and scarring and optimizing improvement in GFR as permanent renal function loss may result.[22]

This case illustrates the quintessential role of drug level monitoring with vancomycin therapy to help mitigate the risk of severe AKI, particularly if treated as an outpatient or if the patient has risk factors. Prompt treatment with corticosteroids after biopsy-confirmed drug-induced AIN can be successful despite ongoing ambiguity of their role.

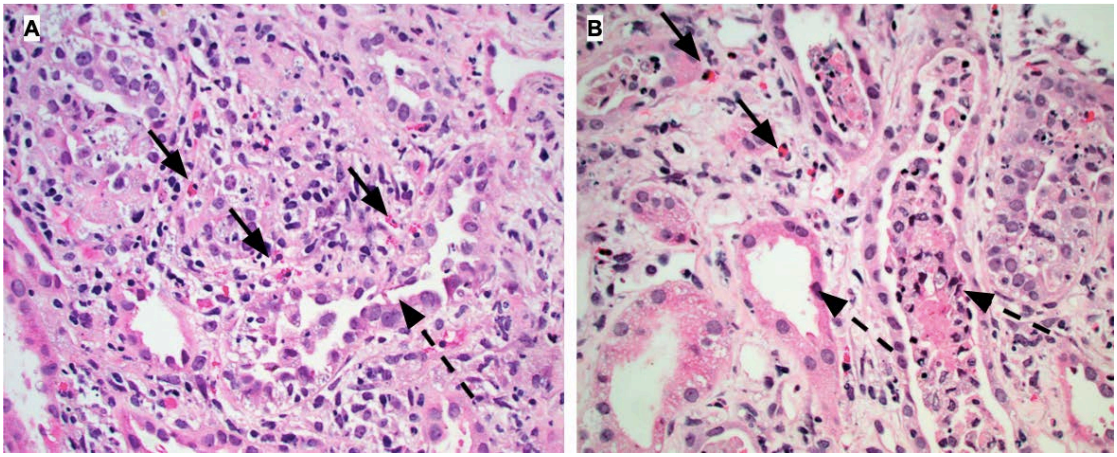

Figure 1
Micrographs from the light microscopic studies (A) area of renal cortex with dense tubulointerstitial inflammation with many eosinophils (B) area of renal cortex with severe proximal tubular injury and cellular necrosis as well as some interstitial inflammation. Solid arrows point towards eosinophils. Dashed arrows point towards injured proximal tubules. H&E stain; 400x magnificent. Constellation of findings suggest severe acute interstitial nephritis with eosinophils and acute tubular injury, concerning for drug related AIN.

REFERENCES

1. **Khalili H, Bairami S, Kargar M**. Antibiotics induced acute kidney injury: incidence, risk factors, onset time and outcome. *Acta Med Iran*. 2013;51(12):871-8. PMID: 24442542.
2. **Levine DP**. Vancomycin: a history. *Clin Infect Dis*. 2006 Jan 1;42 Suppl 1:S5-12. doi: 10.1086/491709. PMID: 16323120.
3. **Rybak MJ, Albrecht LM, Boike SC, Chandrasekar PH**. Nephrotoxicity of vancomycin, alone and with an aminoglycoside. *J Antimicrob Chemother*. 1990 Apr; 25(4):679-87. doi: 10.1093/jac/25.4.679. PMID: 2351627.
4. **Bamgbola O**. Review of vancomycin-induced renal toxicity: an update. *Ther Adv Endocrinol Metab*. 2016 Jun;7(3):136-47. doi: 10.1177/2042018816638223. Epub 2016 Mar 30. PMID: 27293542; PMCID: PMC4892398.
5. **van Hal SJ, Paterson DL, Lodise TP**. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. *Antimicrob Agents Chemother*. 2013 Feb;57(2):734-44. doi: 10.1128/AAC.01568-12. Epub 2012 Nov 19. PMID: 23165462; PMCID: PMC3553731.
6. **Carreno JJ, Kenney RM, Lomaestro B**. Vancomycin-associated renal dysfunction: where are we now? *Pharmacotherapy*. 2014 Dec;34(12):1259-68. doi: 10.1002/phar.1488. Epub 2014 Sep 15. PMID: 25220436.
7. **Elyasi S, Khalili H, Dashti-Khavidaki S, Mohammadpour A**. Vancomycin-induced nephrotoxicity: mechanism, incidence, risk factors and special populations. A literature review. *Eur J Clin Pharmacol*. 2012 Sep;68(9):1243-55. doi: 10.1007/s00228-012-1259-9. Epub 2012 Mar 13. PMID: 22411630.
8. **Oktem F, Arslan MK, Ozguner F, Candir O, Yilmaz HR, Ciris M, Uz E**. In vivo evidences suggesting the role of oxidative stress in pathogenesis of vancomycin-induced nephrotoxicity: protection by erdosteine. *Toxicology*. 2005 Nov 15;215(3):227-33. doi: 10.1016/j.tox.2005.07.009. Epub 2005 Aug 19. PMID: 16112787.
9. **Wai AO, Lo AM, Abdo A, Marra F**. Vancomycin-induced acute interstitial nephritis. *Ann Pharmacother*. 1998 Nov;32(11):1160-4. doi: 10.1345/aph.17448. PMID: 9825081.
10. **Salazar MN, Matthews M, Posadas A, Ehsan M, Graeber C**. Biopsy proven interstitial nephritis following treatment with vancomycin: a case report. *Conn Med*. 2010 Mar;74(3):139-41. PMID: 20391819.
11. **Htike NL, Santoro J, Gilbert B, Elfenbein IB, Teehan G**. Biopsy-proven vancomycin-associated interstitial nephritis and acute tubular necrosis. *Clin Exp Nephrol*. 2012 Apr;16(2):320-4. doi: 10.1007/s10157-011-0559-1. Epub 2011 Nov 16. PMID: 22086124.
12. **Codding CE, Ramseyer L, Allon M, Pitha J, Rodriguez M**. Tubulointerstitial nephritis due to vancomycin. *Am J Kidney Dis*. 1989 Dec;14(6):512-5. doi: 10.1016/s0272-6386(89)80152-0. PMID: 2596477.
13. **Gelfand MS, Cleveland KO, Mazumder SA**. Vancomycin-induced interstitial nephritis superimposed on coexisting renal disease: the importance of renal biopsy. *Am J Med Sci*. 2014 Apr;347(4):338-40. doi: 10.1097/MAJ.0000000000000240. PMID: 24646459.
14. **Sawada A, Kawanishi K, Morikawa S, Nakano T, Kodama M, Mitobe M, Taneda S, Koike J, Ohara M, Nagashima Y, Nitta K, Mochizuki T**. Biopsy-proven vancomycin-induced acute kidney injury: a case report and literature review. *BMC Nephrol*. 2018 Mar 27;19(1):72. doi: 10.1186/s12882-018-0845-1. PMID: 29587650; PMCID: PMC5872390.
15. **Horey A, Mergenhagen KA, Mattappallil A**. The Relationship of nephrotoxicity to vancomycin trough serum concentrations in a veteran's population: a retrospective analysis. *Ann Pharmacother*. 2012 Nov; 46(11):1477-83. doi: 10.1345/aph.1R158. Epub 2012 Oct 16. PMID: 23073306.
16. **Corwin HL, Korbet SM, Schwartz MM**. Clinical correlates of eosinophiluria. *Arch Intern Med*. 1985 Jun;145(6):1097-9. PMID: 4004436.
17. **Nolan CR 3rd, Anger MS, Kelleher SP**. Eosinophiluria--a new method of detection and definition of the clinical spectrum. *N Engl J Med*. 1986 Dec 11;315(24):1516-9. doi: 10.1056/NEJM198612113152404. PMID: 2431314.
18. **Moledina DG, Perazella MA**. Drug-Induced Acute Interstitial Nephritis. *Clin J Am Soc Nephrol*. 2017 Dec 7;12(12):2046-2049. doi: 10.2215/CJN.07630717. Epub 2017 Sep 11. PMID: 28893923; PMCID: PMC5718279.
19. **Muriithi AK, Leung N, Valeri AM, Cornell LD, Sethi S, Fidler ME, Nasr SH**. Clinical characteristics, causes and outcomes of acute interstitial nephritis in the elderly. *Kidney Int*. 2015 Feb;87(2):458-64. doi: 10.1038/ki.2014.294. Epub 2014 Sep 3. PMID: 25185078.
20. **Burgess LD, Drew RH**. Comparison of the incidence of vancomycin-induced nephrotoxicity in hospitalized patients with and without concomitant piperacillin-tazobactam. *Pharmacotherapy*. 2014 Jul;34(7):670-6. doi: 10.1002/phar.1442. Epub 2014 May 22. PMID: 24855041.
21. **Plakogiannis R, Nogid A**. Acute interstitial nephritis associated with coadministration of vancomycin and ceftriaxone: case series and review of the literature. *Pharmacotherapy*. 2007 Oct;27(10):1456-61. doi: 10.1592/phco.27.10.1456. PMID: 17896901.
22. **Nobakht N, Hanna RM, Kamgar M, Sinclair J, Simon L, Emami S, Sisk A, Rastogi A**. Acute interstitial nephritis observed with three different triggering agents. *Clin Case Rep*. 2022 Mar 18;10(3):e05432. doi: 10.1002/ccr3.5432. PMID: 35340649; PMCID: PMC8933633.