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Vancomycin-Induced Leukocytoclastic Vasculitis and Acute Renal Failure Due to Tubulointerstitial Nephritis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

EF 1,2,3
BCEF 1,3,4
Chandra Shekar Pingili
Emmanuel E. Okon

1 Department of Infectious Diseases, Sacred Heart Hospital, Eau Claire, WI, U.S.A.
2 Prevea Health, Eau Claire, WI, U.S.A.
3 Sacred Heart Hospital, Eau Claire, WI, U.S.A.
4 Marshfield Clinic, Eau Claire, WI, U.S.A.

Corresponding Author: Chandra Shekar Pingili, e-mail: skinandtrim@gmail.com
Conflict of interest: None declared

Patient: Male, 79
Final Diagnosis: Leukocytoclastic vasculitis and tubulointerstitial nephritis
Symptoms: Dyspnea • edema of lower extremities • fever • rash
Medication: Vancomycin
Clinical Procedure: He came with fever • shortness of breath • pedal edema and rash. He was in acute renal failure
Specialty: Infectious Diseases

Objective: Unusual or unexpected effect of treatment

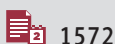
Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and sepsis are commonly treated with intravenous vancomycin. However, vancomycin treatment is associated adverse reactions, including skin rashes and nephrotoxicity. We present a case of acute renal failure due to acute tubulointerstitial nephritis associated with a diffuse leukocytoclastic vasculitic skin eruption following intravenous vancomycin treatment.

Case Report: A 79-year-old Caucasian male patient was treated with intravenous vancomycin for MRSA bacteremia. Prior to treatment, his creatinine was normal at 0.6 mg/dl. He presented one week later with shortness of breath, lower limb edema, and acute renal failure. He had a diffuse maculopapular rash involving the trunk and both upper and lower extremities. A renal biopsy and left arm skin biopsy were examined histologically. The skin biopsy showed leukocytoclastic vasculitis. Renal biopsy showed some sclerosed glomeruli, some with mesangial proliferation, and tubulointerstitial inflammation with eosinophils and plasma cells and mild interstitial fibrosis. Although there was some renal arteriosclerosis, no vasculitic changes were seen, and no vascular thrombosis was present. A diagnosis of leukocytoclastic vasculitis and acute tubulointerstitial nephritis secondary to intravenous vancomycin therapy was made.

Conclusions: Although skin reactions associated with drug therapy are common, vancomycin-associated dermal vasculitis is rare. Tubulointerstitial nephritis is also a rare association with vancomycin treatment. This case report has highlighted that patients being treated with intravenous vancomycin should be carefully observed for acute skin rashes and deterioration in renal function, which can be managed by ceasing treatment with vancomycin, steroid challenge, and preventing future exposure to similar antimicrobial agents.

MeSH Keywords: Methicillin-Resistant *Staphylococcus Aureus* • Nephritis, Interstitial • Vancomycin • Vasculitis, Leukocytoclastic, Cutaneous

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/905214>



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Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and sepsis are commonly treated with intravenous vancomycin. However, vancomycin treatment is associated adverse reactions, including skin rashes and nephrotoxicity [1–6]. Vancomycin has been in use since 1954, and although it is used for the treatment of MRSA infections, it is also used for the treatment of other susceptible organisms when patients are allergic to penicillin [1–6]. During the past few decades, information has accumulated on the therapeutic effects of vancomycin and also on its toxic profile [1–6].

Cutaneous drug reactions are the most common side effects of vancomycin. The term ‘red man syndrome’ is used to describe a reaction to a rapid initial intravenous infusion of vancomycin, and consists of an erythematous maculopapular rash involving the neck, face, and upper torso, associated with pruritis [1,2]. This reaction is mediated by IgE and mast cell degranulation and can be prevented by slowing down the rate of vancomycin infusion, and treatment antihistamines [1]. Other antibiotics, including such as ciprofloxacin, amphotericin B, rifampicin, teicoplanin, and oral vancomycin treatment can also cause a similar type of drug reaction [1]. Renal failure from vancomycin treatment can result from acute tubular necrosis [7,8]. Acute interstitial nephritis is a very rare side effect from this drug [7,8].

We present a case of acute renal failure due to acute tubulointerstitial nephritis associated with a diffuse leukocytoclastic vasculitic skin eruption following intravenous vancomycin treatment.

Case Report

A 79-year-old Caucasian male patient was treated with intravenous vancomycin for Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and sepsis bacteremia. Prior to treatment, his creatinine was normal at 0.6 mg/dl. There was no obvious source of infection. Computed tomography scan of the chest, abdomen, and pelvis was negative for an acute source of infection. A transesophageal echocardiogram was negative for endocarditis.

His past medical history included hypertension, mild-to-moderate aortic stenosis, hypothyroidism, and hyperlipidemia. On hospital admission, he was on taking lisinopril, atorvastatin, levothyroxine, and aspirin.

Two sets of blood cultures had been positive for MRSA, drawn 48 hours apart. MRSA was sensitive to vancomycin with a mean inhibitory concentration (MIC) of 1 microgram/mL. Following vancomycin treatment and when his blood cultures were

negative for MRSA, he was discharged home on intravenous vancomycin via a peripherally inserted central catheter (PICC) line, 2 gm every twelve hours, calculated for the weight of the patient, which was 150 kg.

The patient presented to the emergency room one week following discharge from hospital, with shortness of breath, lower limb edema and a diffuse maculopapular rash involving the trunk, upper, and lower extremities. The patient reported that the rash had started on the trunk and then spread to the buttocks and both upper and lower limbs, and was worse on the back and buttocks. His creatinine, which had been 0.6 mg/dl on first hospital admission, was elevated at 5.6 mg/dl. On this second hospital admission, he was challenged with a single dose of 250 mg intravenous methylprednisolone and showed a dramatic clinical improvement. The following day, he was switched to prednisone treatment 60 mg daily for three days and over the next one week he was completely tapered off the steroids. His home medications were all discontinued. He was also started on hemodialysis.

Because his urine analysis showed microscopic hematuria, which was believed to be an unusual association with vancomycin therapy, the patient underwent serological investigations. The cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) were weakly positive; antinuclear antibodies (ANA), perinuclear ANCA (p-ANCA), and complement C3 and C4 levels were normal; anti-glomerular basement membrane (GBM) antibody was negative; serum protein electrophoresis was positive for acute-phase proteins; serology for antibodies to hepatitis B and hepatitis C were negative; anti-proteinase 3 antibodies, anticardiolipin IgG and IgM were negative.

Skin and renal biopsies were sampled and processed for histology and immunofluorescence. Skin histology showed diffuse leukocytoclastic vasculitis. Immunofluorescence was negative for IgG, IgM, IgA, C3 and fibrinogen. Histology of the renal biopsy showed a few sclerosed glomeruli, other glomeruli showed mesangial proliferation, but were negative for necrotizing lesions or crescents. The renal biopsy showed inflammation with eosinophils and plasma cells, with interstitial fibrosis. Renal vessels showed mild arteriosclerosis, but no vasculitis or thrombus were found. Electron microscopy showed thickening of the glomerular basement membrane and no electron-dense bodies. A diagnosis of acute renal failure due to tubulointerstitial nephritis was made.

The skin lesions gradually resolved following treatment with steroids and stopping treatment with vancomycin. The patient was later discharged home on intravenous daptomycin 10 mg per kg every other day for four weeks. At the time of discharge, levothyroxine and aspirin were resumed. The patient has continued with outpatient clinical follow-up and has

bever had recurrent MRSA infection, but his renal failure persisted, and he continues to require dialysis three times a week.

Discussion

We have presented a case of acute renal failure due to acute tubulointerstitial nephritis associated with a diffuse leukocytoclastic vasculitic skin eruption following intravenous vancomycin treatment. These findings are rare side effects from vancomycin. Because urinalysis showed microscopic hematuria, which is unusual with vancomycin, the patient underwent renal function analysis, serum investigations, and renal biopsy and histology

Skin reactions following vancomycin treatment have been previously reported and include leukocytoclastic vasculitis, extensive fixed drug eruptions, toxic epidermal necrolysis, and exfoliative dermatitis [2–6]. Fever, neutropenia, nephrotoxicity, and ototoxicity are some other adverse effects associated with vancomycin therapy [5,6].

Nephrotoxicity from vancomycin is suspected when tubular necrosis is present [7]. However, this patient had tubulointerstitial nephritis, which is a rare side effect of vancomycin [8,9]. A risk of cross-reactivity between vancomycin and teicoplanin therapy has been reported, but this was not found in this case [10].

Leukocytoclastic vasculitis is a small vessel inflammatory change due to immune complex deposition and activation of the complement cascade. Post-capillary venules are involved with leukocyte migration and local activation of the complement cascade. The histopathology of includes neutrophil infiltration of the vessel wall with fibroid change in the post-capillary venules. Infections, drug reactions, and auto-immune conditions are reported to be triggers of leukocytoclastic vasculitis [11]. Leukocytoclastic vasculitis is reported to affect 15 patients per million in the population, with no gender or seasonal preference, but with an increased risk with increasing age, with 65–74 years being considered the peak age for leukocytoclastic vasculitis [11,12]. Leukocytoclastic vasculitis is a rare side effect of vancomycin treatment [11,12]. Antibiotics, allopurinol, cyclosporine, diuretics, antithyroid drugs, anticonvulsants have all been reported to cause leukocytoclastic vasculitis [13]. Hepatitis B, hepatitis C, human immunodeficiency virus (HIV), and infective endocarditis have also been reported to cause leukocytoclastic vasculitis [14]. Autoimmune diseases, including polyarteritis nodosa, systemic lupus erythematosus (SLE), malignancy, rheumatoid disease, cryoglobulinemia, and antineutrophil cytoplasmic antibodies (ANCA)-positive vasculitis are also associated leukocytoclastic vasculitic changes [15,16]. The macroscopic appearances of skin changes in leukocytoclastic vasculitis include bullae, nodules, maculopapular

and erythematous rashes that usually exclude the palms and soles, and can occur after a single dose of drug or even after a stopping drug treatment [11,16]. Recurrent skin lesions with symptom-free intervals occur with autoimmune disorders. Malignancy, cryoglobulinemia and systemic small-vessel vasculitis are present with chronic leukocytoclastic vasculitis. There is no specific diagnostic test for leukocytoclastic vasculitis [11,16].

As in this case, clinical history, physical examination, serology and tissue biopsy should make the diagnosis of leukocytoclastic vasculitis [16]. A deep skin punch biopsy is the preferred definitive diagnostic technique and should be done within the first 48 hours, with two biopsies being recommended, one for light microscopy and the other for direct immunofluorescence examination [16]. Neutrophilic infiltration within and around the vessel wall with signs of neutrophil degranulation (leukocytoclasia) fibroid necrosis and signs of endothelial damage of the vessel wall confirm the histological diagnosis of leukocytoclastic vasculitis [16]. Biopsy for immunofluorescence is advised within 48 hours of onset of the signs of the rash to detect IgG and IgM in the vessel walls using immunofluorescence [16].

Mild skin reactions are self-limited and resolve over time, but severe reactions with end organ damage need inpatient management with steroids. Although cutaneous and vascular involvement responds to steroids, removing the offending agent, drug or infectious agent, is important. The prognosis of leukocytoclastic vasculitis is favorable, in the case of drug-induced or microbial-induced leukocytoclastic vasculitis, as long as the causative agent is removed, but the extent of tissue damage will influence prognosis [16]. Recurrent lesions are seen in malignancy and autoimmune disorders, and there is an increased risk of recurrence when the patient is challenged with the same drug or any other related drugs [17,18]. De-sensitization is not recommended unless the patient and the clinician are facing multidrug resistant infectious organisms or the patient has multiple drug allergies and should be attempted only in the inpatient setting [17,18]. Leukocytoclastic vasculitis should be distinguished from linear IgA bullous dermatosis, which is a rare, idiosyncratic, autoantibody-mediated skin reaction to vancomycin that can occur between one day to one month after using the drug, and unlike Stevens-Johnson syndrome, the mucosa is spared. Direct immunofluorescence shows linear IgA deposition at the dermal-epidermal basement membrane in vancomycin-associated linear IgA bullous dermatosis [19].

Conclusions

Although skin reactions associated with drug therapy are common, vancomycin-associated dermal vasculitis is rare. Tubulointerstitial nephritis is also a rare association with

vancomycin treatment. This case report has highlighted that patients being treated with intravenous vancomycin should be carefully observed for acute skin rashes and deterioration in renal function, which can be managed by ceasing treatment with vancomycin, steroid challenge, and preventing future exposure to similar antimicrobial agents.

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Conflicts of interest

None.