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Case Report

Vancomycin-associated Henoch-Schönlein purpura

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ABSTRACT

Intravenous vancomycin is a widely used antibiotics, but it causes different types of cutaneous hypersensitivity reactions, ranging from maculopapular rash, red-man syndrome, drug rash with eosinophilia and systemic symptoms, IgA bullous dermatosis, leukocytoclastic vasculitis, Stevens-Johnson syndrome, to IgE-mediated anaphylaxis. We report an elderly patient with the end-stage renal disease presented with diffuse palpable purpura while receiving IV vancomycin therapy for methicillin-resistant *Staphylococcus aureus* septicemia. Histopathology of skin biopsy revealed perivascular infiltrates of leukocytoclastic debris with necrosis of the small-sized blood vessels. Direct immunofluorescence analysis demonstrated vivid IgA plus C3 immune-complex deposits localized to the vessel walls, and no immune complexes were noted on the dermoepidermal junction. There was no IgG or IgM immunoreactivity detected on the tissue specimen. Rheumatologic disease work-ups were negative. A diagnosis of vancomycin-associated Henoch-Schönlein variant of vasculitis was made. Vancomycin was substituted by daptomycin, and the purpuric skin rashes were resolved. Since vancomycin is a commonly used antibacterial agent, clinicians are encouraged to have a heightened awareness of this rare adverse skin reaction. Early recognition and prompt discontinuation of the medication is the key in management. As it is not an Ig-E mediated reaction, desensitization of vancomycin or re-challenge with vancomycin is not recommended as re-exposure to the drug may result in a recurrence of similar manifestations with potential permanent renal failure.

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1. Introduction

Skin rash is a common clinical manifestation. However, identifying the etiology of it may sometimes be challenging, especially in patients who are on multiple medications for a variety of medical ailments. Herein, we describe a 72-year-old man who presented with progressive skin rash over his extremities and upper chest developed on intravenous vancomycin therapy. Skin biopsy was obtained. Based on cutaneous manifestations and histologic findings of skin biopsy, a diagnosis of vancomycin-related Henoch-Schönlein purpura was made. We discussed pertinent differential diagnoses and a thorough literature review was performed. To the best of our knowledge, our patient is the third reported case in the literature.

2. Case report

A 72-year-old elderly male presented with generalized purpuric skin rashes. The patient's past medical history was significant for Parkinson's disease, hypertension, and end-stage renal disease on intermittent hemodialysis. The patient was bed- and wheel-chair bound because of Parkinson's disease, and he resided in the nursing home. Three weeks prior, the patient had developed methicillin-resistant *Staphylococcus aureus* (MRSA) septicemia secondary to an infected arterio-venous graft, which was excised, followed by placement of a new right internal jugular vein tunneled dialysis catheter. Echocardiogram did not reveal vegetation. The patient was discharged to the nursing facility for a 4-week course of intravenous vancomycin administered post-hemodialysis 3 days a week. Other medications on admission included carbidopa/levodopa, aspirin, and amlodipine.

Two weeks into the intravenous vancomycin therapy, the patient noted a faint rash over his arms. Over the next 3 days, the rash progressed to involve the forearms, palms, upper chest, thighs,

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shins, feet, and soles. The patient denied fever, chills, pruritus or pain over the rash, joint pain or swelling, abdominal pain, or diarrhea. A review of the system was otherwise unremarkable. There were no known new medications started in the nursing facility.

On physical examination, the patient was afebrile and had a generalized rash. More specifically, distributed over the arms (Fig. 1A), dorsal surfaces of the hands and feet, and shins (Fig. 1B) were an eruption of confluent, raised, non-blanching, and palpable purpura without any blistering, scaling, or tenderness. Morphologically different rash, petechial in appearance, was noted on the

upper chest, palms (Fig. 1C), and soles. The face, oral mucosa, abdomen, genitalia, and back were spared. Musculoskeletal examination did not reveal evidence of synovitis or deformity. There was no heart murmur heard. No abdominal tenderness or organomegaly was detected. The recently placed dialysis catheter was functioning well without erythema or discharge at the catheter exit site. We suspected vancomycin-related leukocytoclastic vasculitis. Our differential diagnoses included vasculitis rash secondary to recurrent infection (MRSA septicemia), cryoglobulinemic rash,

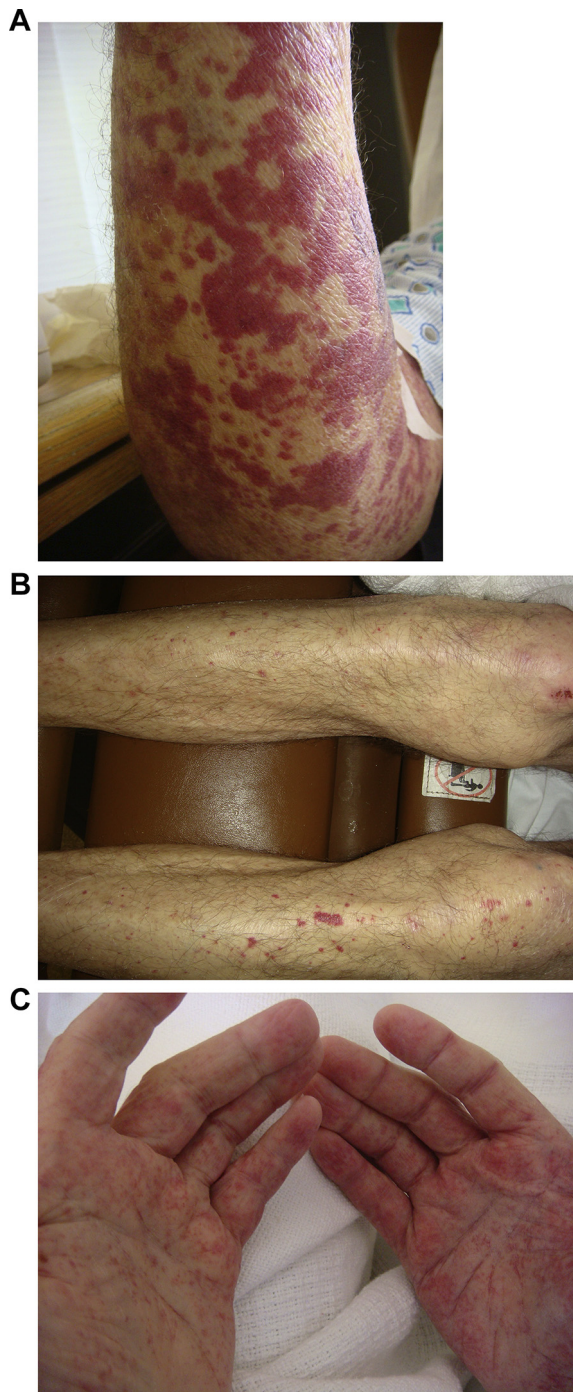


Fig. 1. Cutaneous eruption of coalescing palpable purpura was over the extensor surface of the right forearm (A), dorsal surfaces of the hands and feet, and both shins (B). Petechial rash was noted on both palms (C).

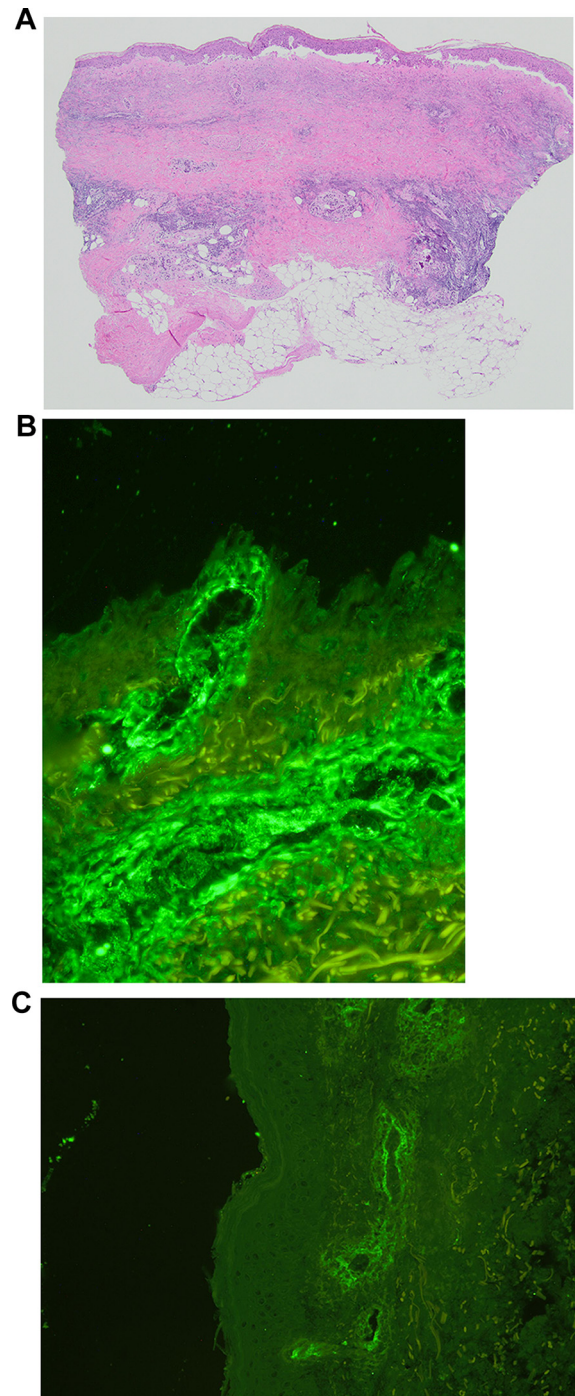


Fig. 2. Histopathology of the skin biopsy. (A) Dermal necrosis and leukocytoclasia surrounding the superficial and deep vascular plexus were seen on hematoxylin & eosin stain (40× magnification). Direct immunofluorescence showed granular deposits of IgA (B) and C3 (C) were present within and around the vessel walls.

Table 1

A list of published reports of vancomycin-associated Henoch-Schönlein purpura.

References	Onset	Vancomycin level (µg/mL) at the onset of the disease	Clinical features	Pertinent laboratory findings	Histopathology	Direct immunofluorescence	Treatment	Outcomes (after stopping vancomycin)
Michail et al. (1998) [2]	Day 1	Not reported	Maculopapular purpuric rash over bilateral lower extremities and buttocks; generalized arthralgia of both upper and lower extremities; abdominal pain; oliguria	Eosinophilia BUN: 183 mg/dL SCr: 6.5 mg/dL ANA, anti-dsDNA, RF, ANCA, cryoglobulins, anti-GBM, complement levels, and CRP: normal IgA: 645 mg/dL SPEP: normal UA: microscopic hematuria, eosinophiluria, proteinuria, renal tubular cells	Skin biopsy: leukocytoclastic vasculitis Renal biopsy: diffuse mesangial proliferation and interstitial tissue dense mononuclear infiltrates	Skin biopsy: IgA, C3, and fibrinogen deposits Renal biopsy: IgA, C3, and fibrinogen deposits in the mesangium and along the basement membrane	Discontinuation of vancomycin	Resolved in 1 day Recurrent of rash, arthralgia, abdominal pain, bloody diarrhea, and oliguria after rechallenge with vancomycin 10 days after discontinuation of vancomycin.
Bataille et al. (2012) [3]	Day 15	Not reported	Purpuric rash on bilateral lower extremities, arthralgia, and macroscopic hematuria	CRP: 124 mg/L IgA: 47.1 mg/dL ANA: 1:200 Cryoglobulin, complement level, SPEP: normal HIV, HBV, HCV, HSV, VZV, CMV, EBV, HHV6, HHV8, Parvovirus B19: negative	1 st and 2nd Skin biopsies: leukocytoclastic vasculitis No renal biopsy performed.	1 st skin biopsy: IgM and C3 deposits 2 nd skin biopsy: IgA and C3 deposits	Discontinuation of vancomycin	Resolved No interval reported
Our patient (2016)	Day 14	25.8	Confluent palpable purpura over the arms, dorsal surfaces of the hands and feet, and shins; petechial rashes over the upper chest, palms, and soles	ESR: 12 CRP: 1.8 mg/dL CBC: no eosinophilia ANA, ANCA, serum C4, cryoglobulin, RPR, HCV serology: negative Serum C3: decreased	Skin biopsy: leukocytoclastic necrotizing vasculitis	IgA and C3 deposits	Discontinuation of vancomycin	Resolved in 3 days

ANA – anti-nuclear antibody; anti-dsDNA – anti-double stranded DNA antibody; RF – rheumatoid factor; ANCA – anti-neutrophil cytoplasmic antibody.

UA – urinalysis; CBC – complete blood count; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein.

BUN – blood urea nitrogen; SCr – serum creatinine.

HIV – human immunodeficiency virus; HBV – hepatitis B virus; HCV – hepatitis C virus; HSV – herpes simplex virus; VZV – varicella zoster virus; CMV – cytomegalovirus; EBV – Epstein–Barr virus; HHV6 – human herpes virus 6; HHV8 – human herpes virus 8.

SPEP – serum protein electrophoresis.

syphilitic rash, or a rheumatologic disease. Vancomycin was substituted by intravenous daptomycin on the first day of hospitalization. All other medications were continued.

Surveillance blood cultures were drawn. Complete blood count showed WBC of $4.62 \times 10^3/\mu\text{L}$ (normal 4.4–11.30) without peripheral eosinophilia, and platelet count $162 \times 10^3/\mu\text{L}$ (normal 145–445). The coagulation parameters were within the normal range. Urinalysis was not performed because of anuria from the end-stage renal disease. The erythrocyte sedimentation rate was 46 mm/h, and C-reactive protein was 1.8 mg/dL (normal <0.8). Serum vancomycin level was obtained approximately 7 h after the last dose of IV vancomycin and it was reported at 25.8 $\mu\text{g/mL}$ (trough reference 15–20, and peak reference 25–50). In addition, the serologic panel for rheumatologic diseases was dispatched, including anti-nuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), complement levels (C3, C4), cryoglobulin level, hepatitis C antibody, anti-neutrophil cytoplasmic antibody (ANCA) panel, and anti-glomerular basement membrane (anti-GBM) antibody. HIV serology and serum rapid plasma reagin (RPR) were also performed given the presence of skin rash over the palms and soles.

The rheumatologic test panel reported negative except low serum C3 at 69 mg/dL (normal 85–193). The blood cultures were negative for bacterial growth. HIV serology and serum RPR were non-reactive. A skin punch biopsy from the right forearm rash was obtained. Hematoxylin & eosin-stained histologic sections showed a superficial perivascular infiltrate of leukocytoclastic debris associated with fibrinoid necrosis of the small caliber vessels (Fig. 2A). Direct immunofluorescence study performed on the sections of frozen skin specimen showed positive immunoreactivity for immunoglobulin A (IgA) and complement 3 (C3) in a finely granular pattern localized to the small vessel walls and perivascularly (Fig. 2B and C). There was negative immunoreactivity for IgG and IgM. The totality of the findings supported the diagnosis of Henoch-Schönlein purpura, a clinical variant of leukocytoclastic vasculitis.

Three days after discontinuation of vancomycin, the purpuric rashes resolved completely without administration of steroids or other immunosuppressant therapy. The patient tolerated intravenous daptomycin and was transferred to the nursing home to complete the course of antibiotic therapy for prior MRSA infection.

3. Discussion

Leukocytoclastic vasculitis secondary to vancomycin is usually associated with IgG immune-complex deposits [1]. IgA-mediated small-vessel vasculitis, a Henoch-Schönlein purpura (HSP) variant, is a very rare complication of intravenous vancomycin therapy. The first case of vancomycin-associated HSP was reported in 1998 [2], and it was followed by the second reported case 4 years later [3] (Table 1). To the best of our knowledge, this is the third reported case of HSP secondary to vancomycin therapy.

Pertinent differential diagnoses in our patient included vasculitis rash secondary to recurrent MRSA septicemia, hepatitis C-associated cryoglobulinemic rash, syphilitic rash, or a rheumatologic disease. There have been reported cases of leukocytoclastic vasculitis secondary to MRSA infection [4,5]. However, the negative blood cultures in our patient militated against that diagnosis. Moreover, the recent outbreaks of hepatitis C virus infection in hemodialysis centers in the United States made us consider if the skin rash could have been due to hepatitis C-associated cryoglobulinemic vasculitis [6,7]. However, the non-reactive hepatitis C antibody and negative cryoglobulin concentration eliminated this diagnosis. A non-reactive serum RPR helped to exclude the cause of exanthem from syphilis. Both the clinical presentation and microscopic findings effectively rule out vancomycin-associated linear IgA bullous dermatosis. That entity usually manifests as cutaneous

bullous blistering lesions (or rarely morbilliform eruptions) [8]. In linear IgA bullous dermatosis, cutaneous histologic sections would show papillary dermal neutrophilic microabscesses, and direct immunofluorescence would demonstrate classic linear immunoreactivity for IgA localized to the dermo-epidermal junction (hence the name) [8]. These features were absent in our patient.

HSP is a small-vessel systemic vasculitis secondary to IgA immune-complex deposition and it predominantly affects children. The disease is characterized by the classic tetrad of clinical features: palpable purpura without thrombocytopenia and coagulopathy, arthritis/arthralgia, abdominal pain, and renal impairment (proteinuria, hematuria, or renal dysfunction) [9]. Adult patients with HSP present with the similar clinical manifestations as in children, however, with more renal involvement [10]. The patient had already been anuric and end stage renal disease, and so it was difficult to comment on the renal manifestations in our case.

The purpuric skin rash in HSP typically appears in symmetrical distribution, primarily in gravity/pressure-dependent areas, such as the lower extremities and buttocks. Face, trunk, and upper extremities can be involved in non-ambulatory patients, as was the case with our patient who had limited ambulatory activity secondary to his Parkinson's disease. Thus, the erythematous purpura and petechial rash were observed in our patient's upper extremities and upper torso. Despite the lack of joint and gastrointestinal symptoms, the patient's classic palpable purpura and characteristic cutaneous histopathologic features (leukocytoclastic vasculitis with florid IgA immunoreactivity) meet the diagnostic criteria of HSP [9,11]. Michail et al. re-challenged the patient with IV vancomycin 10 days after discontinuation of it and similar clinical manifestations were reproduced [2]. Desensitization of vancomycin has no role in this type of skin reaction since it is not an IgE-mediated reaction. It is recommended to avoid the use of IV vancomycin in the future and re-exposure to the drug may have an irreversible renal failure.

In summary, vancomycin is a commonly used antibiotic and histamine-mediated skin rash, known as red-man syndrome, is a well-known adverse reaction from the rapid intravenous vancomycin infusion. Practicing clinicians are also encouraged to be familiar with uncommon side-effects of vancomycin. Vancomycin-associated HSP has rarely been reported, and our patient is the third case reported in the literature to the best of our knowledge. Since the occurrence of this reaction is uncommon, increased awareness of the disease entity is paramount of early diagnosis. The prompt discontinuation of the offending medication, vancomycin in this case, is the most effective and prudent approach with favorable clinical outcome. Vancomycin desensitization or re-challenge has no value and avoidance of future use of vancomycin is recommended.

Conflict of interest

Dr. Bhanot received honorarium for Speaker's Bureau of Astellas and review article for Postgraduate Institute for Medicine. All other authors declare no conflicts of interest.

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References

- [1] Markman M, Lim HW, Bluestein HG. Vancomycin-induced vasculitis. *South Med J* 1986;79:382–3.

- [2] Michail S, Vaiopoulos G, Nakopoulou L, Revenas C, Aroni K, Karam P, et al. Henoch-Schoenlein purpura and acute interstitial nephritis after intravenous vancomycin administration in a patient with a staphylococcal infection. *Scand J Rheumatol* 1998;27:233–5.
- [3] Bataille S, Daumas A, Tasei AM, Jourde-Chiche N, Dussol B, Burtsey S, et al. Vancomycin-induced Henoch-Schönlein purpura: a case report. *J Med Case Rep* 2012;6:106–11.
- [4] Montoliu J, Miro JM, Campistol JM. Henoch-Schonlein purpura complicating staphylococcal endocarditis in a heroin addict. *Am J Nephrol* 1987;7:137–9.
- [5] Maliske SM, Edwards D, Suneja M. Methicillin-resistant *Staphylococcus aureus*-related Henoch-Schönlein purpura treated without systemic immunosuppressants. *Am J Med Sci* 2015;350:514–6.
- [6] Nguyen DB, Gutowski J, Ghiselli M, Cheng T, Bel Hamdounia S, Suryaprasad A, et al. A large outbreak of hepatitis C virus infections in a hemodialysis clinic. *Infect Control Hosp Epidemiol* 2016;37:125–33.
- [7] Muleta D, Kainer MA, Moore-Moravian L, Wiese A, Ward J, McMaster S, et al. Notes from the field: hepatitis C outbreak in a dialysis clinic - Tennessee, 2014. *MMWR Morb Mortal Wkly Rep* 2016;64:1386–7.
- [8] Billet SE, Kortuem KR, Gibson LE, El-Azhary R. A morbilliform variant of vancomycin-induced linear IgA bullous dermatosis. *Arch Dermatol* 2008;144:774–8.
- [9] Mills JA, Michel BA, Bloch DA, Calabrese LH, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Henoch-Schönlein purpura. *Arthritis Rheum* 1990;33:1114–21.
- [10] Blanco R, Martínez-Taboada VM, Rodríguez-Valverde V, García-Fuentes M, González-Gay MA. Henoch-Schönlein purpura in adulthood and childhood: two different expressions of the same syndrome. *Arthritis Rheum* 1997;40:859–64.
- [11] Ozen S, Ruperto N, Dillon MJ, Bagga A, Barron K, Davin JC, et al. EULAR/PreS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis* 2006;65:936–41.