Tigecycline Induced Hemorrhagic Vesiculobullous Leukocytoclastic Vasculitis: A Rare Clinical Presentation

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Received: 5 July 2023

Accepted: 25 September 2023

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DOI 10.5001/omj.2025.31

Abstract

Drug induced leukocytoclastic vasculitis (LCV) is defined as the inflammation of blood vessels caused by the use of pharmacological agents. It may only affect the skin, resulting in cutaneous leukocytoclastic vasculitis, or it may be systemic affecting other organs such as central nervous system, gastrointestinal tract, lungs, kidneys, and joints resulting is organ and tissue damage and even death. Early withdrawal of the causative drug is sufficient to enhance rapid resolution and recovery. Here we report a case of tigecycline induced cutaneous leukocytoclastic vasculitis of hemorrhagic vesiculobullous type in an immunocompromised patient who was being treated with tigecycline for parapneumonic effusion with persistently high inflammatory markers.

Keywords: Drug-Induced Vasculitis; Leukocytoclastic Vasculitis; Tigecycline; Oman

Introduction

Vasculitis is defined as inflammation of blood vessels, affecting their structure and function, resulting weakening, narrowing, and scarring of the vessel wall. Vasculitis presentations are categorized based on the size, type, and location of the affected vessels.[1] Leukocytoclastic vasculitis (LCV) is categorized as 'small vessel vasculitis' where the inflammatory infiltrate is composed of neutrophils.[2] Cutaneous LCV tends to present as palpable purpura in the skin of the lower limbs.[1]

Drugs are among the most common triggers of LCV, and the signs and symptoms start manifesting around 1–3 weeks after the initiation of the drug. Beta-lactams, vancomycin, erythromycin, clindamycin, sulfonamides, allopurinol, NSAIDs, furosemide, thiazides, beta-blockers, gold, phenytoin, valproic acid, metformin, warfarin, and selective serotonin reuptake inhibitors are among the common causes of LCV.[3] Early withdrawal of the offending drug is usually sufficient for rapid resolution and recovery.[4]

Tigecycline induced LCV is rare. One case was reported in 2015 with a sudden skin eruption of macular purpuric rash symmetrically distributed on lower limbs.[5] Here we present a case of tigecycline induced LCV with an atypical clinical presentation.

Case Report

Our patient was a 44-year-old Omani man with a history of uncontrolled hypertension and uncontrolled type II diabetes with end stage renal disease on regular hemodialysis. He had undergone left lower limb above-knee amputation. He also suffered from hepatitis C, ascites, and ischemic heart disease with ejection fraction (EF) 30%–50%. Additionally, he had recurrent bilateral pleural effusion that required multiple pleural tapping.

The patient's current presentation was with right sided pleural effusion complicated with parapneumonic effusion with high inflammatory markers and fever. He was admitted and started on intravenous Tazocin® (a combination of piperacillin and tazobactam). He underwent a right posterolateral thoracotomy for decortication drainage of pleural effusion and was kept on epidural analgesia for pain control. He had persistent leukocytosis and high inflammatory markers, so the infectious disease team stopped Tazocin and started him on tigecycline till the results of the final sensitivity of his screening samples were available.

Three days after starting tigecycline, the patient developed sudden asymptomatic erythematous progressive skin eruptions symmetrically distributed on the upper extremities and ears. There were multiple grouped purpuric papulovesicular lesions coalescing forming plaques on erythematous background distributed symmetrically over the upper extremities and lateral surface of both ears. The palms were spared. Oral examination revealed purpuric maculopapular lesions on the hard palate and healed ulcers on the left buccal mucosa. Face, trunk, lower extremities, and genital area were not affected [Figure 1]. The patient was conscious, alert, afebrile, and had normal vital signs. Dermatoscopy showed hemorrhagic blisters, purpuric globules, and dots on orange-brown background [Figure 2].

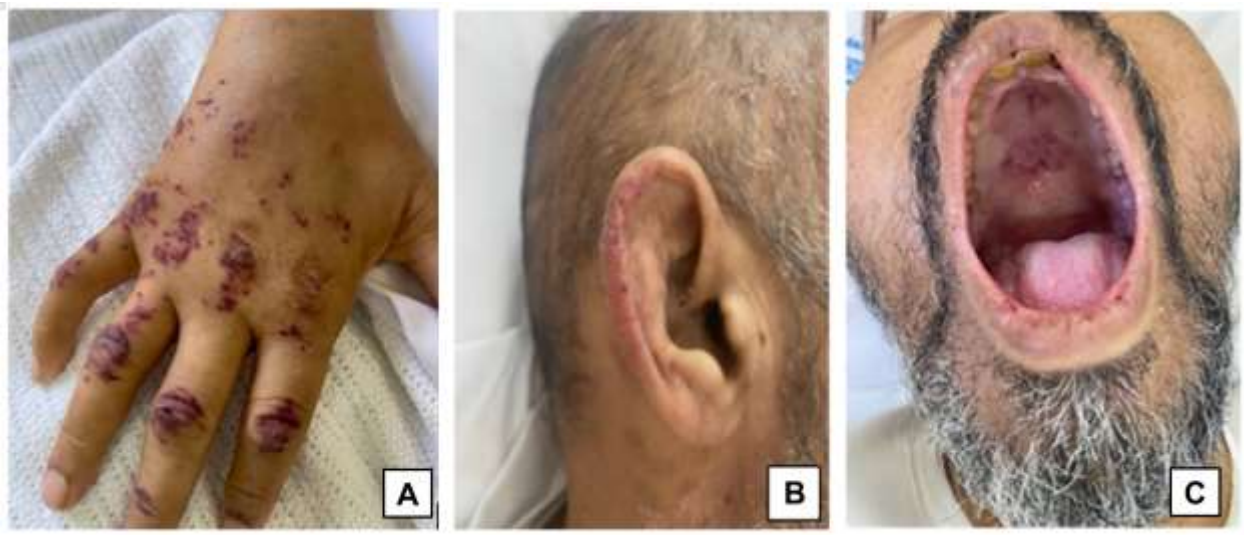

Figure 1: (A) Grouped hemorrhagic blisters with purpuric background in dorsum of right hand. (B) Purpuric macules over the helix of right ear. (C) Grouped hemorrhagic blisters in the hard palate.

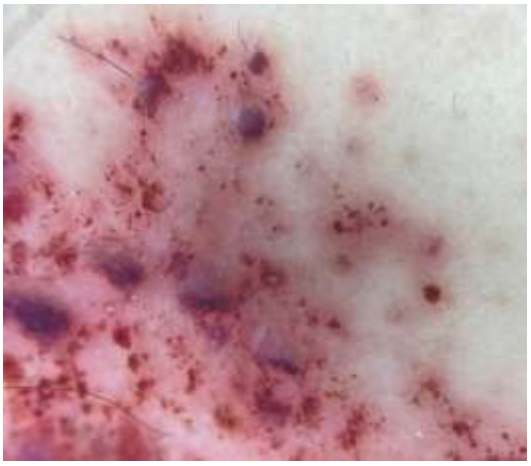

Figure 2: Dermatoscopy image showing hemorrhagic blisters and purpuric globules and dots on orange-brown background.

The clinical impression was that of leukocytoclastic vasculitis likely induced by the new antibiotic, tigecycline, which was immediately replaced with meropenem. As herpes zoster infection with multi-dermatomal involvement was also a possibility, vesicular fluid was sent for polymerase chain reaction for varicella-zoster virus (VZV PCR). While awaiting results, the antiviral acyclovir was started intravenously (IV).

Laboratory results revealed low hemoglobin (8.9 g/dL); mild neutrophilia (5.2 10^9/L); normal platelet count; and raised CRP (167 mg/L). Derangement of coagulation profile yielded prothrombin time (PT): 17.5 sec; activated partial thromboplastin time (APTT): 53.6 sec; thrombin time: 25.8 sec; international normalized ratio (INR): 1.72. Renal function test yielded estimated glomerular filtration rate (eGFR) at 18 mL/min/1.73 m^2; creatinine at 325 umol/L; and potassium ion (K^+) at 5.3 mmol/L. Liver function results were normal except for raised alkaline phosphatase (ALP) (176 U/L) and hypoalbuminemia (22 g/L). When the results for herpes simplex virus (HSV) and VZV PCR came negative, acyclovir IV was discontinued.

Two skin punch biopsies from right forearm were sent for histopathology and immunofluorescence studies. Immunofluorescence result was negative. Histopathological examination revealed clefting at the dermoepidermal junction, and the underlying dermis showed perivascular inflammation [Figure 3]. At higher magnification, neutrophils were visible in the wall of blood vessels with fibrinoid necrosis [Figure 4]. Neutrophilic nuclear dust was also seen in the dermis. These features are typical for LCV. Thus skin punch biopsy confirmed the diagnosis of LCV as predicted.

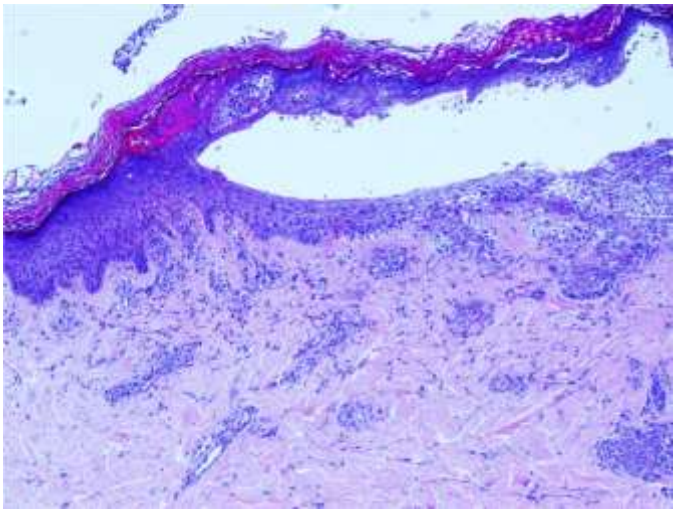

Figure 3: hematoxylin-eosin (H & E) stained slide at 4x magnification shows cleft at dermo epidermal junction with perivascular inflammation.

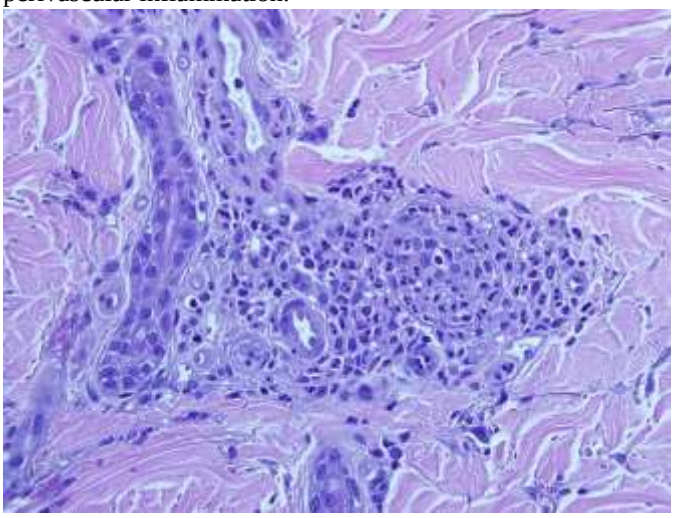

Figure 4: Hematoxylin-eosin (H & E) stained slide at 20x magnification shows neutrophils in the wall of blood vessel with fibrinoid necrosis.

After three days of stopping tigecycline, some vesicles deroofed and there were crusted lesions over right and left hand. The rash became duskier in color and the lesions over the left ear became crusted. The patient was discharged after ten days in stable condition with dramatic improvement in his skin condition.

Discussion

About 10% of LCV cases are drug induced. Some recent cases were associated with COVID-19 vaccination.[6,7] Tigecycline belongs to the newer class of powerful tetracycline-derived antibiotics and has an extraordinarily broad spectrum of activity against many resistant gram-positive, gram-negative, and anaerobic pathogens.[8] On the downside, tetracycline derivatives have been reported to induce autoimmunity such as anti-nuclear cytoplasmic antibody (ANCA)-associated vasculitis, cutaneous polyarteritis nodosa, and drug induced lupus.[9]

In our patient, the clear evidence that tigecycline caused LCV, because the cutaneous lesions improved within three days of the drug's discontinuation without the need of systemic therapy. We could find only one case in the

literature reported as tigecycline induced LCV.[5] Thus our case is the second one. Additionally, to our knowledge ours is the first case reporting tigecycline-induced hemorrhagic vesiculobullous LCV on the upper extremities as the first clinical manifestation.

Leukocytoclastic vasculitis is caused by activation of the complement system and the deposition of immune complex is walls of small blood vessels. After the recruitment of neutrophils, subsequent exudation of erythrocytes, fibrin, and serum occurs along with damage to the vessel walls. Small vessel walls will exhibit fibrinous necrosis as a result of lysosomal enzymes like collagenases and elastases as well as reactive oxygen species. The development of clinical findings is also aided by lymphokines. Increased levels of IL-1, IL-6, IL-8, and tumor necrosis factor may be found in the blood. The lower extremities' turbulence and elevated venous pressure may help to explain why LCV frequently affects the leg.[10]

In our patient, however, the rash started on upper extremities and ears sparing the trunk and lower extremities which is unusual for the cutaneous vasculitis. His skin eruptions were asymptomatic, probably because he was on strong analgesia. The grouped hemorrhagic vesiculobullous lesions resembled those from multidermatomal herpes zoster infection in immune compromised patients, especially the lesions on hard palate. This initially caused diagnostic uncertainty, especially as HCV is known to be associated in the pathogenesis of LCV.[11] The negative results for HSV and VZV PCR tests ruled out that possibility. The unusual presentation of LCV in our patient might be attributable to his complex medical history including peripheral vasculopathy secondary to ischemic cardiac disease and uncontrolled hypertension and diabetes that necessitated a limb amputation.

If LCV is suspected, a skin punch biopsy should be performed with direct immunofluorescence studies. It is recommended to choose a site with blue-gray blotch, being the most specific dermoscopic feature for true vasculitis.[12] Essential laboratory tests include complete blood counts, renal function and liver function tests, and urinalysis, with more extensive work up in case of systemic involvement.[13]

Diagnosing drug induced LCV might be challenging. However, recognizing the clinical features and resolution of cutaneous manifestations after discontinuation of offending drug can aid in the diagnosis.[2] As in the current case, cutaneous LCV has an excellent prognosis if it is limited to the skin and diagnosed early.

Conclusion

LCV is an extremely rare side-effect of the new-generation antibiotic tigecycline, the present case being the second one to be ever reported. Drug-induced LCV should be suspected when a patient develops new skin eruptions following recently started medication. Skin biopsy for routine histological and immunofluorescence studies constitutes the diagnostic gold standard for LCV. It should also be kept in mind that it is not essential for cutaneous vasculitis to start on the lower extremities.

Disclosure

The authors declare no conflicts of interest. Written consent of the patient was obtained to publish this case report.

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