

# Tigecycline Induced Hemorrhagic Vesiculobullous Leukocytoclastic Vasculitis: A Rare Clinical Presentation

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## ***Abstract***

Drug induced leukocytoclastic vasculitis is defined as blood vessels inflammation that caused by use of different 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 in 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 hemorrhagic vesiculobullous type in immunocompromised patient who was treated with tigecycline for parapneumonic effusion with persistent high inflammatory markers.

**Keywords:** Drug-Induced Vasculitis Tigecycline, Induced Vasculitis; Hemorrhagic Vesiculobullous Leukocytoclastic Vasculitis.

## **Introduction**

Vasculitis is defined as inflammation of blood vessels. It affects the structure and function of blood vessels, resulting in weakening, narrowing, and scarring of blood vessel wall. Type of vasculitis depend on size, type and location of affected vessels. It categorized as large vessel, medium vessel, small vessel and variable vessel vasculitis. Vasculitis can be a primary process or a secondary due to different etiologies.<sup>1</sup>

Leukocytoclastic vasculitis (LCV) is small vessel vasculitis. It is a histopathologic term that describe small vessels vasculitis in which the inflammatory infiltrate is composed of neutrophils.<sup>2</sup>

Cutaneous LCV is usually limited to the skin and presented as palpable purpura in lower limbs.<sup>1</sup>

Up to 50% of LCV cases are idiopathic. LCV can be secondary to systemic diseases, infections, malignancies and drugs.

Drugs are considered one of the most common triggers of LCV. The onset of LCV is usually 1-3 weeks of after initiation of drugs. 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 common causes of LCV.<sup>3</sup>

A skin punch biopsy with immunofluorescence study should be performed whenever leukocytoclastic vasculitis is suspected. Most cases of idiopathic cutaneous LCV are self-limited within weeks to months. However, some cases require systemic treatment that range from corticosteroid to other steroid sparing agents. In case of drug induced LCV early withdrawal of the offending drug is sufficient to enhance rapid resolution and recovery.<sup>4</sup>

Tigecycline induced LCV is a rare presentation. One case has been reported in 2015 with a sudden skin eruption of macular purpuric rash symmetrically distributed on lower limbs.<sup>5</sup> Here we are discussing a case report of tigecycline induced LCV with atypical clinical presentation.

## Case Report

A 44 years old Omani man with a history of Uncontrolled hypertension, uncontrolled diabetes type II with end stage renal disease on regular hemodialysis . He has hepatitis C virus and ascites. He has ischemic heart disease with EF 30-50% .He underwent left lower limb above knee amputation . He has recurrent bilateral pleural effusion that required multiple pleural tapping. He was admitted with right sided pleural effusion complicated with parapneumonic effusion with high inflammatory markers and fever . Patient was treated accordingly and started on intravenous Tazocin and he was prepared for right lung decortication. Patient underwent right posterolateral thoracotomy for decortication drainage of pleural effusion. He 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 they get the results of the final sensitivity of his screening samples. After three days from starting tigecycline, the patient developed sudden asymptomatic erythematous progressive skin eruptions symmetrically distributed on upper extremities and ears sparing the face, trunk and lower extremities .

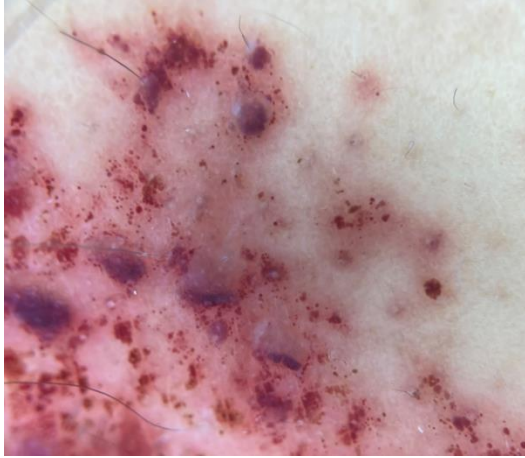
Patient was conscious and alert. He was afebrile and vital signs were within normal.

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 showed purpuric maculopapular lesions at hard palate and healed ulcers at left buccal mucosa. Trunk, lower extremities and genital area were not affected [Figure 1].

Dermoscopy was performed and showed: hemorrhagic blisters, purpuric globules and dots with orange-brown background [Figure 2].



**Figure 1:** (a) Grouped hemorrhagic blisters with purpuric background in dorsum of right hand. (b) Purpuric macules over helix of right ear. (c) Grouped hemorrhagic blisters with purpuric background in the lateral aspect of left forearm. (d) grouped hemorrhagic blisters in the hard palate.

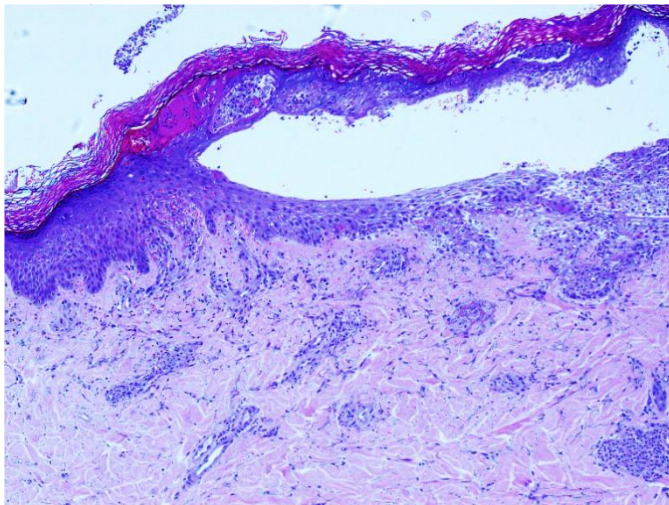


**Figure 2:** Dermoscopy showing hemorrhagic blisters, purpuric globules and dots with orange-brown background.

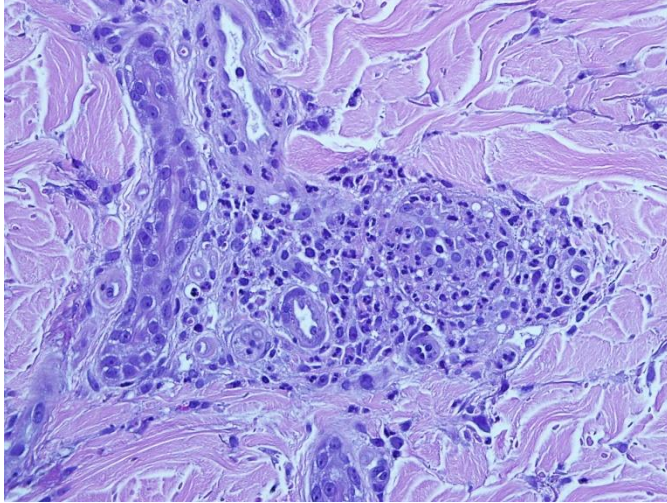
The clinical impression was leukocytoclastic vasculitis probably due to Tigecycline. So tigecycline was stopped immediately and meropenem was started. Herpes zoster infection with multidermatomal involvement was another possibility so vesicular fluid was sent for VZV PCR and IV acyclovir was started .

The performed laboratory testing showed Hb 8.9 g/dL, mild neutrophilia of  $5.2 \times 10^9/L$  with normal platelet count and raised CRP: 167 mg/L. Derangement of coagulation profile with PT:17.5, APTT:53.6, thrombin time: 25.8 and INR: 1.72. Renal function test showed eGFR: 18 ml/min/1.73 m<sup>2</sup>, creatinine: 325 umol/L and K<sup>+</sup>: 5.3. Liver functions test within normal except of raised ALP:176 U/L and hypoalbuminemia of 22 g/L. HSV and VZV PCR came as negative.

Two skin punch biopsies were taken from right forearm and sent for histopathology and immune fluoresce studies. Histopathology examinations showed clefting at the dermoepidermal junction, underlying dermis showed perivascular inflammation [Figure 3]. At high power examination there were neutrophils in the wall of blood vessels with fibrinoid necrosis [Figure 4]. Neutrophilic nuclear dust was also seen in the dermis. These features were typical for LCV. Immunofluorescence was negative.



**Figures 3:** H and E slide at 4 X magnification show cleft at dermo epidermal junction with perivascular inflammation.



**Figure 4:** H and E stained slide at 20 X magnification showing neutrophils in the wall of blood vessel with fibrinoid necrosis.

So, skin punch biopsy confirmed the diagnosis of leukocytoclastic vasculitis possibly tigecycline-induced as predicted. IV Acyclovir was discontinued.

After 3 days of stopping tigecycline, some vesicles already deroofed and there were crusted lesions over right hand and left hand. The rash became more dusky in color and lesions over left ear became crusted.

Patient continued his medical management under the care of cardiothoracic team and was discharged after 10 days in stable condition with dramatic improvement in skin lesions.

## Discussion

Leukocytoclastic vasculitis (LCV) is a small vessel vasculitis. It is a histopathological term that describes neutrophilic infiltrate of blood vessels. LCV is a primary or a secondary process. Up to 50% of LCV cases are idiopathic. Secondary causes of LCV include connective tissue diseases, malignancies, infections and drugs. The latter two are common causes of LCV.<sup>2</sup> There are cases of LCV have been reported following COVID-19 vaccination.<sup>6,7</sup>

10% of LCV cases are drug induced. The onset of LCV is usually 1-3 weeks of after initiation of drugs. 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 common causes of LCV.<sup>3</sup>

Tigecycline is the first of a new class of broad-spectrum antibiotic, glycyl-cyclins, to be developed specifically to treat multidrug resistant isolates to standard antibiotics. It has an extraordinarily broad spectrum of activity against most Gram-positive, Gram-negative and anaerobic pathogens.<sup>8</sup> It is a tetracycline derivative. There are reports of tetracycline derivative induced autoimmunity such as anti-nuclear cytoplasmic antibody (ANCA)-associated vasculitis, cutaneous polyarteritis nodosa and drug induced lupus.<sup>9</sup>

In our patient, tigecycline was the cause of LCV as the cutaneous lesions improved and started to be crusted after discontinuation of Tigecycline in three days without the need of systemic therapy. There is one case reported Tigecycline induced LCV.<sup>5</sup> Our case is the second case report. However, to our best of knowledge this is the first case reporting tigecycline induced hemorrhagic vesiculobullous LCV on the upper extremities as first clinical manifestation.

Leukocytoclastic vasculitis is caused by activation of the complement system and the deposition of immune complex in 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 the clinical findings is also aided by lymphokines. Increased levels of IL-1, IL-6, IL-8, and tumor necrosis factor are found in the blood. The lower extremities' turbulence and elevated venous pressure may help to explain why leukocytoclastic vasculitis frequently affects the leg.<sup>10</sup>

The clinical features of LCV range from asymptomatic skin eruptions to life threatening systemic involvement. Cutaneous LCV is usually limited to skin and rarely has systemic involvement. Clinical manifestations appear usually 1-3 weeks after the triggering event. LCV usually manifests as erythematous macules with palpable purpura or petechiae. It mainly affects the lower extremities. Extracutaneous manifestations are rare. However pulmonary, renal, gastrointestinal or neurological symptoms might present.<sup>2</sup>

In our case, the skin eruptions were asymptomatic which could be attributed to the strong analgesia the patient was on. Clinically the rash started on upper extremities and ears sparing the trunk and lower extremities which is unusual for the cutaneous vasculitis. The grouped hemorrhagic vesiculobullous were resembling multidermatomal herpes zoster infection in immune compromised patient especially the lesions on hard palate which was confusing. These unusual presentation of LCV in this patient can be explained that patient underwent left lower limb above knee amputation and because of peripheral vasculopathy secondary to ischemic cardiac disease and uncontrolled hypertension and diabetes.

The deposition of HCV-containing immune complexes (CIC) in the skin could be the initial pathogenic event for cryoglobulinemic vasculitis; subsequently CIC could spread from the vascular bed to the perivascular tissue and then could be very rapidly eliminated. The direct role of HCV in the pathogenesis of cryoglobulinemic vasculitis get established.<sup>11</sup>

In a known HCV cirrhotic patient, HCV leading to spontaneous bacterial peritonitis as a cause of LCV needs to be excluded by evaluating hematological inflammatory markers. These were not raised in our case.

If leukocytoclastic vasculitis is suspected, a skin punch biopsy should be performed with direct immunofluorescence studies. It is recommended that to choose site for skin biopsy that showed dermoscopic features of blue-gray blotch as it is the most specific dermoscopic feature for true vasculitis. These features represent vascular injury with severe inflammation.<sup>12</sup>

Other laboratory testing depends on clinical presentation. Complete blood counts, renal function tests and liver function test along with urinalysis are recommended to be done once if patient is asymptomatic. More extensive work up is needed in case of systemic involvement.<sup>13</sup>

Management of LCV constitutes of identifying and treating the underlying cause. In case of drug induced LCV, discontinuation of the offending drug is crucial in the resolution of the vasculitis. In idiopathic cutaneous LCV, most cases are self-limited and it takes weeks to months to resolve. Systemic treatment might be needed depending on the severity of LCV. Following systemic agent can be used: corticosteroids, antihistamines, dapsone, nonsteroidal anti-inflammatory drugs, colchicine, potassium iodide, immunosuppressive agents and rarely monoclonal antibodies.

Cutaneous LCV had an excellent prognosis if it is only limited to the skin and diagnosed early. 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.<sup>2</sup>

## **Conclusion**

Drug-induced LCV should be suspected in any patient who developed new onset skin eruptions along with recently started medication. To reach the correct diagnosis a thorough history, physical examination and relating symptoms

resolutions with stopping the culprit drug. Skin biopsy for routine histology and immunofluorescence studies are the gold standard. LCV is rare side effect of tigecycline. It should be kept in mind that cutaneous vasculitis not necessary to start on lower extremities.

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