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Leukocytoclastic Vasculitis after Ceftriaxone Exposure: A Case Report and Literature Review

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Abstract

Leukocytoclastic Vasculitis (LCV) characterizes various small vessel vasculitis types primarily affecting the skin, with occasional internal organ involvement. This inflammation involves immune-complex deposition within dermal capillaries and venues. Although idiopathic in origin, potential triggers, including antibiotic-related factors, must be considered. LCV presents across a spectrum of severity, sometimes extending to ulcers. Diagnosis involves clinical assessment, history, lab tests, and crucially, skin biopsy. Here, we detail the case of a 24-year-old female, free of prior medical issues except hypothyroidism, who developed non-blanching purpuric lesions on her lower extremities and back after ceftriaxone treatment for UTI. Discontinuation of ceftriaxone and steroid administration, prompted by a confirmatory skin biopsy showing leukocytoclastic vasculitis, led to rash resolution during follow-up. In striving for optimal outcomes, early vasculitis diagnosis and causal agent recognition are paramount. While the antibiotic-LCV link is infrequent, investigations into leukocytoclastic vasculitis etiologies warrant careful review of medication-induced factors.

Keywords: Leukocytoclastic Vasculitis; Antibiotic; Ceftriaxone; Case Report

Introduction

Leukocytoclastic vasculitis (LCV) is a histopathological term that the International Chapel Hill Consensus Conference (CHCC) uses to refer to different types of small vessel vasculitis. As the new dermatologic addendum to CHCC 2012 suggests, LCV predominantly affects the skin but can also affect other organs or be a variant or component of systemic vasculitis [1,2].

LCV is characterized by inflammation and necrosis in the small vessels, resulting in palpable purpura. This is the principal clinical presentation of LCV. Additional skin presentations encompass bullae, papules, plaques, nodules, ulcers, and live do reticular is [3,4]. LCV particularly affects the lower extremities; however, about one-third of patients also experience symptoms on their trunk and upper extremities, typically excluding the palmar, plantar, and mucosal areas. Involvement of joints is another facet of LCV. Some patients may initially present with joint pain or arthritis, often involving the knees or ankles [4].

Systemic manifestations of LCV are less common compared to its effects on the skin. These may include fever, microscopic hematuria, elevated creatinine levels, pericarditis, and pleurisies [4].

As per the updated CHCC classification, LCV is categorized into: (1) ANCA-associated vasculitis (AAV), (2) immune complex vasculitis, including cryoglobulinemic vasculitis (CV), IgA-vasculitis (Henoch-Schonlein purpura, HSP), hypocomplementemic urticarial vasculitis (anti-C1q vasculitis, HUV), and IgM/IgG immune complex vasculitis (previously referred to as Hypersensitivity Vasculitis), (3) vasculitis linked to systemic diseases (such as rheumatoid arthritis, systemic lupus erythematosus, and sarcoidosis), and (4) vasculitis associated with probable causes (for example, related to infections, medications, sepsis, or cancer) [2].

While systemic involvement is typically found in about half of LCV cases, the cause of the other half of cases is split between unclassified or idiopathic causes and drug or infection-induced single-organ cutaneous small vessel vasculitis. Among the drugs reported to be associated with LCV are antibiotics, particularly beta-lactams. Sulfonamides, quinolones, and non-steroidal anti-inflammatory drugs (NSAIDs) are most commonly reported [2].

Ceftriaxone, a widely used third-generation cephalosporin antibiotic, though it has been occasionally linked to immune-mediated reactions, is rarely included in vasculitis cases [5,6]. In this case report, we present a compelling instance of Leukocytoclastic vasculitis occurring in a patient following exposure to Ceftriaxone, shedding light on the potential connection between drug exposure and the development of this vasculitic condition.

Case Presentation

A 24-year-old female without a history of previous drug allergy and a medical history of 2 years of hypothyroidism presented with a 3-day history of progressive skin rash development. Presenting as palpable purpura, then evolving into a maculopapular rash, the rash appeared first on the left leg, spread to include the other leg, then ascended to the thigh and, to a lesser extent, to the abdomen, back, chest, and upper limbs. The rash was associated with itching and a burning sensation. (Figure 1)

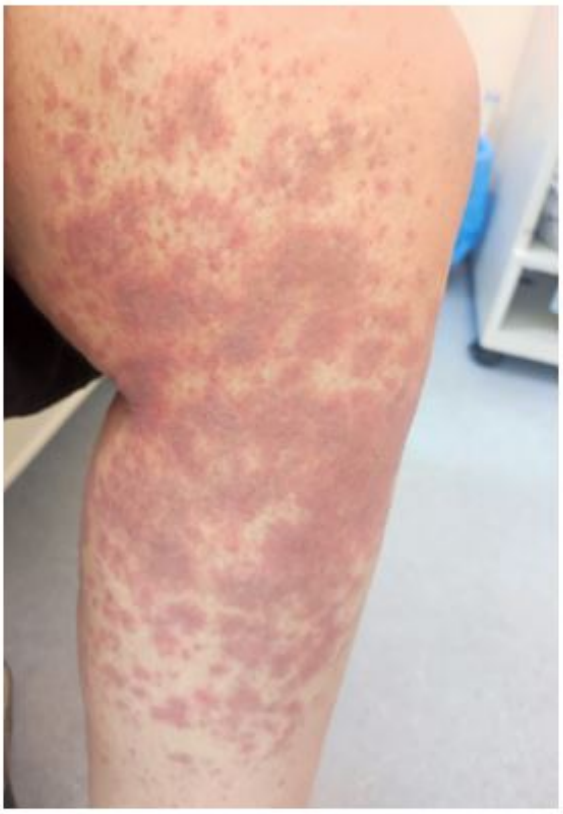

Figure 1: Non-blanching purpuric lesions on lower extremities

Five days before this presentation, the patient had been treated with ceftriaxone, paracetamol, and IV fluids for urinary tract infection, which was confirmed by urine analysis taken after the patient presented at an outpatient clinic complaining of moderate suprapubic abdominal pain associated with dysuria, frequency, urgency, episodic fever, and chills, with no history of diarrhea or vomiting. So, she sought medical help at an outpatient clinic, where she was diagnosed with a urinary tract infection based on urine analysis.

During the physical exam, multiple non-blanching purpuric lesions were noted, limited to the lower extremities with a little extension to the back. Vital signs, including blood pressure, heart rate, respiratory rate, and oxygen saturation, were within normal limits.

Routine lab tests were ordered. The white blood cell count, red blood cell count, platelet count, kidney function tests, and liver function tests were within normal limits. The viral panel was negative. Urine analysis showed moderate bacteria, WBCs of 9, and RBCs of 1.

A skin biopsy was taken from the lesion and revealed leukocytoclastic vasculitis. The superficial, small dermal blood vessels showed fibrinoid necrosis and infiltration of neutrophils with a leukocytoclastic pattern. No evidence of granuloma or malignancy was reported. (Figure 2)

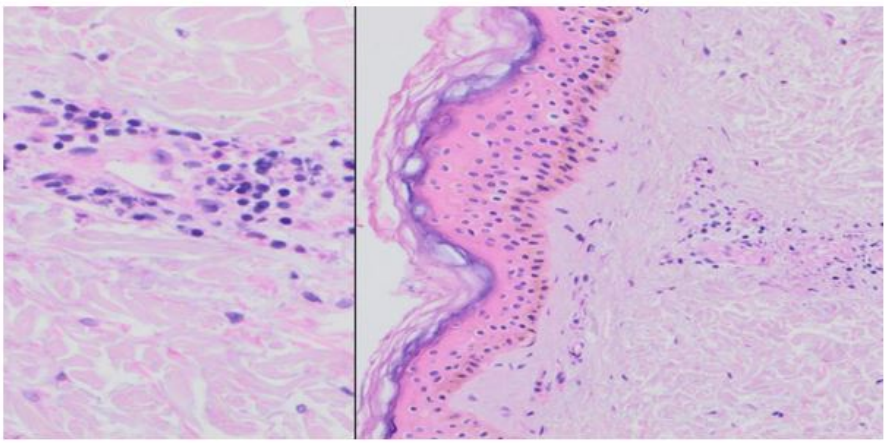

Figure 2: H&E stain: Dermal vasculitis characterized by infiltration capillary sized blood vessels by neutrophils with leuckocytoclasis and fibrinoid necrosis.

Ceftriaxone was discontinued, and the patient was treated with IV steroids in the hospital for 3 days. Upon discharge, the patient was put on tapered oral steroids for 1 week. On follow-up, the rash disappeared, and the patient is doing well.

Discussion

Several factors may contribute to the onset of LCV (Leukocytoclastic Vasculitis) including connective tissue disorders, malignancies, infections, notably those affecting the upper respiratory tract, drugs, and intravenous drug misuse [7]. Drug-induced cutaneous vasculitis (DIV) is categorized as "vasculitis associated with probable etiology" in the updated 2012 CHCC nomenclature. DIV impacts a minority, with studies documenting an 8-11% incidence of DIV among inpatients [8].

The exact mechanism of leukocytoclastic vasculitis remains unclear. Nonetheless, it is suggested that the deposition of immune complexes in the walls of small vessels may play a pivotal role in this process. The deposition of immune complexes in the walls of arterioles, capillaries, and postcapillary venules triggers the activation of the complement cascade, specifically C3a and C5a. As a result, activated neutrophils driven by chemotactic factors and vasoactive cytokines migrate and infiltrate the vessel wall, releasing lysosomal enzymes and free oxygen radicals, leading to damage of the vessel wall and extravasation of red blood cells and fluid to surrounding tissue, clinically leading to purpura formation. Following degranulation, neutrophils experience a subsequent process known as leukocytoclasia, during which they undergo cellular degradation and ultimately die. This process results in the release of nuclear debris, also referred to as nuclear dust, which, along with the fibrinoid deposit, the remaining neutrophils, and swallowed endothelial cells, define LCV histologically [9,1].

Drugs associated with LCV cover a wide range of pharmacologic categories, including antimicrobials, antivirals, anticonvulsants, chemotherapeutics, cardiovascular drugs, diuretics, anticoagulants, thrombolytics, and numerous others. [8]. Fluoroquinolones, especially Ciprofloxacin, are the most common antibiotic medications reported to be implicated in LCV [10]. Our culprit, Ceftriaxone, however, is rarely implicated, with the latest regularly updated report done by eHealthMe to the FDA disclosing that only 24 people (0.07%) out of 33,453 who reported side effects when taking Ceftriaxone had leukocytoclastic vasculitis (true to date, June 21, 2023) [11]. With a thorough review of the literature and other case studies disclosing the finding that only 4 cases asserted LCV due to Ceftriaxone exposure, ours would hence be the fifth case reported [7,10,12,13].

Although skin involvement in LCV can be limited, dominant, or a component of systemic vasculitis, it is mostly skin-limited in the vast majority of drug-induced vasculitis. Skin involvement mainly refers to palpable purpuric lesions that likely appear 7-21 days after being exposed to a certain medication. These lesions mainly show on the lower extremities and, to a lesser degree, on the back, sacral, gluteal region, hands, and forearms [3,14]. This classic pattern of presentation correlates with our patient, who pre-

sented on the fifth day following treatment with Ceftriaxone with a painful, palpable purpura that disseminated to include the bilateral lower extremities extending to the thigh and, to a lesser extent, to the abdomen, back, chest, and the upper limbs. Vesicles, bullae, nodules, or ulcers could also manifest cutaneously, though less commonly. Systemic manifestations involving the abdomen, kidneys, and joints, in particular, can also be associated with DIV [14]. However, our patient didn't have any systemic symptoms.

Based on the American College of Rheumatology criteria, which have a sensitivity of 71% and specificity of 83.9%, LCV is diagnosed if a patient is found to have at least three of five of the following: a patient older than 16 years, palpable purpura, maculopapular rash, history of use of a possible drug that correlates with symptom onset, and skin biopsy findings that are pathognomonic for leukocytoclastic vasculitis [15]. Seeing as our patient scored 5/5, the diagnosis of LCV was likely. However, a skin biopsy examined histologically and under immunofluorescence is considered the gold standard for diagnosis; it is only used to confirm the diagnosis, as the pathognomonic findings of LCV, which include neutrophilic infiltration of vessel walls with necrosis and fibrinoid deposition, can change after approximately 2 days, providing a narrow window of 24-48 hours after the onset of skin lesions for obtaining a biopsy [10,1].

The diagnosis of LCV alone is not enough for effective management, and identifying the offending agent is needed. Discontinuation of the offending agent typically leads to the complete resolution of clinical symptoms without recurrence [2]. However, pinpointing the exact cause can be challenging due to the broad range of medications implicated, especially in the setting of a patient with polypharmacy and concurrent infections [8]. Hence, a thorough history, physical examination, and laboratory workup are indispensable when evaluating patients with vasculitis. Focusing on promptly recognizing associated skin manifestations, correlating drug use chronologically with the onset of skin lesions, and excluding systemic diseases [2,1,16]. With no systemic symptoms and a negative immunological workup, our patient was ruled negative for systemic diseases. The used drug paracetamol seems unlikely to be the culprit since the incidence of LCV following paracetamol use doesn't exceed 0.01%, according to the revised eHealthMe report [17]. And with the viral panel results turning negative, a viral infection was also ruled out. Ruling out other possible differentials in our patient, the vasculitis was assumed to be ceftriaxone-induced, especially seeing as the rash regressed upon withdrawal of ceftriaxone and the use of corticosteroids.

In addition to the etiology of LCV, effective treatment depends on its severity. While mild cases are self-resolved by discontinuing the causative agent with or without symptomatic treatment such as antihistamines or nonsteroidal anti-inflammatory drugs, cases with systemic, severe, or acute forms of the disease may need to be treated with immunosuppressive drugs using steroids alone or combined with other drugs [2,1].

The four cases that we found through our systematic review included two males and two females, aged 17, 35, 49, and 61 years (Table *1*). All patients had a history of infection that required an antibiotic prescription for treatment (colitis, upper respiratory infection (URI), urinary tract infection, and endocarditis). While two of the patients had a past medical history of chronic hepatitis C, one of them had a previous history of Guillain-Barré syndrome (GBS) (Table *1*). Additionally, all patients presented with a non-blanching, palpable, and purpuric rash, mostly over the extremities; however, only one patient had renal involvement. With a maximum of 14 days and a minimum of 2 days, the median time between antibiotic use and the onset of vasculitic symptoms is calculated to be eight days. The patient's diagnosis in all four cases was confirmed by a skin biopsy. For treatment, steroids were given to most, and ceftriaxone was discontinued for all. With that, remission was achieved with a median duration of 10 days (Table *1*) [7,10,12,13]. In our specific case, the patient exhibited the rash after 5 days of Ceftriaxone use and showed complete recovery in less than 2 weeks following the cessation of Ceftriaxone and treatment with antihistamines and IV steroids.

Table 1: Characteristics of patients with Ceftriaxone-induced leukocytoclastic vasculitis.

Reference/author	Age*/sex	Previous diagnosis	Clinical presentation	Duration of antibiotic use	diagnosis	Histopathology finding	treatment	Resolution
[8] Almasoudi AA, et al.	49/F	URI/ GBS	erythematous, maculopapular, simultaneously pruritic and burning skin rash involving the upper and lower extremities, Swelling was confined to the lower lip	2 days	LCV	skin biopsy showed LCV	oral prednisolone	1 month
[9] Agrawal SR, et al.	17/F	colitis	facial puffiness, anasarca, decrease urine output and reddish purpuric rash	5 days	LCV with renal failure	skin biopsy showed LCV	oral prednisolone 40 mg, ceftriaxone discontinued	5 days
[1] Raina AI et al.	61/M	UTI/ hepatitis C	Non-blanching, palpable purpuric maculopapular rash predominantly involving lower extremities and buttocks	3 days	LCV	skin biopsy showed LCV	ceftriaxone discontinued	10 days
[10]Haehn DA, et al.	35/F	Endocardites /HTN,hepatitis C	5-day rash in lower extremities, joint pain	14 days	LCV	skin biopsy showed LCV	Corticosteroids, ceftriaxone discontinued,daptomycin	Not report
Our case	22/F	UTI	Skin rash , itching and burning sensation	5 days	LCV	skin biopsy showed LCV	IV steroids,ceftriaxone discontinued	14 days

UTI: urinary tract infection; URI: Upper Respiratory Infection; GBS: Guillain-Barre syndrome; HTN: hypertension; LCV: Leukocytoclastic Vasculitis; F: female; M: male. * Age in years

Conclusions

Drugs have a potential side effect that could lead to morbidity or even mortality when not identified correctly and timely, Ceftriaxone-induced LCV has an excellent prognosis when identified promptly, however, diagnosing DIV is challenging. This case adds to the limited body of knowledge surrounding Ceftriaxone-induced LCV and underscores the importance of its timely recognition through taking detailed patient history, conducting a thought patient physical evaluation, correctly identifying the skin lesion, and doing laboratory workup. This in turn aides in reaching accurate diagnosis and appropriate management, thus the best possible outcomes for patients affected.

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