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Case report

Oxacillin-induced leukocytoclastic vasculitis

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ABSTRACT

Leukocytoclastic vasculitis (LCV) refers to a histopathological pattern of neutrophil predominant inflammatory process of small vessels associated with fibrinoid necrosis. Cutaneous LCV usually presents as symmetrically distributed palpable purpuric nodules of the lower extremities with or without systemic involvement. Although 50% of LCV cases are idiopathic, it can be secondary to identifiable causes such as malignancy, autoimmune conditions, infections, and medications. Medications have been implicated in up to 25% of cases; sulfonamides, NSAIDs, and beta-lactams have the most frequent association. We herein present a 32-year-old female who developed palpable purpura over hands and lower limbs 12 days after exposure to oxacillin administered for infective endocarditis. Punch biopsy from the skin lesions confirmed the diagnosis of LCV. Given the temporal relationship between oxacillin administration and development of skin findings, the diagnosis of oxacillin-associated LCV was suspected. Discontinuation of drug resulted in resolution of the lesions confirming the diagnosis. To our knowledge, this is the second case of oxacillin-induced cutaneous LCV described in literature.

Introduction

Leukocytoclastic vasculitis (LCV), also known as hypersensitivity vasculitis, is a histopathological term used to describe inflammatory changes driven by neutrophils in small vessels [1]. LCV is a rare condition which frequently presents with palpable purpuric nodules of the lower extremities. It usually presents as isolated cutaneous disease in various morphological presentations, but extracutaneous involvement such as gastrointestinal tract and kidney involvement are not uncommon [2,3]. Although 50% of LCV cases are idiopathic, it can be secondary to identifiable causes such as malignancy, autoimmune conditions, infections, and medications. Medications have been implicated in 10 to 24% of the cases of LCV, the most frequent agents being sulfonamides, nonsteroidal anti-inflammatory drugs, and beta-lactam antimicrobials [4,5]. Treatment depends on the etiology, severity of symptoms, and presence of extracutaneous involvement, and can vary from symptomatic therapy to immunosuppressive medications [2,6]. We present the second reported case of oxacillin-induced LCV, in whom vasculitis was confined to skin, with no other evidence of systemic vasculitis.

Case report

A 32-year-old woman with a history of intravenous drug use and attention deficit/hyperactivity disorder presented for the evaluation of fevers, chills and shortness of breath. She had been in her usual health until a week prior to admission when she started to have fever, chills and generalized weakness. Additionally, a few days before presentation, the patient experienced shortness of breath. Her social history revealed that she was a non-smoker and did not consume alcohol however had been abusing fentanyl intravenously. The patient was only on dextroamphetamine/amphetamine. She denied exposure to any other medications or chemicals.

On admission, her vitals were as follows: Temperature 102.7 °Fahrenheit, blood pressure 102/56 mmHg, pulse 136 beats per minute, and respiratory rate 38 breaths per minute. The oxygen saturation was 94% on room air. Physical examination revealed a well-developed female in moderate respiratory distress; bilateral rhonchi; regular heart rhythm, tachycardia, no murmur, rub or gallop. Investigations revealed a white blood cell count (WBC) of

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12,200/mm3, a hemoglobin of 10.9 g/dL, a platelet count of 85,000/mm3, ESR of 60 mm/hr, and hyponatremia with a sodium of 124 mmol/L. Kidney function tests showed creatinine level of was 2.8 mg/dL with a BUN of 98 mg/dL. NT-proBNP was 1028 pg/mL (normal 0–450 pg/mL). Her ECG showed sinus tachycardia, and a chest radiograph was remarkable for bilateral lower lobe infiltrates associated with small pleural effusions. Patient was given IV fluids and levofloxacin intravenously to cover community acquired pneumonia. Her clinical condition deteriorated a day after admission to the medical floor and she was transferred to the intensive care unit for septic shock and acute respiratory failure requiring pressor support and mechanical ventilation.

Her blood cultures grew gram-positive cocci for which she was started on vancomycin therapy. Transthoracic echocardiogram showed a large vegetation at the tip of anterior leaflet of tricuspid valve measuring 2 cm x 1.2 cm and moderate-to-severe tricuspid regurgitation. Cardiothoracic surgery was therefore consulted. Transesophageal echocardiogram with contrast study further revealed patent foramen ovale with shunt. CT chest showed multiple cavitary peripheral lung nodules, consistent with septic emboli. Furthermore, patient also developed non-oliguric AKI and required renal replacement therapy for acute tubular necrosis secondary to perfusion-related kidney injury in the setting of septic shock.

Blood cultures grew methicillin sensitive *Staphylococcus aureus* (MSSA) on the third day of the ICU stay, therefore oxacillin (2 g IV every 6 h) treatment was initiated. The patient gradually improved on supportive and antimicrobial therapy over the course of two weeks, was eventually weaned off pressors and successfully extubated. Renal function started to recover as well.

12 days after initiation of oxacillin, skin examination revealed bilateral nontender purpuric papules localized predominantly on the dorsal aspect of the patient's hands and feet (Fig. 1). Skin findings evolved into bullous lesions over the following 24–48 hours and similar lesions were noted on the anterior knee and lateral aspect of thighs (Fig. 2). No mucosal or palmar involvement was observed. She did not have abdominal pain, arthralgias, paresthesia, fever or chills.

Laboratory tests were negative as follows: HIV antibody, hepatitis B serology, p-ANCA and c-ANCA, cryoglobulin and rheumatoid factor. ANA was weakly positive at a titer of 1:40 and anti-ds DNA antibody was negative. Complement C3 was low with a level of 14 mg/dL (normal 75–175 mg/dL) and C4 was 28 mg/dL (normal 14–40 mg/dL). Anti−HCV antibody was positive with an HCV viral load of 4.16×10^5 IU/mL. No significant changes in red blood count, leukocyte count, and kidney function were observed. Eosinophil count remained within the normal limits throughout the hospital stay.

Aspirated fluid from her bullous lesions did not grow bacteria, and there were no organisms seen on gram staining. Punch biopsies from the bullous skin lesions showed perivascular neutrophil infiltration with fibrinoid necrosis of small vessels consistent with leukocytoclastic vasculitis (Fig. 3). No bacteria, fungi or evidence of viral inclusions were identified. Given the clinical and pathological correlation as well as the temporal relationship between oxacillin administration and development of skin findings, the diagnosis of oxacillin-associated LCV was suspected. Accordingly, vancomycin was started in lieu of oxacillin, resulting in progressive resolution of skin lesions without scar formation.

The patient later underwent tricuspid valve replacement surgery with no perioperative complications. After one month, the patient was seen in a follow-up appointment and there was no recurrence of skin lesions.

Discussion

Small vessel vasculitides defines a broad spectrum of diseases, in which LCA denotes an entity where inflammation in small vessels is driven by neutrophils, resulting in leukocytoclasia. LCV most commonly presents as cutaneous vasculitis without systemic involvement or glomerulonephritis, which is termed as isolated cutaneous LCV [7]. Its incidence has been estimated to be 15.4–38.6 per million by several studies. Extracutaneous involvement is relatively infrequent, constitutes 15–30% of the cases and most commonly manifest as arthralgias, abdominal pain, and hematuria [8]. The exact pathophysiology is unknown; however, immune complex deposition in vessel walls with subsequent complement activation is believed to be the initial step in the pathogenesis of LCV. The majority of cases are idiopathic, but it can be secondary to

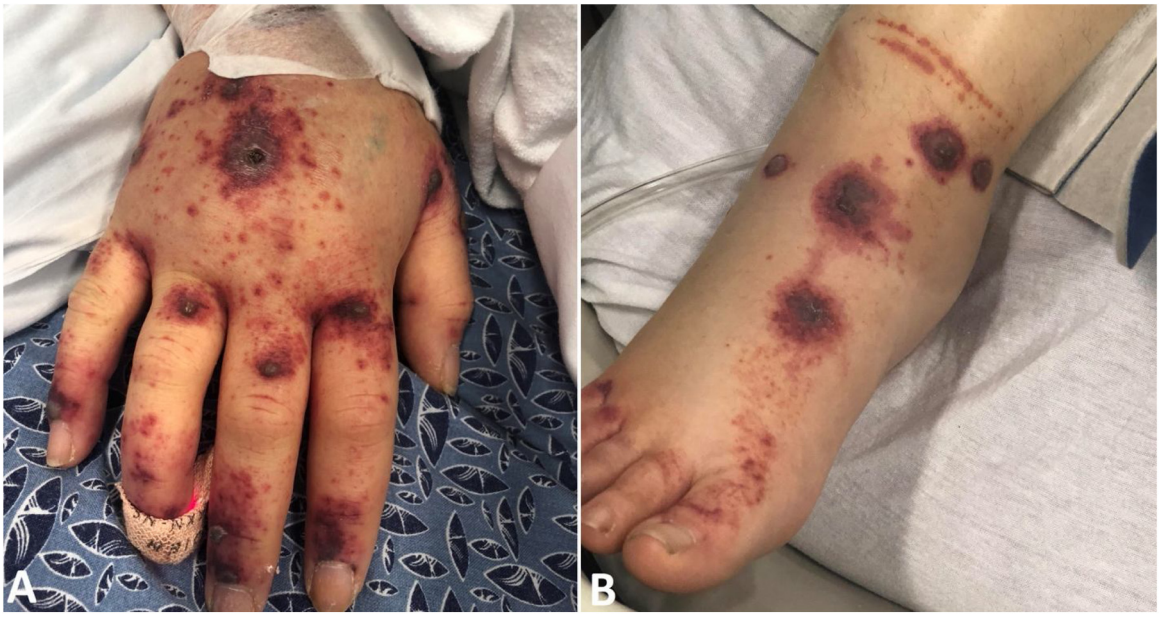

Fig. 1. Palpable purpuric and bullous lesions localized predominantly on the dorsal aspect of hands (A) and feet (B).

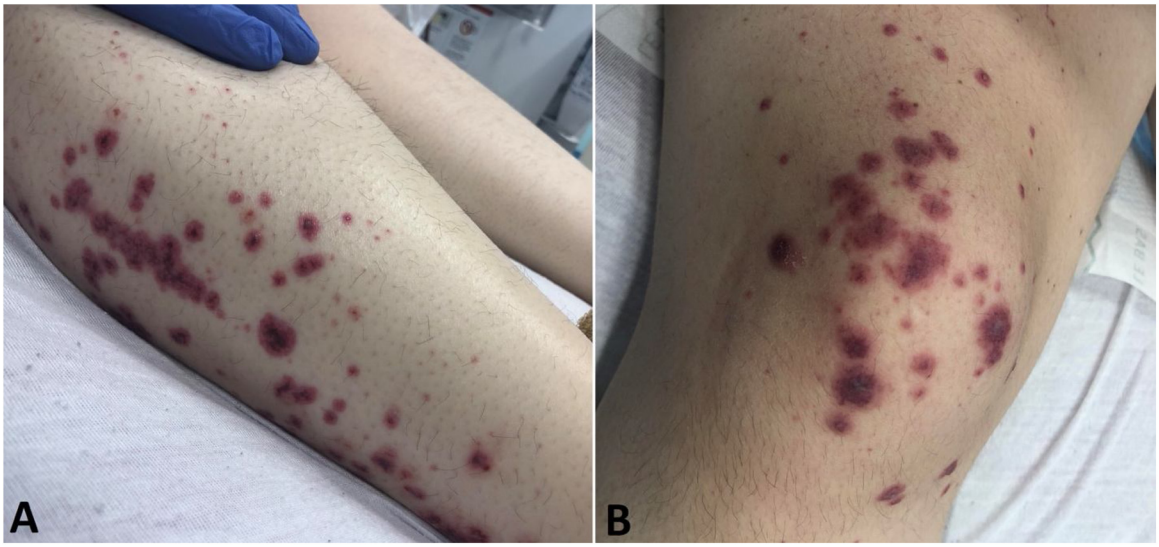

Fig. 2. Multiple palpable round-ovular lesions cover the lateral (A) and anterior (B) aspect of the lower limbs.

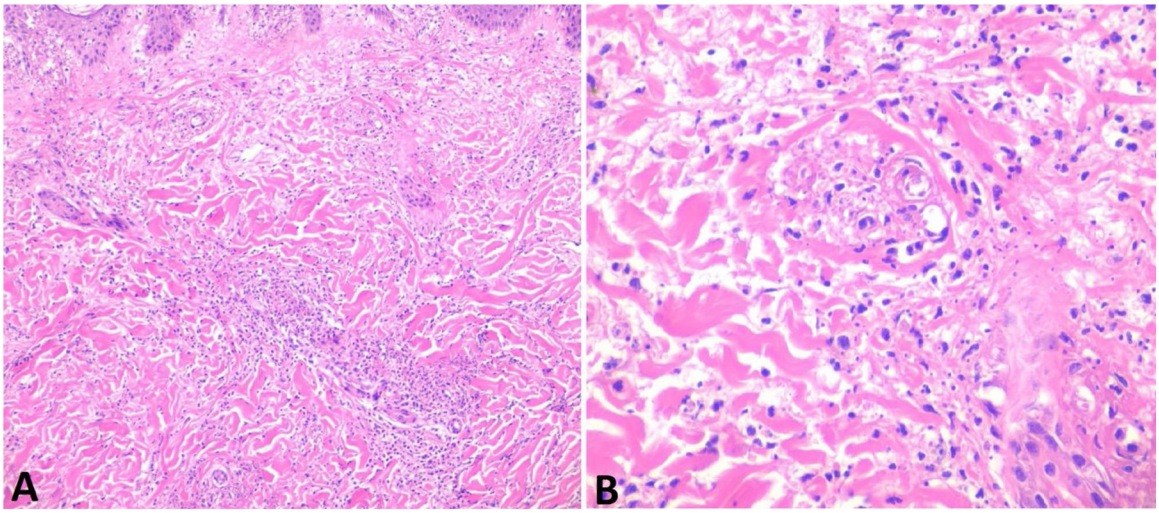

Fig. 3. Histopathological section demonstrating patchy perivascular neutrophil predominant infiltrate with areas of fibrinoid necrosis of blood vessels, nuclear debris and hemorrhage (*H and E,* 10x and 40x, respectively) in the dermis.

defined trigger such as infections, malignancies, autoimmune disorders, and drugs [2]. Up to 25% of the cases are attributed to medications including antimicrobials, nonsteroidal anti-inflammatory drugs, allopurinol and sulfonamides [6,9]. Diagnosis of LCV is based on clinical presentation and histopathologic findings of the skin biopsy. A punch biopsy should be performed in all suspected cases to confirm the diagnosis of leukocytoclastic vasculitis. It is also imperative to investigate target organ involvement and underlying etiologies such as connective tissue diseases, infections or systemic vasculitis based on clinical suspicion [6].

This particular case was a diagnostic challenge, as the patient had active hepatitis C infection and co-existing infective endocarditis. HCV-induced mixed cryoglobulinemia is an immune-complex mediated small vessel vasculitis commonly presents as leukocytoclastic vasculitis [10]. However, in our case, initial and repeated serum cryoglobulin levels were normal which ruled out HCV-induced mixed cryoglobulinemia. Moreover, normal levels of complement C4 and rheumatoid factor levels argued against mixed cryoglobulinemia.

The skin findings also raised a possibility of an embolic phenomena in the setting of infective endocarditis. The lesions in our case were palpable purpura localized on dorsal aspect of hands and feet, in contrast to Janeway lesions that presents most commonly as painless macules in palms and soles [11]. In addition, gram staining and cultures of fluid aspirated from the bullous lesions and subsequent tissue biopsies were negative for bacteria. Bacterial infections, particularly bacteremia have also been implicated as a cause of leukocytoclastic vasculitis. The pathogenesis is not fully understood, but it is likely to result from the immune complex formation and development of antibodies in response to bacterial antigens. Several cases were reported where cutaneous LCV was the presenting manifestations of infective endocarditis and bacteremia [12–14]. However, in the present case, the temporal relationship between oxacillin administration and the appearance of vasculitis as well as resolution of the skin findings after discontinuation of the inciting agent suggests that oxacillin was the likely culprit rather than bacterial endocarditis.

Causality assessment of adverse drug reactions is challenging given the lack of appropriate diagnostic tests, the ethical issues with re-challenging with the same medication and the rarity of the adverse events. Therefore, causality assessment scales have been developed to standardize assessment of causality for all adverse drug reactions [7,8]. According to World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Center (WHO-UMC) and the Naranjo probability scale, our case belongs to the class of 'possible' causality category.

To our knowledge, this is the second reported case of oxacillin-induced cutaneous leukocytoclastic vasculitis. The first case reported by Koutkia et al. [15]. The reported patient developed biopsy-proven LCV which presented as symmetric palpable purpuric lesions in lower extremities eight days after the initiation of oxacillin. The skin findings were similar to our case, including progression to hemorrhagic vesicles and involvement of hands and fingers. In contrast to the previously reported case where gastrointestinal and renal involvement seen, our patient showed no signs of extracutaneous involvement.

Initial management of LCV involves treatment of underlying disorder or prompt discontinuation of the offending agent, if identified. Most of the cases are self-limited and resolve in weeks to months without sequale [16]. Supportive measures such as antihistamines, compression stockings and leg elevation can be used in mild cases where rash involves dependent areas [2,17]. In our case, skin lesions completely resolved within a month with supportive treatments only. A short course of prednisone can be also considered if the disease is widespread, severely symptomatic or associated with visceral-organ involvement. However, precipitating cause cannot be identified in majority patients with leukocytoclastic vasculitis. Recurrent idiopathic cases be treated with dapsone, colchicine or immunosuppressive agents such as mycophenolate, azathioprine or steroids [2,6].

Our case illustrates a rare case of oxacillin-induced cutaneous LCV, masquerading the skin manifestations associated with HCV and IE. To conclude, a high index of suspicion is imperative for diagnosing drug-related cutaneous manifestations as discontinuation of the suspected agent is critical for resolution of the vasculitis and cutaneous lesions.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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The authors declare no sources of funding for the submitted case report.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Authors contribution

Meric Mericliler, MD: Drafting the manuscript.
Aya Shnawa, MD: Drafting the manuscript.
Dalya AlQaysi, MD: Drafting the manuscript.
Jorge Fleisher, MD: Revision and final approval.
Andrew Moraco, MD: Revision and final approval.

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