Received: 15 July 2023 | Revised: 18 December 2023 | Accepted: 28 December 2023

DOI: 10.1002/ccr3.8437

CASE REPORT

Clinical Case Reports Open Access WILEY

Leukocytoclastic vasculitis caused by sulfamethoxazole-trimethoprim

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Key Clinical Message

Leukocytoclastic vasculitis is a rare, small-vessel vasculitis that can be caused by sulfamethoxazole-trimethoprim. Most presentations involve skin rash but serious systemic involvement is possible. The precise mechanism is unclear but genetic and immune-based tissue damage has been postulated. The rash often resolves with discontinuation of sulfamethoxazole-trimethoprim with or without steroids.

KEYWORDS

adverse drug reaction, hapten, N-acetyl transferase 2, rash, vasculitis

1 | INTRODUCTION

Sulfamethoxazole-trimethoprim (SMT) is a drug widely used for both the treatment and prevention of different infectious diseases and it is associated with various side effects, one of which is leukocytoclastic vasculitis (LCV). Our goal in this manuscript is to draw the attention of healthcare providers to this uncommon cutaneous side effect of SMT including a literature review of other common antimicrobials that may cause LCV by acting as haptens. A hapten is a small molecule (drug) combining with a larger carrier (tissue protein) to elicit antibody-mediated injury. The awareness promoted by this article is helpful as LCV can occasionally have systemic involvement, which if not promptly recognized and managed, can lead to more ominous and disastrous consequences. We also include a brief review of published cases of LCV attributable to SMT and draw some similarities to and differences from our case. We suggest that healthcare providers consider LCV as a differential diagnosis of vasculitic rash that occurs after initiation of SMT in any patient.

2 | CASE PRESENTATION

A 23-year-old male presented with a worsening rash, pruritus, and watery diarrhea. The patient had a motor vehicle accident 6 years prior with a left ulnar and radial fracture. He was treated with open reduction and internal fixation (ORIF) which was complicated by a deep infection of the ulnar plate. The hardware was removed and an external fixator was placed. One year later, he returned with a nonunion of the ulna for which he underwent ORIF with bone graft placement. Unfortunately, he developed post-surgical wound and hardware infection with a purulent discharge from the surgical site at the ulna. The hardware was removed once again and operative debridement was done. The cultures from the site grew Methicillin-resistant Staphylococcus aureus (MRSA) for which the patient was started on a 6-week course of Vancomycin. He was later de-escalated to a 2-week course of SMT for suppression.

Three days after starting SMT, he developed an itchy rash on his left foot, which spread to both legs. He

presented to the hospital 6 days after the rash appeared. Under the suspicion the rash was drug-induced, SMT was discontinued. Antimicrobial therapy was switched to clindamycin, and clobetasol ointment and hydroxyzine tablets were prescribed to alleviate itching. The rash, however, continued to worsen, which prompted a return to the emergency room. The rash spread proximally to the thighs and groin and also appeared on the right arm. The patient denied a history of fever, chills, chest pain, shortness of breath, abdominal pain, hematochezia, hematuria, or neck rigidity.

On examination, his vital signs were stable. The rash is best described as multiple non-blanchable purpura and petechiae on the ventral aspect of the right arm, bilateral inner thighs, knees, and lower legs, with several scattered bright pink and firm discrete papules ranging from 3 to 4 mm in size (Figure 1—*Multiple non-blanchable purpura and discrete papules on the bilateral inner thighs, knees, and lower legs*). Those on the feet were worse and larger, in the 5–6 mm range, with violaceous round papules and a surrounding rim of macular purpura coalescing into plaques (Figure 2—*Violaceous round papules and a surrounding rim of macular purpura coalescing into plaques on both feet 8 days after starting sulfamethoxazole-trimethoprim*). The palms, soles, back, buttocks, abdomen, and mucosal area were uninvolved. There were no blisters, erythema, or ulcerations noted, and the rash area was not tender. Skin biopsy of a representative lesion from his right thigh was obtained with histopathology which shows a cutaneous small-vessel vasculitis (leukocytoclastic vasculitis)—(Figure 3—*High-power magnification showing mixed eosinophilic, and neutrophilic infiltrate with degranulation and nuclear dusts (arrowed), extravasated red blood cells, and endothelial damage (H&E; 20×)*). Immunofluorescence was negative for IgG, IgM, IgA, and C3. The patient also had mild renal impairment, with serum creatinine peaking at 1.4mg/dl (baseline 1.1mg/dl). Given the possible systemic involvement of leukocytoclastic vasculitis (LCV), the patient was started on oral prednisone, 40mg daily, pending further work, which included urinalysis, renal ultrasound, and stool for occult blood. The workup for possible renal or gastrointestinal involvement of LCV was negative. Specifically, serum creatinine improved back to baseline within a few days; urinalysis showed only five red blood cells, and microalbuminuria of 100 mg/day with no white blood cells or renal casts. There was normal echogenicity on renal ultrasound and stool was negative for occult blood. Prednisone was

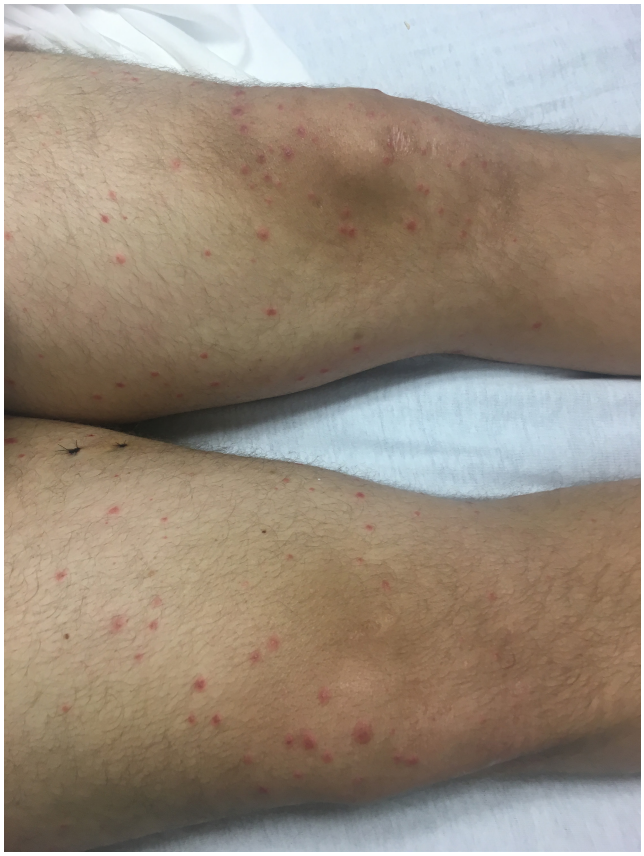

FIGURE 1 Multiple non-blanchable purpura and discrete papules on the bilateral inner thighs, knees, and lower legs.

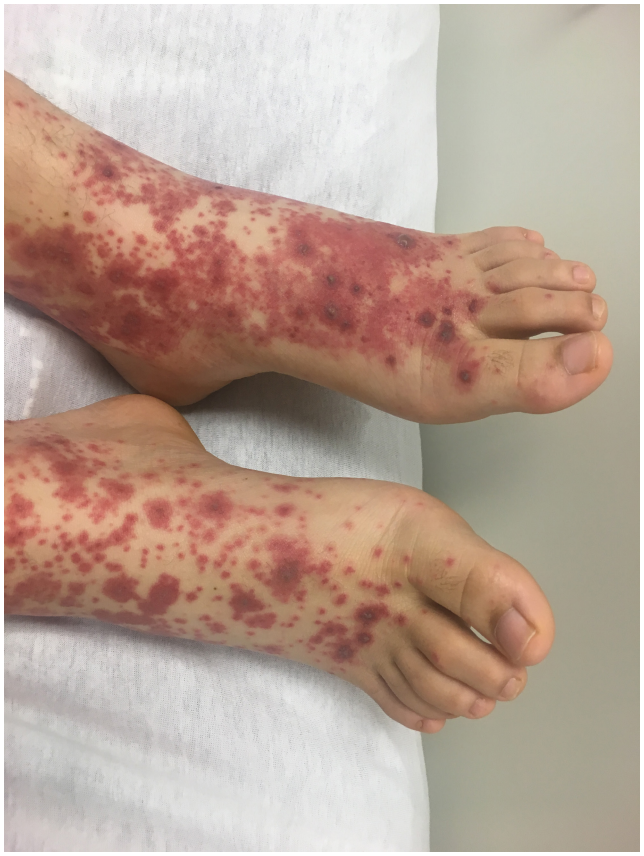

FIGURE 2 Violaceous round papules and a surrounding rim of macular purpura coalescing into plaques on both feet.

discontinued after only a few days while the patient continued on topical clobetasol. The rash improved significantly and resolved completely within a month.

3 | DISCUSSION

LCV is a subtype of small-vessel vasculitis, which affects the skin's capillaries and venules. It can be localized to the skin, causing cutaneous symptoms such as petechial eruption or systemic involvement.[1] LCV can be primary or secondary to drugs, infections, allergies, or inflammatory conditions. Various medications, including nonsteroidal anti-inflammatory, amiodarone, beta-blockers, metformin, warfarin, immune checkpoint inhibitor therapy, and antimicrobials (Table 1), have all been implicated in causing LCV.[1]

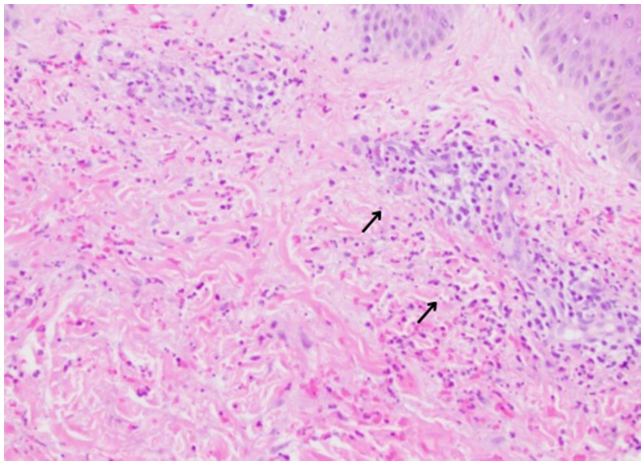

FIGURE 3 High power magnification shows mixed eosinophilic, and neutrophilic infiltrate with degranulation and nuclear dusts (arrowed), extravasated red blood cells, and endothelial damage (H&E; 20×).

A useful tool proposed to classify and diagnose primary cutaneous vasculitis is the KAWAKAMI algorithm.[2] This is a simple classification used when physicians are confronted with cutaneous vasculitis and can help diagnose one of the seven cutaneous vasculitides described in the algorithm. In addition to information obtainable from histopathology, based on this algorithm, LCV is often limited to the upper to the middle dermis, accompanied by a negative workup for antineutrophilic cytoplasmic antibodies, cryoglobulin, or IgA deposition.[2] LCV is a diagnosis of exclusion, and multiple potential differential diagnoses should be ruled out before diagnosing drug-induced LCV. The American College of Rheumatology has provided the following criteria to diagnose LCV in order to maintain uniformity: (i) Age >16 years at the time of disease onset; (ii) medication use and its correlation with disease onset; (iii) palpable purpura, (iv) maculopapular exanthem; and (v) histopathological picture demonstrating arterioles and venules with evidence of peri/extravascular granulocytes. This recommendation has a diagnostic specificity of 83.9% and a sensitivity of 71% if three out of five criteria are present.[3] Our patient fulfilled all five of these criteria, further strengthening the evidence of drug-induced LCV, which in our case was due to SMT. LCV, however, can be easily confused with various other forms of vasculitis involving skin components, such as cutaneous polyarteritis nodosa described in the KAWAKAMI algorithm, infectious rash, hematological petechial eruption, dermatitis, and drug eruption.[2]

A careful history and physical examination will help make the correct diagnosis and separate it from other rashes. Possible differentials for our case include drug-induced eruption, erythema multiforme, IgA vasculitis (previously Henoch Schönlein purpura), and dermatitis. IgA vasculitis was, however, highly unlikely given the

TABLE 1 Shows the list of widely used antimicrobials reported to cause LCV.

Antibiotics	Antitubercular drugs	Antivirals	Antiparasitic	Anti-HIV Meds
Penicillin Amoxicillin Oxacillin	Rifampin	Famciclovir	Quinine	Zidovudine
Cephalosporins Ceftriaxone Cefuroxime	Rifampin and Pyrazinamide	Sofosbuvir	Mefloquine	Indinavir
Vancomycin	Rifampin and Ethambutol		Ornidazole	Dolutegravir
Imipenem-Cisplatin				Efavirenz
Teicoplanin				
Linezolid				
Macrolide–Clarithromycin				
Fluroquinolone–Ciprofloxacin				

absence of renal and joint involvement and the biopsy confirmation of the rash in our case to be small-vessel vasculitis of the leukocytoclastic subtype. The cutaneous side effect of SMT is not limited to LCV. The drug can also cause maculopapular rash, morbilliform lesions, erythema multiforme, purpura, and photosensitivity.[4] More severe cutaneous drug reactions are also possible, including Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[4]

The precise mechanism by which SMT and other antibiotics cause LCV is unclear but is an area of interest. Genetic and immune-based tissue damage has been postulated. This involves immune complex deposition in the vessel wall along with complement activation. The antigens of these medications can act as haptens, absorbed by inflammatory cells and immune complexes, resulting in inflammation of the vessel wall.[1] With inflammation of the vessel wall and injury to vessel walls, neutrophils, and inflammatory mediators are recruited to the site, resulting in secondary exudation of red blood cells, fibrin, and serum. LCV commonly occurs in the legs due to turbulence and increased venous pressure in the lower limbs. Drugs like allopurinol, carbamazepine, and lamotrigine have been linked to the interaction between human leukocyte antigens, T-cell receptor signaling, and lymphocyte activation.[5] Similarly, drugs like isoniazid, hydralazine, dapsone, and sulfonamides show a concept of inherited differences in metabolism,[5] which can also be a contributing cause to the pathogenesis of LCV in patients taking SMT. The N-acetyltransferase-2 (NAT-2) slow acetylator phenotype is associated with sulfamethoxazole-induced cutaneous hypersensitivity.[5] For example, according to a study done by Zelinska and colleagues, the genotype encoding the arylamine NAT-2 polymorphism for slow acetylation is directly related to the prevalence of the side effects of SMT, such as skin lesions, including toxic epidermal necrolysis, decrease in blood counts, altered liver enzymes, fever, and dyspepsia.[6] However, this observation of slow acetylation association with SMT hypersensitivity was not reproduced in HIV-positive individuals, who often require SMT for treatment and prevention of opportunistic infections.[7] Although there is a US Food and Drug Administration label for sulfamethoxazole that warns about hypersensitivity with slow acetylation, there is no testing for NAT-2 acetylation phenotyping to prevent and diagnose such adverse effects.[8] The challenges in testing may be further compounded by conflicting information about this concept, the burden of identification of at-risk individuals, and cost issues. SMT is widely used throughout the world, and given the potentially large number of people at risk for potential adverse drug reactions, including LCV, future studies in this area are warranted. Studies should focus on the reliability of NAT-2 testing to predict the side effects of SMT in these patients. Studies should also explore the cost-effectiveness of NAT-2 testing, pharmacogenetic testing, and the mechanistic basis of SMT hypersensitivity, including cutaneous side effects such as LCV.

Our article also includes a brief review of the literature. SMT is a common antimicrobial prescribed for the treatment and prophylaxis of several infections, including skin, urinary tract, pulmonary, and opportunistic infections, such as Pneumocystis pneumonia and Nocardiosis. Around 16 cases of LCV from SMT were identified from the literature search. Three out of 16 cases were excluded as the full text was not available. Among the 13 cases we have reviewed, females were more affected than males, and ages ranged from 22 to 86. Most subjects developed a rash between 2 days and 2 weeks after starting SMT, with the rash starting on the lower extremities and spreading proximally. One case had a delayed presentation after 4 weeks.[9] The rash ranged from macules to papules to pustular lesions. Four cases had a nonpruritic rash while one case had pruritus. The palm was involved in two of these 13 cases. Two cases had associated retinal and optic disc involvement concomitant with cutaneous vasculitis.[10,11] It is difficult to identify at-risk populations from the review as there were no consistent unifying factors. Most of the cases had a resolution of the rash with the cessation of the offending drugs with or without a steroid taper dose. In one case, the rash evolved into bullae and plaque,[12] and in the other, it reappeared after 2 months, followed by eye involvement.[10] In one LCV case, the rash developed even though the patient was already on high-dose steroids (30 mg/kg) for idiopathic pulmonary fibrosis,[9] which is rather puzzling as steroids are one of the treatment modalities for LCV. A greater steroid dose (40 mg/kg), nevertheless, eliminated the rash after discontinuation of SMT. This case raises the question of whether steroid immunomodulatory activity (likely at higher doses), rather than anti-inflammatory activity (at lower doses) can explain the mechanism of appropriate steroid treatment response for systemic LCV.[13]

LCV has a favorable prognosis if diagnosed early and treated effectively. There should be particular attention paid to ruling out systemic involvement and more aggressive cutaneous differential diagnoses such as SJS/TEN. The first line of treatment is typically discontinuation of SMT, along with a tapering dose of steroids when indicated. Although there have been instances where LCV has progressed, resulting in retinal vasculitis, in most cases, the rash typically resolves without complications. In our case, switching from SMT to clindamycin for suppression, along with the use of topical steroids, led to the spontaneous resolution of the rash within a month. The risk factors associated with systemic involvement are not yet

fully understood, and the clinical significance or impact of NAT-2 genetic testing remains unknown.

The limitations of our case include a lack of information on NAT-2 acetylation phenotype and genetic testing due to cost limitations (uninsured patient). Implementing NAT2 testing for at-risk groups can mitigate drug reactions by identifying slow acetylators linked to SMT rash and subsequently prevent future mishaps. This information can guide providers to be cautious when prescribing drugs metabolized by NAT, especially when encountering patients with a previous history of a rash. In our case, vancomycin was used for 6 weeks before it was de-escalated to SMT. Vancomycin can also cause LCV, as evidenced by published reports.[14–16] However, in our patient, the rash appeared after 3 days of initiation of SMT. The temporal relation between SMT initiation and the appearance of rash, and disappearance of the rash on discontinuing SMT favors SMT as the culprit rather than vancomycin in our case.

In conclusion, this article highlights the significance of recognizing leukocytoclastic vasculitis as a potential side effect associated with the commonly prescribed drug SMT. We have emphasized the underrated importance of NAT-2 genetic testing in identifying individuals who may be at risk of experiencing negative effects from SMT and the need for future research in this area. When LCV is suspected as a result of SMT, the immediate discontinuation of the drug is crucial, followed by a thorough evaluation to rule out any systemic involvement. For cases with limited disease, topical treatments may suffice, but the use of steroids is often necessary for extensive or systemic involvement. Raising awareness among healthcare professionals can improve patient outcomes of this rare but important cutaneous side effect of SMT therapy.

AUTHOR CONTRIBUTIONS

Parjanya Bhatt: Writing – original draft. **Nadine Montreuil:** Writing – review and editing. **Ayoola Olayiwola:** Writing – review and editing. **Tanya Quiroz:** Writing – review and editing. **Felipe Ruiz:** Investigation; writing – review and editing. **FOLUSAKIN AYOADE:** Conceptualization; supervision; writing – review and editing.

FUNDING INFORMATION

This work received no external funding.

CONFLICT OF INTEREST STATEMENT

The authors do not have any conflicts of interest to disclose in relation to this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author, [FA]. The data are not publicly available due to restrictions related to patient privacy and confidentiality.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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How to cite this article: Bhatt P, Montreuil N, Olayiwola A, Quiroz T, Ruiz F, Ayoade F. Leukocytoclastic vasculitis caused by sulfamethoxazole-trimethoprim. *Clin Case Rep*. 2024;12:e8437. doi:10.1002/ccr3.8437