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Leukocytoclastic Vasculitis Induced by Dalbavancin: A Case Report

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Patient: Female, 66-year-old
Final Diagnosis: Leukocytoclastic vasculitis
Symptoms: Arthralgia • fatigue • pruritic rush • purpuric skin lesions
Clinical Procedure: —
Specialty: Infectious Diseases • General and Internal Medicine

Objective: Rare disease

Background: Dalbavancin is a lipoglycopeptide antibiotic largely used to treat serious and complex bacterial infections, particularly those caused by gram-positive bacteria. Its main advantages include a prolonged half-life, which allows for once-weekly dosing, effectiveness against resistant pathogens, most notably, methicillin-resistant *Staphylococcus aureus*, and a good profile of tolerability and patient adherence. Herein we report the first documented case of a patient who developed palpable purpura on both lower limbs following treatment with dalbavancin, which was clinically and histologically diagnosed as leukocytoclastic vasculitis (LV).

Case Report: A 66-year-old woman received dalbavancin due to an acute bacterial skin and skin structure infection (ABSSSI) of her right leg. The patient initially showed a favorable clinical response, with marked improvement of the infection. However, 3 weeks after the administration of dalbavancin, she developed a diffuse erythematous palpable purpura, predominantly affecting the lower limbs, and accompanied by mild arthralgia and generalized asthenia. To further investigate and confirm the underlying cause of these new symptoms, a skin biopsy was performed, revealing histopathological findings consistent with LV. Following the diagnosis, corticosteroid therapy was initiated, resulting in a significant symptomatic improvement.

Conclusions: To the best of our knowledge, this is the first published, histologically confirmed case report of LV developing after treatment with dalbavancin. Given the widespread use of dalbavancin for treating ABSSSIs, clinicians should be aware of the potential adverse effects, including LV, that may arise during its administration.

Keywords: Vasculitis • Skin Diseases, Infectious • Therapy, Soft Tissue

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Introduction

Dalbavancin is a lipoglycopeptide antibiotic that plays a critical role in the management of serious gram-positive bacterial infections [1]. It is approved for acute bacterial skin and skin structure infection (ABSSSI), especially in patients who have either failed to respond to, cannot tolerate, or are allergic to alternative antibiotic therapies [1]. The main advantage of dalbavancin is its long half-life, allowing for a once-weekly dosing regimen, making it an attractive option for outpatient therapy [1-3]. It is administered either as a single 1500 mg dose or as a 2-dose regimen (1000 mg followed by 500 mg 1 week later), as approved for the treatment of ABSSSI [2].

Additionally, dalbavancin exhibits efficacy against resistant gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), positioning it as a valuable tool to fight antimicrobial resistance. Dalbavancin is generally well-tolerated; however, several adverse effects have been reported including gastrointestinal disturbances, elevated liver enzyme levels, headache, rash, pruritus, and rare hypersensitivity reactions such as anaphylaxis [4,5].

Among hypersensitivity reactions, a rare but relevant manifestation is leukocytoclastic vasculitis (LV), a small-vessel vasculitis histologically characterized by neutrophilic infiltration and fibrinoid necrosis of postcapillary venules. LV has an estimated incidence of approximately 30 cases per million people annually and may occur secondary to infections, autoimmune diseases, malignancies, or exposure to certain medications, including antibiotics [6-8]. Herein we present, to our knowledge, the first histologically confirmed case of LV potentially induced by dalbavancin.

Case Report

A 66-year-old woman presented to the emergency department with fever, erythema, and swelling in her right leg. Her past medical history included hypertension, dyslipidemia, colorectal cancer, and recurrent episodes of thrombophlebitis. The patient had no known history of drug allergies or previous hypersensitivity reactions.

For the 2 days prior to presentation, she had been taking paracetamol (acetaminophen) to manage her fever and leg pain. Despite this, her symptoms worsened, and she continued to experience persistent fever. On physical examination she was alert, with normal vitals except for a temperature of 38.2°C. The patient described a burning sensation and swelling in her right leg, resulting in a heavy sensation. The leg was warm, erythematous, and painful, particularly around the edges. Inguinal lymph nodes were tender, and the overlying skin appeared shiny and tight. The remainder of the physical examination was unremarkable.

Laboratory tests revealed leukocytosis (WBC 17 000/mm^3), with neutrophilia (absolute neutrophil count 14 000/mm^3). C-reactive protein (CRP) was markedly elevated at 102 mg/L (normal <5 mg/L), suggesting an active inflammatory process. Liver enzymes and renal function were within normal limits. Serologies for hepatitis C virus, hepatitis B virus, and HIV were negative.

A doppler ultrasound of the affected leg ruled out deep vein thrombosis. A presumptive diagnosis of an ABSSSI was made, and the patient was started on a single 1500 mg intravenous dose of dalbavancin. Dalbavancin was selected for its efficacy against gram-positive organisms, including MRSA, and because the patient preferred to avoid hospital admission.

Three weeks later, the patient developed palpable purpura on her lower limbs and abdomen, accompanied by pruritus, fatigue, and mild arthralgia, although no fever was present (**Figure 1**).

Follow-up laboratory tests showed normalization of inflammatory markers (CRP 4.48 mg/L, WBC 8.9×10^3/mm^3, neutrophils 4.54×10^3/mm^3) and stable liver and renal function. The absence of fever and the temporal association with dalbavancin administration raised the suspicion of a drug-induced hypersensitivity reaction.

A rheumatologic workup for autoimmune disorders (cryoglobulins, complement components C3 and C4, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-cardiolipin antibodies, anti-β2-glycoprotein antibodies, and lupus anticoagulant) was negative.

A skin biopsy revealed leukocytoclastic necrotizing small vessel vasculitis (**Figure 2**).

Infections, particularly those caused by *Staphylococcus aureus* [6], can occasionally trigger LV. However, in this case the marked improvement in local signs of infection and normalization of inflammatory markers (CRP and WBC) by the time purpuric lesions appeared, make an infectious trigger less likely. Moreover, no new medications aside from paracetamol had been taken; the patient's chronic therapies had remained unchanged for years without prior adverse effects and there were no clinical or laboratory findings suggestive of systemic infection or newly diagnosed autoimmune conditions. These findings, along with the clear temporal relationship, strongly suggest that dalbavancin was the most probable cause.

Based on these findings, the patient was treated with oral prednisone at 0.5 mg/kg per day and oral cetirizine at 10 mg/

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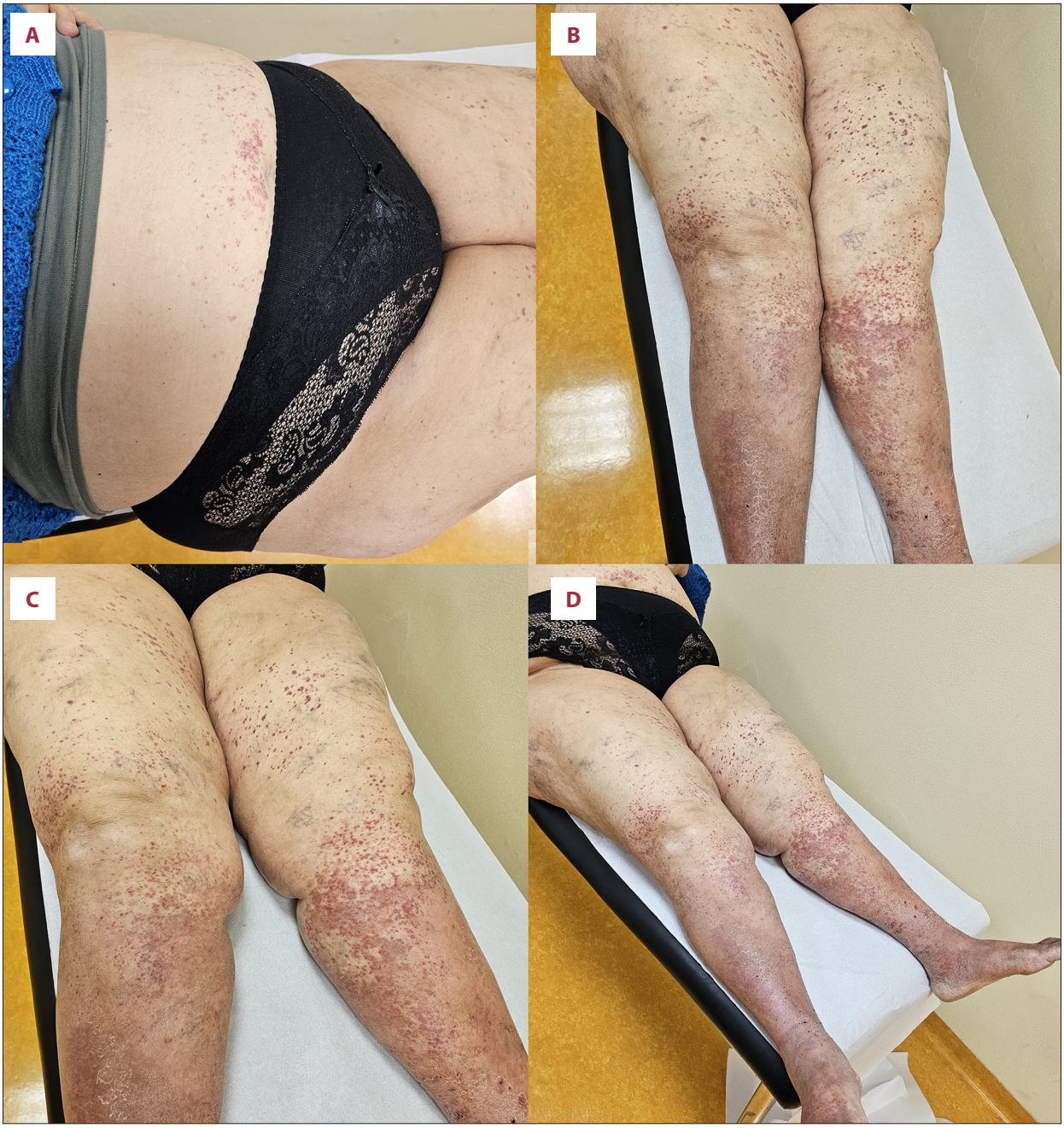

Figure 1. Clinical presentation of abdominal skin involvement in purpura (**A**) and leg skin purpura (**B-D**).

day for 14 days, followed by a gradual tapering of prednisone over 90 days until complete discontinuation. Within 3 weeks of starting steroid therapy, the patient's symptoms markedly improved and the purpura gradually resolved completely.

Discussion

Dalbavancin is a generally well-tolerated therapy with very few patients experiencing adverse effects or treatment interruptions. A systematic review and meta-analysis on dalbavancin's safety reported that the most commonly observed adverse effects were related to the gastrointestinal system (nausea, vomiting, diarrhea, constipation), headaches, infusion reactions, and pruritus, with an overall prevalence of 30.6%. Treatment discontinuation occurred in approximately 3% of cases, supporting the drug's favorable safety profile [4].

A recently published Italian registry indicated that 2.7% of patients reported adverse effects, with 4 patients developing

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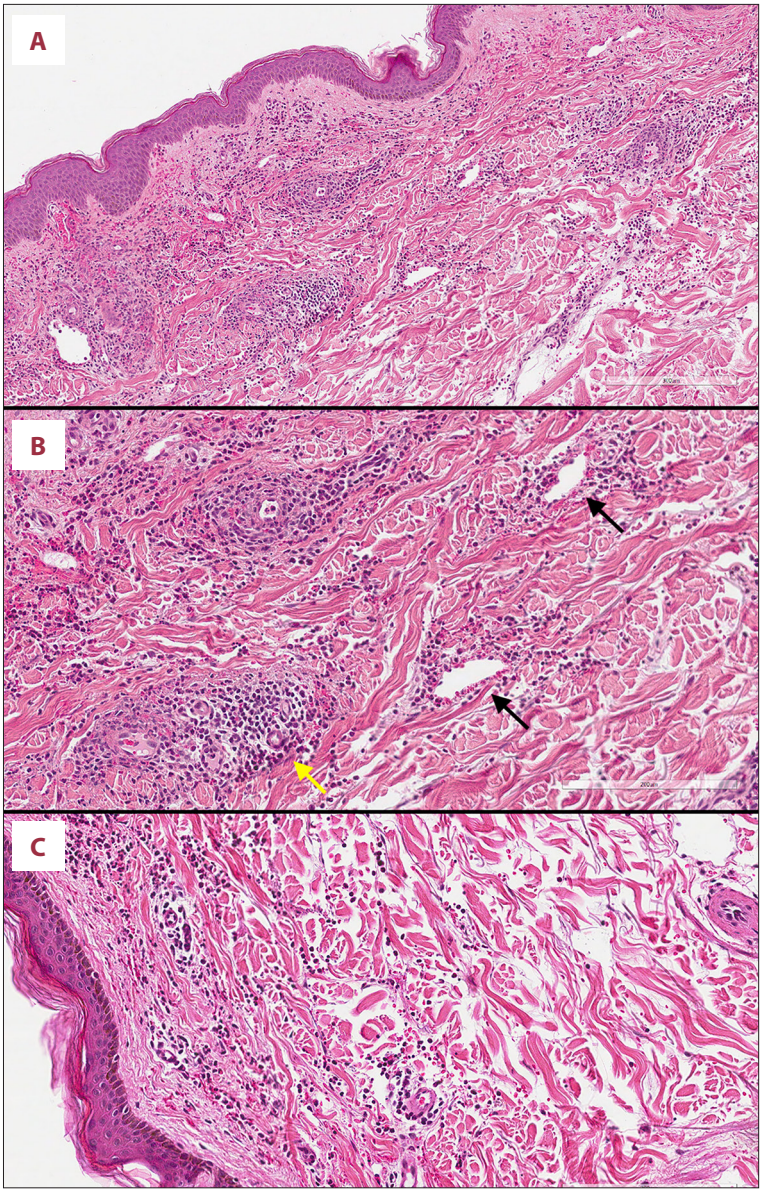

Figure 2. Histological image of the skin biopsy showing a perivascular inflammatory infiltrate in the superficial dermis associated with red blood cell extravasation (**A,** hematoxylin and eosin, original magnification ×100). The inflammatory infiltrate is composed of lymphocytes, neutrophils, and eosinophils and is associated with vascular wall destruction with fibrinoid necrosis (black arrows), and involvement of eccrine glands (yellow arrow) (**B,** hematoxylin and eosin, original magnification ×200). In the last image, karyorrhexis and nuclear dust can be appreciated (**C,** hematoxylin and eosin, original magnification ×200). Overall, these morphological findings are consistent with leukocytoclastic vasculitis.

allergic rashes [9]. Our previous experiences with dalbavancin have shown a strong safety profile, with no severe adverse events noted for both on-label and off-label prescriptions [1,10].

In the current case, a 66-year-old woman developed a palpable purpuric rash on her extremities and trunk after receiving dalbavancin for ABSSSI, and a skin biopsy confirmed the diagnosis of LV. The absence of new medications during the 3-week interval, the resolution of the underlying soft tissue infection, and negative autoimmune and infectious evaluations argue against alternative causes.

Other potential etiologies, such as autoimmune diseases, paraneoplastic syndromes, and long-term medication use were also considered. The patient's chronic therapies had been stable for years and were not previously associated with vasculitis. Laboratory investigations, including autoantibody and complement panels, were unremarkable. No clinical or laboratory findings suggested an underlying malignancy.

Drug-induced LV represents about 10% of LV cases, and is commonly caused by medications like cyclosporine, azathioprine, or antibiotics (notably beta-lactams, sulfonamides, and quinolones) [7,8]. A few cases have also been attributed to vancomycin [11-13] or linezolid [14]; however, to our knowledge no previous cases have involved dalbavancin, despite similar glycopeptide structure and pharmacodynamics.

The exact pathogenic mechanism may involve immune complex deposition in blood vessel walls, leading to complement

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activation and neutrophil recruitment, ultimately damaging vessel walls causing purpura. This condition can affect multiple vascular structures leading to systemic complications if not addressed promptly. As with other triggers, it is likely that dalbavancin may also induce direct drug toxicity, immune complex formation, or hypersensitivity reactions resulting in an autoimmune response mistakenly targeting blood vessels [8,12,13].

The diagnosis is frequently one of exclusion and it includes the complete medical history, physical examination, and laboratory testing. It also adheres to the American College of Rheumatology criteria, which require at least 3 out of 5 specific factors, with a sensitivity of 71% and specificity of 83.9% [15]. The 5 criteria are: age over 16, use of a possible drug in temporal relation to symptoms, palpable purpura, maculopapular skin lesions, and a biopsy of a skin lesion indicating neutrophils surrounding arterioles or venules [15]. Our case met all these criteria, confirming the LV diagnosis.

Generally, vasculitis resolves after discontinuation of the offending drug, leading to complete recovery [16]. In our case, the administration of a long-acting antibiotic resulted in a slow clearance of the drug requiring the additional use of corticosteroids and antihistamines.

Currently, data on management of long-acting antibiotic-induced vasculitis are lacking. Our unique case underscores the importance of a tailored approach to managing patients undergoing dalbavancin therapy, emphasizing the need for a thorough review of any prior drug reaction histories before initiating treatment.

Conclusions

To the best of our knowledge, this is the first published, histologically confirmed case report of LV developing after treatment with dalbavancin. This case provides valuable insight into the drug's safety profile and may stimulate further research into adverse reactions induced by long-acting antibiotics. Given the expanding use of long-acting antibiotics like dalbavancin in clinical practice, clinicians should consider close clinical monitoring in patients with a history of hypersensitivity reactions, and remain vigilant for delayed-onset adverse effects such as LV.

Patient Consent

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images.

Ethics Approval and Consent to Participate

The study was performed in accordance with the Declaration of Helsinki.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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