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Cutaneous vasculitis induced by dapagliflozin (forxiga): a rare adverse effect

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Dear Editor,

While common adverse events associated with sodium-glucose cotransporter-2 (SGLT2) inhibitors, such as genitourinary infections and volume depletion, are well-characterized,[1] rare immune-mediated cutaneous manifestations are increasingly recognized in post-marketing surveillance.[2] Here, we describe a clinically probable case of cutaneous small-vessel vasculitis (CSVV) induced by dapagliflozin, contributing to the limited but expanding body of evidence on this rare and potentially severe complication.

An 83-year-old woman with an established history of type 2 diabetes mellitus, heart failure, and permanent atrial fibrillation was prescribed dapagliflozin 10 mg/day to optimize glycemic control and provide cardiovascular protection. Her baseline glycated hemoglobin was 7.8%, and her baseline renal function was within age-appropriate reference ranges. No other new medications or dietary supplements had been introduced in the months prior to the event, and her chronic therapy had been stable for over a year.

Approximately 8 days after initiating dapagliflozin, the patient developed an acute, multifocal, predominantly bilateral skin eruption consisting of small, palpable purpuric lesions and purpuric papules. The eruption extensively involved the lower limbs (Figure 1), buttocks (Figure 2), abdomen, and hands. Some of these lesions exhibited central darkening and superficial crusting. Clinically, the skin manifestations were associated with severe localized leg pain and marked asthenia. No overt tissue necrosis, ulceration, or mucosal involvement was documented. The overall clinical presentation was highly consistent with drug-induced CSVV, also known as hypersensitivity vasculitis, which represents a significant clinical challenge in the inpatient setting.[3]

Extensive laboratory investigations were performed during the acute phase to rule out systemic involvement and address the wide spectrum of cutaneous vasculitis differential diagnoses.[4] Results revealed a mild elevation of C-reactive protein (15 mg/L), while serum creatinine remained stable at 1.1 mg/dL. Complete blood count parameters, including total leukocytes and the absolute eosinophil count, were within normal reference ranges. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, and tumor markers were negative. Serum complement levels (C3 and C4) were completely normal, effectively ruling out systemic autoimmune conditions, overt hypereosinophilic syndromes, or active consumption related to systemic vasculitis.[5,6]

Dapagliflozin was immediately discontinued upon clinical suspicion. Due to the rapid progression, extensive anatomical distribution of the lesions, and significant constitutional symptoms, systemic corticosteroid therapy was indicated in line with current management strategies for severe or symptomatic cutaneous vasculitis.[7] The patient received intravenous methylprednisolone at a dose of 40 mg twice daily for the first 24 hours, followed by an oral regimen that was gradually and structuredly tapered until total withdrawal. Under this regimen, the skin lesions rapidly halted progression, progressively regressed, and achieved complete clinical resolution approximately 3 to 4 weeks after the discontinuation of the offending drug.

We must acknowledge a significant limitation of our report: no skin biopsy or direct immunofluorescence was performed during the acute episode due to practical clinical constraints. Consequently, according to current diagnostic expert consensus, this case represents a clinically compatible and probable diagnosis rather than a histopathologically proven one. Nevertheless, the strict and compelling temporal relationship (onset 8 days post-initiation), the total exclusion of alternative systemic, neoplastic, or infectious causes, and the prompt, favorable response to drug dechallenge strongly support a drug-induced etiology. Application of the Naranjo adverse drug reaction probability scale yielded a score of 7, formally classifying this event as a "probable" adverse drug reaction.[8]

Drug-induced CSVV typically involves a type III hypersensitivity mechanism, wherein circulating drug-induced immune complexes deposit in the walls of dermal post-capillary venules, activating the complement cascade and prompting neutrophilic infiltration and subsequent vascular damage.[9] While the precise biological mechanism for SGLT2 inhibitors remains uncertain and is likely idiosyncratic, our patient's clinical course closely parallels the index case reported by Bhattacharyya and Ghosh,[10] where a 69-year-old man developed a similar symmetrical purpuric eruption shortly after starting dapagliflozin, with histopathology definitively proving leukocytoclastic vasculitis with C3 deposition. Interestingly, other rare forms of vasculitic spectrum disorders, such as nodular vasculitis, have also recently been described in association with dapagliflozin, reinforcing the hypothesis of a class-related inflammatory trigger in susceptible individuals.[11]

As the clinical indications for SGLT2 inhibitors rapidly expand across international guidelines for heart failure and chronic kidney disease, the exposed patient population is becoming significantly older, multi-morbid, and more frail. This case underscores the cru-

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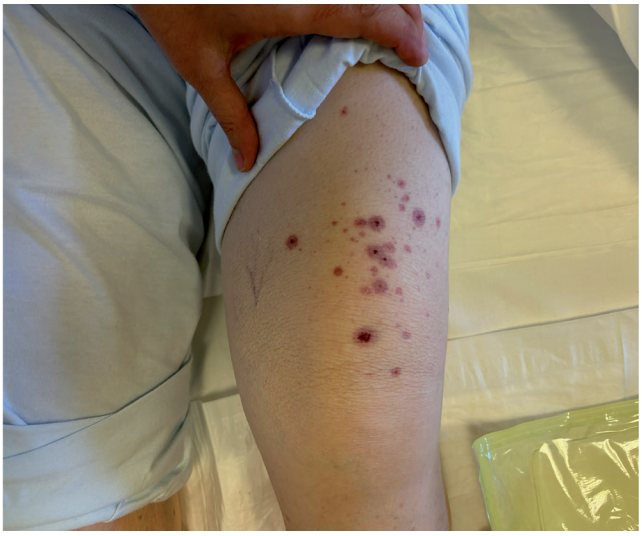


Figure 1. Clustered purpuric lesions involving the left knee/lower limb.



Figure 2. Multifocal purpuric lesions involving the gluteal region.

cial importance for clinicians to promptly recognize uncommon cutaneous reactions to SGLT2 inhibitors, differentiate them from common infectious rashes, rule out visceral systemic involvement, and actively report suspected events to pharmacovigilance networks to better define the safety profile of these widely used agents.

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