

Italian Journal of Medicine

https://www.italjmed.org/ijm

eISSN 1877-9352

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Ital J Med 2026 [Online ahead of print]

Please cite this article as:

Provenzano S, Visioli S, Ribattezzato V, Modugno M. **Cutaneous vasculitis induced by dapagliflozin (forxiga): a rare adverse effect**. *Ital J Med* doi: 10.4081/itjm.2026.2418

Submitted: 05-12-2025
Accepted: 25-10-2026

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

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Key words: dapagliflozin, vasculitis, SGLT2 inhibitors, adverse drug reaction.

Contributions: all authors contribute to the literature search, writing, drafting, and review of the manuscript, refining of sections in alignment with journal guidelines. They also approved the final version.

Conflict of interest: the authors declare no competing interests.

Ethics approval and consent to participate: according to local and national institutional regulations, ethics committee approval is not required for retrospective single case reports.

Patient consent for publication: due to the patient's clinical condition and physical inability to provide a written signature, verbal informed consent for the publication of this case report, including the accompanying clinical images, was obtained in the presence of a witness.

Availability of data and materials: the clinical case data are available.

The authors declare that generative artificial intelligence (AI) or AI-assisted technologies were used solely for language editing and proofreading purposes.

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 crucial 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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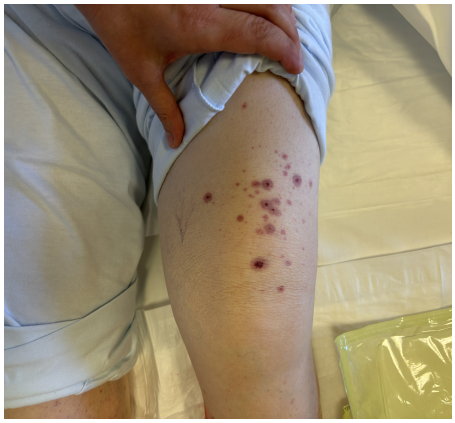


Figure 1. Clustered purpuric lesions involving the left knee/lower limb.



Figure 2. Multifocal purpuric lesions involving the gluteal region.