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INTERMEDIATE

CASE REPORT: CLINICAL CASE

Small-Vessel Vasculitis After ST-Segment Elevation Myocardial Infarction

Clopidogrel or Amiodarone?

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ABSTRACT

We report a case of cutaneous small-vessel vasculitis in a patient treated with clopidogrel after an ST-segment elevation myocardial infarction and with amiodarone caused by persistent atrial fibrillation 6 weeks before. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2022;4:967-971) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 76-year-old woman presented to our outpatient dermatology clinic with palpable purpuric papules on the legs that had lasted for 3 days (Figures 1A and 1B). The skin lesions were asymptomatic, but she complained of limb pain and fatigue. She had no fever or any other clinical signs of infection.

LEARNING OBJECTIVES

- To identify drug-induced small-vessel vasculitis early in patients with symmetric skin rash on the legs so as to prevent extracutaneous organ involvement.
- To coordinate the diagnostic and therapeutic decisions in a patient with drug-induced small-vessel vasculitis after withdrawal of the suspected drug.

PAST MEDICAL HISTORY

Six weeks earlier, she had been diagnosed with ST-segment elevation myocardial infarction (STEMI) (Figure 2). Coronary angiography had revealed closure of the ramus posterolateralis of the right coronary artery, but passage of the wire and stent placement were not possible because of the vessel's small diameter (Video 1). Instead, treatment with clopidogrel 1 × 75 mg/d and apixaban 2 × 2.5 mg/d was introduced. Because of persistent atrial fibrillation, apixaban had already been prescribed at a dosage of 2 × 5 mg/d in combination with flecainide 2 × 50 mg/d 4 months before. Because of the STEMI, the antiarrhythmic therapy was switched from flecainide to amiodarone with an initial dose of 3 × 200 mg/d and reduction to 1 × 200 mg/d after 14 days. Her additional regular medication included amlodipine, ramipril, and metoprolol.

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ABBREVIATIONS AND ACRONYMS

CSVV = cutaneous small-vessel vasculitis

STEMI = ST-segment elevation myocardial infarction

DIFFERENTIAL DIAGNOSIS

The differential diagnosis explaining erythematous spots and papules on the skin included cutaneous small-vessel vasculitis (CSVV), petechiae, steatotic eczema, stasis dermatitis, and pigmented purpuric dermatosis.

INVESTIGATIONS

A skin biopsy specimen was taken from the left thigh for histopathologic and direct immunofluorescence studies. Histology showed superficial perivascular inflammatory cells, mainly consisting of neutrophils and lymphocytes, and thickening of vessel walls with fibrin deposition. Perivascular nuclear dust and extravasation of erythrocytes were also present, all characteristic signs of early leukocytoclastic vasculitis (Figures 3A and 3B). Direct immunofluorescence showed only perivascular immunoglobulin M and no immunoglobulin A deposits.

Blood investigations showed a mild elevation of C-reactive protein level at 11.2 mg/L (normal range <5 mg/L), with normal leukocyte count and a slightly increased serum creatinine level of 1.08 mg/dl (normal range 0.51-0.95 mg/dL), which was previously unreported. Platelet count was within the normal range. Urine analysis was normal. Urine sediment microscopy revealed hyaline casts and few white blood cells, which might be attributed to acute interstitial nephritis.

Antinuclear antibody titer was elevated at 1:200 (normal range <50), without specific extractable nuclear antigens. Antineutrophil cytoplasmic autoantibodies were negative. C4 complement was strongly reduced (0.02 g/L; normal range 0.1-0.4 g/L). Hepatitis B, hepatitis C, and HIV serology results were negative.

MANAGEMENT

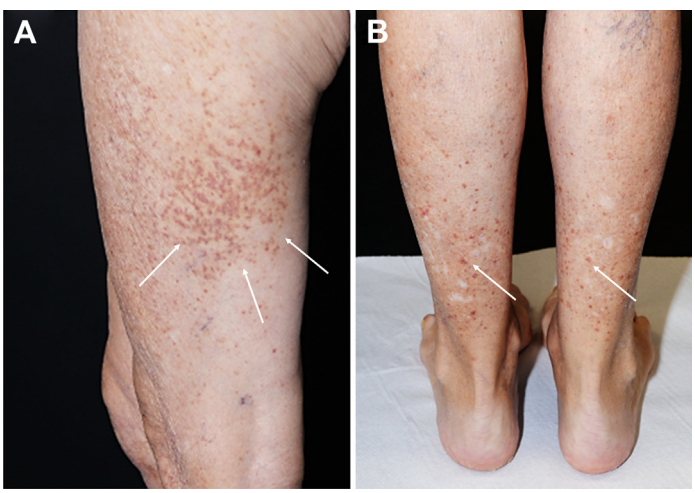
Based on the clinical, histologic, and immunofluorescence findings, we diagnosed CSVV. Considering the newly increased creatinine level in the patient's serum and presence of white blood cells in the urine sediment, incipient kidney involvement was diagnosed. Therefore, we treated the patient with systemic prednisolone (initially with 0.5 mg/kg body weight) next to topical corticosteroids. In addition, we recommended discontinuation of clopidogrel and amiodarone because it has been reported previously that both drugs can cause CSVV. Our diagnostic workup disclosed no evidence for another underlying cause of the patient's skin lesions.

DISCUSSION

CSVV is defined as inflammation of the small blood vessels of the skin and can also involve larger vessels or other organs.[1] The leading symptom of CSVV is palpable purpura, predominantly found on the lower extremities and symmetrically distributed.[1] Diagnosis is made by histopathologic examination, in which small vessels show transmural infiltration and disturbance by neutrophils and fibrinoid necrosis, a pattern specific for leukocytoclastic vasculitis.[2] Of note, the term leukocytoclastic vasculitis is confusingly used as a synonym for CSVV, but it actually refers to the histopathologic characteristics found in several types of vasculitis.[2]

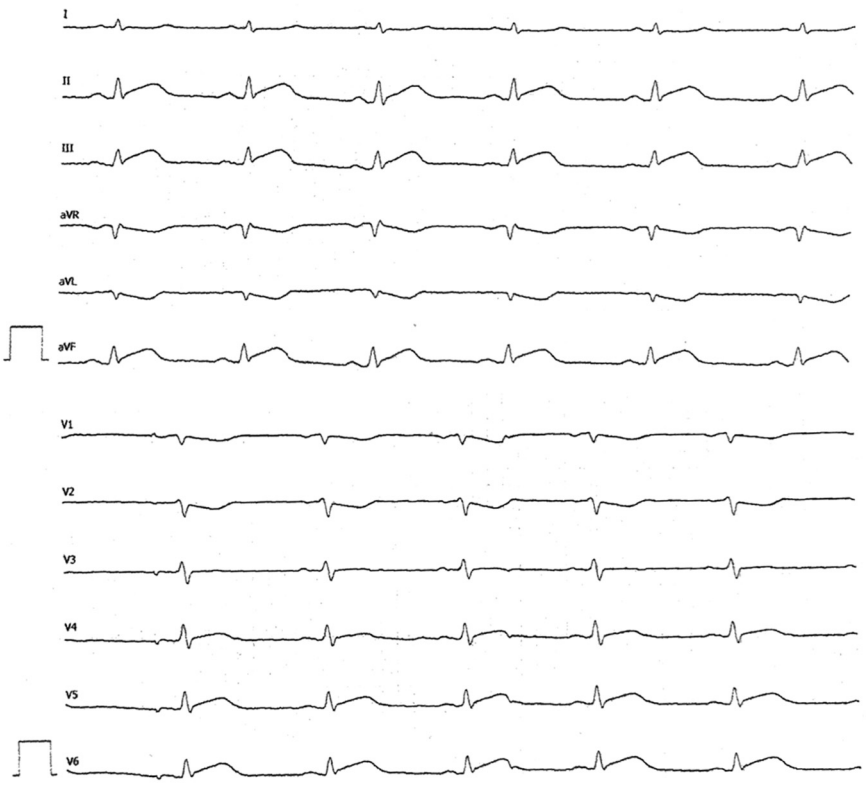
After diagnosing CSVV, the most important aim is to evaluate possible systemic involvement, eg, involvement of the kidneys or intestine, and to find the underlying cause of CSVV.[1] CSVV may be caused by drugs (10%-15%); viral or bacterial infections; malignancies; or other systemic diseases, especially autoimmune disorders.[1] In the case described here, there was no evidence for an infection or another underlying disease, but 2 drugs were recently initiated, clopidogrel and amiodarone. Both were initiated 6 weeks before onset of the CSVV and were withdrawn at the same time. One week after discontinuation, the skin lesions resolved entirely, suggesting drug-induced CSVV.

FIGURE 1 Clinical Pictures of the Patient's Legs



The patient presented with symmetrically distributed palpable purpuric papules on the legs as indicated by **white arrows** on the **(A)** left thigh and **(B)** lower legs.

FIGURE 2 Electrocardiography of the Patient Showing Inferolateral ST-Segment Elevation



Vasculitis is listed as a rare side effect of amiodarone, with only 5 reports of CSVV reported in the literature, with a high temporal variability between the initiation of amiodarone therapy and onset of CSVV (summarized in **Table 1**, cases 1-5[3-7]). Notably, the very long half-time value of amiodarone, ranging from 20 to 100 days, does not necessarily correlate to the time between amiodarone withdrawal and regression of skin lesions, which has been reported to be as short as 1 week.[3] Thus, the fact that the skin lesions in our patient resolved within 1 week after discontinuation of amiodarone does not exclude it being the cause.

Clopidogrel is a very rare cause of CSVV, which, to the best of our knowledge, has been previously reported in only 2 cases (**Table 1**, cases 6[8] and 7[9]). In 1 case, the onset of CSVV was 4 days after the introduction of clopidogrel[8] and in the other, it was as long as 1 year.[9] Complete resolution of CSVV took 7 days and 14 days, respectively, which is comparable to our case.

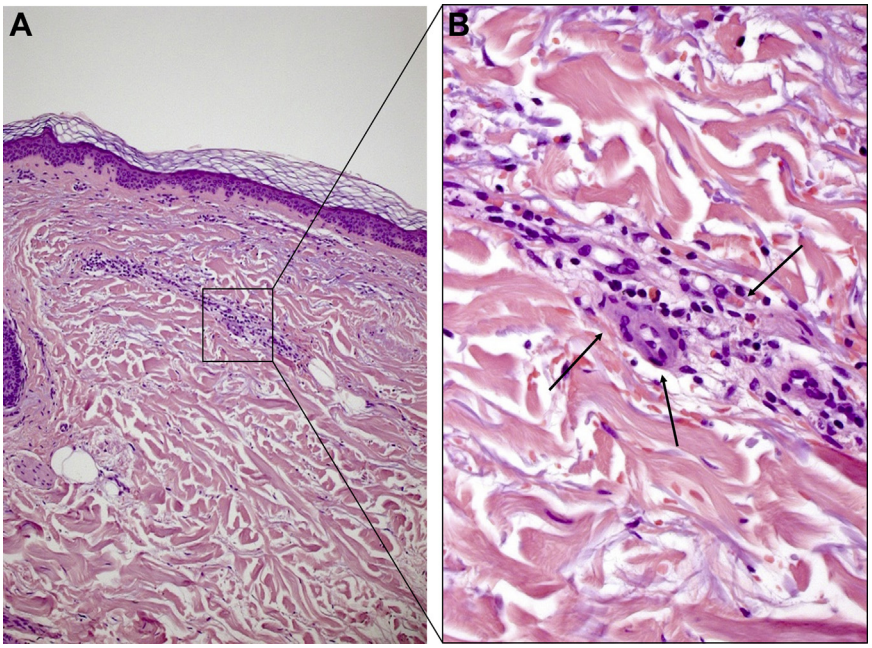
To sum up, a purpuric skin rash on a patient's legs with recently introduced drugs hints toward CSVV and should not be overlooked by the treating physician, because involvement of other organs can be critical. Because drug-induced CSVV is a diagnosis of exclusion, other causes have to be ruled out, and the temporal relation between recently induced drugs and appearance of palpable purpura, as well as the effect of drug withdrawal, have to be taken into account.[2]

Although the exact pathogenesis of drug-induced CSVV is unclear, is thought to be a type III hypersensitivity reaction. Thus, discontinuation of the putative causative drug is essential, along with avoiding subsequent rechallenge and exposition to drugs with similar composition.[10]

FOLLOW-UP

After discontinuation of clopidogrel and amiodarone, the rash regressed completely, and creatinine elevation returned to normal within 1 week. No further clinical signs of organ involvement occurred. Clopidogrel and amiodarone were not reintroduced. Instead of antiarrhythmic drugs,

FIGURE 3 Hematoxylin-Eosin-Stained Histopathologic Sample of a Skin Biopsy Specimen From the Left Thigh



Histology revealed characteristic histologic signs of early leukocytoclastic vasculitis **(black arrows)**, consisting of thickening of vessel walls, perivascular neutrophils and lymphocytes, perivascular nuclear dust, and extravasation of erythrocytes. **(A)** Original magnification ×50 and **(B)** original magnification ×400.

pulmonary vein isolation was performed to treat atrial fibrillation.

CONCLUSIONS

CSVV is a very rare side effect of clopidogrel and amiodarone. Cardiologists should be aware of it and be able to identify and treat CSVV. When in doubt, a skin biopsy should be performed and a dermatologist consulted. Discontinuation of the culprit drug results in remission of the disease.

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TABLE 1 Published Reports of Amiodarone- or Clopidogrel-Induced CSVV in the Literature

Case Number	Causative Drug	Onset of CSVV[a] After Drug Initiation	Treatment	Time to Regression of CSVV After Drug Discontinuation	First Author
1	Amiodarone	7 wk	Discontinuation of amiodarone	4 wk	Ndiaye et al[3]
2	Amiodarone	4 y	Discontinuation of amiodarone	16 wk	Scharf et al[4]
3	Amiodarone	5 d (drug reintroduction)	Discontinuation of amiodarone	2 wk	Staubli et al[5]
4	Amiodarone	9 d	Discontinuation of amiodarone	20 wk	Dootson and Byatt[6]
5	Amiodarone	45 d	Discontinuation of amiodarone	2 wk	Gutierrez et al[7]
6	Clopidogrel	4 d	Discontinuation of clopidogrel	7 d	Erpolat et al[8]
7	Clopidogrel	1 y	Discontinuation of clopidogrel Systemic antihistamines and topical steroids	2 wk	Shetty et al[9]

Organ involvement was limited to the skin in all reported cases. [a]Cutaneous small-vessel vasculitis.
CSVV = cutaneous small-vessel vasculitis.

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KEY WORDS kidney involvement, leukocytoclastic vasculitis, palpable purpura

APPENDIX For a supplemental video, please see the online version of this paper.