Warfarin-induced leukocytoclastic vasculitis and proteinuria

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Abstract

Warfarin is typically prescribed for patients with thromboembolic diseases and atrial fibrillation. In addition to the complications of bleeding, allergic skin reaction is one of its rare adverse effects. We herein report a case of a 79 year old male patient with leukocytoclastic vasculitis and proteinuria secondary to warfarin. The warfarin was discontinued and oral prednisone therapy was initiated. The cutaneous lesions and the proteinuria resolved thereafter.

Keywords: Leukocytoclastic, proteinuria, vasculitis, warfarin

Introduction

Oral anticoagulants are widely used in the prevention and treatment of venous and arterial thrombotic events. Skin reactions associated with oral coumarin-derived anticoagulants are an uncommon occurrence. Bleeding is the major side effect of warfarin therapy, but other nonhemorrhagic adverse reactions are also considerable.[1] Warfarin-induced skin changes are relatively uncommon side effects of warfarin therapy. The cutaneous complications of warfarin therapy include ecchymosis and purpura due to an excessive anticoagulant effect, photosensitivity, maculopapular vesicular urticarial eruptions, purple toes syndrome, skin tissue necrosis, and vasculitis.[2] We report a 79-year-old male patient with leukocytoclastic vasculitis and proteinuria (LCV), secondary to warfarin. The result of skin lesion biopsy confirming LCV, cutaneous lesions, and proteinuria resolved after warfarin was discontinued.

Case Report

A 79-year-old male patient was admitted with a 5-day history of progressive, well-demarcated nonpruritic cutaneous lesions on his lower extremities, which were reddish to violet and 5–10 mm in size. The lesions spread rapidly over his lower extremities (form ankle to mid-thigh bilateral), sparing his upper extremities, trunk, face, neck, and chest wall. He had a history of hypertension and dyslipidemia. His medications include lisinopril, hydrochlorothiazide, and simvastatin. Moreover, he had taken warfarin 2.5 mg p.o daily for 4 weeks as a deep venous thrombosis prophylaxis, after he had right total knee replacement surgery for severe right knee osteoarthritis 4 weeks ago. The patient denied any history of drug or food allergy, he also denied any exposure to laundry detergent, insect bites, poison ivy, or oak. There was no fever, chills, joints pain, or headache. There was no nausea, vomiting, hematuria, or urinary symptoms. No over-the-counter or nonsteroidal anti-inflammatory drugs (NSAIDs) medications used.

His vital signs were normal. Physical examination revealed bilateral lower extremities (form ankle to mid-thigh) and palpable purpura [Figure 1a and b]. The rest of his examination was unremarkable.

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Laboratory studies revealed a hemoglobin of 9.6 g/dL; white blood cell count, 4.5 × 10^3/mm³ (1% eosinophils); platelet count, 125 × 10^3/mm³; creatinine, 1.47 mg/dL; erythrocyte sedimentation rate, 50 mm/h; and normal levels of liver enzymes. The International Normalized Ratio was 1.6 on admission. Total eosinophil count and total IgE were normal. Testing for antistreptolysin-O, antinuclear and anti-neutrophil cytoplasmic antibodies, syphilis, rheumatoid factor, cryoglobulins, human immunodeficiency virus, and hepatitis B and hepatitis C viruses (HCVs) were all negative. Results of assays of coagulation function were normal (factor VIII assay, von Willebrand factor quantitation, ristocetin cofactor activity, and platelet function closure time, normal). In addition, deterioration of renal function and overt proteinuria were also observed at admission. Subsequent workup for acute kidney injury revealed a fractional excretion of sodium of 1.6% and fractional excretion of urea nitrogen of 62%. Urine culture was sterile with no eosinophils in urine, and renal ultrasound showed no evidence of obstructive uropathy. Testing for anti-glomerular basement membrane antibodies was negative, and complement C3 and C4 levels were decreased. Twenty-four hour urinary protein excretion was 420 mg.

Histological examination of the involved skin demonstrated perivascular and interstitial inflammation involving small blood vessels, with predominantly neutrophilic infiltration and extravasation admixed with few eosinophils, in addition to neutrophilic degeneration which goes with LCV [Figure 2a and b].

Warfarin was suspected as the cause of vasculitis, and it was discontinued. Oral prednisone therapy was started at a dose of 40 mg/day, as well as antihistamine. The skin lesions gradually improved after the discontinuation of warfarin and initiation of steroid therapy. Furthermore, his renal function recovered, as well as proteinuria. The patient was discharged, on tapered prednisone, in stable condition free of cutaneous lesions and with recovered renal function.

**Discussion**

LCV is an inflammatory disease involving the small vessels that usually presents as nontrombocytopenic palpable purpura. Cutaneous lesions typically begin as asymptomatic localized hemorrhages that become palpable as blood leaks out of the vessels. Other cutaneous manifestations that may be encountered with LCV include vesicles, nodules, hemorrhagic bullae, and superficial infarctions. The eruptions may be asymptomatic or associated with itching, burning, or edema. Although lesions are commonly seen on the lower extremities, they may occur elsewhere, including areas under local pressure, such as the back in bedridden patients.

It is reported that about half of the cases of LCV have associated systemic effects that may involve the kidney; gastrointestinal tract; or pulmonary, cardiovascular, or central nervous systems (in addition to the cutaneous lesions). Signs and symptoms may include general malaise, myalgia, arthralgia, abdominal pain, nausea, proteinuria, hematuria, and fever.

Cutaneous vasculitis can be associated with infection (15–20%), inflammatory disease (15–20%), malignancy (<5%), or it can be idiopathic (45–55%). Drugs seldom cause cutaneous or systemic vasculitis, and the typical manifestation is cutaneous small vessel vasculitis.

The differential diagnosis of left ventricular (LV) encompasses a wide spectrum of diseases, including Henoch–Schönlein purpura, cryoglobulenic vasculitis, and drug-induced acute allergic interstitial nephritis. LCV-associated Henoch–Schönlein purpura presents as palpable purpura in the lower extremities and buttocks. The condition commonly manifests in children, especially in young boys. Henoch–Schönlein purpura usually follows an upper respiratory tract infection and is characterized by a tetrad of findings: Palpable purpura, arthralgia or arthritis, abdominal symptoms, and renal failure. The cutaneous lesions usually disappear in 10–14 days. Cryoglobulenic vasculitis presents as lower extremity purpura precipitated by cold, prolonged standing, trauma, infection, or drug reaction. A common cause of cryoglobulinemia is HCV, which accounts for approximately 80–90% of cases. The hallmark of cryoglobulinemia is the presence of cryoprecipitates, which are composed of a mixture of monoclonal and polyclonal immunoglobulins. Neutrophilic and/or lymphocytic infiltrates

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**Figure 1:** (a) Physical examination revealed bilateral lower extremities (from ankle to mid-thigh) and palpable purpura. (b) Examination of lower extremities revealed papular rash.

**Figure 2:** (a) Low field and (b) high field. Histopathology revealed perivascular and interstitial inflammation involving small blood vessels, with predominantly neutrophilic infiltration and extravasation admixed with few eosinophils.
with mural necrosis and thrombosis of vascular plexus are seen in the dermis. Warfarin has been associated with leukocytoclastic vasculitis and allergic interstitial nephritis. Hypersensitivity to warfarin simultaneously results in allergic interstitial nephritis and leukocytoclastic vasculitis where they usually present with acute renal failure and skin rash. Kidney biopsy will show allergic interstitial nephritis and skin biopsy will show leukocytoclastic vasculitis. Both biopsies have high eosinophil count, which are highly suggestive of a drug-induced reaction.\[11\]

Drugs are implicated in 10–24% of the cases with cutaneous manifestations of LCV, which usually occur with a long latent period. In the literature review, the interval between the first exposure to warfarin therapy and the symptoms of vasculitis was markedly varied (from days to years). Vasculitis may occur after dose titration or after re-exposure of the causative agent.\[12\] In most of the cases, vasculitis resolved after discontinuation of the drug.\[13\]

Drug-induced LCV presents as palpable purpura is confined to the lower extremities. The mechanism for the development of drug-induced LV is postulated to involve a cascade of immune complex formation and complement activation. Warfarin-induced LCV typically develops in a long-term treatment, and the disease spectrum ranges from relatively benign cutaneous symptoms requiring only discontinuation of warfarin and supportive care to a life-threatening condition requiring intensive care. Pharmacological treatments include topical and systemic corticosteroids, antihistamines, NSAIDs, and immunosuppressants. Patients with severe or life-threatening manifestations have required treatment with corticosteroids (or even pulse corticosteroids), hemodialysis, cyclophosphamide, or plasmapheresis.\[12\]

The latent period of LCV following administration of a causative agent has been shown to be highly variable from as short as 3 days or as long as 12 years. Our patient had begun warfarin therapy 4 weeks before the occurrence of vasculitis, which is within the time frame for the development of LCV. The onset of drug-induced LCV typically occurs 7–10 days after contact with the antigen responsible for the reaction.\[14\] There are two groups according to the interval between first exposure to warfarin and the appearance of the symptoms. The patients with symptom onset within 6 weeks are named “normal latency LCV,” and the patients with latency of more than 6 weeks are called “late-onset LCV.” Among the patients with late-onset LCV, they seemed to have a much higher prevalence of proteinuria. About 87.5% of late-onset LCV patients developed proteinuria and 0% of normal latency LCV patients were reported to have proteinuria.\[10\] There was no significant difference in the histological findings between the normal-latency group and the late-onset group.\[14\]

In summary, warfarin or other coumarin drug-induced vasculitis is very rare. To our knowledge, this is the first case report of warfarin-induced normal latency LCV who presented with proteinuria in addition to skin lesions. It is critical to be aware of this potential adverse effect of warfarin to enable prompt diagnosis and treatment in similar cases.

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Conflicts of interest
There are no conflicts of interest.

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