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PUNCHING FOR THE TRUTH BENEATH THE RASH: A CASE OF WARFARIN-INDUCED LEUKOCYTOCLASTIC VASCULITIS

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ABSTRACT

Warfarin is a commonly used anticoagulant. It is associated with many adverse effects, including major or minor bleedings, purple toe syndrome, and cutaneous manifestations. Although rare, leukocytoclastic vasculitis (LCV) has been reported in the literature. We present the case of a 65-year old male patient who presented with palpable purpura and acute kidney injury with proteinuria five weeks after starting warfarin for an acute lower extremity deep venous thrombosis. A punch biopsy of the lesions revealed leukocytoclastic vasculitis. Renal biopsy showed findings suggestive of pauci-immune glomerulonephritis. The offending agent was discontinued, and intravenous methylprednisolone was given with complete resolution of skin eruptions and renal failure. The patient was discharged home on apixaban without recurrence of the rash. Early recognition, prompt diagnosis and management will prevent morbidity and mortality in people at risk.

KEYWORDS: Leukocytoclastic vasculitis, warfarin, hematuria, acute renal failure, glomerulonephritis.

INTRODUCTION

Warfarin is the pioneer oral anticoagulant, used to prevent and treat arterial and venous thromboembolic disease. It is a widely used medication due to its low cost, availability, and extensive clinician familiarity with the drug. It acts by inhibiting the formation of vitamin K-dependent clotting factors II, VII, IX, & X. Warfarin has a narrow therapeutic index, interacts

with multiple drugs, and its metabolism in the human body is variable.[6] The most common adverse effect is bleeding due to over anticoagulation, and the most common cutaneous adverse effects are ecchymosis and purpura, secondary to increased anticoagulant effect. Nonetheless, other adverse effects, such as skin necrosis or small-vessel vasculitis have been reported in the literature but are rare.

CASE REPORT

We present the case of a 65-year old Hispanic male with history of coronary artery disease, bronchial asthma, gout, and arterial hypertension, who had a five-day history of abdominal pain, hematuria, and painless maculopapular rash. These symptoms began five weeks after starting warfarin 5mg daily for treatment of an unprovoked left lower extremity deep venous thrombosis. The patient denied any use of herbal supplements, NSAIDs (non-steroidal anti-inflammatory drugs), aspirin, new detergents, sun exposure, fever, chills, hemoptysis or joint pain. The patient also denied previous allergies to food, medications, or environmental agents.

On initial physical examination, there was an active and alert, oriented x3 male patient with normal vital signs. However, examination of the skin showed a non-blanching purpuric rash in bilateral forearms, flanks, and lower extremities [Figure 1]. An interdigital small, dried hemorrhagic bulla [Figure 2] was present on the left foot's first interdigital space, and the extremity had swelling to the level of the thigh, with erythema, and tenderness. The rest of the physical examination was otherwise unremarkable.

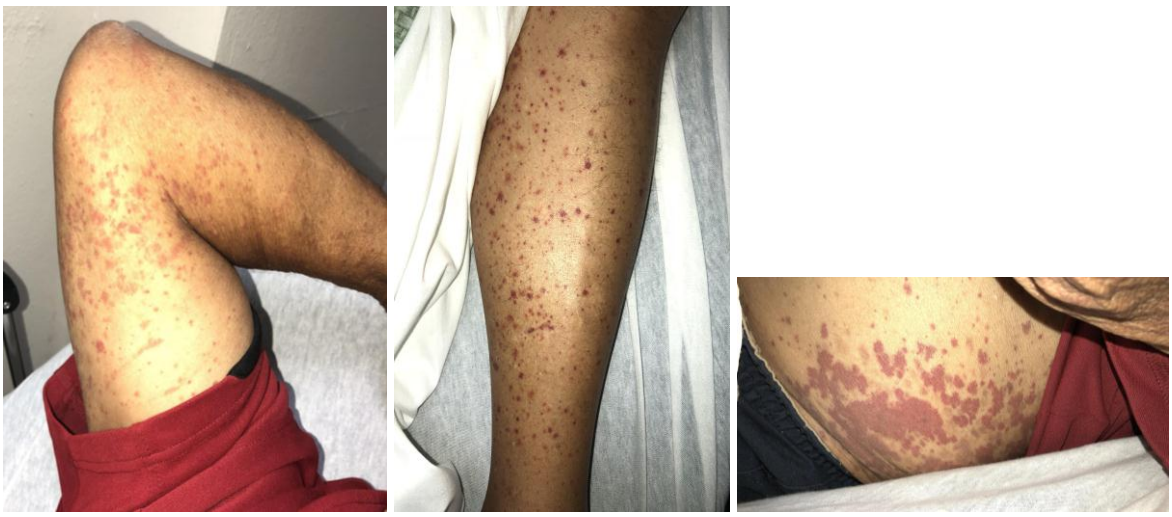

Figure 1: Maculopapular non-blanching purpuric lesions of upper and lower extremities and flank.

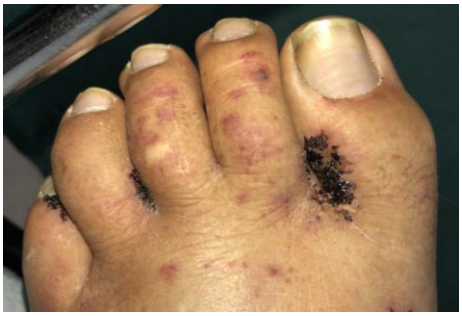

Figure 2: Interdigital dried hemorrhagic bullae.

Laboratories showed multiple disturbances. The complete blood count (CBC) was pertinent for normocytic anemia of 10.5g/dL with a mean corpuscular volume (MCV) of 86.2, thrombocytosis of 614 Thou/uL, and eosinophilia 18.7% on the differential. The coagulation panel showed prolonged PT 54.2 sec and PTT 79.5 sec, resulting in a supra-therapeutic INR of 5.06. The chemistry showed results compatible with intrinsic acute kidney injury with an elevated Creatinine 2.20 mg/dL, compared to 1.30 mg/dL upon discharge one month prior, and a BUN:Cr ratio of 17.7. Urinalysis showed macroscopic and microscopic hematuria (RBC over 50) and proteinuria of 25 mg/dL with WBC 3-9/hpf without casts. Urinary protein excretion was estimated with a urine protein to creatinine ratio of 1.4g/day. Rheumatoid factor was elevated at 16.50 IU/mL and serum cryoglobulin was positive. The patient also presented the following laboratory disturbances: an elevated: ESR 120mm/h, C3 192mg/dL, and C4 89mg/dL. Serologies for MPO, PR3, Human Immunodeficiency Virus and Hepatitis B and C were all negative. An abdominal ultrasound was pertinent for symmetric and normal sized kidneys with increased cortical echogenicity favoring parenchymal renal disease.

Because warfarin-induced vasculitis was suspected, it was immediately discontinued and anticoagulation for DVT was continued with enoxaparin. A punch biopsy of the left thigh showed fibrin in the walls of venules with interstitial infiltrates of neutrophils, consistent with leukocytoclastic vasculitis [Figure 3]. In view of hematuria and acute kidney injury, a renal biopsy was performed, which revealed changes suggestive of pauci-immune glomerulonephritis and acute tubular injury [Figure 4a and 4b]. The patient received treatment with intravenous corticosteroids for three weeks, which resulted in resolution of the rash, decrease in proteinuria to 0.5g/day and normalization of creatinine level to patient's baseline in 1.32mg/dL. The coagulation parameters normalized upon discontinuation of warfarin. The patient was discharged home to continue DVT treatment with apixaban.

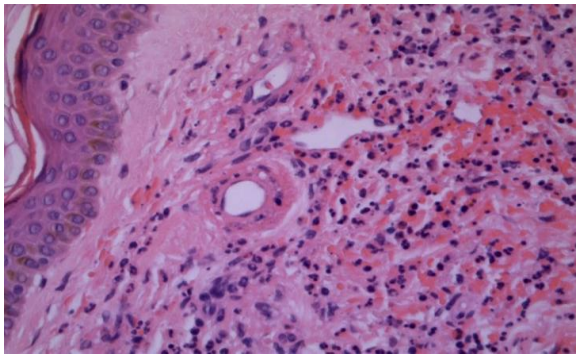

Figure 3: Punch biopsy of lower extremity showing small vessel leukocytoclastic vasculitis.

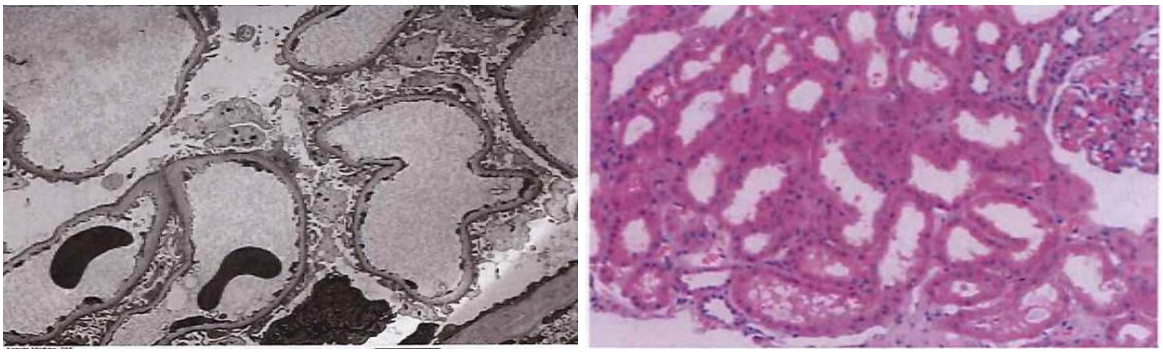

Figure 4: Electron microscopy showed 10-15% podocyte effacement (a), Acute tubular injury (b).

DISCUSSION

In this case, we report the first case of warfarin-induced leukocytoclastic vasculitis reported in Puerto Rico, according to our knowledge and revision of medical literature. LCV is an inflammation of small-sized vessels, that usually presents as a non-blanching maculopapular rash. It may become palpable due to the leak of blood out of the vessels. The lower extremities are the most commonly affected areas, but it can be seen in other parts of the body.[2] Warfarin-induced LCV may also be associated with systemic manifestations in kidneys, gastrointestinal tract, and central nervous system. The diagnosis can be confirmed with a skin biopsy. The described mechanism of disease is not clearly established but is thought to involve immune complexes and complement activation.[3] While it is mostly associated with systemic inflammation (infection, malignancy, rheumatologic diseases), it is rarely an adverse effect of drugs. Once the diagnosis is made it is important to focus on the etiology of such manifestation to avoid further detrimental effects. The prognosis depends on the extent of involvement of internal organs. An elevated INR strongly predicts warfarin-related adverse effects.[6] This was consistent in our case, as the patient presented an INR of

5.06. Warfarin has been associated with leukocytoclastic vasculitis and interstitial nephritis with a variable latency period ranging from days to years.[1] Our patient presented a delayed latency of 5 weeks. Most cases of drug-induced LCV are due to diuretics, beta-lactam antibiotics, and NSAIDs[2] Warfarin-induced LCV is exceedingly rare. Skin biopsy was consistent with leukocytoclastic vasculitis and renal biopsy had findings suggestive of pauci immune glomerulonephritis. The co-presentation of both syndromes has been observed in mice.[5] According to Rutgers, et al (2016) this histopathological finding is either the renal manifestation of Wegener's granulomatosis, microscopic polyangiitis of Churg-Strauss syndrome, or a renal-limited vasculitis. We believe the vasculitis was secondary to warfarin because skin lesions improved after discontinuation of the drug. Nonetheless, re-exposure to the medication was not performed to avoid further kidney injury to a patient with an established history of stage 3A Chronic Kidney Disease, according to the CKD-EPI equation for glomerular filtration rate. In cases of LCV, re-exposure to warfarin (the offending drug) is not contraindicated if a mild cutaneous vasculitis occurred, or in the setting of a life-threatening condition without feasible alternatives.[4] However, our patient suffered a combination of cutaneous and renal (internal organ) manifestations of LCV, for which re-initiation of warfarin was discarded and he successfully completed treatment with apixaban, a direct oral anticoagulant. He responded favorably, due to prompt recognition, and confirmation of diagnosis, discontinuation of warfarin, and anti-inflammatory treatment.

CONCLUSIONS

Warfarin is a frequently used medication with multiple known adverse effects including renal and dermatologic. Arguably, the most documented adverse effect is bleeding. Although rare, it has been associated with LCV. The latency period from use of the drug to clinical presentation of LCV has not been clearly established. Nonetheless, there are cases reporting periods ranging from days to years. Our case presented with signs and symptoms after 5 weeks of warfarin anticoagulation. It is extremely important to be aware of these possible complications even if some time has passed in the treatment. Early recognition, prompt diagnosis and management will prevent morbidity and mortality in people at risk.

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