

Ulcerative IgA vasculitis in the setting of warfarin therapy

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Abstract

Henoch-Schönlein purpura (HSP) is a small vessel vasculitis characterized by the presence of vascular immunoglobulin A deposition that usually presents as non-thrombocytopenic palpable purpura. It primarily affects children and is less common in adults. The incidence of hemorrhagic necrotic skin lesions increases with age, similarly to renal involvement. Warfarin is a widely used oral anticoagulant drug that has rarely been associated with leukocytoclastic vasculitis and allergic interstitial nephritis. We report a patient with HSP who presented with cutaneous ulcerative plaques and proteinuria in the setting of warfarin therapy. We would like to raise the awareness of this potential adverse effect of warfarin for prompt diagnosis.

Keywords: vasculitis, anticoagulant drugs, warfarin, adult, Henoch-Schönlein purpura, IgA

Introduction

Henoch-Schönlein purpura (HSP) is more common among children than adults, although it is more severe in adults. Clinical manifestations mainly involve palpable purpura, arthritis, arthralgias, acute enteritis, and glomerulonephritis, including hematuria, proteinuria. Gastrointestinal and renal involvement are the principal causes of morbidity and mortality in adults. The incidence of hemorrhagic necrotic skin lesions and renal involvement is reported to increase with age [1]. During childhood, the disease generally follows respiratory infection, whereas adult patients exhibit more frequent histories of medication use prior to

the onset of HSP [2]. Leukocytoclastic vasculitis associated with oral coumarin-derived anticoagulants are rarely reported [3].

Case Synopsis

A 49-year-old woman was admitted to our outpatient clinic owing to progressive, painful cutaneous plaques on the lower extremities that had first appeared three weeks previously. Her history revealed that the lesions had started as a reddish-to-violet eruption and transformed into hemorrhagic necrotic plaques over the subsequent three days, spreading rapidly over the thighs and gluteal region. She had a history of hypertension and diabetes mellitus. Medications used included metformin, repaglinide, and valsartan-hydrochlorothiazide for



Figure 1. Crusty ulcerated plaques with a necrotic appearance surrounded by live erythematous halos with well-defined borders on the distal parts of the bilateral lower extremities (A-C) and buttocks (D).

the previous two years. Warfarin and digoxin had been started two months previously for new-onset atrial fibrillation. Dermatological examination revealed necrotic, crusted, ulcerated papules and small plaques with well-defined borders surrounded by an erythematous halo, mostly localized on the distal parts of the lower extremities but also scattered on the buttocks (**Figure 1**).

Skin biopsy showed epidermal ischemic damage with subepidermal separation, fibrinoid degeneration, and neutrophil infiltration in the vessel walls. Perivascular neutrophilic infiltration accompanied by nuclear fragmentation and dermal erythrocyte extravasation was also observed (**Figure 2**). Direct immunofluorescence revealed granular blood vessel wall staining with IgA and C3, but negative results with IgG, IgM, and C4 (**Figure 3**).

Laboratory studies revealed elevated C-reactive protein and erythrocyte sedimentation rate and normal liver enzyme levels and complete blood cell count. Tests for antistreptolysin-O, anti-neutrophil cytoplasmic antibodies, anti-nuclear antibody, anti-ds DNA, rheumatoid factor, cryoglobulins, and complement C3-C4 levels were all normal. Serology studies for syphilis, human immunodeficiency virus, and hepatitis B and C viruses were negative. Protein C and S tests, factor VIII assay, and von Willebrand

factor were also within normal ranges. The patient's international normalized ratio value was 3.13 (in high range) and prothrombin time was 33.4 sec (prolonged). Deterioration of renal function and elevated serum blood urea nitrogen were observed. Overt proteinuria and hematuria were also observed on urinalysis. Twenty-four-hour urinary protein excretion was over one gram.

The patient was diagnosed with HSP complicated with IgA nephropathy. Although it was difficult to definitively state that the direct cause was warfarin, it was discontinued and replaced by enoxaparin. Oral prednisolone therapy was started at 100mg/day. The skin lesions gradually improved after the discontinuation of warfarin and the initiation of corticosteroid therapy. Twenty-four-hour urinary protein excretion decreased to 275mg/day during follow-up. Renal functions also recovered. Prednisolone therapy was discontinued after 8 weeks by dose reduction. No recurrence was seen during the follow-up period of up to three months.

Case Discussion

HSP is a non-thrombocytopenic systemic vasculitis of childhood with a peak incidence in the first and second decades of life. The annual incidence in children is estimated at 14 cases per 100,000, whereas the incidence in adults is only 1.3 per 100,000, with a mean age at onset of approximately 50 years [1]. The clinical manifestations of HSP vary

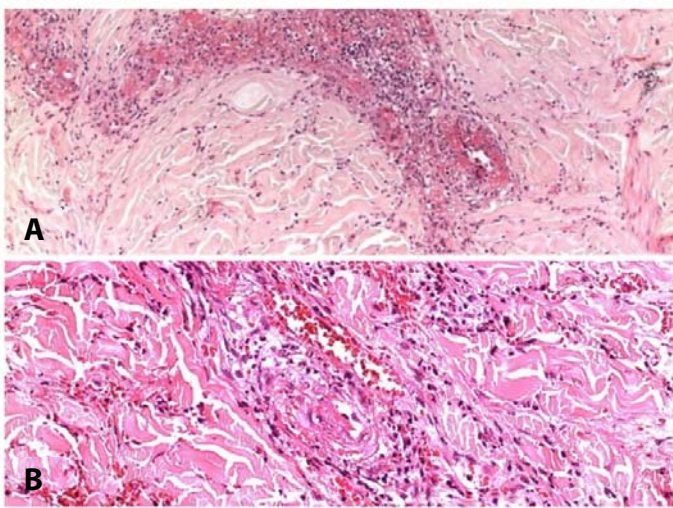


Figure 2. Histopathology of the biopsy material from the left lower extremity showed fibrinoid degeneration and neutrophil leukocyte infiltration in vascular walls of the dermis and neutrophil leukocytes, nuclear fragmentation, and erythrocyte extravasation in perivascular area. H&E, **A)** 10 \times , **B)** 20 \times .

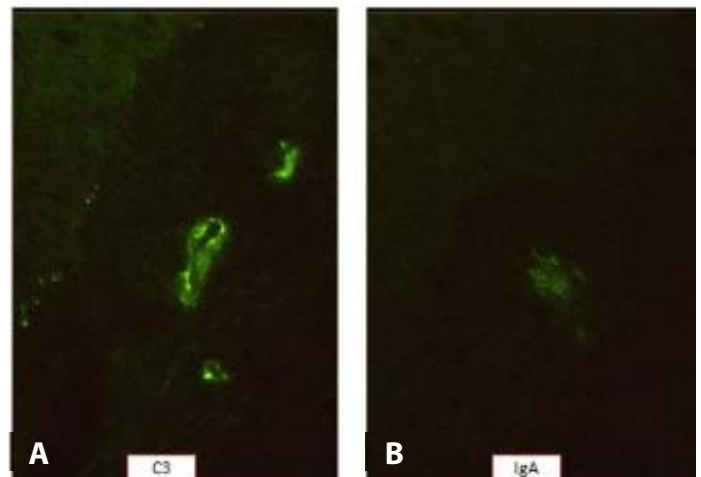


Figure 3. Direct immunofluorescence test, **A)** C3, 20 \times , and **B)** IgA were positive, IgG, IgM, and C4 were negative, 20 \times .

with age and renal involvement and complications with renal insufficiency are more common in older patients [2].

Although rare, drug-induced HSP has been more commonly reported during adulthood, whereas the disease generally follows upper respiratory tract infections in the pediatric population [1]. Drugs suspected of causing HSP include non-steroidal anti-inflammatory drugs, lisinopril, furosemide, and anti-tuberculosis medications [5]. However, warfarin-induced leukocytoclastic vasculitis (LCV) is rare and to the best of our knowledge only 15 cases of LCV induced by warfarin or coumarin have been reported [6,7]. In addition to our patient, there are two more cases of HSP induced by warfarin in the literature [8,9]. In these cases, the interval between first exposure to warfarin therapy and onset of symptoms of vasculitis varied between four days and 12 years. Warfarin therapy was administered to our patient eight weeks before the onset of symptoms, which is within the normal interval for the development of vasculitis. Leukocytoclastic vasculitis is classified under two forms, depending on the interval between first exposure to warfarin and onset of vasculitis. In "normal latency LCV," symptoms occur within six weeks of the drug being started. If latency exceeds six weeks, this is known as "late-onset LCV." Patients with late onset LCV have a much higher prevalence of proteinuria, at approximately 87.5%, whereas renal involvement was not observed in cases of normal latency LCV [6,9]. Our patient's findings were consistent with late-onset LCV. As in our case, the other two cases of HSP associated with warfarin use reported in the literature had 24-hour proteinuria levels above one gram [8,9].

Cutaneous necrosis is not a common finding in childhood HSP and has been reported in fewer than

5% of all cases [10]. Pillebout et al. determined hemorrhagic necrotic purpura in 35% of adult HSP cases and suggested that the incidence of hemorrhagic necrotic skin lesions increases with age, similarly to renal involvement [2]. Our patient also had extensive necrotic skin lesions and palpable purpura was not observed.

Warfarin and digoxin are commonly used concomitantly in the treatment of atrial fibrillation and chronic heart failure. Our patient also received digoxin in addition to anticoagulant therapy. In addition to our patient, there have been seven other reported cases of vasculitis associated with digoxin and warfarin therapies [9,11-13]. Concomitant use of warfarin and digoxin is therefore believed to increase the risk of development of warfarin-induced LCV owing to potential drug interactions [6]. In most cases, vasculitis resolved after discontinuation of warfarin.

Conclusion

In conclusion, to the best of our knowledge, this is only the third case report of coumarin-derived anticoagulant drug induced late onset HSP presenting with severe proteinuria and acute renal failure in addition to necrotic skin lesions. It is important to be aware of this potential adverse effect of warfarin for prompt diagnosis. In these cases immediate discontinuation of warfarin is vital for the prevention of renal failure and other organ involvement.

Potential conflicts of interest

The authors declare no conflicts of interests.

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