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Case Report

Warfarin skin necrosis mimicking calciphylaxis in a patient with secondary hyperparathyroidism undergoing peritoneal dialysis

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Abstract

Warfarin skin necrosis (WSN) is an infrequent complication of warfarin treatment and is characterized by painful ulcerative skin lesions that appear a few days after the start of warfarin treatment. Calciphylaxis also appears as painful skin lesions caused by tissue injury resulting from localized ischemia caused by calcification of small- to medium-sized vessels in patients with end-stage renal disease. We report on a patient who presented with painful skin ulcers on the lower extremities after the administration of warfarin after a valve operation. Calciphylaxis was considered first because of the host factors; eventually, the skin lesions were diagnosed as WSN by biopsy. The skin lesions improved after warfarin discontinuation and short-term steroid therapy. Most patients with end-stage renal disease have some form of cardiovascular disease and some require temporary or continual warfarin treatment. It is important to differentiate between WSN and calciphylaxis in patients with painful skin lesions.

Introduction

Warfarin skin necrosis (WSN) is a nonhemorrhagic complication of warfarin treatment, and its prevalence is reported to be only 0.01–0.1% among patients taking warfarin [1]. Calciphylaxis is a rare, challenging complication of end-stage renal disease (ESRD) with a high mortality rate. WSN and calciphylaxis have common clinical features, and warfarin treatment is a representative risk factor for calciphylaxis [2]. We describe a patient undergoing peritoneal dialysis who exhibited painful ulcerative skin lesions after warfarin administration.

Case report

A 52-year-old man with aortic stenosis was admitted to the thoracic surgery department. He had undergone kidney transplantation 15 years previously but had been on peritoneal dialysis for the past 2 years because of graft failure. He was also diagnosed with secondary hyperparathyroidism accompanied by metastatic pulmonary calcification and had received ethanol injection to a right parathyroid nodule.

On hospital day (HD) 7, he underwent surgery to replace the aortic valve with a titanium-based prosthesis. During the operation, his aorta showed severe wall calcification. The final pathology finding of the original aortic valve was fibrocalcific

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valvulopathy. The day after the operation, warfarin was added to his medication lists without heparin overlapping. On HD 18, hemorrhagic pustules developed suddenly on both feet. The skin lesions were distributed over both feet and were accompanied by xerotic scale (Fig. 1). The lesions were tender. At that time, there was no change in his condition other than the skin lesions.

The patient's medications included renalmin (vitamin B and C complex), sevelamer, cinacalcet, and divalproex, all of which he had been taking before admission, and famotidine, atenolol, risperidone, isosorbide-5-mononitrate, Mypol (ibuprofen/codeine/acetaminophen complex), and warfarin, all of which were added after the surgery. During the hospitalization, serial assessment showed that C-reactive protein concentration was increasing, and intravenous vancomycin was added on HD 19. The initial differential diagnosis of the skin lesions was drug eruption and metastatic infection, and a skin biopsy and microbiology examination were performed. While waiting for the result, the skin lesions changed to necrotic ulcers accompanied by substantial pain and progressed to the thigh level of both legs.

The patient was referred to the nephrology department because of painful skin lesions on HD 21. At that time, laboratory data showed a serum calcium of 8.7 mg/dL, phosphorus of 2.2 mg/dL, and intact parathyroid hormone level of 155.4 (reference range, 11.0–62.0) pg/mL. Chest radiographies showed extensive calcified consolidation in both upper lung fields (Fig. 2). We considered the possibility of calciphylaxis because his lungs and blood vessels showed extensive calcification and the host factors such as ESRD, secondary hyperparathyroidism, and recent warfarin commencement suggested the possibility of calciphylaxis. On HD 23, the pathology report indicated fibrinoid necrosis of entire dermal vessels, epidermal necrosis, and vesicles (Fig. 3A). Of note, no vascular calcification was detectable (Fig. 3B). Further review of the patient revealed no evidence of systemic vasculitis, and tests for antineutrophil cytoplasmic antibodies (antiproteinase 3 and antimyeloperoxidase) were negative.

On HD 27, we decided to withhold warfarin after consideration of WSN and started parenteral steroid (methylprednisolone

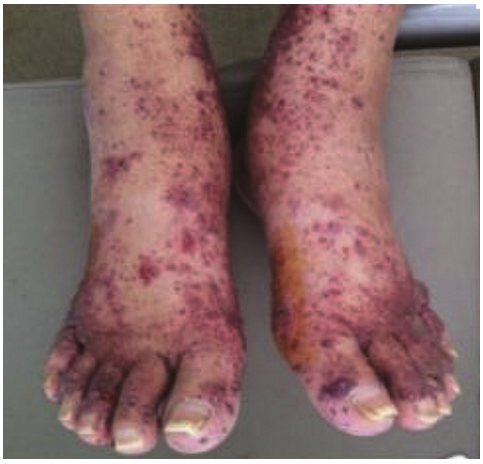

Figure 1. Skin lesions on both feet. On HD 19, 11 days after the start of warfarin, erythematous pustules with tenderness developed suddenly on the lower aspects of both feet. The skin lesions expanded to the thigh level over the next few days.
HD, hospital day.

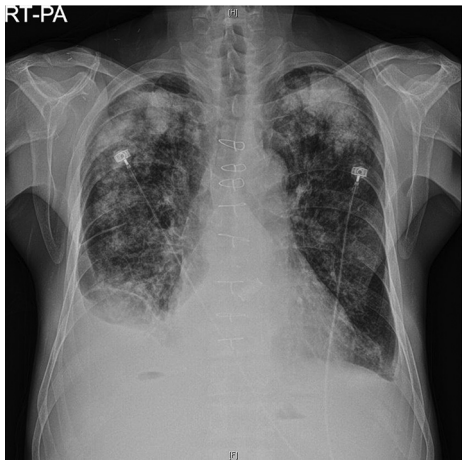

Figure 2. Chest radiography. Calcified consolidation is shown in both upper lung fields.

40 mg every 8 hours) after discussion with the allergy department. On HD 29, he was transferred to his local tertiary hospital for personal reasons. In that hospital, steroid therapy was continued and then tapered without the use of anticoagulants.

Twelve days after discharge, the patient visited our hospital because of epistaxis and was readmitted. At that time, the skin lesions had improved, and the steroid was tapered out. On HD 4 of the second hospitalization, we tried again to give the patient warfarin with enoxaparin. From HD 9 of the second hospitalization, painful skin lesions became aggravated. The reemergence of the painful skin lesions was strong evidence of WSN, and we immediately stopped the warfarin treatment and used short-term systemic steroid. The skin lesions and pain disappeared. We finally diagnosed the skin lesions as WSN, and enoxaparin was used as the anticoagulant. He was discharged after the systemic steroid was stopped and given enoxaparin as the maintenance anticoagulant.

Discussion

WSN is an infrequent nonhemorrhagic complication of warfarin treatment. The first case was described in 1943, and the prevalence is reported to be 0.01–0.1% [1]. In Korea, 2 cases have been reported. One involved a 70-year-old man who presented with hemorrhagic bulla and ecchymosis on the right upper extremity that appeared after 6 days of warfarin treatment for acute stroke. He had no history of medical illness except hypertension [3]. The other case involved a 48-year-old woman who presented with skin necrosis on both breasts about 3 weeks after double valve replacement surgery and warfarin treatment. She also had no other significant medical history [4]. There are no reports of WSN in patients with ESRD. In patients with ESRD, WSN may be more challenging because of the need for an important differential diagnosis from calciphylaxis. When a patient with ESRD presents with painful skin lesions after warfarin treatment, the clinician should consider the possibility of the 2 main differential diagnoses—WSN versus calciphylaxis.

Although the pathogenesis is not fully understood, WSN results from the pharmacologic effects of warfarin. During the early phase of treatment, warfarin creates a paradoxically transient hypercoagulable state because several of the