CASE REPORT

Calciphylaxis induced by warfarin therapy in a patient with anti-phospholipid antibody syndrome associated with systemic lupus erythematosus

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Abstract Calciphylaxis is a life-threatening complication of end-stage kidney disease (ESKD) and leads to cutaneous necrosis and gangrene. Various risk factors for calciphylaxis have been reported, and warfarin therapy is a particularly strong trigger. Here we report the case of 50-year-old woman with ESKD and systemic lupus erythematosus who developed calciphylaxis after anti-thrombotic therapy, including warfarin, for ischemic skin ulcers due to arteriosclerosis obliterans and anti-phospholipid antibody syndrome. Although warfarin improved the thrombotic skin ulcers, it might also be a trigger for calciphylaxis. Discontinuation of the warfarin and the addition of low-density lipoprotein apheresis and sodium thiosulfate infusion failed to improve the gangrene; eventually, her legs had to be amputated to prevent lethal infection. The histology of the dermal and soft tissue obtained from the amputated legs showed typical findings of calciphylaxis. Warfarin is a vitamin K antagonist with inhibitory effects on the calcification of regulatory proteins, such as matrix Gla protein and fetuin-A. Therefore, the warfarin therapy might have induced calciphylaxis in our patient.

Keywords Calciphylaxis · Sodium thiosulfate · Warfarin

Introduction

Calciphylaxis, often called calcific uremic arteriolopathy, is a pathophysiological change caused by the deposition of calcium and leads to cutaneous necrosis and gangrene. Some risk factors, such as ESKD, lower serum albumin levels, female gender, diabetes mellitus, mineral bone disorders, and warfarin therapy have been reported [1, 2]. However, its etiology seems to be multifactorial and remains unclear.

APS increases the risk of recurrent arterial or venous thrombosis. Warfarin therapy is essential for the treatment and prophylaxis of the thrombosis in APS [3]. Here we report the case of a Japanese SLE patient who developed calciphylaxis after warfarin therapy for thrombotic ischemic skin ulcers due to APS.

Case report

A 50-year-old woman was admitted because of a skin ulcer on her foot. She had been diagnosed with SLE in her thirties with erythema, polyarthritides, proteinuria, hematuria, and the presence of antinuclear antibodies. She received steroid therapy and her clinical symptoms improved, but the proteinuria and hematuria still continued. Insulin therapy was started because of steroid-induced diabetes. She refused kidney biopsy, and her kidney function gradually decreased. Six months before admission, she noticed purpura and a small ulcer on her right foot. She was diagnosed with ASO, because the peripheral circulation of her lower limbs was extremely poor. On the other hand, the lupus anticoagulant was positive and a skin biopsy of the ulcer lesion revealed small fibrin thrombi (Fig. 1a). She was also diagnosed with APS, and anti-thrombotic therapy with

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beraprost sodium and warfarin was started to treat both ASO and APS. In addition to the skin ulcer, her kidney function further worsened, which brought her to the admission in our hospital.

On admission, pitting edema and skin ulcers with necrotic tissue were observed on the feet. One of the ulcers had reached the periosteum. A small area of gangrene was also detected on her left ring fingertip. Her laboratory data revealed the presence of nephrotic syndrome with massive proteinuria (7.1 g/day) and hypoalbuminemia (2.3 g/dL), as well as the presence of renal failure with a high creatinine level of 5.9 mg/dL, a high phosphate level of 6.7 mg/dL, and a calcium level of 8.4 mg/dL. The intact parathyroid hormone level was not high (32.7 pg/dL). Hemodialysis was started for kidney dysfunction with uremic symptoms, such as general malaise and appetite loss, and they improved after regular hemodialysis. After the debridement of necrotic tissue around the ulcers and warfarin therapy, the ulcers gradually re-epithelialized, and were almost healed after ten-weeks of treatment. However, small areas of gangrene appeared and spread out across the toes of both feet and her fingers. X-rays and computed tomography confirmed calcification in the small- and medium-sized arteries as well as in the subcutaneous tissues (Fig. 2). A bone scan also confirmed ossification of the arteries and skin. Moreover, the calcium deposition in small-sized arteries was confirmed by skin biopsy (Fig. 1b). Collectively, based on these clinical, radiological, and histological findings, the gangrene was caused by calciphylaxis.

Next, the warfarin was discontinued, and a total of five sessions of LDL apheresis was performed twice a week, using a Liposorber LA-15 system (Kaneka Co. Ltd, Osaka, Japan) with treatment with 3000 mL of plasma during each session to improve the peripheral circulation. In addition, sodium thiosulfate infusion (25 g intravenously over 60 min, 3 times after hemodialysis) was started with

institutional review board approval and informed consent. Although the area of gangrene did not ameliorate, the pain from the gangrene did slightly decrease, and the amount of analgesic drugs decreased. However, her general condition worsened due to the adverse effects of sodium thiosulfate, such as metabolic acidosis, anorexia, and nausea. Therefore, sodium thiosulfate was stopped after the eighth infusion. Although her general condition improved after the discontinuation of sodium thiosulfate, the gangrene progressively extended to her knees and wrists over 4 months (Fig. 3). Therefore, amputations of her legs were necessary to relieve the persistent pain and to prevent a lethal infection. The histology of the dermal and soft tissue, obtained from the amputated legs, showed typical findings of calciphylaxis and ASO; this included calcium deposition in the middle layer of the arterial walls in the subcutaneous fat (Fig. 4a) and cellular proliferation of intima with partial obliteration (Fig. 4b).

Discussion

Herein, we have described a SLE patient who developed calciphylaxis after warfarin therapy for APS. The warfarin was effective for thrombosis, but it may have triggered calciphylaxis. The combination therapy of LDL apheresis with sodium thiosulfate infusion was partially effective. However, we discontinued the sodium thiosulfate infusion due to some adverse effects.

Kidney dysfunction has some role in vascular damage. Abnormalities of calcium and phosphate metabolism and chronic inflammation induced by uremia cause vascular smooth muscle cells (SMCs) to differentiate into osteoblast-like cellular phenotypes and vascular calcification [4, 5]. Moreover, local vascular calcification regulatory proteins, such as matrix Gla protein and fetuin-A, and their signaling pathways decrease under uremic conditions [6].

Fig. 1 **a** Skin biopsy revealed the detachment of the basal epidermal layer. Arrows show small fibrin thrombi in the subepidermal small vessels. **b** Arrows show calcium deposition in the subcutaneous arterioles

Fig. 2 X-rays and CT showed calcified arteries (*arrows*) and subcutaneous ectopic calcifications (*arrow heads*)

Fig. 3 Clinical course after admission. Warfarin therapy improved thrombotic skin ulcers; however, gangrene in the distal extremities rapidly spread after initiation of warfarin therapy. The gangrene finally extended to her knees and wrists

Fig. 4 Histology of the dermal and soft tissue. **a** Calcium deposition in the middle layer of the arteriolar wall. **b** Cellular proliferation of the intima with partial obliteration

Furthermore, warfarin is a vitamin K antagonist that has inhibitory effects on calcification regulatory proteins. Therefore, the progression of kidney dysfunction and warfarin could be a risk for calciphylaxis in our case.

Before our patient showed calciphylaxis symptoms, she was diagnosed with SLE and APS. Autoimmune diseases lead to endothelial damage [7]. SLE patients, especially those with APS, tend to have arterial calcification [8]. In addition to SLE and APS, our patient had other risk factors for calciphylaxis, such as lower serum albumin levels, female gender, diabetes mellitus, systemic steroid use, and warfarin therapy.

Some possible therapeutic approaches for calciphylaxis are known, such as the improvement of the abnormal metabolic parameters (calcium, phosphorus, and intact parathyroid hormone concentrations), wound care and debridement, hyperbaric oxygen therapy, bisphosphonates, and the antioxidant approach using sodium thiosulfate [2]. The effect of sodium thiosulfate has been reported to rapidly bring relief from severe pain within days to weeks and to heal skin ulcerations within weeks to months [6, 9]. The adverse effects of intravenous sodium thiosulfate can be obstacles. They consist of nausea, abdominal discomfort, and metabolic acidosis. In this case, these adverse effects appeared after a few injections, which resulted in the discontinuation of this treatment. It is not possible to distinguish which cases may be sensitive to sodium thiosulfate. A retrospective study [9] showed that a delay in diagnosis and treatment, or the complications of diabetes, coronary artery disease, peripheral artery disease, or heart failure was associated with poor prognosis. In this case, we speculated that the complications of diabetes and ASO with APS were one of the reasons for the ineffectiveness of sodium thiosulfate.

LDL apheresis is an effective therapeutic approach for ASO patients. It improves peripheral circulation through multiple effects, such as anti-inflammatory, vasodilatory, and angiogenic effects, and lowers lipid levels. It was recently reported that LDL apheresis markedly increased

capillary perfusion and promoted ulcer healing during calciphylaxis in one case [10]. We attempted LDL apheresis to improve her peripheral circulatory disturbance; however, the ulcers did not heal, and the gangrene progressed. We believe that the peripheral circulatory failure extended to gangrene, which went beyond the point of no return. Taken together, considering the poor outcome of patients with calciphylaxis like this patient, further investigations on treatment of calciphylaxis are needed.

In conclusion, calciphylaxis consists of heterogeneous backgrounds. Further studies are needed for a clearer understanding of the pathogenesis of calciphylaxis, and optimal treatment which leads to better prognosis in such patient.

Conflict of interest The authors have declared that no conflict of interest exists.

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