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BRIEF REPORT

Warfarin-induced calciphylaxis successfully treated with sodium thiosulphate

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ABSTRACT

Calciphylaxis is a rare life-threatening form of skin necrosis. Although traditionally observed in patients with end-stage renal disease and/or hyperparathyroidism, calciphylaxis has also been reported to occur in 'non-traditional' patients with normal renal and parathyroid function. We report a case of warfarin-induced calciphylaxis treated successfully with sodium thiosulphate and discuss the role of Vitamin K2 as a potential therapeutic option in the management of warfarin-induced calciphylaxis.

Key words: calciphylaxis, sodium thiosulphate, vitamin K2, warfarin.

INTRODUCTION

Calciphylaxis is a rare small vessel vasculopathy, usually confined to patients with renal insufficiency, and estimated to occur in 1–4% of patients on haemodialysis. The pathogenesis of this condition is poorly understood, and the reported mortality rate ranges from 60–80%. Diagnosis is based on clinical, biochemical, histopathological and radiological findings. Warfarin has previously been reported to provoke calciphylaxis.[1] We present a rare case of warfarin-induced calciphylaxis successfully treated with sodium thiosulphate.

CASE REPORT

A 54-year-old man with a history of cardiac failure was admitted with uncontrolled atrial fibrillation. He was warfarinised and 5 days later he developed asymptomatic purple patches on his calves. Warfarin was continued for 9 months and he subsequently developed painful leg ulceration. He had a history of type II diabetes and bronchiectasis for which he took oral doxycycline continuously. Examination revealed deep, well-demarcated, tender ulcers affecting the calves in a symmetrical distribution, on a background of livedoid change (Fig. 1).

Laboratory investigations showed a normal full blood count, renal and liver function, bone profile, parathyroid hormone and protein C and S levels. Antinuclear antibody, anti-neutrophil cytoplasmic antibody, lupus anticoagulant, cryoglobulins and complement were not detected. Inflammatory markers were modestly elevated (c-reactive protein 25 mg/L; erythrocyte sedimentation rate [ESR] 20 mm/h) and the international normalised ratio was elevated at 2.5, consistent with warfarin therapy. Skin swabs excluded any concomitant infection. A diagnostic biopsy from the ulcerated area revealed calcium deposition within the lumen of capillary sized vessels in the subcutis with evidence of medial calcification and intimal hyperplasia associated with fat necrosis. There was no evidence of vasculitis and fibrin thrombi were not seen.

The warfarin was discontinued immediately and enoxaparin commenced as an alternative anticoagulant. Maggot therapy was required for debridement of the necrotic tissue, opioid analgesia for pain relief and sodium thiosulphate infusions (25g intravenously thrice weekly) were initiated. There was complete resolution of the ulcers after 8 months of sodium thiosulphate therapy (Fig. 2).

Calciphylaxis is a metastatic calcification-induced microvascular occlusion syndrome of mural calcification, intimal proliferation, fibrosis and thrombosis leading to target organ hypoperfusion.[2] The lesions of calciphylaxis are typically very painful, with ulceration, secondary infection and end organ hypoperfusion resulting in gangrene, amputation and sepsis with significant morbidity and mortality rates as high as 89%.[3]

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Abbreviation:

ESR	erythrocyte sedimentation rate

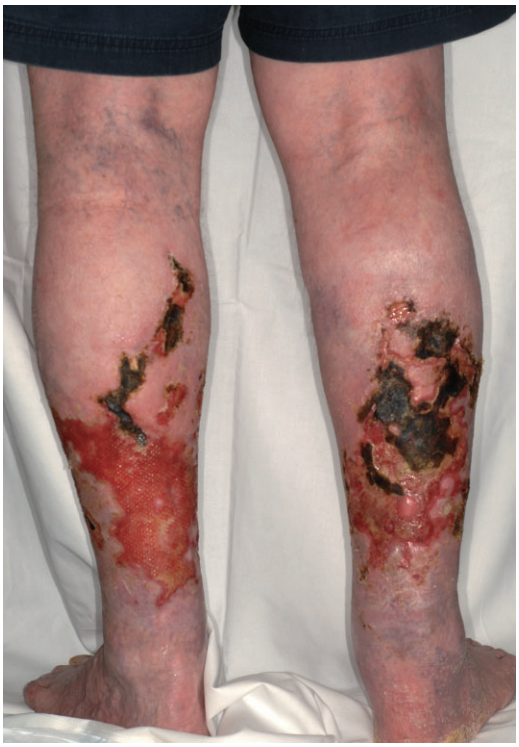

Figure 1 Well-demarcated leg ulcers affecting the lower limbs in a symmetrical distribution with eschar formation and background livedoid changes.

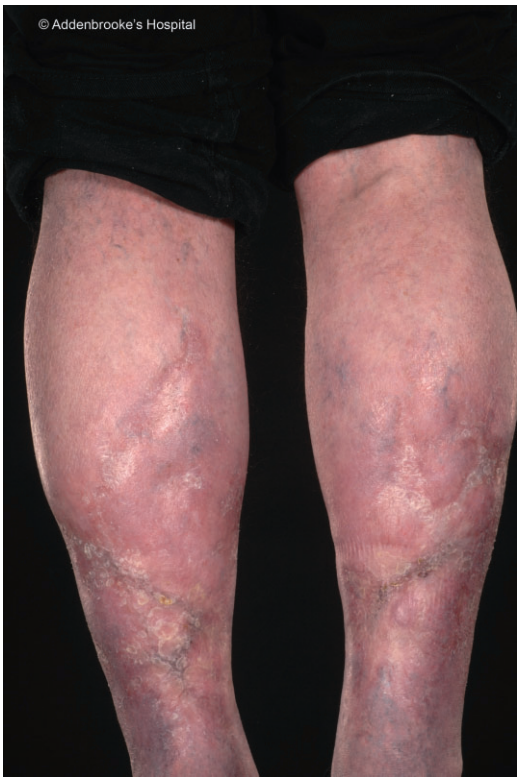

Figure 2 Complete resolution of leg ulceration after 8 months' treatment with sodium thiosulphate infusions.

The pathogenesis of calciphylaxis is poorly understood. Calciphylaxis in patients with normal renal and parathyroid function supports the view of calciphylaxis as a final common end-point, reachable via many pathways involving the interplay of various risk factors. Exposure to sensitisers and challengers is thought to culminate in an increased susceptibility to vascular calcification and luminally narrowed arterioles, which are therefore more prone to thrombosis if exposed to the proper stimuli.[4] The final common pathway involves nuclear factor kappa-β activation, leading to vascular calcification, which, when followed by thrombosis, results in the clinical features of calciphylaxis.

Risk factors for calciphylaxis include obesity, liver disease, systemic corticosteroid use, diabetes, white race, female sex, increased ESR, elevated alkaline phosphatise, protein C and S levels and warfarin usage.[5] Price *et al.*[6] demonstrated warfarin's ability to promote vascular calcification in rodents, probably via the inhibition of gamma-carboxylation of matrix gamma-carboxyglutamic acid proteins that normally function to inhibit endogenous calcification.

Although warfarin-induced skin necrosis (WISN) is a well-recognised entity[7] with a similar clinical presentation to that of warfarin-induced calciphylaxis, this was deemed to be less likely in our patient for a number of reasons. The histological features of WISN typically include thrombotic occlusion in dermal, subcutaneous vasculature with haemorrhage, which was not a feature in our case. In addition, our patient possessed a risk factor profile lending more towards calciphylaxis than WISN: the latter group typically portray a hypercoagualable state, for example, protein C and S deficiency,[8,9] abnormal liver function tests and lupus anticoagulant positivity, which were not seen in our patient. Furthermore, although the clinical presentations can be very similar, the lesions of calciphylaxis have a predilection for the lower limbs, as demonstrated in our case. In contrast, lesions of WISN predominate in areas where there is relatively greater adipose tissue, for example, the breasts, thighs, hips and buttock region.

Management is aimed at making an early diagnosis and adopting a multidisciplinary approach. Wound care is paramount. Specific treatments reported to be useful in the treatment of calciphylaxis include parathyroidectomy, using calcium or aluminium-free phosphate binders, intravenous phosphate binders and bisphosphonates.[10] Recently, sodium thiosulphate, an inorganic salt that promotes the dissolution of calcium deposits via chelating calcium in the form of the highly soluble calcium thiosulphate salts, has shown promising results.[11]

Although our patient refused to take any 'new' oral medication, we feel vitamin K would have been a valuable adjunct in reversing the process of calciphylaxis. Warfarin acts as a vitamin K antagonist, inhibiting the production of both vitamin K1 and K2. Vitamin K1 is involved in the production of coagulation factors and vitamin K2 actively prevents arterial calcification.[12] There are several forms of

vitamin K2 of which two are of interest in this case: menaquinone-4 and menaquinone-7. The average Western diet is relatively deficient in Vitamin K2, which is sourced by intestinal conversion from vitamin K1, meat and fermented food products. This dietary deficiency coupled with chronic antibiotic therapy, as in our case, can further exacerbate vitamin K2 deficiency.[13] We hypothesise that the combination of diabetes (with already present calcium apatite crystals in the vessels ready to form a nidus) and chronic vitamin K2 deficiency caused by long-term antibiotic therapy set our patient up for a catastrophic acceleration of vascular calcification when exposed to warfarin.

Treatment options for calciphylaxis have been largely empirical or supportive, and indeed there are no prospective treatment trials. Although our patient declined to take vitamin K2 supplementation, we feel more research is required into the potential therapeutic utility of vitamin K2 in the management of calciphylaxis with the hope of preventing the devastating consequences of this rare condition.

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