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Case report

Sodium thiosulfate is effective in calcific uremic arteriolopathy complicating chronic hemodialysis

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ABSTRACT

Background: Calcific uremic arteriolopathy (CUA) or calciphylaxis is a severe complication of advanced chronic kidney disease (CKD) and dialysis. Few effective treatments are available and the mortality rate is high. We report 4 cases in which sodium thiosulfate therapy was rapidly effective.
Cases: Sodium thiosulfate therapy was given to 4 Caucasian patients (3 females and 1 male aged 49 to 91 years) with CUA. The causes of end-stage CKD were nephroangiosclerosis ($n = 2$) and diabetic nephropathy ($n = 2$). The lesions developed 1 to 6.5 years after the initiation of hemodialysis and involved the lower limbs in 2 patients, the fingers in 1 patient, and a breast in the remaining patient. They were responsible for pain and skin necrosis in all 4 patients. Local superinfection occurred in 3 patients. Intravenous sodium thiosulfate was given in a dosage of 12.5 to 25 g after each hemodialysis session, for 12 to 24 weeks. The pain and trophic disorders resolved fully in all 4 patients. The side effects consisted of nausea and vomiting ($n = 2$) and a moderate blood pressure decrease ($n = 1$). No recurrences were noted during the follow-up of 5 to 17 months after treatment discontinuation.
Conclusion: The findings from this small case-series suggest that sodium thiosulfate may hold promise for the treatment of CUA.

1. Introduction

Calciphylaxis or calcific uremic arteriolopathy (CUA), first described in 1962, is characterized by calcifications of the cutaneous and subcutaneous arterioles. Ninety percent of cases of CUA develop in patients with end-stage chronic kidney disease (CKD) [1]. CUA is associated with high mortality rates ranging from 40 to 86%. The skin lesions predominate at the lower limbs and are more common in proximal areas. They consist of erythematous mottling and indurated nodules or plaques that are often extremely painful and usually progress to form ulcers. Histological studies show vasculopathy without vasculitis. Calcifications are visible in the media of the small arteries and arterioles of the dermis and hypodermis, which also exhibit intimal hypertrophy and endovascular fibrosis. Calcium deposition within the blood vessels is an early and crucial event in the development of CUA plaques [2]. The calcifications are believed to result chiefly from mineral and bone homeostasis disorders with hyperphosphatemia and elevation of the calcium-phosphate product, abnormally high or low parathyroid hormone levels, adynamic bone disease, excess vitamin D, and/or aluminum toxicity. Other local and systemic factors are involved, such as inflammation, malnutrition with hypoalbuminemia, vitamin K antagonist therapy, endothelial dysfunction, and/or an imbalance between promineralizing factors and calcification inhibitors. The treatment of CUA is difficult and standard measures often lack efficacy. Sodium thiosulfate (STS) has been used for over a century to treat cyanide poisoning. There are reports of successful STS therapy in patients with ectopic calcifications such as recurrent urinary lithiasis and uremic tumoral calcinosis [3]. In case-series of patients with CUA, STS therapy produced inconsistent results. Here, we report 4 cases of CUA in patients on chronic hemodialysis who responded to STS therapy.

2. Case-reports

2.1. Case #1

The first patient was a 91-year-old man who had been receiving standard hemodialysis at our center for 1 year (Table 1). He

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Table 1
Clinical features in 4 patients with calcific uremic arteriolopathy and effects of sodium thiosulfate therapy.

	Patient #1	Patient #2	Patient #3	Patient #4
Age/sex	91/H	55/F	49/F	91/F
Ethnicity	Caucasian	African	Caucasian	Caucasian
CV risk factors	HT, dyslipidemia, MI	HT, diabetes, dyslipidemia, LLOAD, angina	HT, diabetes, dyslipidemia, MI	HT, MI
Type of CKD	Nephroangiosclerosis	Diabetic nephropathy	Diabetic nephropathy	Nephroangiosclerosis
Dialysis	Hemodialysis	Hemodialysis	Hemodialysis	Hemodialysis
Clinical features	Pain, infection, sinus tract, necrosis	Pain, infection, necrosis	Pain, infection, necrosis	Pain, necrosis
Location	Fingers	Right breast	Lower limbs	Lower limbs
Time from HD to onset (years)	1	6.5	1.5	5.5
Previous treatments	Phosphate chelation	Calcium-channel inhibitors	Phosphate chelation	Phosphate chelation, calcium-channel inhibitors
STS dosage	25 g/48 h	12.5 g/48 h	12.5 g/48 h	25 g/48 h
Duration of STS use (weeks)	16	24	16	12
Outcome	Full recovery	Full recovery	Full recovery	Full recovery
Follow-up (months)	0 (died)	5	8	17

F: female; M: male; CKD: chronic kidney disease; CV: cardiovascular; HD: hemodialysis; HT: hypertension; MI: myocardial infarction; LLOAD: lower limb occlusive arterial disease; STS: sodium thiosulfate.

was overweight and had dyslipidemia. His cardiovascular history included hypertension, percutaneous coronary angioplasty to treat myocardial infarction, diffuse arteriosclerosis, and heart failure due to a combination of hypertension, coronary artery disease, and valvular disease. He had early-stage secondary hyperparathyroidism. His chronic medications consisted of the antiplatelet agent clopidogrel, a lipid-lowering agent, and two antihypertensive drugs (a beta-blocker and a nitrate). In February 2006, he was started on chronic hemodialysis, three 4-hour sessions per week, for end-stage renal failure due to nephroangiosclerosis. Extremely painful ulcers and necrotic lesions developed over the fingers of his right hand 21 months later (Fig. 1). Radiographs of the hands visualized subcutaneous calcifications measuring 1 to 4 mm in diameter and located under the skin lesions. These clinical and radiographic features strongly suggested CUA, making a biopsy unnecessary. The skin lesions ran a complicated course, with the formation of sinus tracts, bacterial infection, and ischemic necrosis. Laboratory findings at the diagnosis of CUA were as follows: serum calcium: 2.66 mmol/L; serum phosphate: 1.85 mmol/L; calcium-phosphate product: 4.92 $mmol^2/L^2$; 25(OH) D: 41.40 ng/mL; $1,25(OH)_2D$: 11 ng/L; parathyroid hormone: 80 ng/L; bone alkaline phosphatase: 12.9 μg/L; and CTX: 1320 ng/mL. Markers for systemic inflammation were moderately elevated (C-reactive protein: 7.10 mg/L; and erythrocyte sedimentation rate: 38 mm/h). He initially received analgesics and treatments to eradicate the local infection. Phosphate chelation therapy and a vitamin D analog were given to

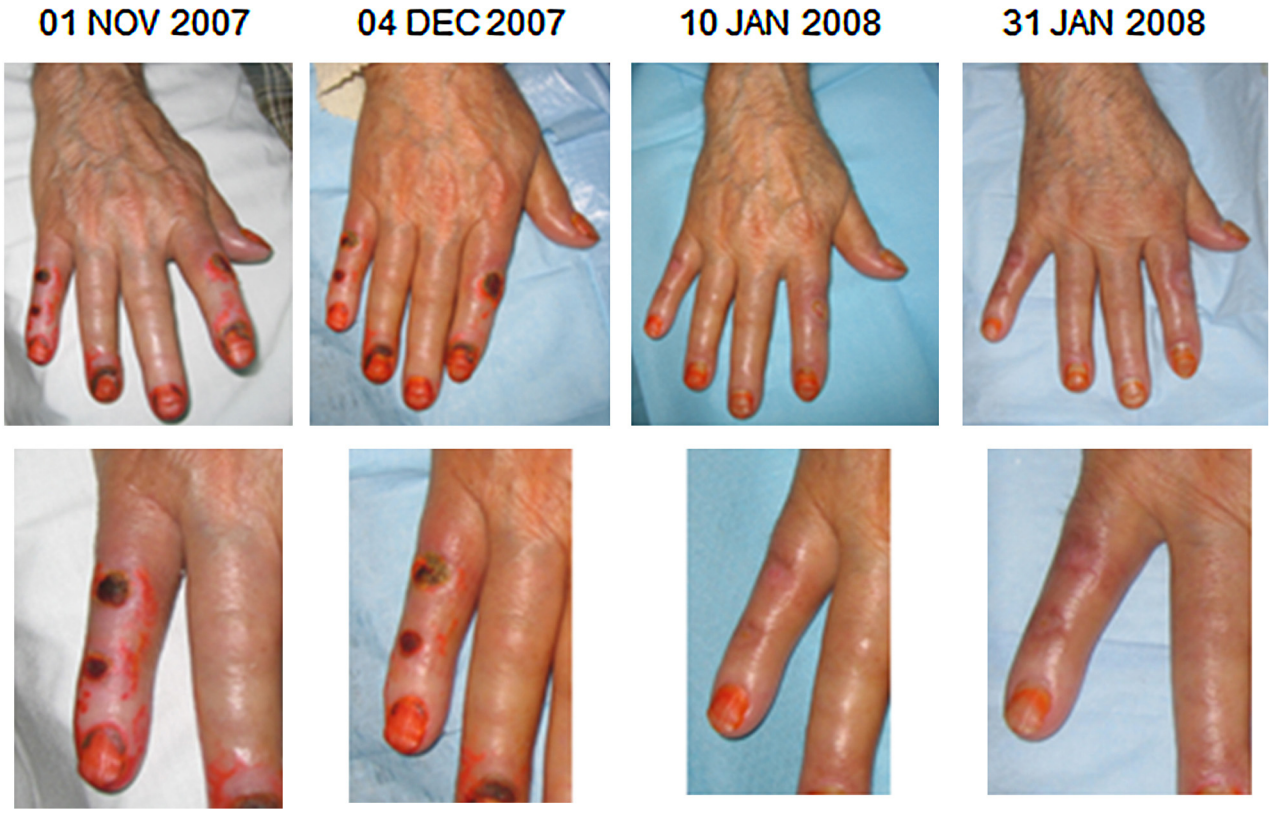

Fig. 1. Patient #1. Course of the ulcerated and necrotic skin lesions during treatment with sodium thiosulfate (STS). The necrotic lesions on the fingers developed after 21 months of chronic hemodialysis. They resolved rapidly with STS therapy.