INTERNAL MEDICINE

□ CASE REPORT □

The Successful Treatment of Calciphylaxis with Sodium Thiosulfate and Hyperbaric Oxygen in a Non-dialyzed Patient with Chronic Kidney Disease

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Abstract

We present the case of a non-dialyzed patient with chronic kidney disease and biopsy-proven calciphylaxis who presented with painful cutaneous ulcers on both legs. The skin ulcers drastically improved within 6 months after the initiation of hemodialysis, aggressive wound care, the control of a mineral and bone disorder, and the administration of sodium thiosulfate and hyperbaric oxygen therapy. Notably, the patient's serum levels of C-reactive protein and calciprotein particles decreased and her serum albumin and fetuin-A levels increased in parallel with the alleviation of her calciphylaxis. This case highlights the importance of applying combined medical treatment to calciphylaxis and suggests the possible involvement of calciprotein particles in the pathogenesis of calciphylaxis.

Key words: calciphylaxis, calciprotein particle, chronic kidney disease, hyperbaric oxygen therapy, sodium thiosulfate

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Introduction

Calciphylaxis is a rare but life-threatening disorder which is associated with a high mortality rate. It is characterized by cutaneous ischemia and necrosis caused by medial calcification, intimal fibrosis, and thrombosis of the pannicular arterioles (1). Calciphylaxis usually affects patients with chronic kidney disease (CKD) who are undergoing dialysis. It is less common in CKD patients who have not undergone dialysis (2). Epidemiological studies have unveiled a variety of risk factors for calciphylaxis, which include (but are not limited to) the use of warfarin, calcium-based phosphate binders, vitamin D receptor activators (VDRAs), and corticosteroids; secondary hyperparathyroidism; a hypercoagulable state; and female gender (1, 3). At the present time, however, no definitive treatment has yet been established for calciphylaxis.

Fetuin-A, which is produced in the liver and which is negatively regulated by inflammation, is an important inhibitor of vascular calcification (4, 5). Fetuin-A decreases in the presence of CKD and is involved in the pathogenesis of vascular calcification (6-8). Recently, calciprotein particles (CPPs) - microparticles composed of calcium, phosphate, fetuin-A, albumin, and other proteins - were reported to be directly involved in the inflammation and vascular calcification associated with CKD (9-12). Fetuin-A also modifies the procalcific potential of CPPs and prevents vascular calcification (13). However, it remains to be determined whether a reduction in fetuin-A and an increase in CPP are involved in the pathogenesis of calciphylaxis.

We herein present the case of a non-dialyzed CKD patient

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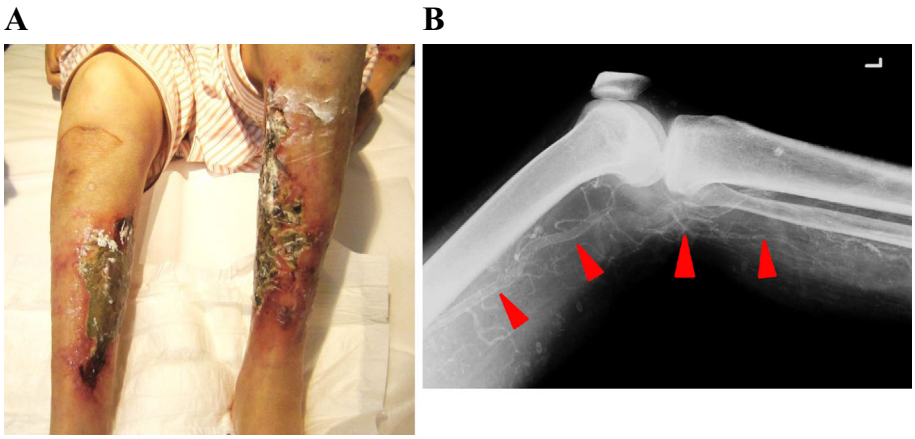

Figure 1. The patient's lower legs at admission. A: Skin ulcers on the pretibial skin. B: A radiograph shows diffuse calcification of the left femoral, popliteal, and peripheral arteries (red arrows).

with skin biopsy-proven calciphylaxis who was successfully treated with a combined medical treatment which included the administration of sodium thiosulfate (STS) and hyperbaric oxygen therapy (HOT). Interestingly, 6 months after the initiation of the treatment, the patient's serum fetuin-A level increased and her serum CPP levels decreased in parallel with healing of the calciphylaxis-associated skin ulcers.

Case Report

A 61-year-old woman with CKD and nephrotic syndrome was admitted to our hospital due to the presence of multiple painful cutaneous ulcers of the lower legs. At age 43 years of age she had developed minimal change nephrotic syndrome, which had been confirmed by a renal biopsy. Although she was treated with a combination of prednisolone, mizoribine, cyclosporine A, and low-density lipoprotein apheresis, the nephrotic syndrome remained, with multiple cycles of relapses and remissions. Her renal function gradually decreased. Eight months prior to the current admission, cutaneous ulcers developed bilaterally in a wide area of pretibial skin. The skin ulcers worsened despite the provision of a standard topical treatment. At that time, the corrected serum calcium level was 9.1 mg/dL, with a phosphate level of 7.5 mg/dL. The patient was treated with calcium carbonate (3 g/day) and alfacalcidol (0.5 μg/day). She was finally transferred to our institution for further evaluation and treatment.

On admission, her height was 148.4 cm, her weight was 55.7 kg, and her body mass index was 25.3 kg/m^2. She was alert, with a blood pressure of 136/74 mmHg, a heart rate of 84 bpm, and a body temperature of 36.6℃. She exhibited anemic palpebral conjunctiva, a moon face appearance, and bilateral painful leg ulcers (Fig. 1A).

The laboratory data on admission are shown in Table. Briefly, the following results were obtained: serum albumin (1.3 g/dL), blood urea nitrogen (99 mg/dL), creatinine (5.92 mg/dL) estimated glomerular filtration rate (6.3 mL/min/1.73 m^2), phosphate (7.6 mg/dL), calcium (5.1 mg/dL), intact parathyroid hormone (345 pg/mL), and serum C-reactive protein (6.2 mg/dL). A urine dipstick test was positive for proteinuria (4$^+$) and hematuria (2$^+$). The proteinuria was 3.5 g/g·creatinine. An examination of the urinary sediment revealed red blood cells [1-4 cells/high power field (HPF)], white blood cells (9-10 cells/HPF), and oval fat bodies.

Based on the above results, the patient was diagnosed with nephrotic syndrome corresponding to CKD stage G5A3. At this point, however, there were several differential diagnoses, including diabetic gangrene, antiphospholipid antibody syndrome, and cryoglobulinemia. She had a history of steroid-induced diabetes. Her casual blood glucose level was 160 mg/dL and her glycosylated hemoglobin (National Glycohemoglobin Standardization Program) level was 5.8% under insulin therapy. However, her skin perfusion pressure was within the normal range, eliminating the possibility of diabetes-related gangrene. Based on the serum biochemistry results, antiphospholipid antibody syndrome and cryoglobulinemia were excluded.

A radiograph of the soft tissue revealed diffuse calcification of the left femoral, popliteal, and peripheral arteries (Fig. 1B). A histological examination of a Hematoxylin and Eosin stained skin biopsy specimen showed arterial medial calcification (Fig. 2A) and thrombosis of the blood vessels (Fig. 2B). Von Kossa staining showed that phosphate deposits were present in the media of the arterioles (Fig. 2C). Elastica-van Gieson staining showed endothelial proliferation (Fig. 2D). The final diagnosis was calciphylaxis.

The patient's clinical course is shown in Fig. 3. She was treated with hemodialysis (5 hours, three times weekly) from the second day of hospitalization. The hemodialysis allowed for greater phosphate removal and compensated for the deterioration of her residual kidney function and led to a reduced level of urinary protein loss. We discontinued the mizoribine and cyclosporine A and decreased the prednisolone dose to reduce the risk of infection and to facilitate wound healing.

During hospitalization days 75-100, sodium thiosulfate

Table. The Laboratory Data on Admission.

			Reference range				Reference range
<Complete blood count>				**<Coagulation>**			
White blood cell	14,960	/μL		Protein C	87	%	
Neutrophils	93.5	%		Protein S	134	%	
Red blood cell, $\times 10^4$	374	/μL		PT-INR	1.12		
Hemoglobin	10.5	g/dL		APTT	31.1	sec	
Platelets, $\times 10^4$	29.1	/μL					
				<Immunological study>			
<Serum biochemistry>				C-reactive protein	6.2	mg/dL	
Total protein	4.2	g/dL		Procalcitonin	0.6	mg/dL	
Albumin	1.3	g/dL		Complement 3	94	mg/dL	
Blood urea nitrogen	99	mg/dL		Complement 4	35	mg/dL	
Cr	5.92	mg/dL		Serum complement titer	49	U/mL	
Uric acid	13.9	mg/dL		Immunoglobulin G	491	mg/dL	
Total bilirubin	0.7	mg/dL		ANA	negative		
Aspartate aminotransferase	13	U/L		Cryoglobulin	negative		
Alanine aminotransferase	9	U/L		ACA	negative		
Alkaline phosphatase	264	U/L		LAC	negative		
γ-Glutamyl transpeptidase	52	U/L		MPO-ANCA	<1.0	U/mL	
Lactate dehydrogenase	685	U/L		PR3-ANCA	<1.0	U/mL	
Total cholesterol	141	mg/dL					
LDL-cholesterol	58	mg/dL		**<Endocrinology>**			
Sodium	136	mEq/L		Intact PTH	345	pg/mL	10-65
Potassium	3.6	mEq/L		Calcitriol	9.9	pg/mL	20-60
Chloride	103	mEq/L		TRACP-5b	556	mU/mL	120-420
Calcium	5.1	mg/dL		BAP	11	μg/L	3.8-22.6
Phosphate	7.9	mg/dL		Osteocalcin	1.1	ng/mL	2.5-13.0
Magnesium	1.8	mg/dL		PTHrP	<1.0	pmol/L	<1.0
Hemoglobin A1c (NGSP)	5.8	%					

Abbreviations: ACA: anti-cardiolipin antibody, ANA: anti-nuclear antibody, ANCA: anti-neutrophil cytoplasmic antibody, APTT: activated partial thrombin time, BAP: bone-type alkaline phosphatase, Cr: creatinine, LAC: lupus anticoagulant, LDL: low-density lipoprotein, MPO: myeloperoxidase, NGSP: national glycohemoglobin standardization program, PR3: proteinase 3, PT-INR: prothrombin time-international normalized ratio, PTH: parathyroid hormone, PTHrP: PTH-related peptide, TRACP-5b: tartrate-resistant acid phosphatase 5b

[(STS), 10 g] was intravenously administered three times a week for 60 minutes during the last hour of each hemodialysis session. Because the administration of STS has previously been associated with the exacerbation of metabolic acidosis (14), we performed blood gas analyses to monitor the patient's acid-base balance. The predialysis pH and serum bicarbonate level (HCO_3^-) were 7.31 and 18.6 mmol/L, respectively. When we administered STS for the first time, the postdialysis pH and HCO_3^- were 7.42 and 23.3 mmol/L, respectively. At the time of the tenth administration, the predialysis pH and HCO_3^- were 7.35 and 17.7 mmol/L, respectively, whereas they were 7.39 and 22.1 mmol/L, respectively, after dialysis. Accordingly, we found that STS treatment had minor effects on metabolic acidosis in our patient.

During hospitalization days 106-233 the patient also underwent 40 HOT sessions (86 minutes at 2 atmospheres for each session). The skin ulcers showed a marked improvement after 6 months of treatment (Fig. 4). At 1 year after discharge, she was on maintenance hemodialysis without a relapse of the calciphylaxis.

Using this treatment approach, the patient's serum levels of phosphate, calcium, and intact parathyroid hormone were controlled and remained within the target ranges. Although cinacalcet is recommended for the treatment of hyperparathyroidism in patients with calciphylaxis (15, 16), we used maxacalcitol, a type of VDRA, because her corrected serum calcium level was below the normal range. The inflammation and her nutritional state were monitored by observing her serum C-reactive protein level, which decreased from 18.0 mg/dL to 0.9 mg/dL, and the serum albumin level, which increased from 1.0 g/dL to 2.8 g/dL. Additionally, her serum fetuin-A level increased from 10 g/L to 27 g/L, and her CPP level decreased from 17% to 9% (9).

Discussion

We successfully treated calciphylaxis in a non-dialyzed patient with CKD. Our treatment protocol included the initiation of hemodialysis, the administration of VDRAs, the discontinuation of a calcium-based phosphate binder, intensive wound care, the intravenous administration of STS, and HOT. After 6 months of these intensive treatments, the patient's serum fetuin-A level increased and her serum CPP level decreased.

The management of mineral bone disease is important in the treatment of calciphylaxis (1). In the present case, to increase phosphate removal and lessen the calcium burden, we initiated hemodialysis therapy and exchanged the calcium-based phosphate binder with a binder that did not contain calcium. We treated her secondary hyperparathyroidism with

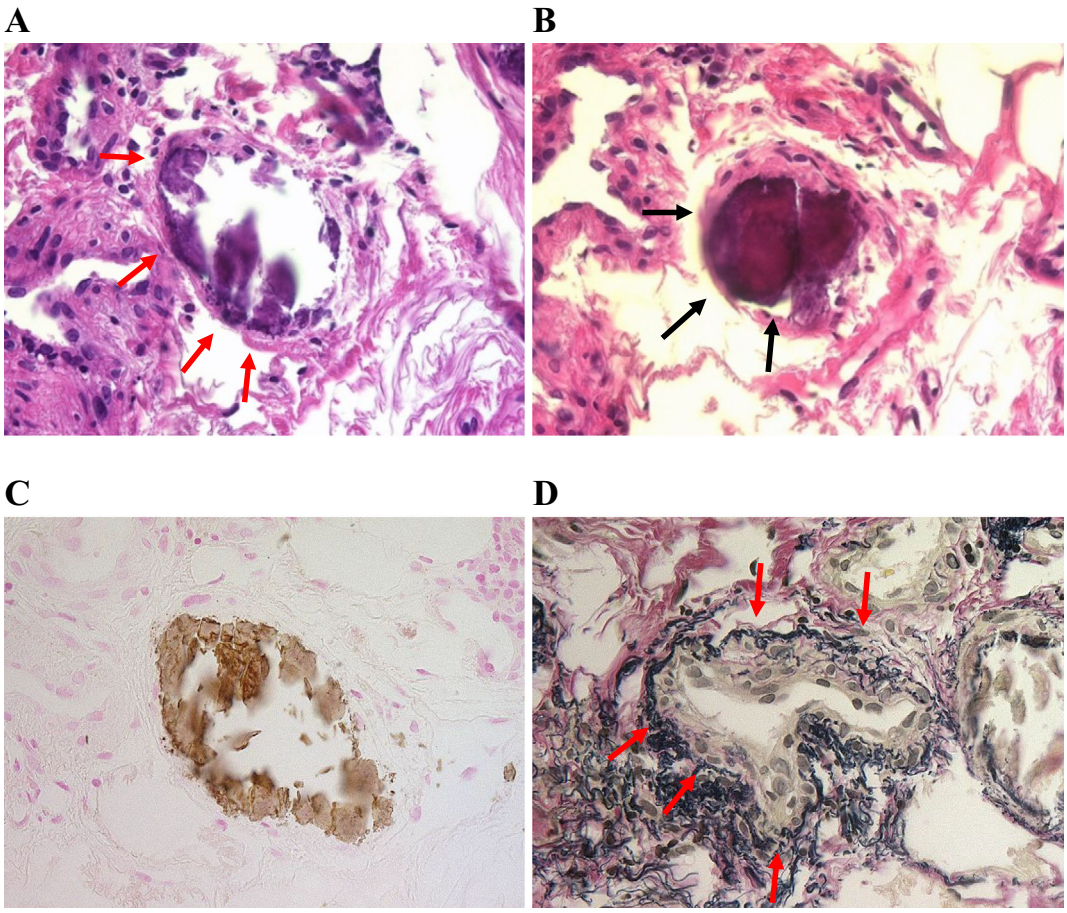

Figure 2. **The histology of a skin ulcer. A: Note the arterial media with basophilic deposits (red arrows) [Hematoxylin and Eosin (H&E) staining, ×200]. B: Vascular thrombosis is apparent (black arrows) (H&E staining, ×200). C: A biopsy specimen of the patient's skin shows arterial calcification (Von Kossa staining, ×200). D: A skin specimen shows intimal proliferation (red arrows) (Elastica-van Gieson staining, ×200).**

maxacalcitol, which is reported to be less hyperphosphatemic. The correction of the dysregulated mineral and bone metabolism partially contributed to the alleviation of calciphylaxis in the present case. Of note, calciphylaxis is a rare disease, despite the high prevalence of mineral bone abnormalities that occur in association with CKD (1, 3). Additionally, calciphylaxis may appear in patients with normal renal function who do not have bone or mineral disorders (17). Taken together, our case suggests that calciphylaxis is not mediated by dysregulated mineral and bone metabolism alone.

Malnutrition, an important risk factor for calciphylaxis, is frequently accompanied by decreases in serum albumin and fetuin-A levels. Basic studies have shown that both albumin and fetuin-A have the potential to act as antioxidants and to mitigate the procalcific property of CPP, thereby preventing vascular calcification (13). In addition, fetuin-A is a stronger calcification inhibitor that involves multiple calcification steps (4). In the present case, the initiation of dialysis greatly contributed to the reversal of malnutrition and the increased serum albumin and fetuin-A levels. In addition, the serum albumin and fetuin-A levels increased in a linear manner after the initiation of dialysis, which can be explained by the decreased urinary loss of both the proteins induced by nephrotic syndrome and their enhanced synthesis in the liver (18). The initiation of dialysis also helped to control the serum phosphate level, which was followed by an improvement in the patient's secondary hyperparathyroidism. Taken together, these results suggest that the initiation of dialysis in the present case had multiple favorable effects on the patient's nutritional status and her mineral and bone disorder, and that it eventually led to the cure of the patient's calciphylaxis-related ulcers.

In the present case, inflammation, a decreased fetuin-A level, and increased CPP levels might have played important roles in the development and healing of calciphylaxis. Calciphylaxis is often accompanied by inflammation, which is partly explained by the coincidental bacterial infection of the ulcerated skin. Inflammation directly drives vascular calcification and reduces fetuin-A production in the liver (5, 19). Because fetuin-A modulates the procalcific property of CPPs and plays a role in the macrophage-dependent clearance of CPPs from circulation (13, 20), it is possible that a decrease in fetuin-A could promote calciphylaxis. CPPs induce inflammation, leading to a vicious cycle of inflammation, decreased fetuin-A, and further CPP pro-

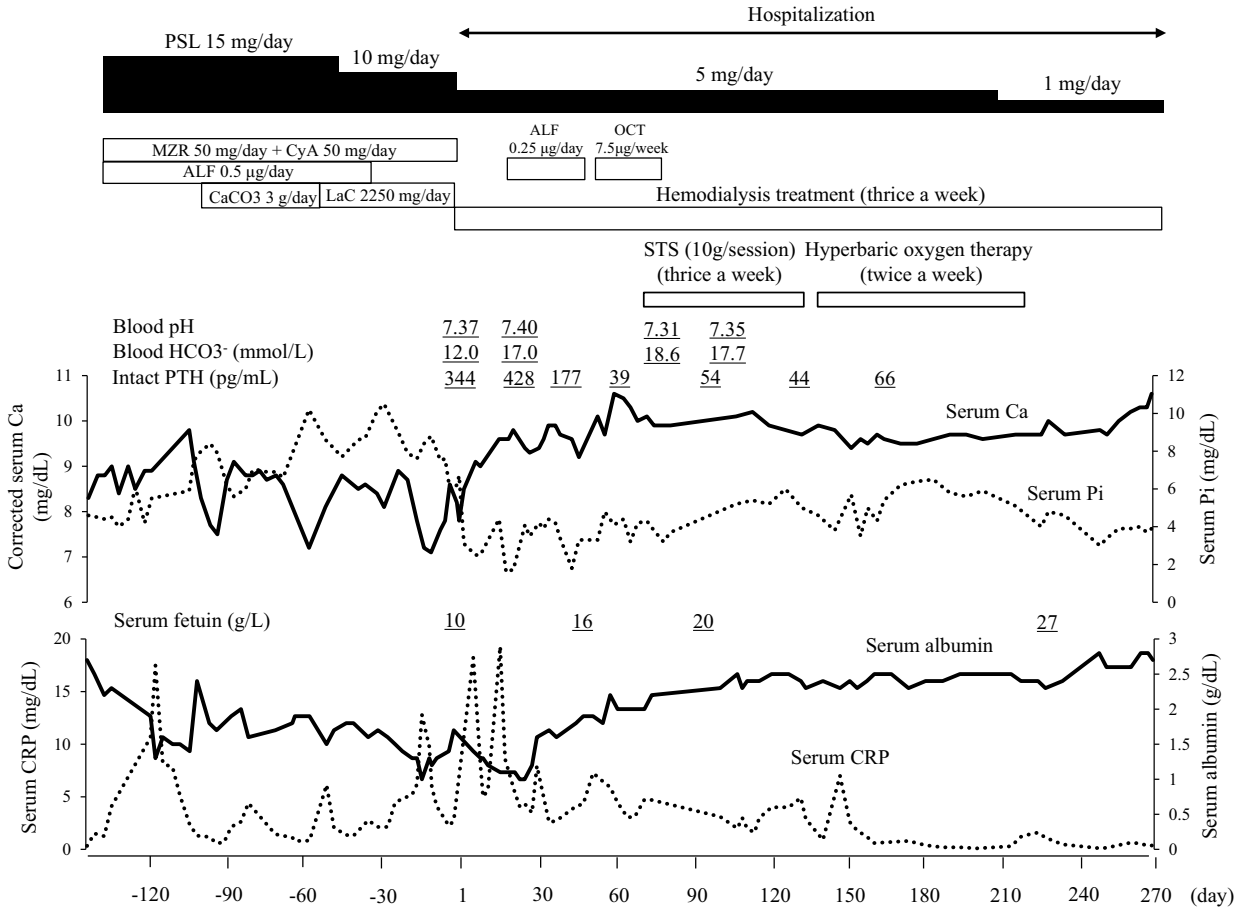

Figure 3. The patient's clinical course before and after the combined medical treatment. ALF: alfacalcidol, Ca: calcium, $CaCO_3$: calcium carbonate, Cr: creatinine, CRP: C-reactive protein, CyA: cyclosporine A, PTH: parathyroid hormone, LaC: lanthanum carbonate hydrate, MZR: mizoribine, OCT: maxacalcitol, Pi: phosphate, PSL: prednisolone, STS: sodium thiosulfate

duction. Recent studies have shown that high serum levels of CPPs were found in patients with calciphylaxis and that they were cleared from the serum during hemodialysis (8, 21). Additionally, nephrotic syndrome might contribute to a fetuin-A decrease through urinary loss of this protein (as occurred in the present case) (18). Our patient initially had high serum levels of CPPs and a low serum fetuin-A level with increased levels of inflammation markers, which reversed after medical treatment. This reversal suggests that in the present case, the patient's inflammation and the decrease in her fetuin-A level and increase in her CPP levels were involved in the pathogenesis of calciphylaxis. We cannot, however, rule out the possibility that the increase in fetuin-A and the decrease in the serum CPP level were merely parallel phenomena, and that they were not directly involved in the pathogenesis or the healing of calciphylaxis. Interventional studies are therefore needed to determine the role of a systemic decrease in fetuin-A followed by a systemic increase in the CPP levels regarding the pathogenesis of the patient's calciphylaxis.

Recent clinical studies have shown the efficacy of STS and HOT in patients with calciphylaxis (17, 22, 23); STS has been shown to directly chelate calcium at the tissue level and to inhibit the oxidative stress that promotes vascular calcification. A retrospective review of 53 hemodialysis patients with calciphylaxis showed that the calciphylaxis diminished in 73% of patients after STS treatment (22). In addition, HOT is thought to facilitate wound healing through the reversal of tissue hypoxia (23). Although these newly introduced treatment modalities lack definitive evidence to support their use, the combination of STS and HOT should be considered in the treatment of calciphylaxis because the calciphylaxis-related mortality rate is still unacceptably high and because no interventions have proven to be totally effective.

The primary cause of death in patients with calciphylaxis is frequently sepsis secondary to bacterial infection of the affected skin ulcer. Wound management with a combination of exudate control, the facilitation of wound healing, and the surgical debridement of necrotic devitalized tissue can prevent local bacterial infection; however, surgical wound debridement remains a controversial procedure (24, 25). Special attention should therefore be paid to wound care in patients with calciphylaxis, which should be administered according to the daily status of their ulcers.

The present case is associated with some limitations.

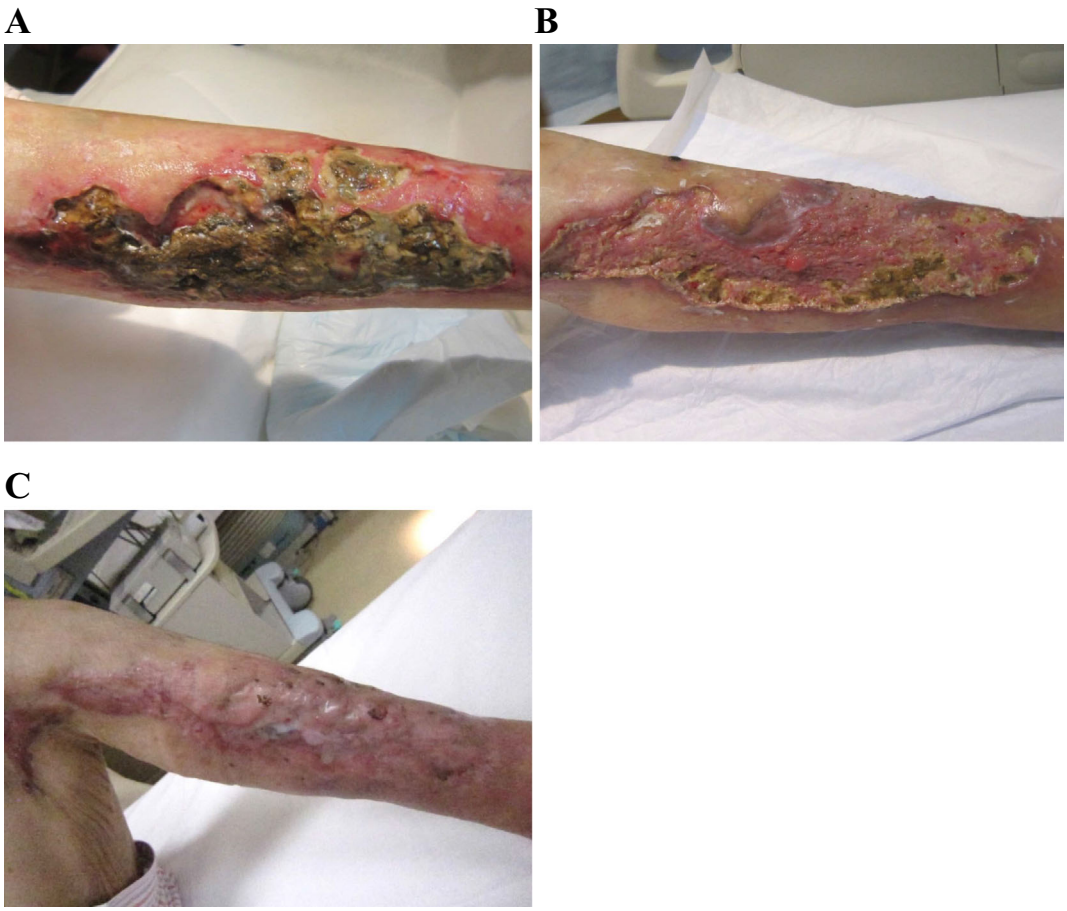

Figure 4. **The serial changes in the skin ulcers before and after the combined medical treatment. A: On admission. B: Three months after the initiation of the treatment. C: Six months after the initiation of the treatment.**

First, cinacalcet (instead of maxacalcitol) should have been selected for the treatment of the patient's secondary hyperparathyroidism. VDRA is a known risk factor for calciphylaxis. In contrast, the administration of a calcimimetic agent is recommended because it reduces the serum parathyroid hormone level without increasing the serum calcium and phosphate levels. It also has direct protective effects on calciphylaxis (15, 16). Second, we did not determine the serum CPP levels serially. Hence, we could not know which treatment contributed to the decrease in the patient's serum CPP level. In addition, it remains unclear whether the reduction in the patient's serum CPP level was involved in the healing of her ulcers or whether it was merely a parallel change induced by the initiation of dialysis.

In summary, the present case emphasizes that patients with CKD can develop calciphylaxis even before the initiation of dialysis. We suggest that combination of medical treatments including STS, HOT, and the initiation of dialysis were an effective treatment strategy for our patient with calciphylaxis. Further studies which provide more robust evidence are needed to determine which of the treatments (including STS and HOT), were safer and more effective. Such studies could also determine whether a systemic increase in fetuin-A followed by a systemic decrease in CPP is critical to the healing of calciphylaxis in patients with predialysis CKD.

Author's disclosure of potential Conflicts of Interest (COI).
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