

Minimal Change Nephrotic Syndrome Sequentially Complicated by Acute Kidney Injury and Painful Skin Ulcers due to Calciphylaxis

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Abstract

Calciphylaxis is rare cutaneous manifestation associated with painful skin ulceration and necrosis. It primarily occurs in patients with end-stage chronic kidney disease. In this report, we would like to show our experience with a male patient presenting with minimal change nephrotic syndrome that was sequentially complicated by acute kidney injury and painful ulcerative cutaneous lesions due to calciphylaxis. There seemed to be several contributing factors, including a disturbance of the patient's mineral metabolism and the systemic use of glucocorticoids and warfarin. Various concerns regarding the diagnostic and therapeutic conundrums that were encountered in the present case are also discussed.

Key words: minimal change nephrotic syndrome, acute kidney injury, calciphylaxis, warfarin

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Introduction

Calciphylaxis has been focused on as a rare cutaneous manifestation associated with painful skin ulceration and necrosis (1). Medial calcification and intimal hyperplasia in small and medium arteries are the major pathological characteristics of this disease, however, numerous other histopathological features have also been described (1, 2). Although calciphylaxis primarily occurs in patients with end-stage chronic kidney disease (1, 3), it has occasionally been reported in nonuremic patients (4, 5). In this report, we would like to show our experience in a male patient with minimal change nephrotic syndrome (MCNS) sequentially complicated by acute kidney injury (AKI) and painful ulcerative cutaneous lesions due to calciphylaxis.

Case Report

A 38-year-old man presented to a local physician in the

middle of August 2012 with complaints of abdominal distension and progressive swelling of his legs. Despite having no apparent history of renal disease, he was found to have ascites with serum albumin (sAlb) and serum creatinine (sCr) levels of 1.0 g/dL and 1.6 mg/dL, respectively. He denied using any drugs, and his medical history was unremarkable. The swelling in his extremities further progressed and he gained approximately 15 kg in body weight over the next two weeks. He was thus referred and admitted to our hospital for further work-up.

The patient's blood pressure was 127/78 mmHg, his pulse was 86 beats/min, his respiratory rate was 12 breaths/min and his temperature was 36.5°C. No rashes or petechiae were observed. A chest X-ray showed bilateral blurred costophrenic angles, suggesting the accumulation of fluid in the thorax. Renal sonography revealed that the right and left kidney measured 113×60 mm and 115×66 mm, respectively, with normal renal cortex echogenicity. The laboratory data obtained on admission are summarized in Table. A 24-hour urine specimen contained 9.6 g of protein with a creatinine

Table. Laboratory Data on Admission.

White blood cell	11,300/ μ L	Aspartate aminotransferase	23 U/L
Hemoglobin	17.3 g/dL	Alanine aminotransferase	14 U/L
Platelet count	25.7×10^4 / μ L	Triglyceride	504 mg/dL
		LDL cholesterol	360 mg/dL
Blood urea nitrogen	22 mg/dL		
Serum creatinine	2.71 mg/dL	C-reactive protein	0.14 mg/dL
Total protein	3.9 g/dL		
Serum albumin	1.1 g/dL	fibrinogen degradation product	5.4 μ g/mL
Sodium	137 mmol/L	D-dimer	2.0 μ g/mL
Potassium	4.1 mmol/L		
Chloride	106 mmol/L	IgG	159 mg/dL
Ca	7.7 mg/dL	IgA	250 mg/dL
Pi	4.6 mg/dL	IgM	125 mg/dL

Ig: immunoglobulin

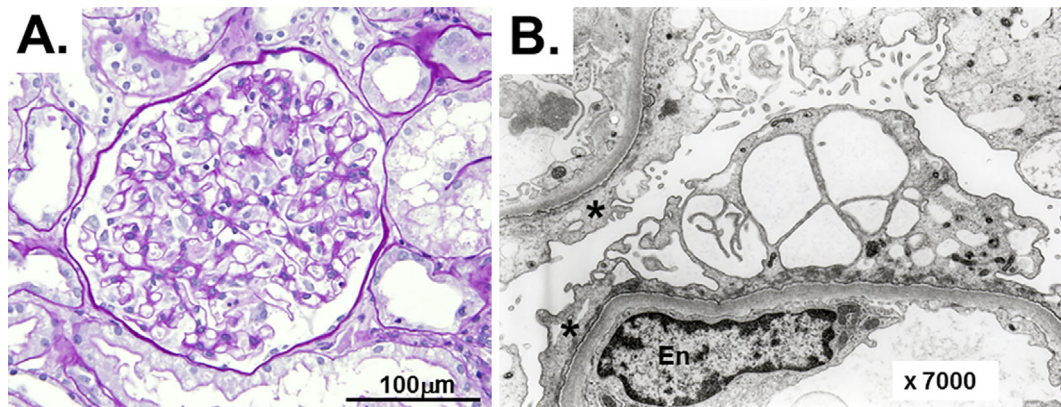


Figure 1. The renal biopsy findings. A light micrograph of the glomerulus (A) shows no glomerular changes (Periodic acid-Schiff stain), while an electron micrograph of a portion of the glomerulus (B) demonstrates diffuse foot process effacement (asterisks) and vacuolation. En: glomerular endothelial cell. The scale bar and scale are indicated in each panel.

clearance of 28.4 mL/min.

A renal biopsy consisting of four cores of renal parenchyma with twenty-nine glomeruli was performed on clinical day four. The specimen exhibited no glomerular changes and the interstitium appeared to be normal. An immunohistochemical analysis failed to reveal any immune complex deposits, while electron microscopy showed a flattening of the foot processes of the glomerular visceral epithelial cells without any apparent electron dense deposits within the glomerular basement membrane or mesangial area, which was consistent with minimal change disease (MCD) (Fig. 1). Intravenous prednisolone sodium succinate (PSL-SS) (60 mg/day) was initiated on the day after the renal biopsy. This was switched to oral prednisolone (PSL) (50 mg/day) about two weeks later. The intravenous administration of unfractionated heparin (10,000 U/day), which had been initiated on the day after admission in an attempt to maintain an active partial thromboplastin time of between 1.5 and 2 times the control value, was changed to warfarin (2.5 mg/day) on clinical day 20. The patient underwent a transient session of extracorporeal ultrafiltration method (Ecum) because the control of anasarca, which had gradually developed after admission despite the administration of furosemide, was insuf-

ficient. Oral mizoribine (MZB) (150 mg/day) and a single session of low-density lipoprotein apheresis (LDL-A) were also added to the therapeutic regimen; however, the patient's decline in renal function steadily progressed, and became severe enough to commence a transient session of hemodialysis (HD). In the same period, he complained of slight redness and tenderness with an increased temperature around his left thigh. These symptoms were successfully relieved by treatment with empiric antibiotics and intravenous immunoglobulin. Finally, after treatment with oral cyclosporine A (CyA) (150 mg/day) for approximately two weeks and five sessions of double filtration plasmapheresis (DFPP), his urine output began to increase (Fig. 2).

About one month after the last HD session, he started to complain of several small firm and painful nodules with purple discoloration on the lower extremities (Fig. 3A). A skin biopsy revealed arterial calcium deposits with intimal proliferation (Fig. 3E). The lesions became much larger and ulcerative with surrounding erythema over the next two to five weeks (Fig. 3B and C), and a bone scan revealed an increased tracer accumulation in the soft tissue of both legs (Fig. 3F). The serum levels of intact parathyroid hormone (iPTH) and 1,25 dihydroxy-vitamin D (VitD) on clinical day

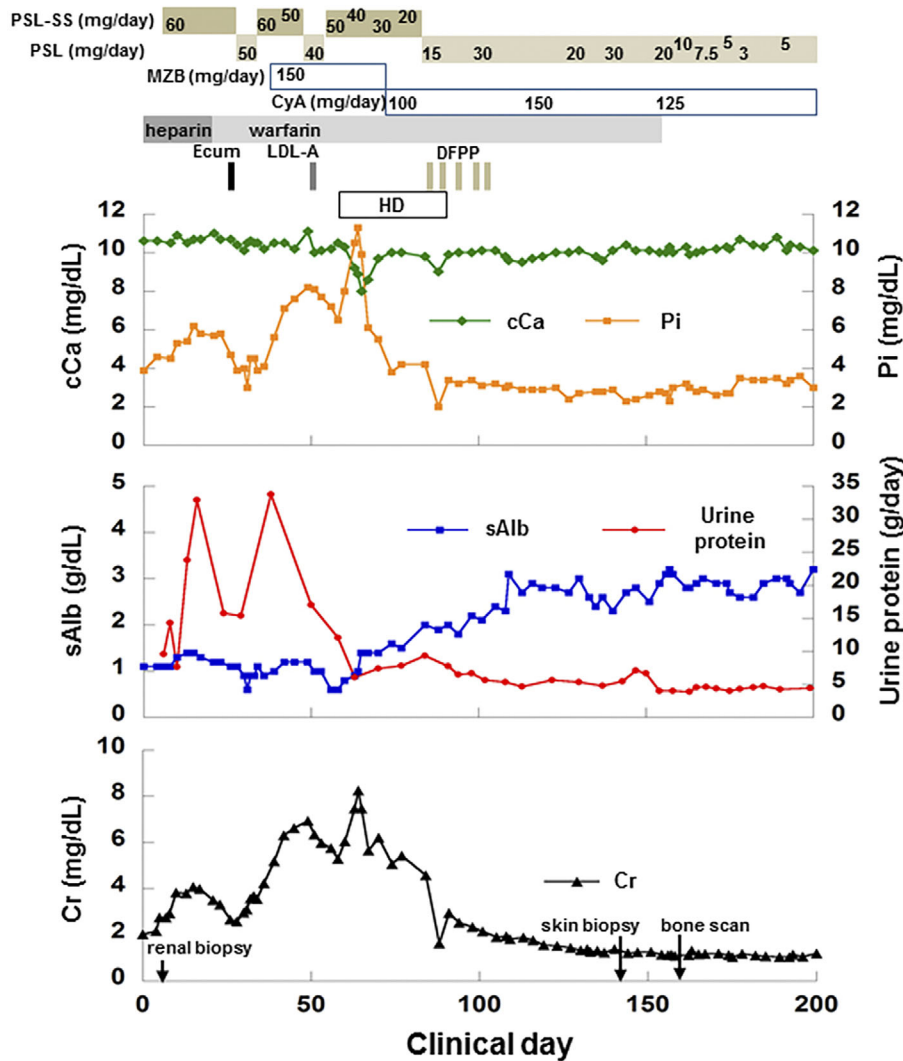


Figure 2. The clinical course of the patient. Serial changes in several clinical parameters and therapeutic regimens during the observation period are shown. Clinical day 0 is designated as the point of admission. The patient's renal function steadily worsened despite treatment with glucocorticoids, immunosuppressants, and LDL-A, and a HD was subsequently performed three times a week from clinical day 64. Note that the patient was switched from MZB to CyA on clinical day 71.

152 were within the normal ranges of 24 pg/mL and 23.6 pg/mL, respectively, while an elevated urinary level of N-telopeptide cross-links of type I collagen (NTx) of 132.3 nmol BCE/mmolCr was noted at the same time point. The patient's medications at this point included furosemide, lansoprazole, PSL, CyA, narcotics for the pain from his ulcers, calcium carbonate, and warfarin. According to the diagnostic criteria of calciphylaxis (1) as well as the clinical and pathological findings, he was diagnosed to have the disease, and the last two agents, calcium carbonate and warfarin, were then discontinued and oral alendronate sodium hydrate (5 mg/day) combined with beraprost sodium (120 µg/day) were administered. A culture obtained from the patient's wound grew *Pseudomonas aeruginosa*, which was treated with intravenous ceftazidime for one week, while topical wound care was applied (silver sulfadiazine with cleansing and debridement). After approximately five weeks, the tenderness substantially improved and the wounds demonstrated granu-

lation tissue growth. The pain and cutaneous manifestations continued to improve and the patient's urinary NTx level was confirmed to have normalized to 57.1 nmol BCE/mmolCr on clinical day 322; at that time he had been treated with a vitamin K2 analogue menatetrenone (45 mg/day) for approximately three months. The wounds were confirmed to have fully healed ten months later (Fig. 3D). At that time, his sCr and sAlb levels were around 1.4 mg/dL and 3.6 g/dL, respectively, and his 24-hour urinary protein level was 0.6 to 0.7 g/day.

Discussion

AKI is a well-recognized complication of MCNS (6, 7). The concurrent use of PSL and some immunosuppressive agents, including MZB and CyA, has been a therapeutic option for the MCNS patients in whom PSL treatment is not sufficient to achieve either a complete or partial remis-

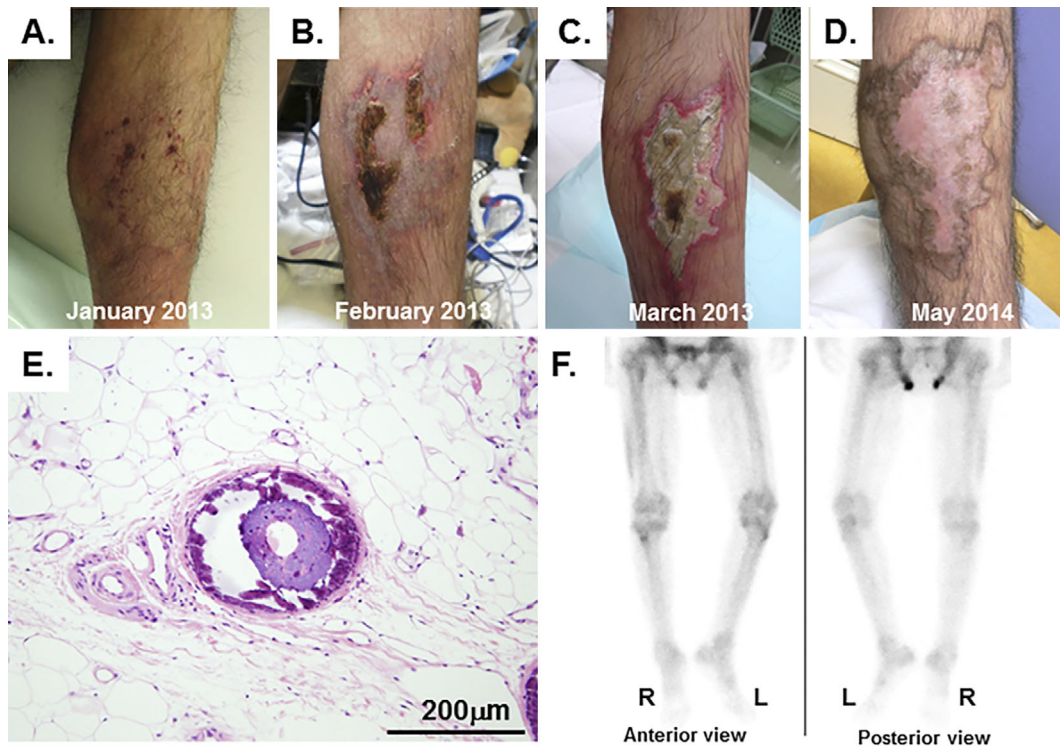


Figure 3. An early skin lesion in the left leg showed a palpable painful petechial rash (A). It developed into dusky violaceous purpuric plaque with overlying eschars (B) and became ulcerative with surrounding erythema (C) at one and two months after the onset of symptoms, respectively. The fully healed wound on same aspect was confirmed in May 2013 (D). A skin biopsy specimen showed a small artery with medial calcification accompanied by edematous intimal thickening (E, Hematoxylin and Eosin staining). A scale bar is shown. A bone scan performed in the middle of February 2013 demonstrated the superficial location of radiotracer activity in the subcutaneous region of the lower extremities although the uptakes were most prominent in the right thigh (F).

sion (8, 9). Some subsets of MCNS patients may require extensive volume control with Ecum and/or adjunct apheresis because of the refractory nature of nephrotic syndrome (10, 11). Consequently, one may argue that the therapeutic managements for MCNS with AKI are too common to be described; however, the clinical significance of the current patient should be evaluated carefully due to the subsequent complication of cutaneous lesions due to calciphylaxis.

Currently, various metabolic disorders and therapeutics that are associated with advanced chronic kidney disease, including secondary hyperparathyroidism, hyperphosphatemia, hypercalcemia, elevated calcium-phosphorus product, VitD administration, and calcium-containing phosphate binders have come into focus as precipitating factors for calciphylaxis (1, 2, 4). Low sAlb, high serum alkaline phosphatase levels, a female sex, liver disease, and the use of systemic corticosteroids and warfarin have also been regarded as independent risk factors (1, 12). Calciphylaxis may also occur in patients with serum calcium (Ca), serum phosphorus (Pi), calcium-phosphorus product, and PTH levels in the reference ranges (2, 4, 12-14). Thus, the mechanism of the disease is likely to be extremely complex and it may represent common pathologic findings of tissue injury in response to a

variety of heterogeneous insults (4).

We consider it to be reasonable that some medications and comorbidities might have predisposed our patient to develop calciphylaxis. One of the candidates is hypoalbuminemia, which has been focused on as an indicator of poor health, increased tissue fragility, and impaired wound healing (15). Warfarinization has been considered to induce the disease through the inhibition of the vitamin K-dependent carboxylation of the matrix-Gla protein, which reduces the ability of the protein to inhibit regional vascular calcification (2, 4, 15, 16). The reduction of the functional protein C and/or S activities has also been implicated in some subsets of calciphylaxis patients with warfarinization (16); however, a quantitative analysis performed one day after the cessation of warfarin in our patient found that neither of these activities had decreased. The association between glucocorticoids and calciphylaxis has been reported anecdotally (17, 18). Such agents have been shown to promote vascular injuries and endothelial damage (17); however, their role in the pathogenic process of the disease has not been precisely clarified. In the current patient, we believe that the significant increase in the urinary level of NTx should mirror the concomitant disturbance of the bone and calcium metabolism which was induced by the systemic administration of

glucocorticoid (19). Although the patient was no longer dependent on HD at the onset of calciphylaxis, the temporal decline in his renal function might also have predisposed him to the disease through the concurrent mineral disturbance characterized by hyperphosphatemia, which encouraged us to use calcium carbonate as a phosphate binder. Of note, his corrected serum calcium (cCa) levels determined by Payne's formula (20) ranged from 8.6 to 10.1 mg/dL, while the maximum cCa-phosphate (Pi) product level was 100.57 mg²/dL² approximately two months prior to the onset of painful nodules with petechiae. Additionally, we may need to focus on the inflammatory event associated with the patient's left thigh that developed during almost the same period of time. One may argue that it might be one of the cutaneous phenotypes of calciphylaxis. However, prompt relief with empiric antibiotics combined with intravenous immunoglobulin therapy encouraged us to attribute such symptoms to fasciitis and/or cellulitis due to latent bacterial infections, which might have resulted from a compromised immune status characterized by the prominent decrease in immunoglobulin levels, which could be associated with an attenuated immune status (21). Nevertheless, we feel that this might lay the groundwork for a sustained calcium accumulation, thereby predisposing our patient to calciphylaxis. This concept is purely hypothetical, although a local inflammatory milieu resulting from repetitive traumatic tissue damage, periarticular forces, and bleeding from microtrauma causing exaggerated reparative responses have been regarded as potential pathogeneses of soft tissue calcification in patients complicated by tumoral calcinosis (22, 23). Finally, we speculate that the development of the disease in our patient can be ascribed to the additive or synergistic effects of multiple factors, although it is difficult to precisely determine their individual contribution. The specific impact of the concurrent NS remains unclear; however, it is apparent that such pathology integrated the concomitant above-described factors.

Warfarin is highly effective in the prevention of thromboembolic disorders and it is widely used for this reason (24), while hypercoagulability has been demonstrated among patients with nephrotic syndrome (NS) by their increased risk for the development of various pathologies, including venous and/or arterial thromboembolism and renal vein thrombosis (25). However, prophylactic anticoagulation has not been accepted as the standard of care for patients with NS (25), and a selective or individualized approach still seems justified in ordinary medical practice (26). In our case, the prominent and protracted decreases in the sAlb levels of below 2.0 g/dL, which may be one of the clinical parameters predicting thromboembolic events in patients complicated by NS (25, 26), encouraged us to administer prophylactic anticoagulation. Of note, warfarin has also been demonstrated to act as an inducer of skin necrosis resulting from the occlusion of dermal vessels by fibrin thrombi, with a high propensity for subcutaneous involvement in several areas, including the abdomen, thighs, and legs, thereby

mimicking calciphylaxis (24). Thus, we were facing, as do most physicians at various times, therapeutic and diagnostic dilemmas. We believe that a skin biopsy should have provided a clinical benefit in the current patient since it allowed us to reach a precise diagnosis of the cutaneous manifestations; however, the careful application of the procedure on a case-by-case basis is mandatory because a skin biopsy may result in poor wound healing with increased risks of infection and mortality (1, 13, 16, 27). Alternatively, an imaging analysis using bone-seeking tracers may aid in the diagnosis of calciphylaxis (12, 28). Considering the result obtained in the current case, however, the diagnostic impact of this modality in other patients with the disease may require a careful evaluation. Indeed, it appears likely that extensive baring of the subcutaneous region rids the limbs of calcified tissue, thereby modulating the magnitude of the tracer uptake (27).

Despite the accumulation of anecdotal or systemic studies disclosing the nature of calciphylaxis (1, 2, 4, 13-17, 27), we feel that the ability to accurately diagnose the disease in the early stage and awareness of the disease itself remain challenges that must still be overcome by physicians. Although there are several reports mentioning the potential of prostacyclin and vitamin K₂ as well as bisphosphonate as therapeutic options for the disease (29-31), the present case did not allow us to precisely assess the clinical benefit of individual agents. Rather, the current report may emphasize the pitfalls of managing patients with NS who are subjected to warfarinization. We must be careful about skin complications, especially in nephrotic subjects who require prophylactic anticoagulation, and calciphylaxis should always be included in the list of causes of painful cutaneous ulcers, thereby leading to a higher index of suspicion and prompt recognition of the disease. We believe that the accumulation of more experience with additional cases similar to ours would aid in the establishment of an optimal management for nephrotic patients complicated by calciphylaxis.

The authors state that they have no Conflict of Interest (COI).

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