

Pre-uremic Calciphylaxis

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Calciphylaxis is characterized by calcification and thrombosis of arteries resulting in ischemic necrosis of predominantly skin and subcutaneous tissue. Primarily affecting patients with end-stage renal disease, calciphylaxis is diagnosed rarely in the absence of renal replacement therapy. We report an elderly obese woman presented with leg pain and ulceration. She had chronic kidney disease, diabetes mellitus, hypertension, and peripheral vascular disease. Angiography revealed occlusion of the left superficial femoral, popliteal, and distal tibial arteries. Amputation was performed. Histological examination demonstrated medial calcification, intimal hyperplasia, and thrombosis of small- and medium-sized arteries in the subcutaneous tissue. This case features calciphylaxis in a patient with chronic kidney disease before the onset of uremia. Calciphylaxis and atherosclerotic peripheral vascular disease have several risk factors in common. This report calls attention to a disorder that can be masqueraded as leg ulceration due to peripheral vascular disease in the absence of renal replacement therapy.

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INTRODUCTION

Calciphylaxis, also known as calcific uremic arteriolopathy, is a rare devastating disorder characterized by slowly progressive necrosis of skin and subcutaneous tissue.¹⁻³ Histologically, calciphylaxis is characterized by medial calcification, intimal hyperplasia, and thrombosis of small- and medium-sized blood vessels.¹ The etiology and pathophysiology of calciphylaxis are poorly understood. However, there are well-established risk factors for calciphylaxis (Table 1).^{1,2} Calciphylaxis affects mainly patients with end-stage renal disease and those after kidney transplantation. However, calciphylaxis can also be observed in patients who are not receiving renal replacement therapy.⁴ Calciphylaxis and atherosclerotic vascular disease share several risk factors.⁵ When affecting the lower legs in individuals with atherosclerotic peripheral vascular disease, calciphylaxis can be missed.

Table 1. Risk Factors for Calciphylaxis

Risk Factor
Kidney disease
Reduced glomerular filtration rate
Type and duration of dialysis
Kidney transplantation
Deranged calcium-phosphate-bone Metabolism
Hyperphosphatemia
Hypercalcemia
Hyperparathyroidism
Increased alkaline phosphatase
Vitamin D intake
Intake of calcium-based phosphate binders
Others
Female sex, Caucasian race, diabetes mellitus, obesity, liver disease, warfarin, glucocorticoids, hypoalbuminemia, aluminum toxicity, hypercoagulable states

CASE REPORT

A 72-year-old woman with chronic kidney disease (CKD) presented with leg pain and ulceration. The patient was in her usual state of health until 6 months prior to the current presentation when she developed worsening pain in the left lower leg. The pain was exacerbated by ambulation and palpation. She also noticed purple-blue discoloration of the left foot. Past medical history was notable for type 2 diabetes mellitus diagnosed 25 years ago complicated by retinopathy, neuropathy, and nephropathy with a baseline serum creatinine concentration of 2.4 mg/dL. She also suffered from obesity, secondary hyperparathyroidism, hypertension, peripheral vascular disease, coronary artery disease, dyslipidemia, hypothyroidism, and deep venous thrombosis in the left leg. Medications included insulin, amlodipine, valsartan, torsemide, metolazone, aspirin, cinacalcet, sevelamer, levothyroxine, and ezetimibe. Review of systems was notable for recent weight gain and left leg swelling. She denied anorexia, nausea, vomiting, abnormal taste, generalized pruritus, decreased mental acuity, and insomnia.

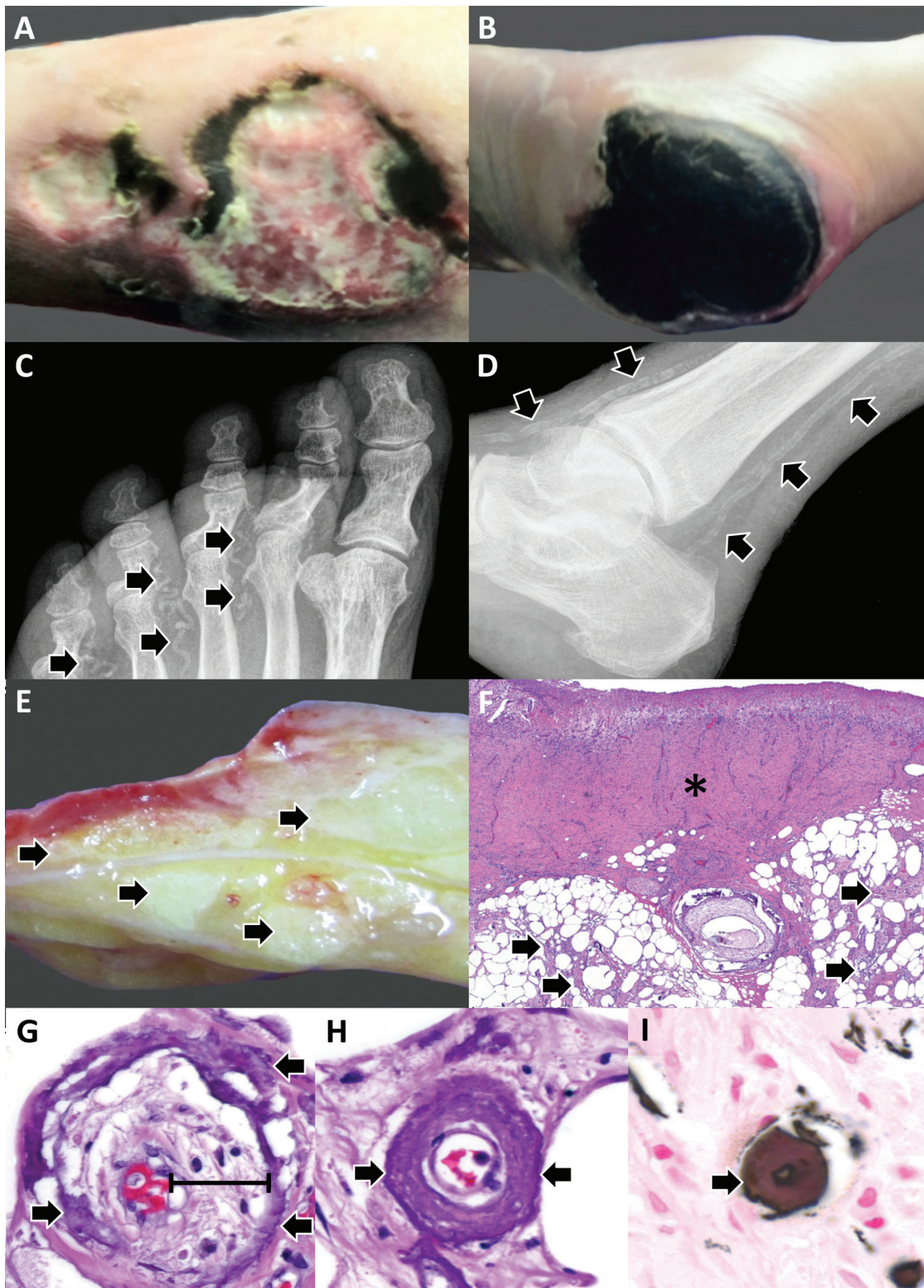
On physical examination, the patient was an elderly obese Caucasian woman in no acute distress. The temperature was 37.0°C; the blood pressure, 172/89 mm Hg; the pulse, 104 beats/min; the respiratory rate, 10 breaths/min; and oxygen saturation, 97% on room air. Two ulcers with irregular erythematous margins were noted on the left lateral calf (Figure A). There were eschars on the left third toe, dorsal foot, and heel (Figure B). The left calf and foot were tender to palpation. There was mild pitting edema throughout the entire left leg. No pulses were felt in the left leg. Laboratory data are summarized in Table 2. There were leukocytosis, neutrophilia, normocytic normochromic anemia, hyperglycemia, hypoalbuminemia, proteinuria, and impaired kidney function. Daily urinary protein excretion was 1.2 g/d based on a random urine protein-creatinine ratio. Plain radiography of the left foot showed marked vascular calcification (Figures C and D). Bone scan showed no evidence of osteomyelitis.

Following positive wound cultures for multiple pathogenic bacteria, intravenous antibiotics were administered. Angiography revealed occlusion of the left superficial femoral, popliteal, and distal tibial arteries. Percutaneous angioplasty with stent placement was unsuccessful. A left above-the-knee

Table 2. Laboratory Data*

Parameter	Value on Admission	Reference Range
Blood chemistry		
Sodium, mmol/L	138	135 to 145
Potassium, mmol/L	4.5	3.4 to 4.8
Chloride, mmol/L	104	99 to 109
Bicarbonate, mmol/L	27	21 to 30
Urea nitrogen, mg/dL	102	7 to 22
Creatinine, mg/dL	2.9	0.5 to 1.4
Glucose, mg/dL	201	65 to 200
Hemoglobin A1c, %	5.1	4.2 to 5.8
Albumin, g/dL	1.8	3.5 to 5.5
Calcium, mg/dL	7.7	8.6 to 10.3
Phosphorus, mg/dL	4.7	2.3 to 5.0
Alkaline phosphatase, U/L	139	20 to 130
Leukocyte count, × 10 ⁹ /L		
Neutrophils, × 10 ⁹ /L	12.3	4.8 to 10.8
Lymphocytes, × 10 ⁹ /L	11.0	1.5 to 7.0
Monocytes, × 10 ⁹ /L	1.0	1.0 to 3.7
Eosinophils, × 10 ⁹ /L	0.2	0.0 to 0.7
Basophils, × 10 ⁹ /L	0.1	0.0 to 0.4
Hematocrit, %	0.0	0.0 to 0.1
Hemoglobin, g/dL	24.6	40.0 to 49.0
Platelet count, × 10 ⁹ /L	8.2	13.6 to 16.7
aPTT, sec	261	130 to 350
PT, sec	25	24.5 to 35.7
APC resistance, ratio	11.6	10.1 to 12.6
Prothrombin G20210A	> 2.1	> 2.1
Urinalysis		
Color	Yellow	Yellow
Appearance	Hazy	Clear
pH	6.0	4.6 to 7.8
Specific gravity	1.020	1.001 to 1.035
Glucose	Negative	Negative
Ketones	Negative	Negative
Bilirubin	Negative	Negative
Blood	Trace	Negative
Protein, mg/dL	100	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
White blood cells, /HPF	0 to 2	0 to 2
Red blood cells, /HPF	2 to 4	0 to 2
Urine protein-creatinine ratio	1.2	0.02 to 0.13
Lupus anticoagulant panel		
DRVVT ratio	Negative	Negative
Hexagonal PL, sec	< 1.2	< 1.2
Anti-cardiolipin Ab	< 8.0	< 8.0
IgG, U/mL	Negative	Negative
IgA, U/mL	3.5	< 10
IgM, U/mL	4.0	< 8.0
Protein C activity, %	0.2	< 10
Protein S activity, %	72	70 to 140
AT III activity, %	111	58 to 150
AT III activity, %	71	52 to 128

*Ab indicates antibodies; APC, activated protein C; aPTT, activated partial thromboplastin time; AT, antithrombin; DRVVT, dilute Russell viper venom time; PL, phospholipid; and PT, prothrombin time.



A, Two large cutaneous ulcers partially surrounded by an eschar seen on the left lateral calf. **B**, The left heel demonstrating an eschar with erythematous margins. **C** and **D**, Vascular calcifications (arrows) seen on plain radiography of the left foot and ankle. **E**, Cross-section through cutaneous ulcer demonstrating fat necrosis in the subcutis (arrows). **F**, Microphotograph demonstrating cutaneous ulceration, subcutaneous fibrosis (asterisk) and fat necrosis (arrows). **G**, Microphotograph of a medium-sized blood vessel showing luminal narrowing, intimal expansion (bar) and medial calcification (arrows). **H** and **I**, Microphotograph of two small blood vessels with marked medial calcification (arrows). Tissue sections were stained with hematoxylin-eosin (F to H). Calcium deposits were stained using von Kossa method (I).

amputation was performed. Gross examination revealed several cutaneous ulcers (Figures E and F). Severe calcific atherosclerosis of popliteal and tibial arteries was present. Popliteal vein thrombosis was noted. Histological examination demonstrated medial calcification, intimal hyperplasia, and thrombosis of small- and medium-sized blood vessels in the subcutaneous tissue (Figures G to I). A histological diagnosis of calciphylaxis was rendered.

DISCUSSION

Calciphylaxis is rarely reported in patients with CKD before the initiation of renal replacement therapy. A review of the literature by Nigwekar and colleagues identified only 36 cases of calciphylaxis in the absence of renal replacement therapy.⁴ Most patients were older than 30 years (89%), Caucasian (83%), and women (75%). The lower legs were affected in 72% of cases. The most common conditions associated with calciphylaxis were corticosteroid therapy (61%), diabetes mellitus (28%), primary hyperparathyroidism (28%), warfarin use (25%), malignancy (22%), alcoholic liver disease (17%), connective tissue disorders (11%), and protein C or S deficiency (11%). Far exceeding the prevalence of connective tissue disorders, glucocorticoids were used in the treatment of calciphylaxis in 14% of patients. While elevated calcium and phosphate concentrations in blood were reported in 38% and 15% of patients, respectively, a calcium-phosphate product greater than 50 was observed in only 21% of patients. A serum creatinine concentration above 1.2 mg/dL was noted in 42% of patients. The mortality rate was 52% during the follow-up period, with sepsis being the leading cause of death.

In a retrospective study, Weenig and colleagues identified 15 nondialysis patients with calciphylaxis.⁵ Most patients were women (93%) of advanced age (mean age 60 years). The legs were affected in all cases followed by buttocks or hips (33%), trunk (20%), and arms (7%). Fourteen patients (93%) had impaired kidney function. The estimated glomerular filtration rate was below 20 mL/min in 3 patients, between 21 mL/min and 40 mL/min in 8 patients, and between 41 mL/min and 60 mL/min in 3 patients. Additional risk factors for calciphylaxis included systemic glucocorticoid therapy (80%), warfarin use (60%), autoimmune or inflammatory disorders (60%), obesity (47%), diabetes mellitus

(33%), hepatobiliary disease (33%), and calcium supplementation (33%). Systemic glucocorticoid therapy was administered mostly for systemic autoimmune and inflammatory disorders such as systemic lupus erythematosus, sarcoidosis, rheumatoid arthritis, and polymyositis. Our patient had many of the risk factors reported in the studies by Nigwekar and Weenig, ie, impaired kidney function, female sex, Caucasian race, advanced age, site of involvement, diabetes mellitus, obesity, and deranged calcium-phosphate metabolism.

The clinical manifestations of calciphylaxis depend on the distribution, severity, and duration of the underlying vasculopathy.¹ Early cutaneous manifestations consist of painful dusky red to violaceous indurated lesions tender to palpation. Cutaneous infarction results in deep ulcerative lesions often covered by an eschar. The legs are affected in most cases. The differential diagnosis of calciphylaxis includes cutaneous ulceration secondary to atherosclerotic vascular disease, neuropathy, infection, malignancy, hematological disorders and trauma.⁶ Atherosclerotic arterial disease is particularly prevalent in CKD and end-stage renal disease patients.^{7,8} As we have shown in this report, atherosclerotic arterial disease may coexist with calciphylaxis in CKD patients.

Microvascular thrombosis is a salient histological feature of calciphylaxis.^{1,2} In the study by Weenig and colleagues, thrombosis of pannicular or dermal arterioles was observed in 86% of patients with calciphylaxis.⁵ The etiology of microvascular thrombosis in calciphylaxis is incompletely understood. Endothelial cell injury and a systemic hypercoagulable state are believed to be involved in the pathogenesis of calciphylaxis.^{3,9} A recent meta-analysis demonstrated that reduced protein C and S levels were found in 38% and 43% of patients with calciphylaxis, respectively.¹⁰ Calciphylaxis has also been associated with antiphospholipid antibodies, factor V Leiden mutation, antithrombin deficiency, and homocysteinemia.¹⁰⁻¹² Although the prevalence of reduced protein C and S activity in the study by Harris and coworkers was much higher than that reported by Nigwekar and colleagues, the common theme in these and other studies is the presence of a hypercoagulable state in a significant subset of patients with calciphylaxis. Our patient had a history of deep vein thrombosis, and gross examination of the amputated leg demonstrated a thrombus in

the popliteal vein. However, protein C, protein S, and antithrombin levels were normal. In addition, antiphospholipid antibodies, prothrombin G20210A mutation, and activated protein C resistance were not detected. Blood homocysteine concentrations were not measured. It is conceivable that the procoagulant microenvironment due to endothelial cell injury was aggravated by a low-flow state due to occlusive vascular disease leading to microvascular stasis and thrombosis.

Although restoration of blood flow is the main therapeutic goal in severe atherosclerosis, there is no standard treatment for calciphylaxis. Available treatment options can be divided into three categories: (1) comprehensive multidisciplinary supportive care, (2) strategies to aggressively address deranged calcium-phosphate metabolism and vascular wall calcification, and (3) measures to improve tissue perfusion and oxygenation.^{1,2,13,14} Sodium thiosulfate is gaining popularity in the treatment of calciphylaxis.^{2,15} Although its oral bioavailability is poor, sodium thiosulfate is extensively distributed into the extracellular fluids following intravenous administration. Sodium thiosulfate forms water-soluble complexes with certain metals including calcium. In addition, it is a reducing agent that exerts potent anti-oxidative effects. Parathyroidectomy is reserved for patients with severe hyperparathyroidism.^{1,13} The efficacy and safety of tissue plasminogen activator as an adjuvant treatment for calciphylaxis was examined in a recent retrospective study.¹² Although there was a trend for improved survival with tissue plasminogen activator, life-threatening bleeding occurred in 20% of patients. Our patient was treated with wound care, antibiotics, sevelamer, cinacalcet, sodium thiosulfate, and angioplasty. However, an above-the-knee amputation was undertaken due to advancing gangrene.

This case highlights calciphylaxis in a patient with CKD before the onset of uremia and initiation of renal replacement therapy. Calciphylaxis and atherosclerotic peripheral vascular disease share several risk factors and may coexist. This case calls for heightened awareness of this coexistence and possible masquerading of calciphylaxis by peripheral vascular disease.

CONFLICT OF INTEREST

None declared.

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