Non-Uremic Calciphylaxis: Case Report and Review

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Non-uremic calciphylaxis is a rare cause of ischemic ulcerations. Calciphylaxis occurs when the levels of calcium and phosphate in the blood exceed their solubility range leading to deposition within arteriolar walls. Calciphylaxis is seen secondary to hyperparathyroidism, diabetes, obesity, warfarin treatment, protein C or S deficiency, and autoimmune disorders. Deep skin biopsy containing subcutaneous adipose tissue will show medial calcification of dermal and subcutaneous arterioles.

Calciphylaxis is diagnosed most commonly in patients with end stage renal disease. Its diagnoses in patients with normal renal function and in whom calcium and phosphorous levels are normal is rare. This clinical condition is associated with a delay in diagnosis and is often entirely missed. Given the increased morbidity and potential limb loss associated with misdiagnosis and mistreatment, calciphylaxis is an important subject for students, residents, and clinicians alike.

Key words: calciphylaxis, gangrene, non-uremic, ulcer, end stage renal disease

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Non-uremic calciphylaxis is defined as a chronic, progressive syndrome of arteriolar media calcification and thrombotic ischemia leading to necrotic ulceration [1]. Calciphylaxis occurs when the levels of calcium and phosphate in the blood exceed their solubility range, leading to arteriolar wall deposition. Calciphylaxis is a rare vasculopathy, which usually affects patients with end-stage renal disease, with an incidence of 1-4% of dialysis dependent individuals per year [2]. Reports of calciphylaxis in patients with normal renal function, as well as normal calcium and phosphorus serum levels, are scarce [2].

Identified risk factors for the development of calciphylaxis include hyperparathyroidism (primary or secondary to renal failure), diabetes, obesity, warfarin treatment, protein C or S deficiency, and autoimmune disorders. Autoimmune disorders seen in association with calciphylaxis include systemic lupus, rheumatoid arthritis, and giant cell arteritis. Though calciphylaxis is most commonly seen in patients with end stage renal disease, renal involvement is not obligatory [3-5]. The central mechanism for development of calciphylaxis is calcifying arteriolopathy, with pathologic transformation of vascular tissue into osteoid-like tissue [3].
Clinically, calciphylaxis presents as purpuric and livedo plaques, which may spontaneously ulcerate and necrose, rapidly advancing into painful deep necrotic lesions [1-3]. Due to the rapid progression of calcification, some have described the disease as "metastatic-like"[3]. A deep skin biopsy, including subcutaneous adipose tissue, is required to verify diagnosis [6]. Histological examination of skin reveals medial calcification of dermal and subcutaneous arterioles [7]. A von Kossa stain is utilized to visualize calcified vascular walls. The most common histopathological findings are septal calcifying panniculitis [3]. The following is a case report of a patient found to have calciphylaxis with normal renal function and normal serum levels of calcium and phosphorous.

Case Report

We report on a 55 year old morbidly obese, non-diabetic female admitted for digital gangrene of the fingers and toes. Past medical history is significant for rheumatoid arthritis (RA) with long-term steroid therapy, a non-healing abdominal wound, non-hemorrhagic cerebrovascular accident (CVA), and peripheral neuropathy of bilateral hands and feet. The patient initially described the development of blue discoloration of her fingers and toes over a period of two weeks, which rapidly progressed into necrosis. Coinciding with the development of gangrenous digits was the development of ulcerations to the lower extremities, including a large wound on the posterior right calf and several wounds over the dorsum of both feet. The patient denied prior episodes of digital discoloration, with or without cold exposure or Raynaud's phenomenon. Electromyography revealed a mononeuritis multiplex syndrome affecting the median, ulnar, and femoral nerves superimposed on a generalized non-necrotizing myopathy with underlying axon loss sensorimotor polyneuropathy.

On physical examination, pedal pulses were non-palpable, but audible upon Doppler examination. Loss of protective sensation was noted distal to ankle level bilaterally. Dermatologic examination revealed necrosis of digits 1-5 left and 1-2 right (Figure 1). Necrotic eschar extended to level of the dorsal midfoot bilaterally. Underlying serous fluid with mild fluctuance was noted. Erythema, increased warmth, tenderness to palpation, and edema were observed in the right calf. No lymphangitis was noted. The remainder of the neurovascular and musculoskeletal examination were unremarkable.

Figure 1: Clinical photographs of affected extremities. Gangrenous changes can be visualized to the digits with peri-gangrenous erythema.

Radiographic evaluation revealed faint soft tissue calcifications. Small foci of gas were noted within 1st webspace of the right foot, consistent with overlying ulceration (Figure 2).
Figure 2. Radiology: 3 views bilateral feet. Small foci of gas in the first web space, which may be related to skin ulceration. Faint subcutaneous soft tissue calcifications are seen bilaterally. No erosive changes or periosteal reactions noted. Generalized osteopenia noted.

Serologic testing showed no evidence of impaired renal function. Calcium and phosphorous levels were also found to be within normal limits. The duplex ultrasound was positive for acute proximal deep vein thrombosis in the common femoral vein, femoral vein, and popliteal vein of the right lower extremity. Vascular testing included pulse volume recordings (PVR’s) (Figure 3). Normal waveforms were visualized at the ankle and transmetatarsal level bilaterally. Complete loss of multiphasic flow waveform pattern was identified at the digital level bilaterally.

Figure 3. PVR waveforms show complete loss of multiphasic flow pattern at the digital level.

Upon histological testing, specimens exhibited rare interstitial calcium deposits within deep dermis and adipose tissue. Focal calcium deposits were found within the subcutaneous blood vessels. Small, thin, calcified filaments were present on the background of fibrosis in the deep subcutis. These findings are consistent with a diagnosis of non-uremic calciphylaxis (Figure 4).

Intravenous sodium thiosulfate treatment was initiated while surgical debridement was deferred due to the dry, non-infected nature of the soft tissue. Daily wound care consisted of betadine covered with silver absorbent dressing until demarcation was complete. The deep vein thrombosis was treated with a heparin to Coumadin bridge anticoagulation therapy.

Figure 4. Histological specimens showing rare interstitial calcium deposits within deep dermis and adipose tissue. Focal calcium deposits within a subcutaneous blood vessel. Small, thin, calcified filaments are noted on background of fibrosis in the deep subcutis.

Figure 5. 10 month follow-up, intravenous sodium thiosulfate treatment showed healing and possible revitalization of previous gangrenous soft tissue.
Discussion

Treatment of calciphylaxis requires control of the calcium-parathyroid hormone axis [8-10]. Sodium thiosulfate is a chelating agent with anti-oxidant efficacy that is utilized in calcifying nephrolithiasis and tumor-induced calcinosis [8]. Sodium thiosulfate increases calcium solubility in vascular wall deposits and improves hemodialysis clearance. Amino-bisphosphonates inhibit soft tissue calcification by binding to calcified vascular smooth muscle cells, thereby inhibiting progression of the process [9-10].

Prevention of systemic infection is vital. Diligent wound care and avoidance of trauma are imperative to successful treatment. There is debate as to whether or not aggressive wound debridement is warranted in calciphylaxis, due to possible re-aggravation or creation of necrotic ulcers. Advocates argue that aggressive debridement reduces wound infection rates, thus decreasing the likelihood of sepsis and organ failure. Routine debridement of bacterial biofilm and necrotic eschar is necessary. Surgical debridement can be combined with split-skin mesh-graft transplantation. Negative pressure wound therapy may be used adjunctively to increase skin graft survival in chronic leg ulcers. Revascularization can further enhance the limb salvage rate [7].

In conclusion, non-uremic calciphylaxis is a rare cause of ischemic ulcerations. Deep skin biopsy containing subcutaneous adipose tissue will show medial calcification of dermal and subcutaneous arterioles to confirm the diagnosis. This condition must be managed both from a local wound care standpoint, along with overall systemic management by controlling the calcium solubility within the blood. Regular debridement without the use of a calcium chelating agent has the potential to worsen the disease. The wounds must be followed closely to proactively treat any potential infection. Greater awareness of this debilitating disease will lead to proper treatment and improved patient outcomes.

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References


