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Non-uremic calciphylaxis in a patient with multiple rheumatologic diseases

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Abstract

Non-uremic calciphylaxis is a rare, life-threatening condition characterized clinically by cutaneous necrosis and histologically by calcium deposition in small vessel walls. The etiology of non-uremic calciphylaxis remains the subject of ongoing speculation and debate. Herein we present a patient with calciphylaxis who had normal kidney function and numerous rheumatologic diseases, namely systemic lupus erythematosus (SLE), Sjogren syndrome (SS), and myasthenia gravis (MG). We review the pathophysiology, possible mechanisms, and management for non-uremic calciphylaxis.

Keywords: non-uremic calciphylaxis, calcific uremic arteriopathy, metastatic calcification, pathophysiology, sodium thiosulfate, management

Introduction

Calciphylaxis, also known as calcific uremic arteriolopathy or uremic gangrene syndrome, is a severe and life-threatening form of metastatic calcification that occurs primarily in the setting of chronic kidney disease. In 1968-69, two cases of cutaneous calcification and necrosis in humans with chronic kidney disease were published and the term calciphylaxis was applied to these cases [1, 2]. Since then, calciphylaxis has been identified as one of the two major forms of metastatic calcification, that is, tissue calcification occurring in the setting of calcium dysregulation. Metastatic calcification typically occurs in chronic kidney disease complicated by secondary hyperparathyroidism and is believed to be a result of the increased serum phosphate that is associated with these states. Patients with primary hyperparathyroidism may also develop calciphylaxis [3], but this is less common. Herein we present an unusual case of calciphylaxis occurring in a patient without chronic kidney disease or gross parathyroid abnormalities.

Case Synopsis

A 60-year-old woman was transferred to a tertiary medical center for evaluation of multiple, intensely painful ulcerated plaques on both lower extremities that had appeared over several weeks. The patient had a complex medical history notable for systemic lupus erythematosus (SLE), Sjogren syndrome (SS), myasthenia gravis (MG), and deep vein thrombosis (DVT), for which she was taking hydroxychloroquine 200mg PO twice daily, azathioprine 150mg daily, methotrexate 10mg PO weekly, prednisone 80mg

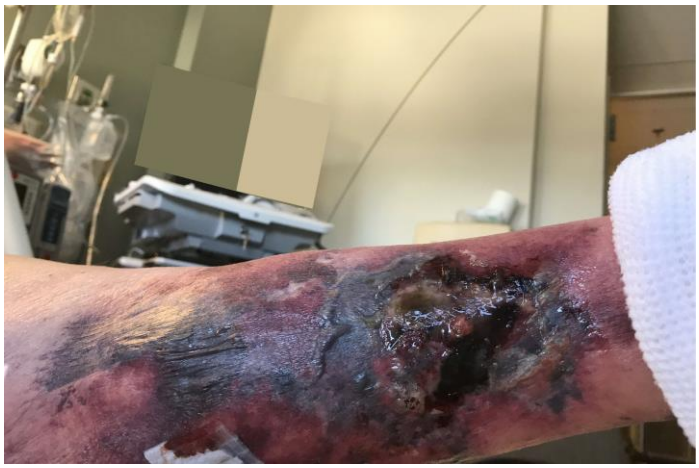

Figure 1. *A frank necrotic ulcer on a background of retiform and stellate purpuric patches and erythema was noted on the patient's left medial calf.*

daily, and apixaban 5mg twice daily. Initial examination revealed large necrotic plaques with reticulated purpuric borders and ulcers, including several large necrotic ulcers on the medial thighs and a 10×5cm ulcer extending to fascia on the right posterior calf (**Figure 1**). Laboratory studies revealed normal serum urea nitrogen, creatinine, glomerular filtration rate, potassium, phosphorus, and calcium. Serum parathyroid hormone (PTH) and total 25-hydroxy-vitamin D were 95ng/l (normal range 10-65ng/l) and 19ng/ml (normal range 30-80ng/ml), respectively, consistent with mild secondary hyperparathyroidism related to vitamin D deficiency. An extensive evaluation for thrombophilia and rheumatologic disease was unrevealing (**Table 1**). Biopsies of the left calf and right lower extremity were performed for tissue culture and histologic evaluation. The tissue cultures did not reveal any evidence of fungal, bacterial, or mycobacterial infection. The routinely prepared tissue sections showed pseudoxanthoma elasticum-like fibers. Von Kossa and Voerhoff-Van Gieson elastic staining highlighted dystrophic perivascular and intravascular calcification and accentuated the pseudoxanthoma elasticum-like fiber formation, respectively. **(Figure 2, Figure 3)** There were no signs of vasculitis. A diagnosis of non-uremic calciphylaxis was rendered and the patient was started on sodium thiosulfate 25mg intravenous three days per week. Her wound-associated pain diminished and she was discharged with wound care, close follow up, and sodium thiosulfate infusions 5 days per week. Post-discharge, an outside provider admitted the patient for operative debridement. Her course was complicated by peri-operative DVT and pulmonary embolus, requiring hospitalization. During this time, a nephrology consultation was obtained to manage her sodium

Table 1. *Rheumatologic and hematologic lab values obtained as part of initial workup for the patient in this case.*

Rheumatologic labs	Patient Value	Reference Range
IgA	207 mg/dl	70-400 mg/dl
IgG	511 mg/dl	700-1600 mg/dl
IgM	96 mg/dl	40-230 mg/dl
Myeloperoxidase anti-neutrophil cytoplasmic antibody IgG (MPO ANCA)	1 AU/ml	0-19 AU/ml
Serine protease 3 anti-neutrophil cytoplasmic antibody IgG (PR3 ANCA)	0 AU/ml	0-19 AU/ml
Anti-dsDNA antibody	10 IU	0-24 IU
Antinuclear antibody	Positive	Negative
Anti-ribonucloprotein antibody	0.9 U/ml	0-4.9 U/ml
Anti-Smith antibody	<0.8 U/ml	0-6.9 U/ml
SS-A antibody	>240.0 U/ml	0-6.9 U/ml
SS-B antibody	<0.3 U/ml	0-6.9 U/ml
Angiotensin converting enzyme	10 U/L	9-67 U/L
Beta-2 glycoprotein 1 IgA antibody	5 SAU	0-20 SAU
Beta-2 glycoprotein 1 IgG antibody	1 SAU	0-20 SAU
Beta-2 glycoprotein 1 IgM antibody	9 SAU	0-20 SAU
Anti-cardiolipin IgG antibody	<10 GPL	0-14 GPL
Dilute Russell's Viper Venom Time, Patient	40.0 seconds	N/A
Dilute Russell's Viper Venom Time, Ratio (Pt/control)	1.21	<1.20
Dilute Russell's Viper Venom 1:1 Mix Time, Patient	36.3 seconds	N/A
Dilute Russell's Viper Venom 1:1 Mix Time, Ratio (Pt/control)	1.10	<1.20
Rheumatoid factor	<10 IU/ml	0-13 IU/ml
Hematologic lab values		
Prothrombin time	11.17 seconds	9.7-12.5 seconds
Partial thromboplastin time	39.0 seconds	25-35 seconds
International normalized ratio	1.1 units	0-1.1 units
C-reactive protein	6.70 mg/l	<0.5 mg/l
Erythrocyte sedimentation rate	38 mm/hr	0-30 mm/hr
C3	87 mg/dl	90-180 mg/dl
C4	23 mg/dl	10-40 mg/dl

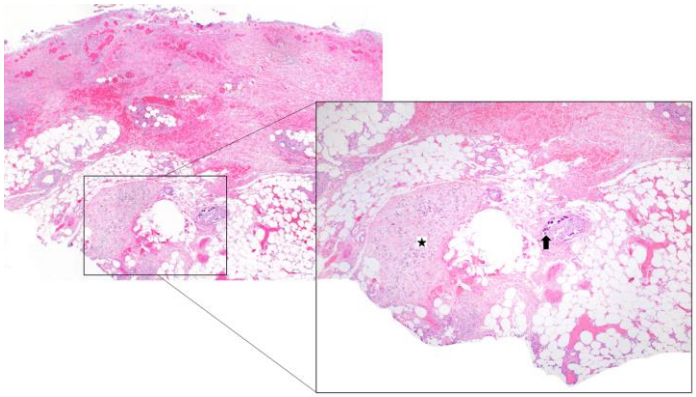

Figure 2. *Right lower extremity incisional wedge biopsy demonstrating complete denudation of the epithelium with hemorrhage and vascular sludge within superficial dermal vessels (left, H&E, 4×). Soft tissue calcification of elastic fibers in a pattern suggestive of pseudoxanthoma elasticum is evident (right insert: star), as are basophilic intraluminal calcific deposits within deep subcutaneous vessels (right inset: arrow, 20×).*

thiosulfate and she was started on oral cinacalcet 30mg daily. She fortunately stabilized, was discharged with continued sodium thiosulfate, and re-established dermatology outpatient follow up. At her last follow up, after 6 months of sodium thiosulfate therapy at 25mg IV Monday through Friday, the wounds on her left leg had completely healed and her right leg was significantly improved, with only two small ulcers remaining (**Figure 4**). Furthermore, her wound-associated pain had completely resolved.

Case Discussion

Calciphylaxis classically presents as reticulated erythematous to viol aceous patches on the torso or proximal lower extremities. Calciphylaxis of other areas, including the face and genitalia [4], has rarely been reported. The lesions are extremely painful, often out of proportion to their clinical appearance. Bullae, ulceration, and gangrenous necrosis of the affected skin follows. Pooled blood in the affected dermal layers promotes rapid bacterial growth. Death by sepsis is the ultimate outcome in many cases. Calciphylaxis carries a one-year mortality rate of 40-50% [5], and the prognosis is even poorer once ulceration develops, with cause-specific mortality exceeding 80% [6].

Calciphylaxis appears to be more common than previously thought, with an estimated prevalence of approximately four percent in a recent study of chronic kidney disease patients [6]. Most cases of calciphylaxis occur in patients with significant renal disease and calciphylaxis in this context is also known as calcific uremic arteriolopathy (CUA). Female sex, obesity, diabetes mellitus, warfarin use, glucocorticoid use, and hypercoagulable state (particularly protein C deficiency and presence of lupus anticoagulant, according to a 2018 case-control analysis [7]) increase risk of calciphylaxis, including in patients with kidney disease [8, 9].

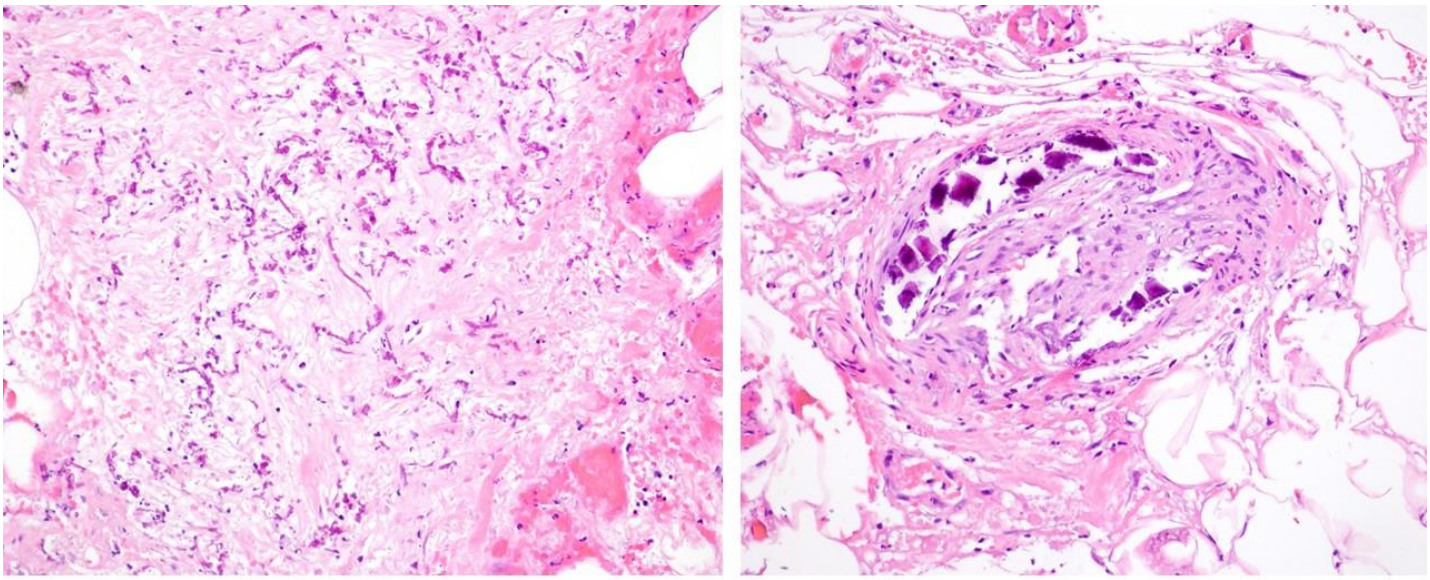

Figure 3. *Higher magnification view of soft tissue calcification (left). Higher magnification view of intraluminal calcific deposits within deep subcutaneous vessels (right). H&E, 20×.*

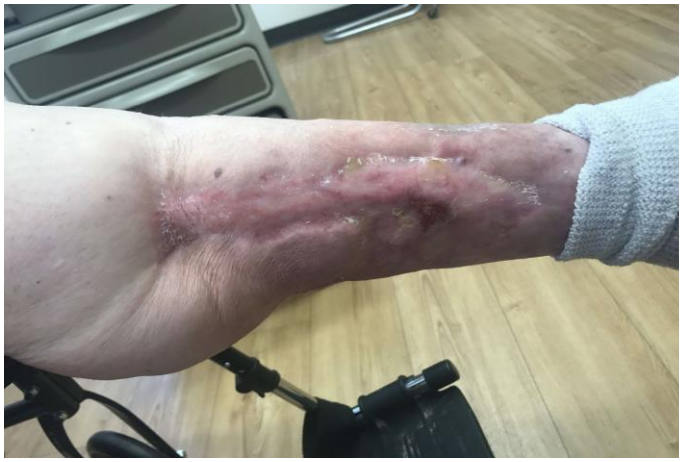

Figure 4. *After 6 months of therapy with sodium thiosulfate, the patient's left medial calf had healed completely with scarring.*

Calciphylaxis is exceedingly rare in patients who are not uremic or whose hyperparathyroidism does not result in significant calcium and phosphate derangements [10, 11].

Table 2. *Primary associated condition of non-uremic calciphylaxis not related to hyperparathyroidism, by frequency.*

Primary Associated Condition	No. of cases (% of cases)
Malignancy**	9
Bisphosphonate use*	8
Alcoholic liver disease	7
Rheumatoid arthritis	5
Systemic lupus erythematosus	2
Warfarin or acenocumarol use	4
POEMS syndrome	2
Diabetes mellitus	2
Giant cell arteritis	1
Sarcoidosis	1
Chagas' Disease	1

Adapted from Nigwekar et al., 2008 and updated with cases reported since that time[16]. Because most patients who develop calciphylaxis have multiple medical conditions and are taking multiple medications, we rely on the authors' best hypothesis of the primary cause of calciphylaxis in their patients. *Meiller et al. have recently argued that bisphosphonate-induced osteonecrosis should be considered a subtype of non-uremic calciphylaxis, based on emerging clinical and histologic evidence [31]. **Includes ovarian cancer, cholangiocarcinoma, chronic myelocytic leukemia, Hodgkin lymphoma, malignant melanoma of the soft parts (clear cell sarcoma), metastatic breast cancer, and multiple myeloma.

Non-uremic calciphylaxis (NUC) in euparathyroid patients has been reported in patients with underlying malignancy [12-17], alcoholic liver disease [12], giant cell arteritis [13], rheumatoid arthritis [14], Crohn disease [15], POEMS syndrome, vitamin D deficiency, and weight loss [16]. Warfarin [17], corticosteroids [18], chemotherapeutic agents [19], and nadroparin calcium [20] have also been implicated in NUC (**Table 2**). A systematic review of non-uremic calciphylaxis found that, after primary hyperparathyroidism, most cases of NUC occurred in patients with underlying malignancy, alcoholic liver disease, and connective tissue disease [16]. Given the rarity of NUC and the fact that many of the affected patients have multiple medical problems, causal relationships are difficult to establish. However, it is notable that NUC has usually been reported in patients with chronic disease rather than healthy patients [16].

The precise pathological mechanisms driving NUC are incompletely understood, but ultimately result in calcification of cutaneous vessels and subsequent tissue infarction. The mechanisms believed to underlie known risk factors for NUC are summarized in **Table 3**.

Diagnosis of NUC requires biopsy, as the differential diagnosis of cutaneous necrosis is broad. Biopsies should be taken from the margins of expanding lesions rather than the necrotic centers and should be deep enough that the dermal and subcutaneous vasculature may be adequately visualized. On histologic analysis, panniculitis and calcifications are frequently seen in NUC (and CUA), though these are not specific findings for either NUC or CUA. Medial calcific stippling and thrombosis of arterioles are specific findings, but they are not present in many cases; thus, diagnosis based exclusively on readings of hematoxylin and eosin (H&E) stained sections would likely lead to many missed diagnoses. Calcium-specific stains, such as the von Kossa stain or alizarin red stain, can increase sensitivity when calciphylaxis is clinically suspected. An emerging histologic feature of NUC is pseudoxanthoma elasticum (PXE)-like changes, which were present in our patient. PXE is an autosomal recessive disease caused by mutations in the *ABCC6* gene, which

Table 3. *Risk factors for calciphylaxis, including uremic calciphylaxis and non-uremic calciphylaxis, with summaries of proposed or speculated mechanisms.*

Risk Factor	Proposed or speculated mechanism
Chronic renal failure [9]	Reduced clearance of phosphate in renal failure, leading to increased calcium-phosphate product and precipitation of calcium phosphate.
Female gender [5]	Unknown
Obesity [25]	Possible pro-inflammatory state from increased adipocyte signaling, leading to low serum fetuin A levels (fetuin A is a serum glycoprotein that normally binds both calcium and phosphate, decreasing the free calcium x phosphate product).
Diabetes mellitus [25]	Endothelial injury and apoptosis related to hyperglycemia promotes deposition of calcium phosphate in tunica intima.
Warfarin or acenocumarol use [17]	Matrix G1a protein normally inhibits arterial calcification; synthesis of active matrix G1a protein requires Vitamin K-dependent gamma carboxylation, which is inhibited by warfarin use.
Glucocorticoid use [14]	Glucocorticoids decrease expression of matrix G1a protein in pericytes in vitro, suggesting they may reduce expression of a calcification-inhibiting protein, as above.
Hypercoagulable state [7]	In any hypercoagulable state, small arteries and arterioles are more likely to thrombose, resulting in necrosis of the end organ (skin and subcutaneous tissue).
Malignancy [25]	1. Lysis of tumor cells leads to phosphate release into bloodstream. 2. Pro-thrombotic state of malignancy, pro-inflammatory cytokines and pro-coagulant substance release from tumor cells. 3. Calcium release into bloodstream (primary osseous malignancies, bone metastases, multiple myeloma).
Bisphosphonate use* [31]	Bisphosphonate use increases serum free phosphate, increasing calcium x phosphate product and risk of calcium phosphate precipitation.
Alcoholic liver disease [12]	1. Albumin infusions for decompensated liver failure (particularly in patients with ascites/at risk of spontaneous bacterial peritonitis). Albumin may act as a "challenger" as in the mouse experiments of Selye et al. 2. Prednisone given for liver disease-associated vasculitis.
Rheumatoid arthritis [14]	1. In many patients, chronic glucocorticoid use decreases expression of calcification-inhibiting matrix G1a protein (see above). 2. Some patients with rheumatoid arthritis also produce anti-protein S antibodies; this leads to a mild hypercoagulable state, possibly increasing risk of arterial and arteriolar thrombosis.
Systemic lupus erythematosus [28-30]	1. Elevation of inflammatory cytokines leading to decreased matrix G1a protein, promoting vascular calcification. 2. Mild renal dysfunction in many patients leading to hypovitaminosis D, and secondary hyperparathyroidism.
POEMS syndrome [16]	Excess IL-6 and VEGF promote an overall inflammatory state, facilitating intimal calcium deposition and thrombosis.
Giant cell arteritis [16]	Monocyte attack of dermal vasculature in the setting of existing intimal damage and age-related calcifications.
Sarcoidosis [5]	Renal dysfunction causing secondary hyperparathyroidism. Possibly, increased production of 1,25 hydroxyvitamin D within granulomas.
Chagas Disease [32]	Increased production of inflammatory cytokines in adipocytes infected with *T. cruzi*.

encodes a cell membrane protein expressed in the skin, gastrointestinal tract, liver, eyes, and vasculature. Clinically, PXE presents very differently from calciphylaxis, with yellowish papules on the neck and axilla, visual changes, and cardiovascular disease. However, fragmentation and calcification of elastic fibers, a histological hallmark of PXE, are being increasingly identified in association with calciphylaxis [21]. PXE-like features were first identified in calciphylaxis in 1996, in a patient with CUA by Nikko and colleagues [22]. One study of 13 calciphylaxis samples found 6 exhibited PXE-like changes and these changes were uniquely localized to subcutaneous fat [23].

Management of calciphylaxis, whether uremic or non-uremic in etiology, begins with stopping all medications that increase the risk of calciphylaxis,

namely, warfarin, iron, and calcium-containing medications. Careful wound care and dedicated pain management are alfbioso beneficial. Hyperbaric oxygen therapy (HBOT) has been studied in calciphylaxis and appeared to improve outcomes in more than half of patients in a series of 34 CUA patients who received a full course of HBOT [24]. Narcotics are generally required for pain control and some authors prefer fentanyl over morphine owing to decreased risk of hypotension with the former agent [25]. The most commonly-used agent used specifically to manage calciphylaxis (both CUA and NUC) is sodium thiosulfate. As many as 70% of patients with calciphylaxis respond favorably to sodium thiosulfate therapy [26]. This agent, perhaps best known for its use in cyanide toxicity (along with amyl nitrite), is an effective calcium chelator in vitro. However, it may operate through other mechanisms in calciphylaxis, as studies have shown that the calcium-phosphate product is not normalized even in patients who respond well to sodium thiosulfate therapy [26, 27]. In non-uremic patients (eGFR>60mL/min/1.73 m^2), 25 grams administered intravenously up to 5 times per week is a commonly used dose. However, as most patients with this condition are on dialysis, studies on optimal dosing of sodium thiosulfate in non-dialysis patients are lacking.

Our case illustrates the difficulty of ascertaining the precise etiology of calciphylaxis. This patient was suffering from multiple rheumatologic diseases and was taking numerous powerful immune suppressant medications. Including our case, non-uremic calciphylaxis has been reported in systemic lupus erythematosus (SLE) on four occasions [28-30], (**Table 4**). Indeed, it is possible that our patient's SLE contributed to her development of calciphylaxis. In addition, although our patient also suffers from Sjogren syndrome, this disease has not been directly connected with non-uremic calciphylaxis. Mild secondary hyperparathyroidism may have potentiated or exacerbated calciphylaxis in our case, but is viewed as an unlikely primary etiology given the minimal laboratory abnormalities and presence of other significant risk factors. Many patients with SLE are thrombophilic and as thrombophilia is independently associated with calciphylaxis, it is conceivable that SLE-associated thrombophilia may play a role in some cases. Our patient's DRVVT ratio was slightly prolonged, but as this corrected completely with 1:1 mixing, it was felt to be incompatible with lupus anticoagulant and likely an incidental finding (**Table 1**). Finally, our patient was also female and taking prednisone, both of which are associated with increased risk of calciphylaxis. In total, our patient had five known risk factors for calciphylaxis — female gender, obesity, glucocorticoid use, (mild) hyperparathyroidism, and systemic lupus erythematosus.

Conclusion

Calciphylaxis can be a challenging diagnosis to make. The initial presentation can be subtle and dermatologic manifestations can vary. Pain out of proportion to physical findings and that persists

Table 4. *Published cases of non-uremic calciphylaxis in systemic lupus erythematosus.*

No.	Publication	Age	Sex	Risk factors*	RC**	Treatment	Outcome
1	Zechlinksi et al.	76	F	SLE, female, alendronate, warfarin, vitamin D deficiency	None	Unknown	Lost to followup
2	Aliaga et al.	34	F	SLE, female, methylpred-nisolone,	None	Methylprednisolone Cyclopho phamide	Sepsis, death
3	Pek et al.	77	F	SLE, female, warfarin use	None	Sodium thiosulfate	Sepsis, death
4	This case	60	F	SLE, female, obesity, prednisone, hyper-PTH	Sjogren syndrome, myasthenia gravis	Sodium thiosulfate Cinacalcet	Improved

*In each of the four cases, systemic lupus erythematosus was considered to be the ultimate cause of non-uremic calciphylaxis. Though uremic calciphylaxis has been relatively better described in systemic lupus erythematosus, there are three known cases of non-uremic calciphylaxis aside from this case. Here we summarize their salient characteristics and relevant risk factors including lupus. *Established risk factors, as described in* **Table 3**. ***RC, rheumatologic comorbidities, i.e. other rheumatologic diagnoses besides lupus.*

despite use of strong analgesics are important clues. NUC poses an additional challenge, as clinicians may be less likely to suspect calciphylaxis in patients who do not have kidney or parathyroid disease. However, patients with autoimmune, connective tissue, and oncologic disease may develop calciphylaxis in the absence of uremia. Regardless of its etiology, NUC carries significant morbidity and mortality and remains incompletely understood. Therefore, continued study of this disease, its pathogenesis, its risk factors, and its optimal management is warranted.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. Rees JK, Coles GA. Calciphylaxis in man. *Br Med J*. 1969;2(5658):670-2. [PMID: 5783125].
2. Anderson DC, Stewart WK, Piercy DM. Calcifying panniculitis with fat and skin necrosis in a case of uraemia with autonomous hyperparathyroidism. *Lancet*. 1968;2(7563):323-5. [PMID: 4173738].
3. Joukhadar R, Bright T. Calciphylaxis in Primary Hyperparathyroidism: A Case Report and Brief Review *South Med J*. 2009;3:318-21. [PMID: 19204621]
4. Endly D, Irfan M, Piliang M. Tender, necrotic plaques of the glans penis due to calciphylaxis. *Dermatol Online J*. 2015;21(6). [PMID: 26158362].
5. Weenig RH, Sewell LD, Davis MD, et al. Calciphylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol*. 2007;56(4):569-79. [PMID: 17141359].
6. Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: Risk factors, outcome and therapy. *Kidney International*. 2002;61(6):2210-7.
7. Dobry AS, Ko LN, St John J, et al. Association Between Hypercoagulable Conditions and Calciphylaxis in Patients With Renal Disease: A Case-Control Study. *JAMA Dermatol*. 2018;154(2):182-7. [PMID: 29238798].
8. Floege J, Kubo Y, Floege A, et al. The Effect of Cinacalcet on Calcific Uremic Arteriolopathy Events in Patients Receiving Hemodialysis: The EVOLVE Trial. *Clin J Am Soc Nephro*. 2015;10(5):800-7. [PMID: 25887067].
9. Mazhar AR, Johnson RJ, Gillen D, et al. Risk factors and mortality associated with calciphylaxis in end-stage renal disease. *Kidney Int*. 2001;60(1):324-32. [PMID: 11422768].
10. Roy R, Lee JA. Calciphylaxis due to hyperparathyroidism. *Endocr Pract*. 2011;17 Suppl 1:54-6. [PMID: 21324820].
11. Duh QY, Lim RC, Clark OH. Calciphylaxis in secondary hyperparathyroidism. Diagnosis and parathyroidectomy. *Arch Surg*. 1991;126(10):1213-8; discussion 8-9. [PMID: 1929821].
12. Chavel SM, Taraszka KS, Schaffer JV, et al. Calciphylaxis associated with acute, reversible renal failure in the setting of alcoholic cirrhosis. *J Am Acad Dermatol*. 2004;50(5 Suppl):S125-8. [PMID: 15097947].
13. Brouns K, Verbeken E, Degreef H, et al. Fatal calciphylaxis in two patients with giant cell arteritis. *Clin Rheumatol*. 2007;26(5):836-40. [PMID: 16871353].
14. Korkmaz C, Dundar E, Zubaroglu I. Calciphylaxis in a patient with rheumatoid arthritis without renal failure and hyperparathyroidism: the possible role of long-term steroid use and protein S deficiency. *Clin Rheumatol*. 2002;21(1):66-9. [PMID: 11954890].
15. Barri YM, Graves GS, Knochel JP. Calciphylaxis in a patient with Crohn's disease in the absence of end-stage renal disease. *Am J Kidney Dis*. 1997;29(5):773-6. [PMID: 9159315].
16. Nigwekar SU, Wolf M, Sterns RH, Hix JK. Calciphylaxis from nonuremic causes: a systematic review. *Clin J Am Soc Nephro*. 2008;3(4):1139-43. [PMID: 18417747].
17. Yu WY, Bhutani T, Kornik R, et al. Warfarin-Associated Nonuremic Calciphylaxis. *JAMA Dermatol*. 2017;153(3):309-14. [PMID: 28099971].
18. Maroz N, Mohandes S, Field H, et al. Calciphylaxis in Patients With Preserved Kidney Function. *J Am Coll Clin Wound Spec*. 2014;6(1-2):24-8. [PMID: PMC4566866].
19. Goyal S, Huhn KM, Provost TT. Calciphylaxis in a patient without renal failure or elevated parathyroid hormone: possible aetiological role of chemotherapy. *Br J Dermatol*. 2000;143(5):1087-90. [PMID: 11069528].
20. Campanelli A, Kaya G, Masouye I, Borradori L. Calcifying panniculitis following subcutaneous injections of nadroparin-calcium in a patient with osteomalacia. *Br J Dermatol*. 2005;153(3):657-60. [PMID: 16120161].
21. Nathoo RK, Harb JN, Auerbach J, et al. Pseudoxanthoma elasticum-like changes in nonuremic calciphylaxis: Case series and brief review of a helpful diagnostic clue. *Journal of cutaneous pathology*. 2017;44(12):1064-9. [PMID: 28869660].
22. Nikko AP, Dunningan M, Cockerell CJ. Calciphylaxis with Histologic Changes of Pseudoxanthoma Elasticum. *Am J Dermatopathol*. 1996;18(4):396-9. [PMID: 199608000].
23. Penn LA, Brinster N. Calciphylaxis with pseudoxanthoma elasticum-like changes: A case series. *J Cutan Pathol*. 2018;45(2):118-21. [PMID: 29086985].
24. An J, Devaney B, Ooi KY, et al. Hyperbaric oxygen in the treatment of calciphylaxis: A case series and literature review. *Nephrology (Carlton)*. 2015;20(7):444-50. [PMID: 25707425].
25. Nigwekar SU, Kroshinksy D, Nazarian RM, et al. Calciphylaxis: Risk Factors, Diagnosis, and Treatment. *Am J Kidney Dis*. 2015;66(1):133-46. [PMID: PMC4696752].
26. Nigwekar SU, Kroshinsky D, Nazarian RM, et al. Calciphylaxis: risk factors, diagnosis, and treatment. *Am J Kidney Dis*. 2015;66(1):133-46. [PMID: 25960299].
27. Yu Z, Gu L, Pang H, et al. Sodium Thiosulfate: An Emerging Treatment for Calciphylaxis in Dialysis Patients. *Case Rep Nephrol*. 2015;5(1):77-82. [PMID: PMC4386105].
28. Zechlinski JJ, Angel JR. Calciphylaxis in the Absence of Renal Disease: Secondary Hyperparathyroidism and Systemic Lupus Erythematosus. *J Rheumatol*. 2009;36(10):2370-1. [PMID: 19820228]
29. Aliaga LG, Barreira JC. Calciphylaxis in a patient with systemic lupus erythematosus without renal insufficiency or

hyperparathyroidism. *Lupus*. 2012;21(3):329-31. [PMID: 21997968].

30. Pek EA, Joseph PL, Al Habeeb AS, Albert LJ. A Fatal Case of Calciphylaxis in a Patient with Systemic Lupus Erythematosus and Normal Renal Function. *J Rheumatol*. 2016;43(2):456-8. [PMID: 26834255]
31. Meiller T, Almubarak H, Weikel D, et al. Bisphosphonate-associated osteonecrosis of the jaw: are we dealing with a localized non-traditional calciphylaxis? *Open Dent J*. 2012;6:5-7. [PMID: 22276079].
32. Vicco MH, Ferini F, Rodeles L, et al. Non-uremic calciphylaxis and Chagas disease. *Rev Clin Esp*. 2014;214(5):55. [PMID: 24698001].