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Calciphylaxis: A Rare Clinical Presentation in a Patient with End-Stage Renal Disease (ESRD)

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Calciphylaxis, also known as calcific uremic arteriolopathy (CUA), affects small arteries of the skin in patients with end-stage renal failure, dialysis patients, and patients with hypercalcemia. The condition is characterized by the calcification of small blood vessels leading to skin necrosis without

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inflammation. It is frequently complicated by superimposed infection and bleeding and has a high mortality rate.
The rare condition is yet to be documented on the islands of Saint Vincent and the Grenadines. The authors have, therefore, made efforts to document, educate, and discuss this rare presentation in a 65-year-old local Vincentian male with 30 years history of poorly controlled diabetes mellitus and hypertension who commenced hemodialysis two years prior to the presentation for end-stage chronic renal failure. With the increasing incidence and prevalence of diabetes mellitus, hypertension, and complications of chronic kidney disease, and renal failure, this article is written as a case study with a concise literature review on calciphylaxis to provide continuing medical education and increase the level of awareness among medical students and index of suspicion among healthcare providers.

Keywords: Calciphylaxis; calcific uremic arteriopathy; end-stage renal failure; Diabetes mellitus; Saint Vincent and the Grenadines; Thiosulphate.

1. INTRODUCTION

Calciphylaxis, also known as calcific uremic arteriolopathy (CUA), was coined in 1961 by Dr. Selye. It is a rare arteriolopathy primarily seen in patients with end-stage renal disease and chronic renal failure or with warfarin use for different medical indications. It is characterized by extraskeletal calcifications. [1] The clinical presentation is very similar to warfarin-induced skin necrosis (WISN). However, differentiation can be made with findings on histology [1].

Calciphylaxis is seen in 1 to 4.5% of patients on hemodialysis, with an increased rate of occurrence among obese, diabetic patients and those on a high dose of calcium supplements, vitamin supplementation, and steroids. Patients typically present with tender escharification that tends to bleed, described as livedo-reticularis-like in most texts, and observed in our patient, who presented with a generalized lesion. Management is multidisciplinary, with a team comprising nephrologists, dermatologists, surgeons (wound care specialists), infectious disease physicians, and the nursing team. The use of thiosulphate for treatment is becoming essential, as in this case [2,3]. Bisphosphonates (Etidronate) use has also been proposed for treatment; however, it may not be suitable for patients on hemodialysis [4,5]. The presentation of calciphylaxis in patients connotes a poor prognosis with high mortality from systemic infection and sepsis [3-5].

2. CASE STUDY

A 65-year-old Caribbean male of Afro-Indian descent presented to the clinic with generalized and worsening dark nodular pigmentations on the skin, more on the lower limbs. The rashes were itchy, painful, and bleeding. The patient has been a known hypertensive and diabetic for about three decades and was diagnosed with end-stage renal disease and placed on hemodialysis for the past two years prior to this presentation. His routine daily medications included calcitriol 0.5mg, nifedipine 60mg, lisinopril 20mg, atenolol 50mg, vitamin D 2000mg, Lasix 40mg, Epogen 800units, glyburide 5mg, and Glucophage 500mg. The patient has no history of allergies and denied the use of warfarin or herbal medications for his medical conditions.

Physical examination revealed an ill-looking, edematous, and afebrile patient, in mild respiratory distress, with facial and bilateral pitting ankle edema. Vital signs showed oxygen saturation (SpO2) of 89%, BMI of 30.57kg/m^2, PR of 97/min, RR of 22 cycles/min, and a BP of 192/61mmHg.

Skin exam showed generalized nodular eschars, varying from 0.2mm to 1cm in dimension, on the face, abdomen, pelvic area, back, and lower limbs. The lesions were dark and tender, with rims of hyperemia, and were extensive on the lower limb (Fig. 1-2). A mild bilateral edema was present in the shin area (Fig. 1).

Chest examination was positive for bilateral crepitations at the lung bases, displaced apex beat with S1, S2 heart sounds, and an S3 gallop rhythm, but no murmur. Abdomen examination was positive for moderate distension, generalized tenderness, and ascites (shifting dullness ++) (Fig. 3).

The investigation results on presentation are as follows:

Blood Tests:

No.	Tests	Patient results	Reference range
1	RBC Count	3.71 x 10^6/uL	4.7 – 6.1 x 10^6/uL
2	Hb Concentration	11.0g/dL	14.0 – 18.0g/dL
3	HCT	34.8%	41% - 50%
4	MCV	93.8fL	80.0 – 100.0fl
5	MCH	29.6pg	27.0 – 31.0pg
6	MCHC	31.6g/dL	32.0 – 36.0g/dL
7	RDW-SD	56.7fL	40.0 – 55.0fL
8	RDW-CV	16.6%	11.0 – 15.0%
9	MPV	12.2fL	7.0 – 9.0fL
10	WBC Count	9.14 x 10^3/Ul	4,500 – 11,000/Ul
11	Platelet count	200 x10^3/uL	150 – 400 x10^3/uL
12	Blood glucose	305mg/dL	<200mg/dL
13	Serum Troponin	0.357	<0.014
14	HIV Serology	Negative	
15	HTLV-1 Serology	Negative	
16	HBsAg	Negative	

Serum Electrolytes, Urea & Creatinine:

No.	Tests	Patient results	Reference range
1	Serum Sodium	147mmol/L	135 – 145mmol/L
2	Serum Potassium	4.8mmol/L	3.5 – 5.0mmol/L
3	Serum Chloride	105mmol/L	95 – 105mmol/L
4	Urea	25.8mmol/L	1.8 – 7.1mmol/L
5	Serum Creatinine	1140.0umol/L	62 – 115umol/L
6	eGFR	4.8mL/min	>90ml/min
7	Serum Calcium	2.79mmol/L	2.20 – 2.55mmol/L
8	Serum Magnesium	1.41mmol/L	0.75 – 0.95mmol/L
9	Serum Phosphorus	2.97mmol/L	1.12 – 1.45mmol/L

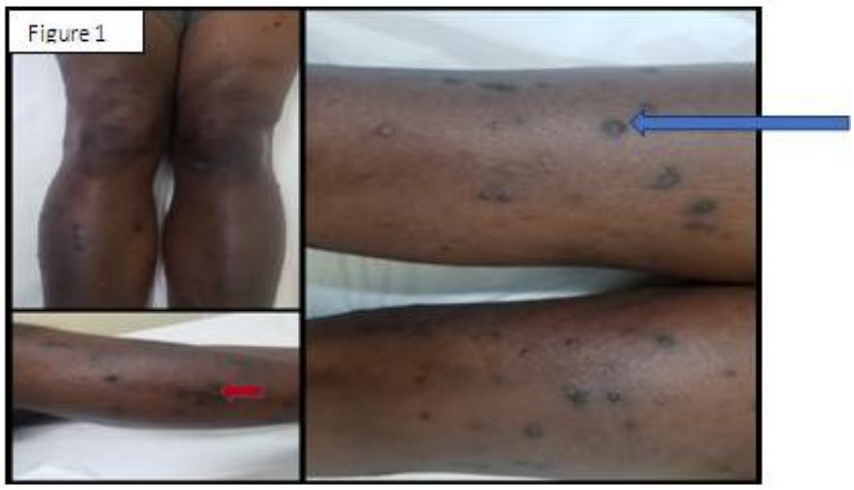

Fig. 1. [Pics]: aggregates of nodular rashes (dark) of varying dimensions. A long blue arrow points towards a large nodular lesion with healed ulcerated central dimple. A short red arrow pointing towards darkened aggregates of multiple nodular rashes. (Lower limbs)

Source: Archive of Caribbean Kidney Medical Center, Saint Vincent, and the Grenadines

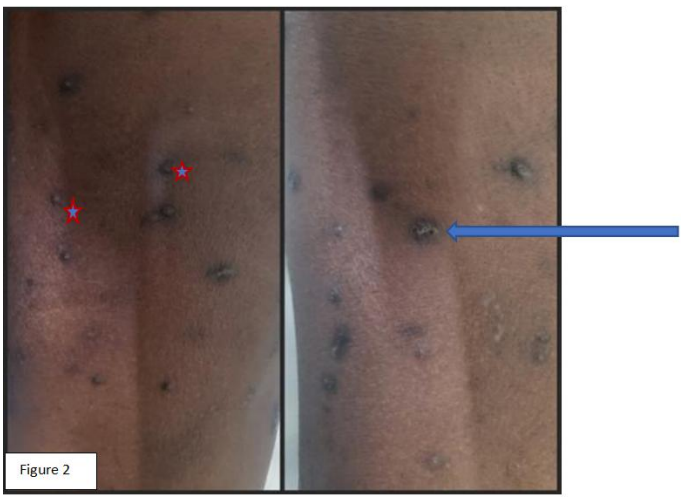

Fig. 2. [Pics]: Close shot of the skin lesions. The left picture shows an area of skin necrosis with multiple nodules (star). The right picture shows areas of healed skin ulcer (long blue arrow)

source: Archive of Caribbean Kidney Medical Center, Saints Vincent, and the Grenadines.

Fig. 3. (pics): Top image showing a lateral view of abdominal distension, marked by fluid accumulation (Ascites). Pic showing ascites (below)

Source: Archive of Caribbean Kidney Medical Center, Saint Vincent, and the Grenadines

Urine analysis was positive for blood and protein. A chest radiograph reveals cardiomegaly with mild pleural effusion. Echocardiography showed vegetation on the heart valves, and blood culture was positive for Serratia marcescens. Brain CT scan, EKG (Fig. 4), and thyroid function tests were normal.

Based on these findings, an assessment of calciphylaxis was suspected, and the patient was scheduled for a skin biopsy. In addition, a trial of intravenous thiosulphate 25mg thrice weekly was planned for a month. The frequency of follow-up visits and hemodialysis were optimized, and the patient was advised to ensure compliance with his routine medications. Images of the cutaneous lesions weeks after the initiation of treatment are shown in Fig. 2.

Follow-up was scheduled for a week, along with the next session of dialysis and biopsy. The patient died of cardiopulmonary arrest from overwhelming septicemia within one week of being diagnosed with Calciphylaxis. Histopathological findings of Calciphylaxis are shown below (Fig. 5).

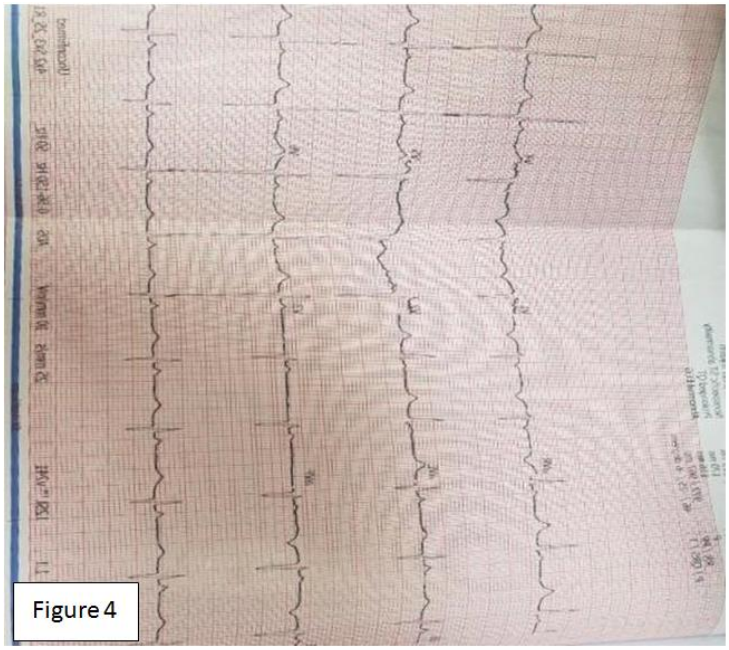

Fig. 4. Normal findings on EKG done on the last visit. Source: Archive of Caribbean Kidney Medical Center, Saint Vincent, and the Grenadines

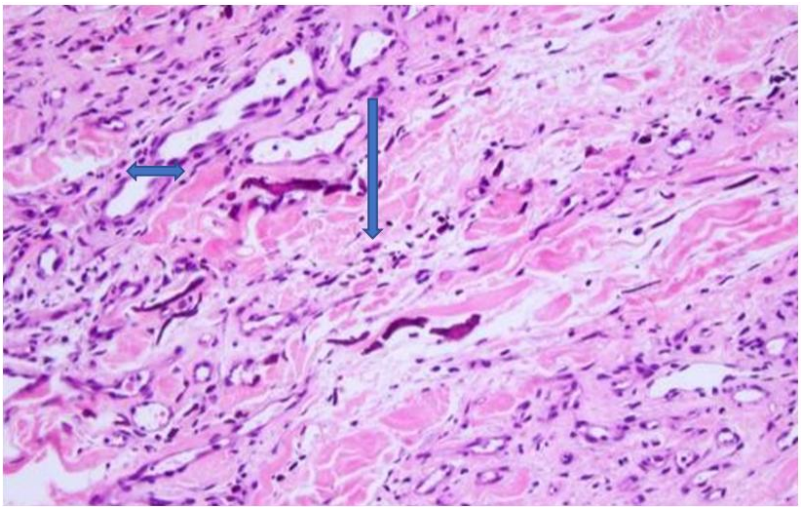

Fig. 5. Histopathological section of the blood vessels showing mild calcification of the blood vessels with minimal inflammatory response (Blue arrows)

Source: Archive of Caribbean Kidney Medical Center, Saint Vincent, and the Grenadines. https://www.pathologyoutlines.com/imgau/skinnontumorcalciphylaxisasadbeigi01.jpg.

3. DISCUSSION

Calciphylaxis results from calcium deposition in the media and intima of small cutaneous blood vessels. The condition leads to necrosis, poor wound healing, and dark eschar formation with indurations seen at the rim of lesions. Calciphylaxis is primarily associated with end-stage renal disease but may also occur in non-uremic clinical conditions. In the general population, the reported incidence is generally low, at 0.04% in Germany, and 0.35% in the USA, while the presentation is seen in about 4% of patients undergoing hemodialysis. The incidence of the condition is higher in Caucasians, females, and patients with diabetes and obesity [5,8]. Prognosis is generally poor, with a 1-year survival rate of 45% and a 5-year survival rate of 35% [6-8].

Extraskeletal calcifications similar to those seen in patients with calciphylaxis may be observed in patients with other clinical presentations. These include patients with metastatic calcification caused by sarcoidosis, hyperparathyroidism, milk-alkali syndrome, hypervitaminosis D, diabetes mellitus, chemotherapy-induced protein C and S deficiency, Crohn's disease, alcoholic liver disease, malignancies, weight loss, trauma or in patients on vitamin D supplementation, calcium-based phosphate binders, warfarin and steroid use, blood, and albumin transfusion [7,9,10,11].

The disease mechanism is not well understood. However, some hypotheses have been made from various risk factors that are known to be associated with the presentation [2]. The deficiency of vascular calcification inhibitors ferin A (fetuin) and matrix G1a protein and the dysfunction of NF-kB, RANK, and RANK-L on osteoclasts, monocytes, and osteoprotegerin are believed to play an important role in extraskeletal mineralization seen in calciphylaxis [12-15]. In Cushing disease, chronic liver disease, and hyperparathyroidism state, activation of NF-kB or degradation of the NF-B inhibitory proteins leads to increased expression of RANK-L with subsequent reduction in the expression of osteoprotegerin [9,10,13,16]. Warfarin use inhibits vitamin K-dependent clotting factors carboxylation of matrix-G1a protein, which reduces the activity of inhibitors of calcification locally [14,15]. There is some evidence of genetic involvement in the pathogenesis of calciphylaxis, implicating the roles of promoter genes of Bone morphogenic proteins 2 and 4, and osteocalcin in calcification [8,10,16,17].

Calciphylaxis is characterized by skin mottling, induration of a livedo reticularis pattern, and ulceration with black, leathery eschar, and an adherent black slough is found [18-20]. The lesions mostly seen in the lower limbs, abdomen, and pelvic areas are painful and extremely tender. Superimposed bacterial infections are common and are associated with poor wound healing [18]. Heart calcifications leading to diastolic heart failure have been reported in patients with severe cases [10,12,17]. The diagnosis is usually made on a clinical basis. A skin biopsy may, however, be considered in some patients but is known to carry the risk of poor wound healing, superimposed bacterial infections (sepsis), and the need for repeat episodes due to a high false negative outcome. In a survey of 1000 patients in the USA, diagnosis in 55% of the patients required a skin biopsy, with 45% diagnosed solely on clinical presentation [8,13,20]. Typical findings on skin biopsy usually include a small mural artery, vein calcification, fat necrosis (panniculitis), thrombus formation, and occlusion without obvious inflammation. X-ray of the bone, bone scintigraphy, and anti-nuclear antibody may also be done in some patients [5,13,21]. The patient in this review fits the description and presentation of calciphylaxis. He was a known hypertensive and diabetic patient with end-stage renal disease and chronic renal failure managed with hemodialysis. He was not on warfarin and presented with characteristic painful skin lesions. The patient also admitted to poor compliance with his prescribed medications.

Treatment of the underlying condition is key as the prognosis is poor, even with specific medications. Treatment guidelines include an increase in the frequency of dialysis in patients with ESRD, adequate wound care, topical antibacterial, use of thrombolytic agents, hyperbaric oxygen, and sodium thiosulfate are frequently employed [13,22-25]. Non-orthodox treatment options, like maggot larval debridement for extensive ulcerations and plasma exchange, have also been employed [14,23,25]. A multidisciplinary approach to intervention comprising optimum nursing care, a dermatologist, plastic surgeon, nephrologist, dietician, wound care specialist internist, and a psychologist are required [8]. However, the prognosis remains poor, with an annual mortality rate between 40 to 80%.

4. CONCLUSION

Calciphylaxis is a life-threatening and devastating complication primarily associated with end-stage renal disease. Diagnosis in most patients can be made from clinical evaluation and should be highly suspected in patients with chronic renal failure presenting with painful skin lesions. Skin biopsy, with histopathological examination and radiologic analysis, may be necessary for a few patients to diagnose this disease. The patient met the criteria and had an excellent response to therapy.

The treatment of calciphylaxis requires a multidisciplinary intervention approach involving pharmacologic therapy, wound care, surgical debridement, nephrologist, and routine dialysis in patients with underlying ESRD, and the patient was managed accordingly. However, compliance

was a major challenge, generally seen in patients with chronic medical conditions on long-term management. Patients with calciphylaxis tend to have a poor prognosis, with a 5-year survival rate of less than 35%, even with adequate care and management. Our patients in this review perfectly fit into the narratives.

DISCLAIMER

There is no conflict of interest between the authors, facilities, and the government. The research is solely for academic purposes in advancing medical knowledge with the sole aim of improving the lives of our patients. Also, no financial support from any source exists, and the Authors solely fund it.

CONSENT AND ETHICAL APPROVAL

The Ministry of Health and Wellness, Saint Vincent the Grenadines, approved the research.

Consent form signed by the patient, witness, and physicians.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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