Case study

A RARE CASE OF END STAGE RENAL DISEASE (ESRD) ASSOCIATED CALCIPHYLAXIS IN SAINT VINCENT AND THE GRENADINES.

ABSTRACT

Calciphylaxis, also known as calcific uremic arteriopathy affects small arteries of the skin of patient with end-stage renal failure, dialysis patients and mostly patient with hypercalcemia. It is characterized by calcification of the blood vessels without obvious inflammation leading to necrosis of the skin. It is usually complicated by superimposed infection and bleeding with high mortality rate.

The rare condition is never documented on the islands of Saint Vincent and the Grenadines, which further explains its rarity. The authors have made efforts to document, educate and briefly discuss this rare complication in a 65-year-old local Vincentian male with 30 years history of poorly controlled diabetes mellitus and hypertension who commenced hemodialysis 2 years ago on account of end-stage chronic renal failure. The article written as part of Continuous medical education(CME) is a case study with a concise literature review on Calciphylaxis aim at increasing the level of awareness and high index of suspicion among medical students and health care providers on the Island because of the increasing incidence and prevalence of diabetic mellitus, hypertension, and chronic renal failure.

Keywords: Calciphylaxis, Calcific uremic arteriopathy, Endstage renal failure, Diabetes mellitus, Saint Vincent and the Grenadines, Thiosulphate.

INTRODUCTION

Calciphylaxis, also known as calcific uremic arteriopathy first coined in 1961 by Dr. Selye. It is a rare arteriopathy characterized by extraskeletal calcification seen in patient with chronic kidney disease or patient on warfarin for different medical conditions. [1] It has similar manifestations with Warfarin induced skin necrosis (WISN), and can be differentiated from WISN by histology. [1]

It can be seen in 1 to 4.5% of patient on hemodialysis, with increase rate of occurrence among obese, diabetic, those on patients on high dose of calcium, vitamin supplements and steroids. The escharification of the skin usually described as livedo-reticularis-like in most texts is tender and have tendency to bleed, like in the case of our patients who has a generalized lesion but worse in the lower limbs. Management is usually multidisciplinary, involving the nephrologist,

dermatologist, surgeons (wound care specialist), infectious disease physicians and the nursing team. The use of thiosulphate is becoming essential as in this case. [2][3]

Bisphospanates (Etidronate) use has been proposed in the management also, but may not be suitable in our patient because he is on hemodialysis [4][5][18,19]. The presence of calciphylaxis connotes bad prognosis with high mortality usually as a result of systemic infection and sepsis. [3][4][5]

CASE STUDY

A 65-year-old Caribbean male of African-Indian extraction presents to the clinic with progressive multiple generalized dark nodular pigmentations on the skin marked in the lower limbs. The rashes are itchy, painful and bleeds .He is a known hypertensive and diabetic patient for about 3 decades. He was diagnosed with endstage renal disease, and has been on dialysis for 2 years. He is presently on calcitriol 0.5mg, nifedipine 60mg, lisinopril 20mg, atenolol 50mg, vitamin D 2000mg, and laxis 40mg, Epogen 800units, glyburide 5mg and Glucophage 500mg. He has no known history of allergy or contacts, and he has never been placed on warfarin or herbal medications for his hypertensive heart disease.

Physical examination revealed edematous and afebrile patient, in mild respiratory distress, facial and bilateral pitting ankle edema. Vital signs are SpO2 -89%, BMI -30.57kg/m^2, PR -97/min, RR-22cycles/min and BP-192/61mmHg.

Skin exam shows multiple generalized nodular eschars (varying 0.2mm to 1cm) in pelvis area, abdomen, back, groin and face; dark and tender with rims of hyperemia extensive in the legs.[Figure 1-2]There is mild bilateral ankle edema in the shin area. [Figure 1]

Chest examination reveals crepitations in lung bases, S1, S2, and S3 gallop rhythm, no murmur with displaced apex beat. Abdomen is distended with significant ascites (shifting dullness ++) and generalized tenderness. [Figure 3]

WBC- 9.14 x 10^3/UI, RBC -**3.71** x 10^6/uL, HGB -**11.0** g/dL, HCT- **34.8** %, MCV - 93.8fL, MCH-29.6pg, MCHC-31.6g/dL, PLATELETS- 200 x10^3/uL, RDW-SD - 56.7, RDW-CV -16.6 %, MPV -12.2fL. SODIUM - 147mmol/L, POTASSIUM - 4.8 mmol/L, CHLORIDE- 105 mmol/L, UREA-25**.8**mmol/L, CREATININE- **1140.0**umol/L, eGFR- **4.8**mL/min, CALCIUM -**2.79**mmol/L, MAGNESIUM -**1.41**mmol/L, PHOSPHORUS - **2.97** mmol/L .Blood sugar is 305mg/dl, urine analysis is positive for blood and protein, Troponin-0.357(<0.014).HIV, HBsAg and HTLV-1 serology were negative.

Chest radiograph reveals cardiomegaly with mild pleural effusion. Echocardiography shows vegetation on the heart valves and positive serratia marcescens on blood culture. Brain CT Scan, EKG (figure 4) and thyroid function test are normal.

An assessment is suspected calciphylaxis is made based on this findings and patient scheduled for skin biopsy. He is scheduled to commence a trial intravenous thiosulphate 25mg 3 times weekly for a month and increase frequency of appointment and dialysis with continuation aforementioned medications. Images of the cutaneous lesions shown weeks after initiation of treatment [figure 2].

Follow up was scheduled for a week along with 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 the Calciphylaxis is shown below. [Figure 5]

Figure 1[Pics]: multiple aggregations of nodular rashes (dark) of varying sizes and shapes. Long blue arrow pointing towards large nodular lesion with healed ulcerated central dimple. Red short arrow pointing towards darkened aggregates of multiple nodular rashes. (Lower limbs)

Source: Archive of CARIBBEAN KIDNEY MEDICAL CENTER, SAINT VINCENT AND THE GRENADINES.

Figure 2[Pics]: Closer shot at the lesion. Right showing areas of skin healed ulcer (Long blue arrow).Left pic showing area of skin necrosis with multiple nodules spreading distally (star)

Source: Archive of CARIBBEAN KIDNEY MEDICAL CENTER, SAINTS VINCENTS AND THE GRENADINES.

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

Source: Archive of CARIBBEAN KIDNEY MEDICAL CENTER, SAINTS VINCENTS AND THE GRENADINES.

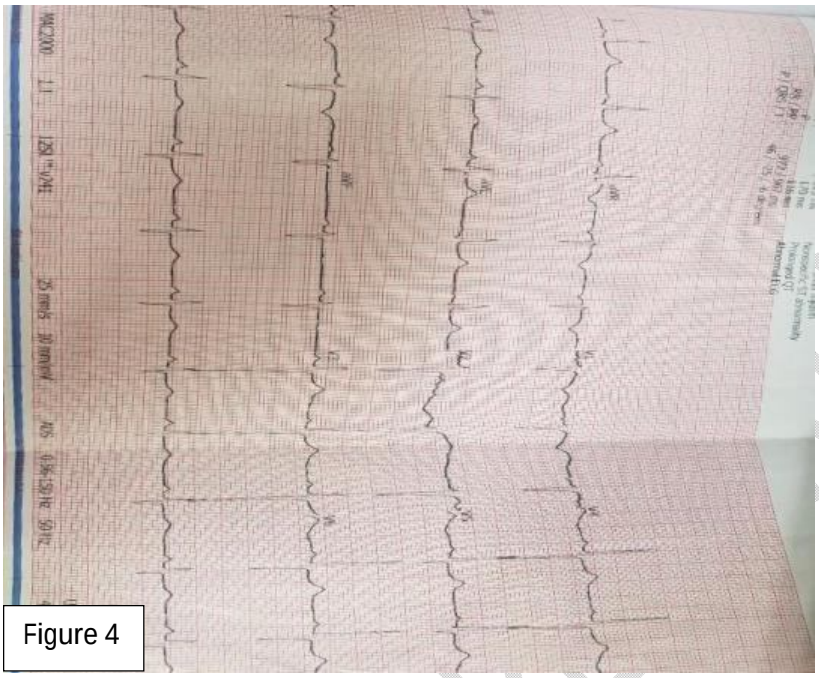

Figure 4

Figure 4: normal findings on EKG done on the last visit.

Source: Archive of CARIBBEAN KIDNEY MEDICAL CENTER, SAINTS VINCENTS AND THE GRENADINES.

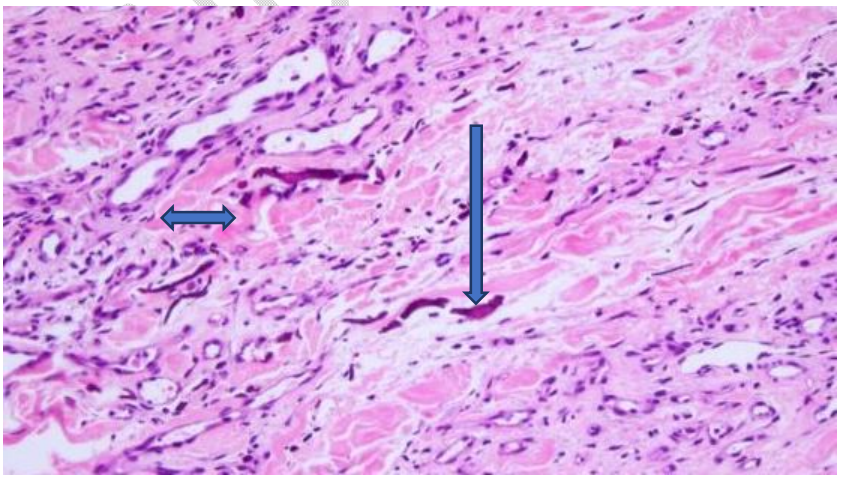

Figure 5: Histopathological section of the blood vessels showing mild calcification of the blood vessels with minimal inflammatory response. (Blue arrows)

Source: https://www.pathologyoutlines.com/imgau/skinnontumorcalciphylaxisasadbeigi01.jpg. [Archive of CARIBBEAN KIDNEY MEDICAL CENTER, SAINTS VINCENTS AND THE GRENADINES]

DISCUSSION

Calciphylaxis is deposition of calcium in the media and intima of small cutaneous blood vessels leading to necrosis, poor would healing and dark eschar formation with indurations at the rim and usually connotes bad prognosis with 1-year survival rate of 45% and 5 year survival rate of 35%. [6][7][8]The incidence is about 4% of the population but it is as low as 0.04% in Germany and 0.35% in the USA, more from uremic causes than non-uremic causes. The incidence is higher in female, Caucasians, diabetic and obese patients. [5][8]Calciphylaxis is primarily associated with end stage renal diseases with increasing incidence and high mortality ,and associated with about 4 % of patient undergoing hemodialysis ,but similar extraskeletal calcifications can be seen in patients with metastatic calcification caused by sarcoidosis, Vitamin D supplementation, calcium based phosphate binders, hyperparathyroidism, milk alkali syndrome ,hypervitaminosis D and rarely in warfarin use, steroid use, weight loss, blood and albumin transfusion trauma, diabetes mellitus, chemotherapy induced protein C and S deficiency, Crohn disease, Alcoholic liver disease and malignancy.[7][9][10][11]

The mechanism is not well understood, but there are hypothesis depending on various risk factors.[2]Deficiency of ferin A (fetuin) and matrix G1a protein which are vascular calcification inhibitor factors, abnormality activities of NF-kB, RANK and RANK-L on osteoclasts and monocytes, osteoprotegerin are believed to play an important role in extraskeletal mineralization .[12][17] In Cushing disease, Chronic liver disease, and hyperparathyroid state there is activation of NF-kB or degradation of the NF-B inhibitory proteins leading increase expression of RANK-ligand with subsequent reduction in expression osteoprotegerin.[9][10][13][16]In case of warfarin, it acts by inhibiting vitamin K-dependent clotting factors carboxylation of matrix -G1a protein which further lead to reduce activity of the protein that inhibit calcification locally.[14][15]There is evidence of genetic involvement in Calciphylaxis and the genes are calcification promoter like Bone morphogenic protein 2 and 4 and osteocalcin [8][10][16][17]

The condition is characterized by skin mottling and induration in livedo reticularis pattern, black, leathery eschar in an ulcer with adherent black slough are found. The lesions are painful and extremely tender mostly seen in the lower limbs, abdomen, and buttocks. It can be secondarily infected by bacteria infection and associated with poor wound healing. Patients can also present with calcification of the heart leading to a diastolic heart failure in severe cases.

[10][12][17].The diagnosis can be made solely on clinical basis, but can be supported by skin biopsy which carries the risk of poor wound healing, superimposed bacteria infections(sepsis) and need for repeat biopsies because of high occurrence of nondiagnostic biopsies are greatly considered. In a survey of 1000 patients in the USA, 55% were diagnosed with skin biopsy, 45% solely on clinical grounds. [8][13]The skin biopsy usually shows mural small artery and vein calcification, fat necrosis (panniculitis), thrombus formation and occlusion without obvious inflammation. X-ray of the bone can be done, bone scintigraphy and Anti-nuclear antibody in very few patients [5] [13]].The patient in this review perfectly fits into the descriptions of Calciphylaxis. He is known hypertensive and diabetic patient with end stage renal failure on dialysis with characteristic painful skin lesions, not on warfarin with poor compliant to prescribed management.

Treatment of the underlying condition is key as the prognosis is generally poor even with specific medications. Increase the frequency of dialysis in patient with ESRD, adequate wound care and topical antibacterial, thrombolytic, Hyperbaric oxygen and Sodium thiosulfate are frequently employed.[6][8][13] There are non-orthodox treatment like maggot larval debridement in extensive ulcerations and use of plasma exchange. [14]The prognosis is very poor with annual mortality rate of 40 to 80%, despite involving multidisciplinary intervention from optimum nursing care, dermatologist, plastic surgeon, nephrologist, dieticians, and wound care specialist internist to psychologist. [8]

CONCLUSION

Calciphylaxis is a life-threatening disease associated with devastating complications. Its diagnosis mainly required clinical evaluation and should be highly suspected in a chronic renal failure patient presenting with new painful skin lesions. Skin biopsy, with histopathological examination and radiologic analysis may be necessary for the diagnosis of this disease. The patient met the criteria and had a good response to therapy.

The treatment of calciphylaxis required a multidisciplinary intervention involving pharmacotherapeutic management, wound care, surgical debridement, nephrologist, and routine dialysis in patients with underlying ESRD. The index patient enjoyed most of the multidisciplinary approach in the management but compliance was a great problem. Patients with calciphylaxis tend to have a very poor prognosis with a 5-year survival rate of less than 5% even with adequate care and management. Our patient 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 works.
Consent form signed by the patient, witness, and physicians.

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