Penile Calciphylaxis – A Rare, Yet Medically Treatable Disease

Abstract

Calciphylaxis or calcific uremic arteriolopathy (CUA) is an infrequent complication in patients with renal failure. Its manifestations range from ischemia to gangrene especially in areas of adiposity. Penile calciphylaxis is very rarely seen. Treatment can be medical or surgical. Sodium thiosulphate has shown to be an efficient treatment. Here were present a case of 74-year-old male who presented with penile calciphylaxis and was treated successfully with oral sodium thiosulphate.

Keywords: *Calciphylaxis, sodium thiosulphate*

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Introduction

Calciphylaxis[1] is an obliterative calcific vasculopathy most commonly occurring in end-stage renal disease (ESRD) patients on hemodialysis (HD) or peritoneal dialysis (PD) or renal transplant recipients. It typically presents as ischemic necrosis involving areas of adiposity in the body such as the trunk, buttocks, or proximal extremity. However, non-adipose regions can also be involved, and such patients can present with digital ischemia[2] and, rarely, penile gangrene.[3] Penile calciphylaxis is rare because of its rich vascular network, and the prognosis is also poor, with a reported overall mortality rate of 64% and mean time to death of 2.5 months.[4] Treatment involving the benefit of penectomy is still under debate. This is a rare entity with less than 60 cases reported in the literature.

Clinical History

A 74-year-old male, a known case of ESRD on continuous ambulatory peritoneal dialysis, Type 2 diabetes, and hypertension, was admitted with complaints of excruciating penile pain, burning micturition, and fever for 1 day associated with recent history of Foley's catheterization 10 days back when he sustained a minor injury to the glans penis. Examination showed an uncircumcised phallus with a black necrotic area on the distal glans without any erythema and no urethral discharge [Figure 1a and b]. The shaft and base of the penis were minimally tender with no other ischemic lesions in the body detected clinically.

Serum calcium and phosphate were 10.9 and 6.2 mg/dL, respectively. Intact parathyroid hormone (PTH) level was 1080 pg/mL (normal 15–65 pg/mL). Prior vasculitis and autoimmune workup were negative, and he had no history of steroid or warfarin intake. Urosepsis with calciphylaxis was suspected. Radiological studies in our patient showed calcification of cavernosal arteries and dorsal penile arteries.

After discussing about the condition and treatment including conservative and surgical management options with the patient and his relatives, they opted for conservative management with wound care, and pain management was planned. The patient needed intravenous (IV) formulation of sodium thiosulfate (STS). Unfortunately, it is not available in the market. Oral STS is, however, available in the market for nonmedical industrial use. After obtaining consent from the patient and his relatives, we administered 2 molars masses of STS (5.2 g) per day.

As in the olden days, we ordered the hospital pharmacist to make this formulation. His penile lesions were healing and symptomatically he got better. The dose was gradually escalated, and he was discharged home after treatment for 2 weeks. He did not have any side effects

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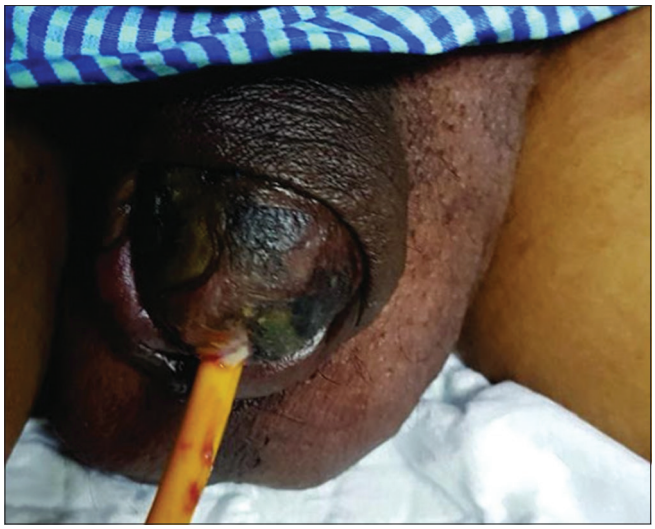

Figure 1: After therapy: The penile lesions have rapidly healed

due to the medication, and his bicarbonate levels were maintained. Pain resolved within 2 weeks, the lesions healed completely in 12 weeks, and STS was discontinued. Patient was on regular follow-up for the next 6 months, when no further lesions were found. He had an optimal mineral bone disease care, including a low-phosphorus diet, appropriate medications, adequate dialysis, cinacalcet, and sevelamer. His calcium, phosphorus, and iPTH levels normalized gradually. Unfortunately, the patient passed away the next year due to acute myocardial infarction.

Penile necrosis[5] due to vasculopathy is seen in patients with diabetic ESRD patients on HD. It was first described by Bryant and White in 1898, though the term calciphylaxis was coined by Hans Seyle in 1962. It is also called as calcemic uremic arteriolopathy. Also, 1%–4% of patients with ESRD on hemodialysis or renal transplant recipients can have calciphylaxis, which is characterized by medial calcification and intimal fibrosis of medium and small arteries. It has a high mortality rate of >60% within 6 months, indicating grave prognosis[4] Calciphylaxis is rarely described in patients on peritoneal dialysis. The hypothesized mechanism[6] is due to reduction in the arteriolar blood flow, which is caused by calcification, intimal fibrosis, and thrombus formation primarily involving the media of dermo-hypodermic small arterioles and capillaries (600 µm in diameter), with fibrosis and thrombosis leading to tissue necrosis.

It can affect proximal or distal tissues causing cutaneous necrosis, which is a characteristic clinical presentation. Most common sites affected are buttocks, thighs, and, less frequently, the penis. Macroscopically, it presents with skin ischemia and necrosis and is histologically characterized by calcification of arterioles in dermis and subcutaneous adipose tissue. Isolated gangrene of the penis[7] represents a localized manifestation of vascular calcification, which occurs in patients with ESRD. Diabetic vasculopathy can also contribute to the disease, especially with superimposed infection.

Risk factors[8-10] include the following:

- hyperphosphatemia;
- medications including warfarin, calcium-based binders, vitamin D analogs, systemic glucocorticoids;
- female sex;
- obesity (body mass index [BMI >30]);
- hypercoagulable states such as protein C and S deficiency and antiphospholipid syndrome;
- hypoalbuminemia;
- diabetes;
- longer dialysis vintage;
- inflammatory and autoimmune conditions;
- recurrent skin trauma; and
- high phosphate concentration.

When to Suspect?

Calciphylaxis should be suspected in patients with painful, non-ulcerating, subcutaneous nodules or plaques. Nonhealing ulcers and/or necrosis are most commonly present in the thigh and other areas of increased adiposity. Additional clinical reasons to suspect the diagnosis are increasing calcium × phosphate (Ca × P) product and PTH levels over the preceding several months and/or concurrent warfarin use. The initial cutaneous changes present as tender serpiginous indurated plaques or livido reticularis with palpable subcutaneous deposits of calcium or thickened blood vessels. Ulceration is a late presentation. The hallmark is severe pain that is unresponsive to analgesics.

How to Diagnose

Gold standard for diagnosis is skin biopsy. However, a skin biopsy is contraindicated in patients who have infected lesions or lesions in extremities.[11] Imaging modalities that have been used include plain radiographs, high-resolution computed tomography (CT) scans, mammography, and bone scans; widespread calcification of vascular smooth muscles and fibrinous thrombi occluding vessel lumina in the absence of inflammation confirms the diagnosis.[12,13]

Hence, diagnosis is clinical: painful, non-ulcerating subcutaneous nodules or plaques, nonhealing ulcers and/or necrosis, which are most commonly present in the thigh, areas of increased adiposity, and the penis. Calciphylaxis should be differentiated from the diseases that could have similar clinical presentations such as warfarin skin necrosis, cryoglobulinemia, vasculitis, cellulitis, nephrogenic fibrosing dermopathy, and cholesterol l embolization. Differential's penile lesions[14] include balanitis, Bechet's syndrome, sexually transmitted diseases, malignancy, Peyronie's disease, and syringoma calcification, which are all unlikely in the patient presented here based on history of physical examination, laboratory results, and imaging.

How to Treat?

Treatment usually consists of a combined medical and surgical approach. The surgical management involving circumcision or partial penectomy versus debridement has been controversial, and internal iliac artery stent, revascularization surgery, and parathyroidectomy have all been described as surgical therapies. There are no guidelines for the optimal treatment of CUA. Treatment consists of dialysis, wound care, correction of calcium–phosphate abnormalities, cinacalcet, parathyroidectomy (if the PTH is elevated), and supportive care. The most recent treatment advance may be the use of STS, with increasing reports of successful reversal of pain and ischemic tissue damage.

Few case reports have shown that penile calciphylaxis was successfully treated with STS.[15-17]

The possible mechanism of STS is unknown, but it is speculated that it is due to chelation of calcium ions, dissolution of insoluble calcium deposits, and restoration of endothelium; also, its role as a potent antioxidant has been noted to promptly decrease pain. In a retrospective study of 27 patients with calciphylaxis in other locations, 52% resolved with STS administration.[18] STS can be administered IV, intralesional, or topically. Intraperitoneal administration is usually not recommended due to risk of chemical peritonitis. The ideal dose[19] of IV STS is 25 g diluted in 100 mL of 0.9% normal saline administered over 30–60 min thrice weekly (for HD patients, it is to be given during the last hour of each hemodialysis session) for 3 months, followed by a maintenance oral dose of 2.6 g three times a week (for HD patients, after each hemodialysis session) till the complete resolution of symptoms. Oral bioavailability of STS is 10%. So, mostly, the oral form is not used for treatment. The common side effect is anion gap acidosis, and oral formulation causes emesis and diarrhea. Close control of phosphatemia with phosphate-binding agents is crucial to prevent the clinical development of penile calciphylaxis.

Calciphylaxis is a treatable disease with a high morbidity and mortality. Early recognition of the condition, appropriate treatment with analgesics, and prevention and treatment of the infection by wound care with antibiotics and STS are critical to allow wound healing, which significantly decreases morbidity and mortality in these patients.

In conclusion, calciphylaxis in ESRD is usually found in hemodialysis patients, but rarely discovered in peritoneal dialysis patients. It is characterized by calcification of subcutaneous arteries and infarction of the subcutaneous cellular tissue and overlying skin. The diagnosis is usually based on clinical signs, symptoms, and calcification in radiology examination. Although the treatment is still debatable, however, we decided to treat the patient with partial penectomy, debridement, and antibiotic. Despite its poor prognosis, the patient in this case showed improvement after the procedure. Proper studies are needed to further investigate calciphylaxis in peritoneal dialysis patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest

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