

## Calciophylaxis leading to penile necrosis

Imran Haider,<sup>1</sup> Muhammad Siddiqui,<sup>2</sup> Wisam Naji,<sup>3</sup> Maria Sheikh,<sup>4</sup> Ayesha Waqar<sup>5</sup>

### Abstract

Penile gangrene is a rare disease. It represents a poor prognostic sign in end stage renal disease (ESRD) patients and an indicator of metastatic vascular calcification. Pathogenesis of this life threatening condition is not clearly understood and treatment is also controversial.

We describe the case of a 61-year-old man known to have diabetes mellitus, chronic renal failure on haemodialysis, who was complaining of worsening groin pain for 4 weeks. On examination dry gangrene of glans penis was noted. Cultures from the penis showed multiple organisms. Computed tomography (CT) showed diffuse calcification of external and internal iliac arteries. Later, he developed calciophylaxis of right anterior thigh. His overall condition did not improve in spite of adequate antibiotics and he was shifted to intensive care unit (ICU) where he required high doses of vasopressors. Clinically he kept deteriorating and passed away due to septic shock.

**Keywords:** Calciophylaxis, Penile, Renal disease, Necrosis.

### Introduction

Calciophylaxis is a rare but frequently reported disease in dialysis patients. Penile calciophylaxis is rare and has poor outcome unless treated aggressively. There are few case reports and case series reported from all over the world including developing countries.<sup>1,2</sup> In patients of chronic renal failure (CRF), it is an indicator of extensive vascular calcification due to secondary hyperparathyroidism also known as calcific uraemic arteriopathy (CAU), which usually affects distal extremities. Penile gangrene secondary to various causes like priapism, vasculitis, penile prosthesis, Fournier's gangrene, and uraemia has been reported. Treatment is complicated and ranges from conservative measures to more aggressive approaches such as penectomy. We are presenting a dialysis dependent diabetic patient who was diagnosed with penile gangrene due to possible calciophylaxis and in spite of appropriate medical management, his condition deteriorated and he expired.

.....  
<sup>1-4</sup>St. Luke's Hospital, St. Louis, MO, USA, <sup>5</sup>Great River Hospital, Burlington, Iowa, USA.

**Correspondence:** Imran Haider. Email: drimranhaider6@yahoo.com

### Case Report

A 61-year-old African American male was seen at the Saint Luke's Hospital, in April 2013, with past medical history of diabetes mellitus, ischaemic cardiomyopathy (EF of 20-25%, status post biventricular defibrillator), chronic atrial fibrillation, peripheral vascular disease, ESRD who had been on maintenance peritoneal dialysis for one year presented with worsening groin pain for one month. He was shifted on haemodialysis one month ago because of fluid overload and scrotal oedema from peritoneal dialysis.

He was seen in dialysis unit one day before the admission when he had a temperature of 38.1°C during dialysis session. He was pancultured and given vancomycin and cefepime. He tolerated dialysis well but was somnolent and lethargic after that. On presentation, he was confused, having severe pain in his groin area with temperature of 37.6°C, blood pressure of 93/51 mmHg and pulse rate of 84 bpm. On examination, groin area was foul smelling, the glans and the skin involving the coronal sulcus was black, hard, and firm, suggestive of dry gangrene. There was no erythema or fluctuance.

Initial data showed haemoglobin and haematocrit of 10.2g/dl and 31.3%, white blood cell (WBC) count 11.5 K/ul, platelet count 129 K/ul, sodium 141mmol/L, potassium 4.3mmol/L, chloride 97mmol/L, bicarbonate 26mmol/L, glucose 120mg/dl, BUN 22mg/dl, creatinine 3.6mg/dl, albumin 2.9g/dl, total protein 6.5g/dl, ALT 26 U/L, AST 43 U/L, total bilirubin 2.9g/dl, INR was 1.3.

The patient was evaluated by infectious disease specialist and was started on intravenous (I/V) cefazolin and metronidazole along with I/V hydration. Staff urologist and nephrologist were consulted and the initial plan was to watch him closely and consider for partial penectomy but the patient refused any surgical interventions. Although his blood, peritoneal and urine cultures were negative, cultures from the penis showed heavy growth of corynebacterium, staphylococcus aureus and gamma haemolytic streptococci. Later he also developed discolouration in the anterior aspect of his right thigh, which was hard and very tender to touch, consistent with calciophylaxis. Para thyroid hormone (PTH) level was 260pg/ml (normal= 11-54pg/ml). A clinical diagnosis was made. Optimally, a biopsy should



**Figure:** CT scan showing calcification of external and internal iliac arteries.

have been performed, but because of the potential complications that was not considered. We were not able to get the sodium thiosulfate for him due to unavailability; Coumadin was held.

His condition was deteriorating; later he was transferred to intensive care unit (ICU) because of hypotension and worsening mental status. He was started on levophed and vasopressin. CT of abdomen and pelvis showed diffuse aortic calcification and dense calcification of internal and external iliac arteries (Figure). His WBC count kept rising and his antibiotic coverage was broadened to meropenem and vancomycin. The patient was not improving in ICU and required high doses of vasopressors. On the 14th day, his breathing became very agonal. We discussed his condition with the family and they did not want any resuscitative measures. The patient passed away; cause of death was likely septic shock.

## Discussion

Calciphylaxis is a rare and serious disorder of smaller arteries, arterioles and capillaries. The characteristic "subcutaneous necrosis" is a result of medial calcification of the arterioles leading to ischaemia. Most commonly it occurs in haemodialysis dependent patients who have ESRD or renal transplant recipients. Other less common non-renal etiology include primary hyperparathyroidism.<sup>3</sup>

Isolated gangrene of the penis represents a localized manifestation of vascular calcification which occurs in patients with ESRD. Diabetic vasculopathy can also contribute especially with superimposed infection, as in index case. By conducting a review of the medical literature, very few of these cases were found to be reported.

Although pathogenesis is not clearly understood, abnormalities in mineral metabolism that predispose to vascular calcification might play a role. Histologically

there is calcific infiltration of tunica media with subsequent intimal hyperplasia leading to marked luminal compression.<sup>4</sup>

Some patients may have increased levels of calcium, phosphorous, PTH, and  $[Ca^{2+}] \times [PO_4^{3-}]$  product. Risk is higher when product exceeds 70 mg<sup>2</sup>/dl<sup>2</sup>; the product was 65.4mg<sup>2</sup>/dl<sup>2</sup> in our case.

The characteristic ischaemic skin lesions and their distribution usually suggest diagnosis of calciphylaxis. If there are no contraindications, skin biopsy is recommend, which shows medial calcification of the arterioles with intimal hyperplasia leading to arterial occlusion and ischaemia. Other diagnostic modalities are bone scans and x-ray mammographic techniques.<sup>5</sup> Treatment of penile gangrene associated with calciphylaxis ranges from conservative measurements to more aggressive approaches as total or partial penectomy with or without subtotal parathyroidectomy. Abnormalities in calcium and phosphorus concentrations should be corrected, with lowering of the Ca X P product below 55mg<sup>2</sup>/dl<sup>2</sup>. Dialysis dose should also be increased among those with inadequate dialysis.

Among dialysis patients with hyperphosphataemia, non-calcium containing phosphate binders are suggested,<sup>6</sup> and those with elevated PTH levels, use of cinacalcet is advisable.<sup>7</sup> Warfarin should also be discontinued.

Intravenous sodium thiosulfate has been used successfully in patients with calciphylactic necrotic lesions in ESRD.<sup>8</sup> With the progression of gangrene and sepsis, penectomy becomes inevitable. Among patients with refractory hyperparathyroidism, prompt parathyroidectomy may be considered. However, a retrospective case control study did not show a survival advantage as compared to non-surgically-treated patients.<sup>9</sup>

A number of novel and experimental therapies have been evaluated in calciphylaxis. These include; administration of bisphosphonate,<sup>10</sup> hyperbaric oxygen, prednisone, low-dose infusion of tissue plasminogen activator,<sup>11</sup> and intracavernosal prostaglandin.<sup>12</sup>

A high mortality rate is reported even with aggressive management given the severity of associated systemic illness and infection is the leading cause of death.

## Conclusion

Patient in the index case had multiple comorbidities, septic shock, local ischaemia superimposed by calciphylaxis, and showed disease progression in spite of appropriate medical management; predicting a poor

prognosis. Analyzing the case retrospectively, may be more aggressive treatment with triple antibiotics and surgical debridement or perhaps partial resection might have given us better results but unfortunately the patient refused. Because of high mortality of this life threatening and disabling condition, prevention appears to play the key role in management.

## References

1. Bappa A, Hakim F, Ahmad M, Assirri A. Penile gangrene due to calcific uremic arteriopathy. *Ann Afr Med* 2011; 10: 181-4.
2. Kjaerskov MW, Comstedt LR, Bygum A, Yderstraede KB. Penile calciphylaxis. *Ugeskr Laeger* 2009; 171: 1864-5.
3. Nigwekar SU, Wolf M, Sterns RH, Hix JK. Calciphylaxis from non uremic causes: a systematic review. *Clin J Am Soc Nephrol* 2008; 3: 1139-43.
4. Weenig RH. Pathogenesis of calciphylaxis. *Am Acad Dermatol* 2008; 58: 458-71.
5. Bleibel W, Hazar B, Herman R. A case report comparing various radiological tests in the diagnosis of calcific uremic arteriopathy. *Am J Kidney Dis* 2006; 48: 659-61.
6. Don BR, Chin AI. A strategy for the treatment of calcific uremic arteriopathy (calciphylaxis) employing a combination of therapies. *Clin Nephrol* 2003; 59: 463-70.
7. Robinson MR, Augustine JJ, Korman NJ. Cinacalcet for the treatment of calciphylaxis. *Arch Dermatol* 2007; 143: 152-4.
8. Cicone JS, Petronis JB, Embert CD, Spector DA. Successful treatment of calciphylaxis with intravenous sodium thiosulfate. *Am J Kidney Dis* 2004; 43: 1104-8.
9. Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR. Calciphylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol* 2007; 56: 569-79.
10. Price PA, Omid N, Than TN, Williamson MK. The amino bisphosphonate ibandronate prevents calciphylaxis in the rat at doses that inhibit bone resorption. *Calcif Tissue Int* 2002; 71: 356-63.
11. el-Azhary RA, Arthur AK, Davis MD, McEvoy MT, Gibson LE, Weaver AL, et al. Retrospective analysis of tissue plasminogen activator as an adjuvant treatment for calciphylaxis. *JAMA Dermatol* 2013; 149: 63-7.
12. Singhinolfi MC, De Stefani S, Mofferdin A, Micali S, Celia A, Bianchi G. Intracavernosal prostaglandin E1 infusion in diabetes with associated ischemic necrosis of the glans penis. *J Urol* 2004; 17:238.