Glans penis necrosis caused by calcific uremic arteriolopathy

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Abstract

Calcific uremic arteriolopathy (CUA) or calciphylaxis is a syndrome characterized by calcification of vessels located in the dermis and adipose tissue. It commonly occurs in patients with diabetes mellitus, hypertension, and end-stage renal disease. Clinical presentation generally begins with severe pain, followed by the presence of liveloid or purpuric plaques. Later the formation necrotic ulcers occur. This condition is associated with a poor prognosis, with a high rate of mortality within months of the diagnosis. Penile involvement is an uncommon but severe manifestation. We present an 81-year-old man with a history of diabetes mellitus, hypertension, and end-stage renal disease with a one-month evolution of painful necrotic ulcers on his glans penis. He was diagnosed with CUA. Owing to infection complicated by sepsis; penectomy was performed. Unfortunately, the patient died of myocardial infarction during his hospitalization.

Keywords: penile calciphylaxis, calcific uremic arteriolopathy, glans necrosis

Introduction

Calcific uremic arteriolopathy (CUA) also known as calciphylaxis is a syndrome characterized by vascular occlusion and calcification of the blood vessels located in the dermis and adipose tissue. This condition predominates in patients with end-stage renal disease. Its prevalence in this population is one to 4% and is more common in those managed with peritoneal dialysis. Other associated factors are obesity, diabetes mellitus, hypercalcemia, hyperphosphatemia, and hyperparathyroidism [1].

Anatomic affected areas are divided as central (areas rich in adipose tissue e.g. abdomen and thighs) or peripheral (areas with less adipose tissue, e.g. fingers). Patients suffering with this condition have a poor prognosis; 50% die during the first year [2].

Case Synopsis

An 81-year-old man with a history of long-standing type 2 diabetes mellitus, hypertension, and end-stage renal disease was managed with peritoneal dialysis for the last two years. He was hospitalized for a one-month history of two 1.5cm necrotic ulcers with fibrinous base on his penis; one was located near the external urethral meatus, the other on the glans penis. They exhibited purulent discharge and

Figure 1. *Glans penis necrosis*

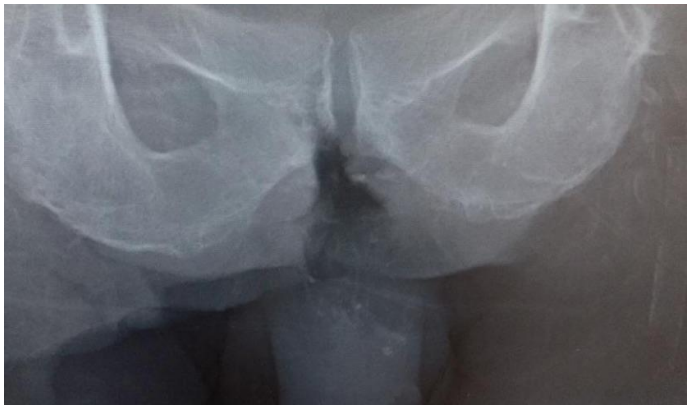

Figure 2. *Calcified vessels on penile radiography.*

decreased temperature (**Figure 1**). The patient described them as very painful. Prior to his hospitalization, he was managed with topical antibiotics without clinical response. He was febrile and had tachycardia; the remaining physical examination was without abnormalities.

The patient´s workup showed leukocytosis of $12\times10^3/\mu L$ with neutrophil predominance, serum calcium of 8.4mg/dl, phosphorus of 3.14mg/dl, calcium-phosphate product of $26.56mg^2/dl^2$ (normal range $<70mg^2/dl^2$), parathyroid hormone (PTH) of 85pg/ml (normal range 10-65pg/ml), creatinine of 6.76mg/dl, urea of 96mg/dl, and urea nitrogen of 44mg/dl. Wound culture from one of the ulcers was positive for *Klebsiella pneumoniae* resistant to beta-lactam antibiotics. With the presumptive diagnosis of CUA a plain penis radiograph was taken, revealing calcification of the penile vasculature (**Figure 2**).

A change from peritoneal dialysis to hemodialysis was performed. Treatment with meropenem and sodium thiosulfate was initiated. Despite medical therapy, the patient persisted with fever, tachycardia, and a tendency to hypotension. He had two points on his Sepsis Related Organ Failure Assessment (SOFA) and spread of the necrotic lesions, covering all the glans. The urology department decided to perform a partial penectomy. After the procedure, the patient had no signs of an ongoing infection and he did not develop new necrotic lesions. The pathological report confirmed the presence of small arterial calcification, narrowing, and fibrous expansion of the intima of the lumen. The vessel size was 380 micrometers (**Figure 3**). These findings were compatible for CUA. Unfortunately, the patient died during his hospitalization related to a myocardial infarction.

Case Discussion

Penile necrosis caused by CUA is uncommon. Clinical presentation generally begins with pain, followed by the appearance of well-delineated purpuric, liveloid, or violaceous plaques of variables sizes, which evolve to necrosis and ulceration. The condition can be localized to the glans or other genital areas [3].

The underlying pathogenesis in this condition is poorly understood. There is a deficiency of carboxylated matrix Gla protein (MGP), a potent calcification inhibitor and under normal conditions inhibits bone morphogenetic protein 2 (BMP-2) and bone morphogenetic protein 4 (BMP-4), which are procalcifying factors. With no carboxylated MGP, BMP-2 and BMP-4 levels rise. There is also down-regulation of fetuin-A, another calcification inhibitor involved in the transportation of mineral nanocrystals. In addition, in adipose tissue, mature adipocytes exposed to elevated levels of phosphate, induce calcification of vascular smooth muscle cells [4].

Although histological findings are the gold-standard, the skin biopsy may show variable changes because of the high infection risk, bad healing, and potential extension of the necrotic lesions [5]. Several series have acknowledged the use of plain

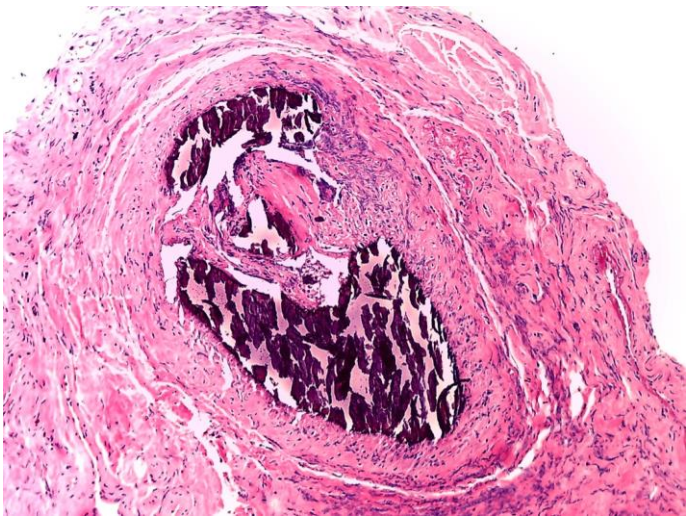

Figure 3. *Calcification of small sized arteries with perivascular inflammatory cells. H&E, 20×.*

radiographs or computed tomography as non-invasive and useful diagnostic interventions for visualizing the calcified vasculature [6]. In patients who undergo biopsy or surgical intervention, histological findings exhibit an intimal fibroblastic proliferation of small-medium sized arteries, luminal narrowing, and calcification, identified as basophilic material within the lumen [7]. Mönckeberg arteriosclerosis is in the differential diagnosis., However, in this case there is calcification of the tunica media in small-medium sized arteries [8].

Serum calcium and phosphorus can be elevated, but the former is normal in 86% and the latter in 40% of the cases [9]. The calcium-phosphate product cannot confirm or exclude CUA because it has a 21% sensitivity and a 95% specificity. More than 50% of the patients with CUA have a product less than 50 [10]. PTH levels are usually high as a result of secondary hyperparathyroidism. However, the expected levels for this condition are usually 2-9 times the upper normal limit [11]. This patient had 85pg/ml, so the diagnosis of Adynamic Bone Disease (ABD) could be an underlying associated disease linked to CUA. The adynamic bone disease is characterized by a low-bone turnover and PTH suppression. It prevails in patients with end-stage renal disease and has been associated with CUA [12]. In this entity PTH levels are <150pg/ml; its presence has been linked to coronary calcifications [13].

Penile calciphylaxis is a predictor of a bad prognosis: 60% of the patients die within the same year, generally within the next 2.5-months from diagnosis. Most of the patients die from infection. Surgical treatment is controversial if performed, the only indication is for uncontrollable pain in spite of analgesics or infection without response to antibiotic therapy. Survival of patients with partial-complete penectomy is 42.9% versus 52% in those without [14].

One of the main medical therapies indicated in calciphylaxis is sodium thiosulfate, a calcium chelating agent with vasodilator activity. With this treatment, complete resolution in 26-52%, and partial in 19% of patients has been reported [4]. For those patients with ABD, therapy includes stopping medications favoring PTH suppression such as calcitriol and calcium-mimetic agents such as cinacalcet. In addition, patients are generally changed from peritoneal dialysis to hemodialysis [15].

Conclusion

Penile CUA is associated with a bad prognosis. Even though sepsis is the main cause of death in these patients, one must consider the underlying cardiovascular burden, especially when associated with ABD, which potentiates the risk of vascular complications. Our patient died from a myocardial infarction rather than sepsis

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. Malthouse T, Lam W, Brewin J, Watkin N, Ayres B, Nitkunan T. Penile lesion in end-stage renal failure -cancer or otherwise?: Calcific uremic arteriolopathy presenting with a penile lesion. *Can Urol Assoc J.* 2015;9(3-4):136-7. [PMID: 26085872].
2. García-Lozano JA, Ocampo-Candiani J, Martínez-Cabriales SA, Garza-Rodríguez V. An Update on Calciphylaxis. *Am J Clin Dermatol.* 2018;19(4):599-608. [PMID: 29808451].
3. Marenco JL, Saíz R, Suarez A, Castiñeiras J. Penile necrosis as clinical presentation of systemic Calciphylaxis: Report of two cases and bibliographic review. *Arch Esp Urol.* 2015; 68(5):505-8. [PMID: 26102055].
4. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. *N Engl J Med.* 2018;378(18):1704-14. [PMID: 29719190].
5. Abrahams JL, Maranda EL, Nichols AJ. Necrosis of the glans penis secondary to calciphylaxis. *Clin Exp Dermatol.* 2018;43(5):645-647. [PMID: 29740852].
6. Morrison M, Merati M, Ramirez J, Cha HC, LaFond A. Penile calciphylaxis diagnosed with computed tomography. *J Eur Acad Dermatol Venereol.* 2016;30(2):352-3. [PMID: 25363283].
7. Bashir SO, Aamer MA, Omer HA, Morsy MD. Penile calcific uremic arteriolopathy occurring postparathyroidectomy in a hemodialysis patient. *Saudi J Kidney Dis Transpl.* 2016;27(6):1265-1269. [PMID: 27900978].
8. Castling B, Bhatia S, Ahsan F. Mönckeberg's arteriosclerosis: vascular calcification complicating microvascular surgery. *Int J Oral Maxillofac Surg.* 2015;44:34-6. [PMID: 25457834].
9. Brandenburg VM, Kramann R, Rothe H, et al. Calcific uraemic arteriolopathy (calciphylaxis): data from a large nationwide registry. *Nephrol Dial Transplant.* 2017; 32: 126-32. [PMID: 26908770].

10. Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR. Calciphylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol*. 2007;56(4):569-79. [PMID: 17141359].
11. Ketteler M, Block GA, Evenepoel P, et al. Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder: Synopsis of the Kidney Disease: Improving Global Outcomes 2017 Clinical Practice Guideline Update. *Ann Intern Med*. 2018;168(6):422-430. [PMID: 29459980].
12. Mawad HW, Sawaya BP, Sarin R, Malluche HH. Calcific uremic arteriolopathy in association with low turnover uremic bone disease. *Clin Nephrol*. 1999;52(3):160-6.
13. Sista SK, Arum SM. Management of adynamic bone disease in chronic kidney disease: A brief review. *J Clin Transl Endocrinol*. 2016;5:32–35. [PMID: 29067232].
14. Yang TY, Wang TY, Chen M, et al. Penile calciphylaxis in a patient with end-stage renal disease: a case report and review of the literature. *Open Med(Wars)*. 2018;13:158-163. [PMID: 29756051].
15. Brandenburg VM, Floege J. Adynamic bone disease—bone and beyond. *NDT Plus*. 2008;1(3):135–147. [PMID: 25983860].