Inflammation and infection

Penile calciphylaxis treated with daily Tadalafil: Case report

Carlos Castro Moya\textsuperscript{a}\textsuperscript{*}, Aníbal Salazar Huerta\textsuperscript{b}, Isidora Salazar Sarrat\textsuperscript{c}

\textsuperscript{a}Hospital de Carabineros, Chile
\textsuperscript{b}Clínica Dávila, Chile
\textsuperscript{c}Facultad de Medicina Universidad de los Andes, Chile

ARTICLE INFO

Keywords:
Penile calciphylaxis
End-stage renal disease
Tadalafil

ABSTRACT

Calciphylaxis is a rare vascular disorder, characterized by a progressive systemic calcification of dermo-hypodermic arterioles. We present a case of end-stage renal disease (ESRD) patient on Hemodialysis, with calciphylaxis, whose clinical manifestation were ulcerated lesions on the penis, treated with phosphodiesterase-5 (PDE5) inhibitors, with good clinical response.

INTRODUCTION

Calciphylaxis, also known as Calcific Uraemic Arteriolopathy, is a rare vascular disorder, with high morbimortality, characterized by a progressive systemic calcification of dermo-hypodermic arterioles, affecting almost exclusively hemodialysis or renal transplant patients. Penile calciphylaxis generally manifests as distal necrosis, and although multiple treatments have been proposed, there is no standardized management.

Case presentation

57-year-old patient, with poorly controlled diabetes mellitus and hypertension, in whom hemodialysis treatment was started because of ESRD caused by diabetic nephropathy. He was referred to our institution for the appearance of 3 painful, nonhealing ulcers with a yellowish-white necrotic pseudomembrane that covered 50% on the glans penis during a 2-month period. (Fig. 1).

Laboratory results highlights serum creatinine of 5.7 mg/dl, normal calcium phosphate product and parathormone levels of 351 pg/ml [10.8–79.4 pg/ml].

Pelvis X-Ray shows a calcified image of the penile vessels (Fig. 2).

Treatment with Tadalafil was started to increase and improve glans irrigation, achieving a good clinical response after 6 months, with almost total remission of the ulcerated lesions present in the glans and complete pain reduction (Fig. 3).

After one year 6 months of the consultation in the urology service, the patient remains in three-week hemodialysis, under control by the nephrology team and with periodic controls by the urology team, maintaining a daily dose of Tadalafil, without recurrence of the ulcers.

Discussion

Definition

Calciphylaxis, also known as Calcific Uraemic Arteriolopathy, is a severe rare vascular disease, with high morbimortality, characterized by a progressive systemic calcification of dermo-hypodermic arterioles, with ischemic necrosis of skin and soft tissues,\cite{1} prevalence fluctuates between 1 and 4% of ESRD patients on hemodialysis, affecting almost exclusively hemodialysis or renal transplant patients.\cite{1}

Etiopathogenesis

The pathogenesis for calciphylaxis remain poorly understood, but it is attributed to several risk factors, secondary hyperparathyroidism stands out, and elevation of calcium phosphate product, with normal or elevated calcium levels. On ESRD, vitamin D production is altered, causing a lower absorption of calcium in the intestine, producing hypocalcemia, which stimulates the production of parathormone, causing secondary hyperparathyroidism, generating greater bone resorption and hyperphosphatemia, all these alterations of phosphocalcic metabolism can promote vascular calcifications.

Another theory is the deregulation of calcium deposition in cutaneous vessels, triggered by a decrease in endogenous calcification inhibitory factors, as serum fetuin-A and Osteoprotegerin\cite{2}, produced by the persistence of inflammatory processes. In turn, the elevation of proinflammatory cytokines such as interleukin 6 and tumor necrosis factor alpha cause endothelial dysfunction, calcification and atherosclerosis.
Histopathology shows a small vessel vasculopathy, with mural calcification and intimal hyperplasia, extravascular calcium deposit, ischemic vaso-oclusion and thrombosis, generating ischemia, of cutaneous vessels and subcutaneous tissues, being able to affect other parenchyma.1(2)

**Histopathology**

Histopathology shows a small vessel vasculopathy, with mural calcification and intimal hyperplasia, extravascular calcium deposit, ischemic vaso-oclusion and thrombosis, generating ischemia, of cutaneous vessels and subcutaneous tissues, being able to affect other parenchyma.1(2)

**Diagnosis**

Clinically, it presents as nodular skin lesions and violaceous, purpuric or ecchymotic, pruritic or painful patches, evolving to necrotic ulcers.

The diagnosis is confirmed with radiological and histological study. The most sensitive radiological procedure is a radiography using the mammography technique.1

The laboratory may be in normal parameters, not excluding the diagnosis, low serum calcium levels may be due to the precipitation of calcium with phosphate in the blood vessels and other sites. It should be noted that the CaXP product greater than 70 has a specificity of 21% and a sensitivity of 95% for the diagnosis of calciphylaxis.2

The definitive diagnosis will be confirmed after the histological study, but the realization of skin biopsies has been ample reason for debate given the risk of superinfection or local dissemination of the ulcer.3

Differential diagnoses include vasculitic syndromes, cryoglobulinemia, atheroembolic disease, coumarin necrosis, disseminated intravascular coagulation, pyoderma gangrenosum, antiphospholipid syndrome, cellulitis, necrotizing fasciitis, infectious endocarditis, but none of these cases present arterioles calcification.2(3)

**Penile calciphylaxis**

Generally, penile calciphylaxis manifests as distal necrosis, in patients with ESRD on hemodialysis or renal transplantation. Penile necrosis is mainly associated with systemic diseases such as diabetes mellitus, hypertension and because of the placement of penile prostheses. Penile calciphylaxis has a reported incidence of 6% in patients with ESRD.4

**Treatment**

Once the vascular deposits of Calcium have been produced, it is irreversible and the therapeutic measures are not very effective, Phosphate chelators, such as Sevelamer or Cinaclet, have been used in patients on dialysis with secondary hyperparathyroidism, and patients who do not respond to medical treatment can be candidates to parathyroidectomy.1

Bisphosphonates have an inhibitory effect on osteoclastic activity and bone resorption, in addition to inhibiting the secretion of proinflammatory cytokines at the level of the vascular wall.

**Phosphodiesterase-5 inhibitors**

PDE5 inhibitors, main phosphodiesterase in the corpus cavernosum, hydrolyze the Cyclic Guanosine Monophosphate, producing relaxation of the smooth muscle, allowing a greater blood flow to the penis, which is why it is used in erectile dysfunction.

**Prognosis**

Although calciphylaxis is infrequent, it is a serious pathology that, despite dialysis techniques, has a poor prognosis, with an estimated one-year survival rate close to 45.8%. The high mortality is due to the superinfection of the lesions and sepsis.

**Conclusions**

Calciphylaxis is a disease that mainly affects patients with ESRD in hemodialysis. Given the low effectiveness of current treatments and their high lethality, efforts should be increased in the prevention of modifiable risk factors and in the early recognition of the disease.

Penile calciphylaxis requires an integral and multidisciplinary management, where the search of new therapeutic alternatives to
optimize the management using different mechanisms is necessary, enhancing the tissue blood supply, with the purpose of prolonging the survival, anatomical integrity and quality of life, agreeing with the premise of the most aggressive surgical treatment in patients with superinfected lesions.

Due to the decreased blood flow given by arteriolar calcification in penile calciphylaxis, we have thought about increasing the flow with PDE5 inhibitors, we believe that the use of Tadalafil may be helpful in patients diagnosed early and before the necrosis is extensive.

Conflict of interest

None.

References

1. Polaina Rusillo M, Sanchez Martos M, Biechy Baldan M, Liebaña Cañada A. Calciphylaxis Semin Fund Esp Reumatol. 2009;10(4):124–127.
2. Zapata-González F, Del Río-Cobaleda DY, Ruiz AC. Calciphylaxis, reporte de un caso. Rev Cés Med. 2013;27(2):235–241.
3. Rojas Estrada J, Castelo Villalón X, Alfonso Sat F, Semanat Vaillant D. Arteriopatía calcificante urémica. Rev Cuba Med. 2011;50(2):209–215.
4. Bolio-Laviada FM, Zamora-Varela FR, Carvajal-García y R. Necrosis de pene por calcificosis en paciente nefrópata. Rev Mex Urol. 2014;74(2):108–111.
5. Herrera Muñoz S, Buitrago Villa C, Serna Toro M, Rostrepo Valencia C. Arteriopatía calcificante urémica, reporte de un caso tratado con tiosulfato de sodio. Rev. Colomb. Nefrol. 2015;21(1):63–70.