Calciphylaxis: a rare but potentially fatal event of chronic kidney disease. Case report*

Calcifilaxia: complicação rara, mas potencialmente fatal da doença renal crônica. Relato de caso

Silvio Alencar Marques[1]
Thais Jung Mendaçolli[2]
Mariângela Esther Alencar Marques[4]
Aline Cruz Kakuda[2]
Luciana P. Fernandes Abbade[3]

DOI: http://dx.doi.org/10.1590/abd1806-4841.20132280

Abstract: Calciphylaxis or calcific uremic arteriolopathy is a rare cutaneous-systemic disease occurring in patients with advanced chronic kidney disease. The classical clinical picture is that of a necrotic and progressive skin ulcer of reticular pattern, mostly in the lower legs and susceptible to local infection. It is a product of mural calcification and occlusion of cutaneous and sub-cutaneous arteries and arterioles. The authors report the case of a 73-year-old male patient in his late stage of renal disease presenting severe necrotic cutaneous ulcers on lower legs followed by local and systemic infection and death due to sepse after parathyroidectomy.
Keywords: Calciphylaxis; Kidney failure, chronic; Leg ulcer; Skin ulcer; Vascular calcification

Resumo: Calcifilaxia ou arteriolopatia urêmica calcificante é quadro cutâneo-sistêmico raro em paciente com doença renal crônica em fase de diálise. Caracteriza-se por úlcera cutânea, necrose de padrão retiforme, evolução progressiva, localizada principalmente nos membros inferiores e suscetibilidade à infecção secundária. Decorre de calcificação da parede arterial e oclusão de arteríolas e artérias cutâneas e subcutâneas. Os autores relatam caso de paciente do sexo masculino de 73 anos de idade com doença renal em estadio tardio e úlceras cutâneas nos membros inferiores com necrose, evolução grave, infecção local e sistêmica e, óbito por sepse após paratireoidectomia
Palavras-chave: Calcificação vascular; Calciofilaxia; Falência renal crônica; Úlcera cutânea; Úlcera da perna

INTRODUCTION

Calciphylaxis or calcific uremic arteriolopathy is a rare cutaneous-systemic disease occurring, most frequently, in patients in the late stage of chronic kidney disease.[1] The terminology "calciphylaxis" was introduced by Selye in 1961, based on his experience of promoting vascular calcification in animal model as a consequence of anaphylactic reactions, using hyperparathyroidism and hypervitaminosis D as sensitization factor and trauma, among others, as a challenging factor.[1,2] Although what was described by Selye as "calciphylaxis" in rodents does not fit exactly that observed in patients, the term calciphylaxis has been used since them to describe a syndrome with rapid subcutaneous tissue calcification and cutaneous necrosis in patients with chronic renal disease. Its synonym "calcific uremic arteriolopathy" is an adequate descriptive term, even though the disease can occur in patients with normal renal function.[3] Calciphylaxis

Received on 14.11.2012.
Approved by the Advisory Board and accepted for publication on 06.12.2012.
* Work performed at the Department of Dermatology and Radiotherapy, Botucatu Medical School, São Paulo State University "Júlio de Mesquita Filho" (FMB-Unesp) – Botucatu (SP), Brazil.
Financial Support: None
Conflict of Interest: None

[1] MD, PhD. Department of Dermatology and Radiotherapy. Botucatu Medical School, São Paulo State University "Júlio de Mesquita Filho" (FMB-Unesp) – Botucatu (SP), Brazil.
[2] MD, Dermatologist. Member of the Brazilian Society of Dermatology. Private clinic – São Paulo (SP) – Brazil.
[3] MD, PhD. Department of Dermatology and Radiotherapy. Botucatu Medical School, São Paulo State University Júlio de Mesquita Filho" (FMB-Unesp) – Botucatu (SP), Brazil.
[4] MD, PhD. Department of Pathology. Botucatu Medical School, São Paulo State University "Júlio de Mesquita Filho" (FMB-Unesp) – Botucatu (SP), Brazil.

has been reported to occur in 1% to 4.5% of patients in dialysis, mostly in hemodialysis, with preponderance in patients who are obese, diabetic, present liver disease, are using systemic corticosteroids or have a calcium-phosphate product of more than $70mg^2/dL^2$.[1,3] The classical clinical picture is that of an initial skin lesion, livedo reticularis-like on the lower limbs, which progress to violaceous, painful, plaque or subcutaneous nodules, followed by ischemic/necrotic ulcers of reticular pattern.[4,5] Usually, the patients present hyperphosphatemia, hyperparathyroidism and an elevated plasma calcium and phosphate product.

We describe the case of a 74-year-old male patient with end-stage renal disease requiring peritoneal dialysis that developed severe, progressive calciphylaxis on both lower distal limbs, eventually fatal.

CASE REPORT

The patient was referred from a nephrological unit with a two-week history of painful cutaneous plaques soon followed by necrotic ulcers on both lower limbs. He had been in peritoneal dialysis for five years due to a chronic hypertension-related kidney disease. On physical examination a necrotic ulcer of 3 cm diameter with a reticular area of purpuric lesion was present on both limbs (Figure 1). Laboratory investigation showed elevated plasma levels of calcium, phosphate, ($Ca^+ \times P^+ = 66,7mg^2/dl^2$), parathormone, alkaline phosphatase and C-reactive protein. Calciphylaxis was diagnosed based on clinical, radiological and histological data and antibiotics, diet regimen to reduce calcium and phosphate balance plus local hydrogel dressing were prescribed (Figure 2-5). Regardless of therapeutic support the lesions pro-

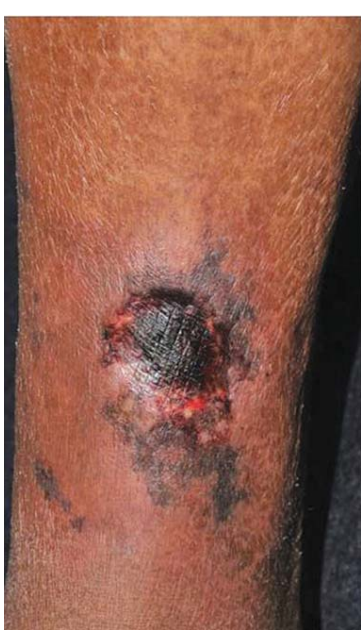

Figure 1: Calciphylaxis: necrotic ulcer with purpuric halo and reticulate pattern of lesion on the leg

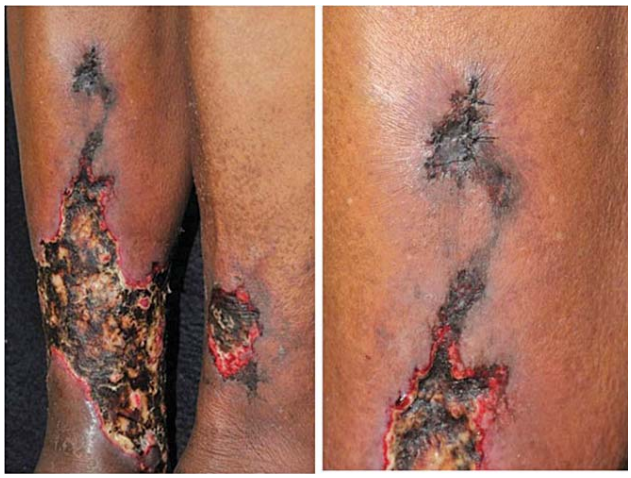

Figure 2: Calciphylaxis: progression of lesion with large area of necrosis on reticulate pattern

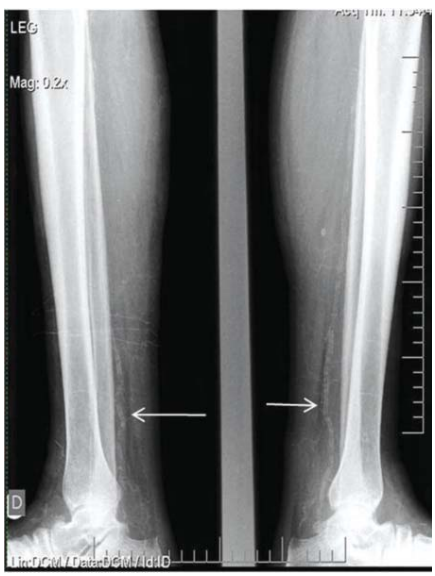

Figure 3: Calciphylaxis: computed tomography of legs showing calcification of posterior tibial artery (arrow)

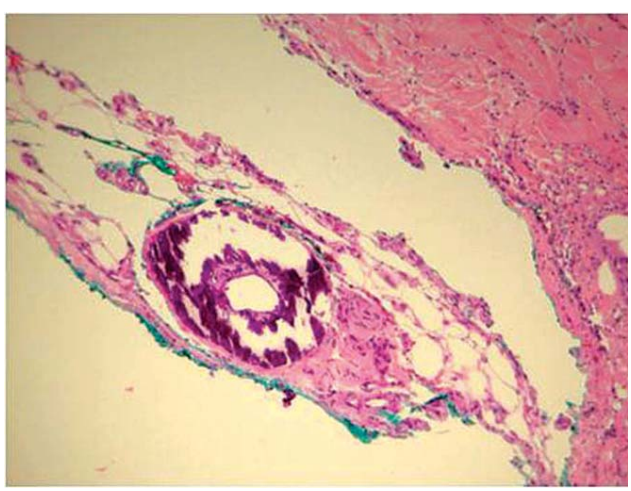

Figure 4: Calciphylaxis: subcutaneous arteriole with calcium deposit on the wall and proliferation of endothelial cells. (H.E. X 200)

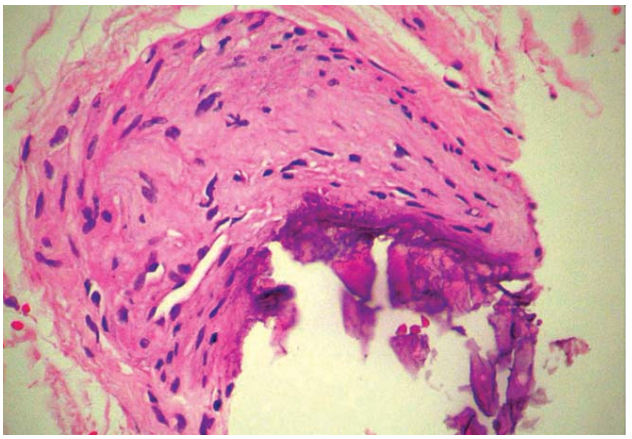

Figure 5: Calciphylaxis: higher power view of calcium deposit on the arteriole wall (H.E. X 400)

gressed into necrotic ulcer of phagedenic pattern (Figure 6). Following the failure of clinical approach an extensive surgical debridement was performed associated with new antibiotics plus intensive local dressing. Despite such procedures the lesion progressed, the clinical condition worsened and eventually the patient was submitted to a parathyroidectomy but he died few days later due to septic shock.

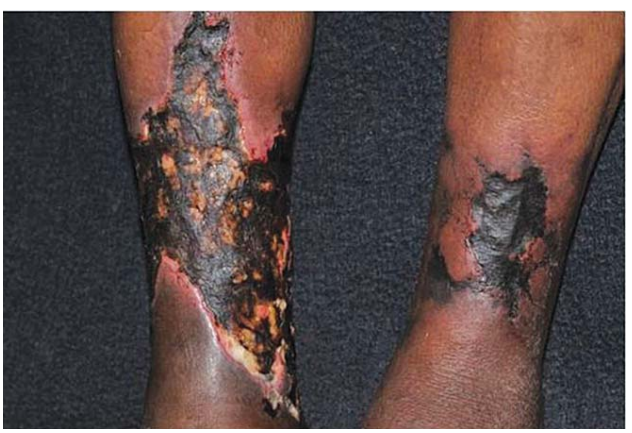

Figure 6: Calciphylaxis: late follow-up with extensive necrotic lesions

DISCUSSION

Calciphylaxis, once thought to be particularly rare, is becoming more frequent as the number of patients requiring hemodialysis or peritoneal dialysis is more prevalent.[2,4] Although classically reported as associated to chronic renal disease, calciphylaxis can be diagnosed in patients with cancer, inflammatory bowel disease or presenting primary hyperparathyroidism with normal renal function.[4] Even though the etiopathogenesis is not well understood, abnormalities present in the uremic patient as hyperphosphatemia, hyperparathyroidism, elevated plasma calcium and phosphate product, active vitamin D supplementation and deficiency of vascular calcification inhibitors have been implicated in the process.[4-6]

The cutaneous lesions are described as the sudden development of tender, violaceous skin lesion of livedoid or reticular pattern that progress to necrotic ulcerations, which frequently become superinfected. These ulcers heal poorly and are very painful. Areas commonly affected are the lower limbs and those with thick adipose tissue, such as the breasts, abdomen and gluteal region. Besides the skin other organs and systems can be involved as lung, heart, kidneys, skeletal muscle, tongue, pancreas and gastrointestinal tract.[1]

The diagnosis can be based on clinical grounds, supported by histological analysis if necessary. The laboratory workout must cover all the possible implications of chronic kidney disease with special attention to Ca^{+} and P^{+} values and evidence of skin or systemic infection.

The treatment must focus on local wound care and metabolic control. It is essential to prevent local and systemic infection. Wound care involves the use of enzymatic debriding agents, hydrocolloid or hydrogel dressings, avoiding tissue trauma or excessive manipulation and prescribing systemic antibiotics as needed.[5-7] Surgical debridement is controversial due to increased risk of sepsis and worsening pain.[7]As calciphylaxis is a very painful and debilitating disease nutritional and psychological support as well as specialized pain management must be provided. Efforts must be made to correct the plasma calcium and phosphorus concentrations in order to achieve a calcium and phosphorus product below 55.0 mg^2/dl^2 and serum levels of phosphate between 2.7 mg/dl and 4.6 mg/dl.[8] Normalization of serum parathyroid hormone levels needs to be also a priority and some patients have obtained improvement after being submitted to a parathyroidectomy. [8]

Sodium thiosulfate has been proposed as a novel and efficient therapy for calciphylaxis as marked improvements with reduction of pain, inflammation and healing of lesions have been demonstrated within a few days to months of use.[2; 4; 8; 9] The suggested mechanism of action is that it would dissolve the insoluble calcium salts embedded in tissue. The doses vary from 5 g to 25 g given intravenously over 1 h after high-flux hemodialysis three times a week for months.[4; 8,9] Bisphosphonates have also been proposed as effective in some cases.[10]

Calciphylaxis is reported to be a lethal complication with an estimated 1-year survival rate of 45.8%. Mortality is usually reported as a result of local and systemic infections and sepsis, similar to that observed in this present case report.[1]

Although uncommon, calciphylaxis must be known by dermatologist as early diagnosis and proper management can be decisive for better prognosis. ❑

REFERENCES

1. Brandenburg VM, Cozzolino M, Ketteler M. Calciphylaxis: a still unmet challenge. J Nephrol. 2011;24:142-8.
2. Brandenburg VM, Kramann R, Specht P, Ketteler M. Calciphylaxis in CKD and beyond. Nephrol Dial Transplant. 2012;27:1314-8.
3. Roncada EV, Abreu MA, Pereira MF, Oliveira CC, Nai GA, Soares DF. Calciphylaxis, a diagnostic and therapeutic challenge: report of a successful case. An Bras Dermatol. 2012;87:752-5.
4. Hayden MR, Goldsmith D, Sowers JR, Khanna R. Calciphylaxis: calcific uremic arteriolopathy and the emerging role of sodium thiosulfate. Int Urol Nephrol. 2008;40:443-51.
5. Panuncialman J, Falanga V. Unusual causes of cutaneous ulceration. Surg Clin North Am. 2010;90:1161-80.
6. Goel SK, Bellovich K, McCullough PA. Treatment of severe metastatic calcification and calciphylaxis in dialysis patients. Int J Nephrol. 2011;2011:701603.
7. Bishop J, Brown E, Podesta A, Troy C, Dong XE. Surgical management of calciphylaxis. associated with primary hyperparathyroidism. A Case report and review of the literature Int J Endocrinol. 2010;2010. pii: 823210; doi:10.1155/2010/823210.
8. Ross EA. Evolution of treatment strategies for calciphylaxis. Am J Nephrol. 2011;34:460-7.
9. Hayden MR, Goldsmith DJ. Sodium thiosulfate: new hope for the treatment of calciphylaxis. Semin Dial. 2010;23:258-62.
10. Torregrosa JV, Durán CE, Barros X, Blasco M, Arias M, Cases A, ***et al***. X. Successful treatment of calcific uraemic arteriolopathy with bisphosphonates. Nefrologia. 2012;32:329-34.

MAILING ADDRESS:
Silvio Alencar Marques
Departamento de Dermatologia e Radioterapia - Faculdade de Medicina
Distrito de Rubião Junior S/N - Botucatu
18618-970 - São Paulo - SP
Brazil
E-mail: smarques@fmb.unesp.br

How to cite this article: Marques SA, Kakuda AC, Mendaçolli TJ, Abbade LPF, Marques MEA. Calciphylaxis: a rare but potentially fatal event of chronic kidney disease. Case report. An Bras Dermatol. 2013;88(6 Suppl 1):S44-7.