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Authors
Danset, Marie
Lesort, Cécile
Jullien, Denis
et al.

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Cutaneous calciphylaxis of the glans penis presenting as a gangrenous ulceration

Marie Danset, Cécile Lesort, Denis Jullien, Jean Kanitakis

Affiliations: Dermatology Department, Edouard Herriot Hospital, Hospices Civils de Lyon, Claude Bernard Lyon I University, Lyon, France

Corresponding Author: Jean Kanitakis, Department of Dermatology, Edouard Herriot Hospital Group, 69437 Lyon Cedex 03, France, Tel: 33-472110301, Email: jean.kanitakis@univ-lyon1.fr

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Abstract

Calciphylaxis is a rare microvascular disorder causing necrotic skin ulcers. It is characterized by deposits of calcium within vascular walls but its precise pathogenesis remains poorly understood. A major risk factor is end-stage renal disease on dialysis. We report a 67-year-old man with calciphylaxis revealed by an unusual necrotic ulcer of the glans penis. The patient also presented with bilateral panniculitis of the thighs and a calf ulcer. All those lesions were painful, highlighting the value of pain as a diagnostic clue. Penile involvement of calciphylaxis is rare and biopsy is often avoided in this area. However, rapid diagnosis of calciphylaxis is important because early treatment has a better chance of being successful. Our patient's condition deteriorated rapidly with development of bilateral retinal artery occlusion and he died shortly thereafter. This case further highlights the fact that calciphylaxis is a systemic vascular disease with an ominous prognosis.

Keywords: calciphylaxis, genital ulcer, chronic kidney disease, hemodialysis, retinal artery occlusion

Introduction

Calciphylaxis (also known as calcific uremic arteriolopathy) is a rare cause of necrotic ulcers. It affects mainly patients with end-stage renal disease (ESRD) on dialysis. The disease is more common in women and affects predominantly the proximal extremities (especially the thighs), the abdomen, and the buttocks. Anogenital, including penile, involvement by calciphylaxis is rare and portends a poor prognosis. Rapid diagnosis of calciphylaxis is important because early treatment has a better chance of being successful. However, patients may delay seeking medical advice in the case of genital lesions. We report herein a patient with calciphylaxis who presented with a painful necrotic ulcer of the penis. Despite intensive care his condition deteriorated with development of bilateral retinal artery occlusion and sepsis; he died 15 days later.

Case Synopsis

A 67-year-old man with a history of type II diabetes mellitus, arterial hypertension, arrhythmic cardiopathy (on preventive anticoagulation with fluindione), dyslipidemia, and obesity presented to the nephrology department. He also had ESRD related to IgA glomerulonephritis and had been on peritoneal dialysis for four years. He was admitted to the hospital for non-febrile deterioration of his general condition that had started six months prior to admission. During hospitalization, the patient complained of severe pain of his penis. Physical examination revealed whitish fibrinoid and adherent deposits on the glans suggestive of superficial necrosis (**Figure 1A)**. The patient presented concomitantly with painful lesions of panniculitis on both thighs (**Figure 2**) and a necrotic ulcer of the calf, which had been spontaneously improving, by his own description (**Figure 3**). The differential diagnosis of the superficial penile ulcer included calciphylaxis, irritative (caustic) contact dermatitis (although no history of contact with a caustic substance was recalled), vasculitis, vascular embolism, thrombosis, and Fournier gangrene, even

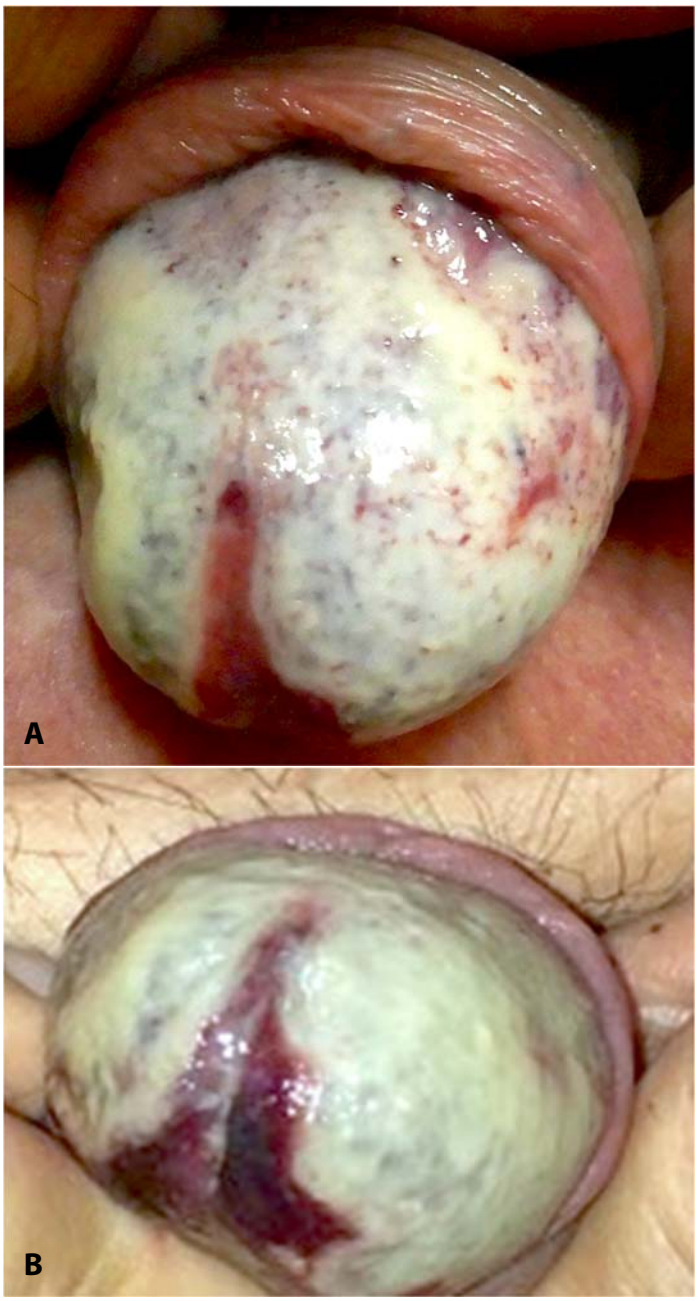

Figure 1. ***A)*** *Necrosis of the glans penis; note the white fibrinoid wet aspect.* ***B)*** *After a week of evolution, the lesion became violaceous.*

though there was no septic syndrome and the course had been slow. Squamous cell carcinoma was also considered as this can manifest with a misleading, chronic (usually painless) ulcer. Laboratory workup revealed increased levels of parathyroid hormone (294ng/L, normal range 15-65pg/mL), decreased albumin levels (28g/L), and normal calcium phosphate (2.23mmol/L). Histopathological examination of a skin biopsy obtained from a lesion

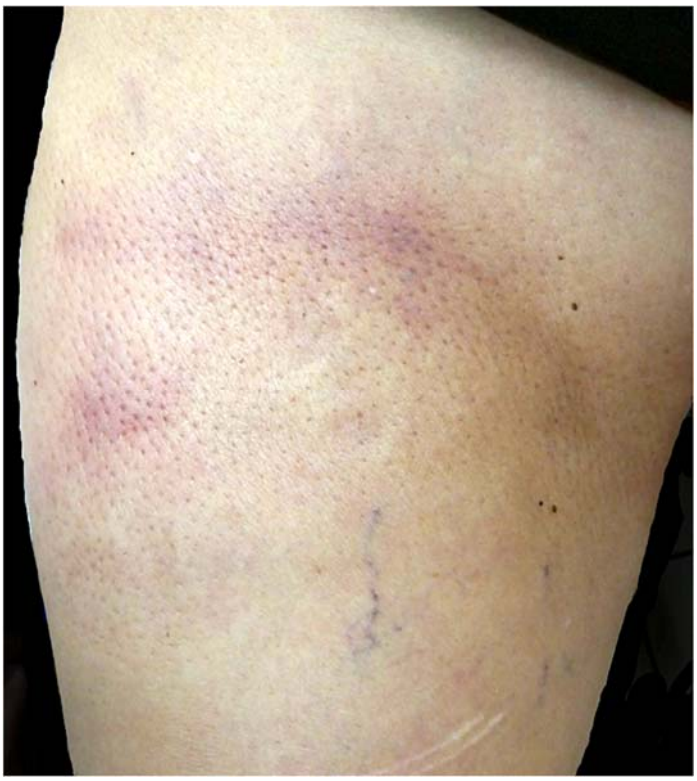

Figure 2. *Proximal lesions of calciphylaxis (symmetric induration with overlying erythema on the right thigh).*

of the thigh showed typical findings of calciphylaxis, i.e., calcium deposits in the medial layer of the wall of subcutaneous vessels that were visible on routinely stained sections and highlighted with the von Kossa histochemical stain (**Figures 4, 5**).

Within a week, the lesion of the glans penis became violaceous (**Figure 1B)**. The patient's condition deteriorated and was complicated by intractable pain of the penis. He was transferred to the intensive care unit and treated with intravenous sodium thiosulfate infusions, hemodialysis, and sessions of rheopheresis. Fluindione and vitamin D were discontinued, even though they had been administered for more than 10 years. Two weeks later the patient developed septic shock to *Staphylococcus aureus* (possibly of cutaneous origin) and left temporal hemianopsia progressing to blindness. Cerebral CT scan was normal. Fundus examination showed a bilateral grayish pallor of the posterior retina with sparing of the central fovea producing the typical appearance of a cherry red spot, suggesting the diagnosis of retinal artery occlusion. The patient and his family opted for

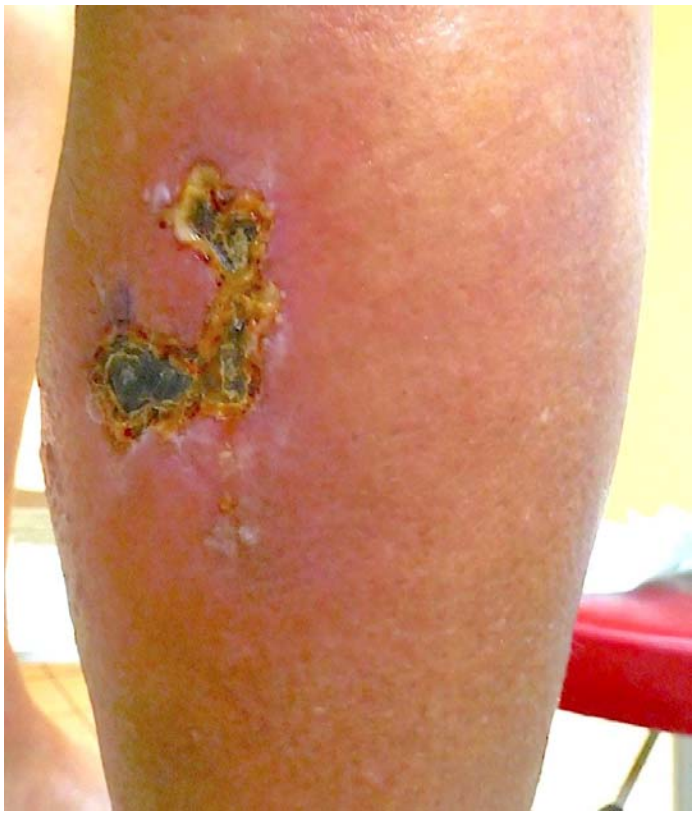

Figure 3. *Necrotic ulcer of the calf.*

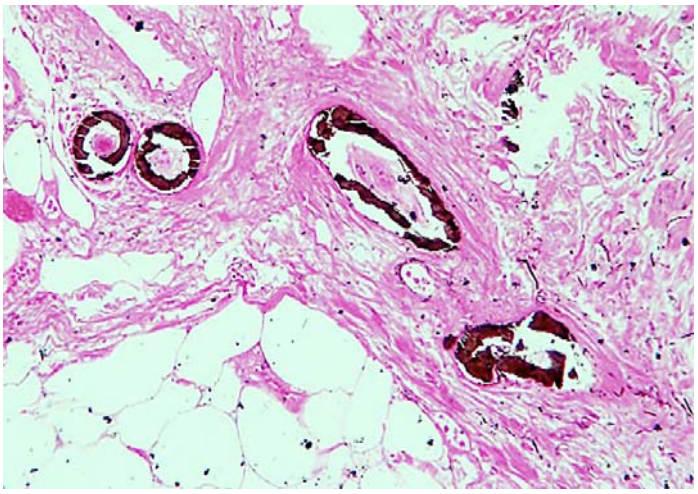

Figure 4. *The vascular deposits stain black with the von Kossa histochemical stain, proving they consist of calcium.*

palliative care. The patient died two weeks after his admission to the intensive care unit.

Case Discussion

Calciphylaxis (or calcific uremic arteriolopathy) is a rare microvascular disorder associated with ESRD, obesity, diabetes mellitus, liver disease, elevated

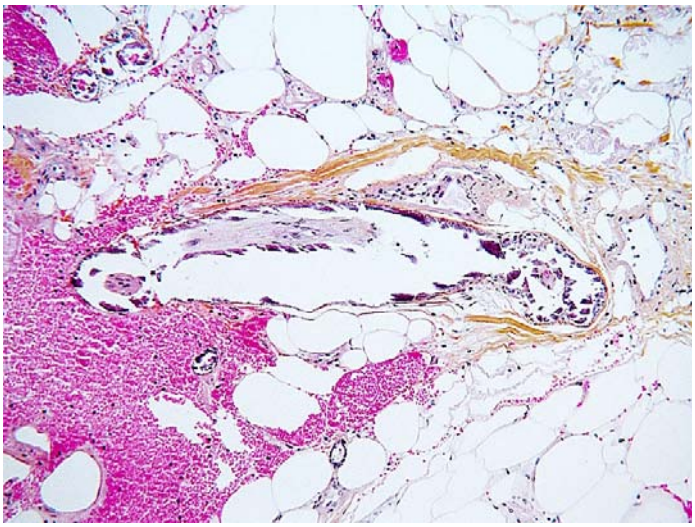

Figure 5.*Microscopic examination of a skin biopsy obtained from the thigh shows basophilic deposits on the wall of blood vessels within the dermal-hypodermal junction.*

calcium-phosphate product, hyperparathyroidism, supplemental vitamin D, cinacalcet, and warfarin treatments [1,2]. Its pathogenesis remains poorly understood. It has been postulated that abnormalities in mineral metabolism induce vascular calcification and endothelial injury, leading to microthrombosis and infarction [3]. The vascular damage induces cutaneous ischemia and necrosis accounting for pain, which is a major symptom. Pain may precede the appearance of skin lesions and is often associated with tactile hyperesthesia.

The cutaneous manifestations of calciphylaxis are polymorphous and include induration, plaques, nodules, livedo, purpura, and ulcers. The lesions are typically multiple and bilateral. Early lesions have often a non-specific appearance causing a delay in diagnosis. However, their recognition is critical in order to implement timely treatment [4]. According to the underlying cause, calciphylaxis may be classified as uremic (in patients with ESRD) or non-uremic. According to lesion localization, calciphylaxis is classified as proximal/central, involving central subcutaneous adipose tissue areas, or distal/peripheral, when it is restricted to peripheral sites with limited adipose tissue.

When the presentation is typical, calciphylaxis can be diagnosed clinically [5]. Microscopic examination of a skin biopsy is diagnostic, provided it contains the

dermal-hypodermal junction. To this end, a double-punch technique can be used, wherein a second punch is inserted through the center of the first. This allows one to retrieve deeper skin tissue with less tissue loss than a surgical biopsy [6]. Microscopic examination shows calcium deposits in the wall of blood vessels, thromboses, and dermal angioplasia [7]. Unfortunately, skin biopsy entails a risk of infection and wound worsening [8], even more so on acral sites such as the penis, where biopsy risks may be concerning to some authors [9]. Elevations in serum calcium or phosphate are not specific. Imaging techniques (such as computed tomography, X-rays, or scintigraphy) are useful for the diagnosis [10-12], but have not yet been definitively validated; furthermore, vascular calcifications are not uncommon in the population at large.

Penile involvement is a rare distal manifestation of calciphylaxis; it manifests with black eschars and necrosis mimicking a wound [13-15]. Our case suggests that mucosal necrosis may have a moist and whitish appearance. The differential diagnosis of penile gangrene includes irritative/caustic dermatitis, vasculitis, vascular embolism, thrombosis, penile prosthesis, priapism, Fournier gangrene, and squamous cell carcinoma. The prognosis is generally poor; one-year mortality for patients with ESRD varies between 45 and 80% [16]. In a series of 34 patients with penile calciphylaxis, the disease-associated mortality reached 64% and the mean survival time was merely 2.5 months. [17].

The treatment of genital calciphylaxis is challenging. No standardized local or systemic treatment exists. Therefore, the management should be discussed in a multidisciplinary group. If the lesions progress to gangrene and sepsis, surgical intervention may be necessary. However, a pathergic reaction can cause progression of necrosis. Therefore, the patient's preference and his life expectancy should be taken into consideration.

Our patient developed simultaneously two rare manifestations of calciphylaxis, penile and ocular involvement. The blindness could be multifactorial, related to chronic arteriopathy (arteriosclerotic disease, hypertension, diabetes), ischemic neuropathy, and/or acute severe arterial hypotension. However, the typical aspect of retinal artery occlusion, the timing, and the bilateral involvement suggest a causal role of calciphylaxis. Only one similar case of penile calciphylaxis associated with anterior ischemic optic neuropathy, to our knowledge, has been previously reported [18].

Conclusion

Penile involvement in calciphylaxis is rare and manifests as a white (wet) or black (dry) necrotic lesion. Physical examination allows the diagnosis in typical cases, obviating the need of a diagnostic biopsy in this sensitive body zone. However, imaging techniques or biopsy may be necessary, although the latter may cause complications. Calciphylaxis should be considered as a possible cause of penile necrotic lesions. Since the vascular involvement in calciphylaxis is systemic, the patients can present with multiple localizations of the disease, as highlighted by the patient presented whose cutaneous and retinal manifestations caused skin ulcers and blindness. Since no standard local or systemic treatment is available, management should be based on a multidisciplinary approach.

Potential conflicts of interest

The authors declare no conflicts of interest.

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