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CALCIPHYLAXIS IN CHRONIC RENAL FAILURE: ABOUT ONE CASE

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ABSTRACT

Summary: Calciphylaxis or uremic and calcifying arteriolopathy is a rare, life-threatening condition, mainly affecting dialysis patients or patients with renal insufficiency. It is characterized by the rapid onset of infiltrated, inflammatory, purplish and livid patches of skin, resulting in deepening and necrotic ulcerations, surrounded by livedo purpuricus, sitting on the trunk, in the adipose areas, or on the limbs. Cutaneous histology reveals calcifications of the media of the deep dermal and hypodermal arterioles, intimal hyperplasia and necrotic panniculitis. Images of thrombosis and extravascular calcifications are also reported. The treatment combines several simultaneous strategies aimed at decreasing the phosphocalcic product, dissociating and removing calcium deposits, clearing necrosis and avoiding potentially fatal septic complications. We report an observation of a histologically confirmed calciphylaxis and review the pathogenesis, clinical, biological, therapeutic and evolutionary characteristics of this complication in the literature.

KEYWORDS: Calciphylaxis - Chronic kidney failure - Haemodialysis - Calciphylaxis - Chronic kidney failure – Haemodialysis.

INTRODUCTION

Calcifying arteriolopathy or calciphylaxis (CA) is a severe pathology with a poor prognosis[1] It is mainly encountered in patients with chronic renal failure (CKD), particularly hemodialysis (HD), where it is called calcifying arteriolopathy uremic (CAU). It is a rare critical disorder characterized by mediacalcinosis of the arteries leading to tissue ischemia in patients with end-stage renal disease who are on dialysis or who have received a kidney transplant.[2] It may result from other causes of hypercalcemia.[3] Certain predisposing conditions in the background of renal failure are found such as diabetes, obesity, arteritis, diffuse vascular calcifications, heart disease and undernutrition. Diagnosis must be rapid and adequate management must be provided to avoid an often fatal progression to sepsis.[4] Despite this, all treatment remains disappointing and the prognosis is bleak with high mortality.[5]

OBSERVATION

Patient aged 32 years, non-obese (BMI = 23 kg/m2), not known diabetic without any other particular pathological history, chronic haemodialysis for 7 years for chronic end-stage renal failure related to an undetermined nephropathy, hospitalised in our unit for tertiary hyperparathyroidism with painful bilateral ulcero-nectrotic nodules superinfected in the thighs (see image 1) appearing for 3 months. It should be noted that the patient was taking neither corticosteroids nor anticoagulant.

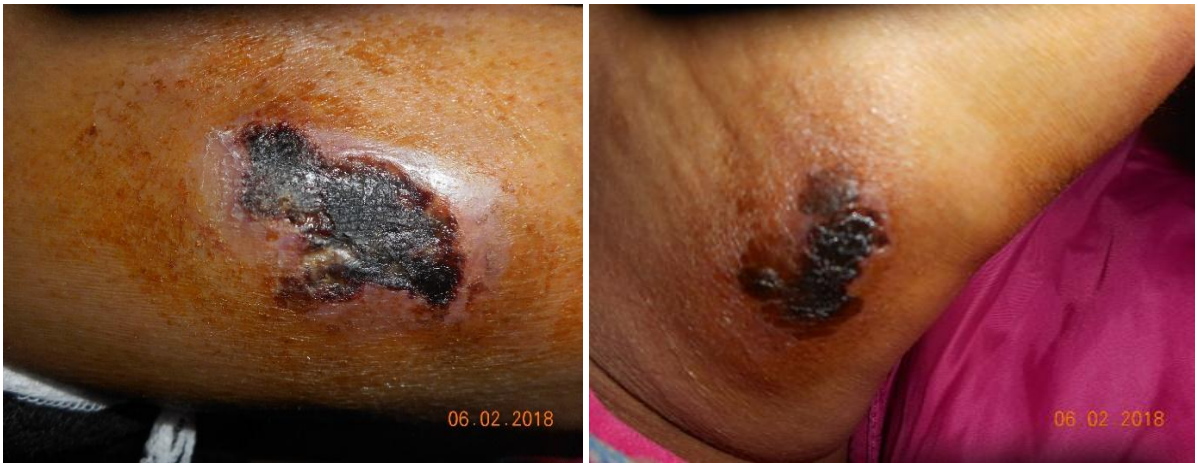

Image 1: Indurated ulcero-nectrotic nodules, hypodermic.

To biology
Hgb=11.9 g/dl RDW = 88.2 fL MCHC =31.1 g/dl; WBC = 5730; Platelet = 226,000 /ul
Calcaemia = 101 mg/L; phosphorus = 71 mg/L; Phosphocalcic product = 7171mg2/L2
Alcaline phosphatase = 480 IU/L; Parathormone= 3700 pg/mL ; Protidemia = 93 g/L; Albuminemia = 38.1g/L
Vit D (D2+D 3) = 11,8 ng/ml

To imaging

Standard radiography showed arterial calcifications in the forearm (see picture 2).

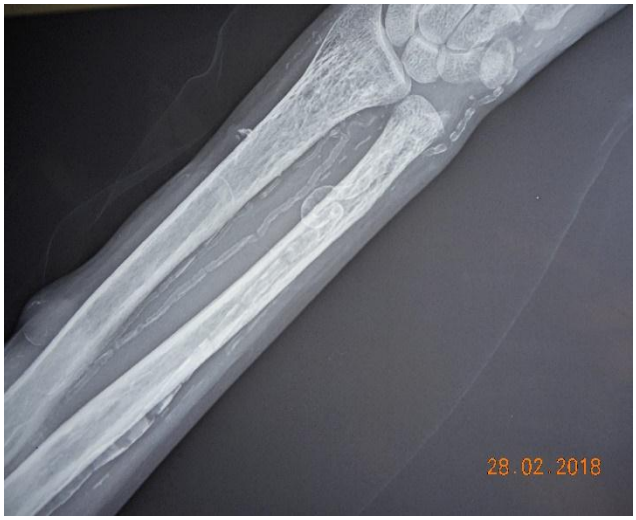

Image 2: Vascular calcifications in the forearm.

Cardiac ultrasound does not show valvular calcifications with retained ejection fraction.
Cervical ultrasonography revealed two retro-thyroid nodular formations related to pathological parathyroid disease without ectopic focus.
A skin biopsy was carried out and an anatomical-pathological study showed that a blood vessel contained violent calcium deposits at the dermal-hypodermal junction (see image 3,4).

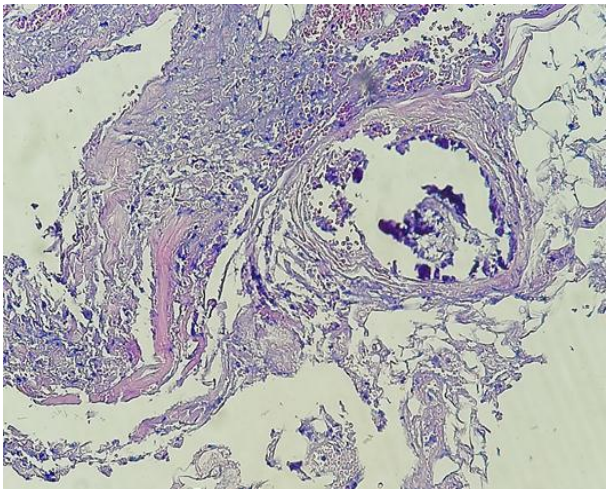

Image 3: Magnification ×200 Von kossa staining.
Calcium deposition at the dermal-hypodermal junction on a red background

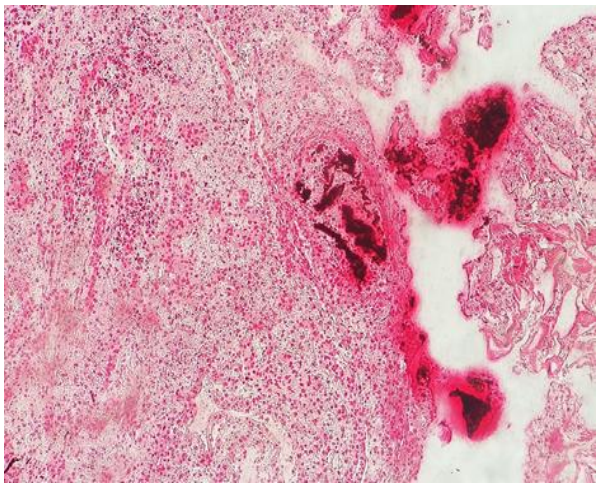

Image 4: Magnification×200 HES staining.
Violin calcium deposition in a blood vessel at the dermal-hypodermal junction.

A parathyroidectomy was indicated and performed without incident with a post-operative phosphocalcic balance (PTH= 316 Pg/ml; Ca++= 56 mg/l; Ph = 33mg/l; PAL=51 UI/L) proving its success.

Complementary therapeutic management consisted of putting the patient on level II analgesics, broad-spectrum antibiotics, vitamin therapy and daily local care with surgical detersion after softening of the lesions.

The evolution was favourable with stabilisation of the necrotic lesions, disappearance of signs of superinfection and reduction of pain.

DISCUSSION

Calciphylaxis was first described by Selye in 1962 with reference to an animal model. Since then, more than one hundred cases have been reported in humans.[6] The prevalence of this complication is 4.1% in a series of dialysis patients with an annual incidence of 1%.[7] These figures would be higher since this lesion is most often under-diagnosed. It is a condition that affects relatively young females with an average age of 48 ± 16 years.[6,8,9] Calciphylaxis occurs almost exclusively in patients with chronic renal failure or in patients undergoing extra-renal therapy, with a preponderance of patients undergoing hemodialysis, the duration of which increases the risk.[6,7,9] However, it can occur after kidney transplantation, especially after treatment of acute rejection episodes, suggesting the precipitating and aggravating role of corticosteroids on calciphylaxis lesions.[6] The effect of corticosteroids on the onset or aggravation of calciphylaxis is unclear; they are thought to stimulate cyclic MPA in vitro with increased parathyroid response and vascular calcifications.[10]

Because calciphylaxis is an infrequent entity, studies are usually conducted on only a small number of cases. Many risk factors have been reported but few are statistically supported. Nevertheless, a retrospective study of 64 patients was published in 2007. It confirms that the most significant risk factor is renal failure. Seventy-seven percent of the patients were on dialysis and 69% of the others had moderate to severe CKD.[11]

A frequently mentioned factor is the disturbance of bone metabolism parameters: hyperparathyroidism, hyperphosphatemia, hypercalcaemia and increased phosphocalcium product. In the study mentioned above, only the phosphocalcium product above 70 mg2/dl[12] was found to be statistically significant (five times more frequent in the group of patients with UCAS). Obesity was also a statistically significant risk factor in this study as was treatment with corticosteroids.

Trauma, such as insulin injection[13], skin compression, or ice application, can cause CUA lesions.

The Caucasian race is also a well-accepted risk factor, with the frequency of occurrence in other races being much lower; so is the female sex, with women being three times more affected than men.[14]

Hypo albuminemia has been shown to be significantly correlated with the risk of developing AUC.[15] Anti-vitamin K anticoagulation (VKA) is also frequently cited as a predisposing factor. Other risk factors sometimes cited include immunosuppressive therapy, dyslipidemia, hypotension, and protein C and S deficiency.

Arteriolar calcifications are therefore at the origin of AUC. These develop silently over a period of years, in contrast to infarction of the skin tissue, which is acute in onset.

It was first thought that a passive process was at the origin of vascular calcifications, with disturbances in calcium-phosphate homeostasis favouring the precipitation of hydroxyapatite crystals. Recent experiments on cell cultures and *knockout* mice support the hypothesis that this is an actively regulated mechanism.

Hyperphosphatemia could induce the transformation of vascular smooth muscle cells into osteoblastic-type cells. Genes would be positively regulated, giving these cells the ability to produce bone proteins.[16]

Some of these proteins are believed to act as calcification inhibitors and others as promoters. Uremia is thought to contribute to an imbalance in favour of procalcifying factors.[17]

Skin and subcutaneous tissue are the main sites involved. Lesions are proximal in 68% of cases.[18] The lesions are localized in the adipose regions (thighs, buttocks, abdomen).

Initially, the lesions most frequently present as erythematous or purplish mottles that may resemble livedo, bruises or nodular or plate-like indurations, erythematous or not, very painful and quite often symmetrical, lying along the inner side of the limbs that come into contact. These lesions usually progress to ulcerations and bedsores.

The pain is severe, neuropathic, and sometimes resistant to treatment.
The differential diagnosis is broad and includes cellulitis or panniculitis, infectious or not, as well as all etiologies of ulcers, haematomas and skin necrosis.

Identification of characteristic skin lesions in the context of TRI is usually sufficient to evoke the diagnosis. A biopsy is often performed to confirm the suspicion and rule out other diagnoses such as infectious necrosis or cholesterol embolism. The biopsy is objective for non-vascular vasculopathy of the arterioles of the dermis and hypodermis, characterized by media calcification and intimal fibrosis resulting in lumen narrowing. Sometimes fibrin thrombi are also observed. This obliterative vasculopathy leads to ischemia of the perfused area followed by necrosis of the adipose tissue and/or skin tissue, responsible for the clinical manifestations.

The treatment of calciphylaxis is multidisciplinary, based on clinical cases from the literature or short series. No drug has a marketing authorisation for this pathology and no prospective therapeutic studies are currently available given the small number of patients and their heterogeneity. Therapeutic management strongly involves the nephrological team in case of dialysis and combines several therapeutic strategies used simultaneously.[19,20] Correction of associated or aggravating risk factors : - limitation of calcium intake, particularly in dialysis baths (≤ 1.25 mmol/L); - limitation of active vitamin D intake; - cessation and contraindication of VKA, relayed by heparin therapy if necessary; - vitamin K supplementation; - intensification of the rate and/or duration of dialysis to reduce phosphatemia (5 to 7 dialysis sessions per week), and to maintain hemodynamics as stable as possible.[21] 2. Local treatment of necrosis: - surgical or mechanical and autolytic detersion (MEOPA dressings) depending on the extent and depth of the necrosis. Surgical detersion could improve survival, probably by reducing the risk of septic complications by superinfection of the necrotic areas; - hyperbaric oxygen proposed by some teams, particularly in the distal forms, at the rate of 5 sessions per week for 4 to 8 weeks[19]; - infection control by broad-spectrum antibiotic therapy; - occlusive dressings, skin grafts. 3. Specific treatments: TSS is a chelator of calcium ions (formation of calcium thiosulphate, eliminated by the kidneys or dialysis) which, through its high solubility, acts by dissociating tissue and vascular calcium salts. It also has an antioxidant power by acting on oxygenated radicals (hydrogen peroxide and superoxide ion) and a local vasodilatory action by interaction with the endothelial synthesis of nitrogen monoxide (NO). It is administered intravenously, at the end of dialysis, at a dose of 5 to 25 g, 3 times a week, until 2 months after the healing of the lesions. Its side effects are mainly headaches, nausea and sodium overload. It may induce metabolic acidosis corrected by the administration of sodium bicarbonate and symptomatic hypocalcemia. Its efficacy has been reported in dialysis patients but also in cases of non-uremic calciphylaxis[22], on pain and healing of lesions within a few days to a few weeks.[19] In a recent retrospective series of dialysis patients where TSS was used in combination with other treatments such as antibiotics and cinacalcet, complete or partial remission was achieved in about 70% of cases.[20] Finally, some observations report the use of TSS topically[23,24] on ulcerated calcified lesions, or orally.[25] Parathyroidectomy or cinacalcet (Mimpara) These treatments are currently reserved for patients with proven hyperparathyroidism. Parathyroidectomy should be discussed in cases of secondary hyperparathyroidism, which cannot be controlled by the usual medical treatments. The medical treatment of secondary hyperparathyroidism by oral administration of cinacalcet is an alternative to surgery and should be tried as a first-line treatment, before a possible parathyroidectomy for some authors.[26] However, their respective efficacy on calciphylaxis is difficult to evaluate. Some small retrospective series report an improvement in survival with parathyroidectomy and others do not.[27,19] Intravenous or oral biphosphonates have been used in a few dialysis patients. Their mechanism of action on calciphylaxis is unclear: direct inhibitory action on bone resorption, independent action on tissue calcification, inhibition of phosphocalcic crystal formation, or anti-inflammatory action. Biphosphonates are eliminated by dialysis, which raises doubts about their effectiveness in dialysis patients.[28]

The prognosis is bleak, with 1-year mortality of about 50%[27,29], mainly due to septic complications. In case of surgical detersion, the prognosis would be better (survival at 1 year; 61.6% versus 27.4%). However, in this retrospective study, surgical detersion may have been performed only in patients with mild or paucified lesional involvement.[30] Finally, the distal forms, located on the lower limbs, are reported as having a better prognosis than the proximal forms, without this prognostic difference having been confirmed in a recent study.[27]

CONCLUSION

Calciphylaxis is a rare complication, affecting 0.5% of patients in our experience, but potentially serious, as it is indicative of severe vascular damage. It justifies the identification of patients at risk in order to optimize mineral and bone metabolism disorders in diabetic, obese, arterial or VKA patients. Identified triggering circumstances should also be avoided. In addition to prevention, early recognition of calciphylaxis, most often clinically based, should allow the rapid initiation of a comprehensive therapeutic strategy that aims to interrupt the ischemic process and promote healing to reduce mortality most often related to superinfections and undernutrition.

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