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Case report

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Calcific Uremic Arteriolopathy, report of a case treated with Sodium Thiosulfate

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Summary

We describe a case of calcific uremic arteriolopathyinitially associated with skin lesions within the context of a patient with chronic kidney disease on automated peritoneal dialysis therapy. Among the most relevant findings, the patient hadhyperphosphatemia, normocalcemia and severe hyperparathyroidism without nodular hyperplasia. Clinical improvement with multimodal management of enhancement in dialysis therapy and intravenous sodium thiosulfate is highlighted. Calciphylaxis is a disorder that has a high morbidity and mortality, secondary to sepsis. It occurs more frequently in patients with chronic renal failure who are on hemodialysis. It is characterized by systemic medial calcification of the arterioles, triggering ischemia and subcutaneous necrosis of skin and soft tissues. Histopathological evaluation helps to confirm the diagnosis.

Key words: Calciphylaxis, Sodium thiosulfate, Chronic kidney disease, Hiperparathyroidism.

Arteriolopatía calcificante urémica, reporte de un caso tratado con tiosulfato de sodio

Resumen

Describimos un caso de arteriolopatía calcificante urémica asociada, inicialmente, a lesiones cutáneas,en un paciente con insuficiencia renal crónica, en terapia de diálisis peritoneal automatizada, como hallazgos más relevantes presentaba hiperfosfatemia, normocalcemia e hiperparatiroidismo severo sin hiperplasia nodular. Se destaca la mejoría clínica con manejo multimodal de intensificación en la terapia dialítica y tiosulfato de sodio intravenoso.

La calcifilaxis es un trastorno que debuta con alta morbilidad y mortalidad, secundaria a sepsis, ocurre con mayor frecuencia en pacientes con insuficiencia renal crónica que se encuentran en hemodiálisis. Se caracteriza por calcificación sistémica en la media de las arteriolas, desencadenándose isquemia y necrosis subcutánea de piel y tejidos blandos. La evaluación histopatológica ayuda a confirmar el diagnóstico.

Palabras clave: calcifilaxis, tiosulfato de sodio, enfermedad renal crónica, hiperparatiroidismo.

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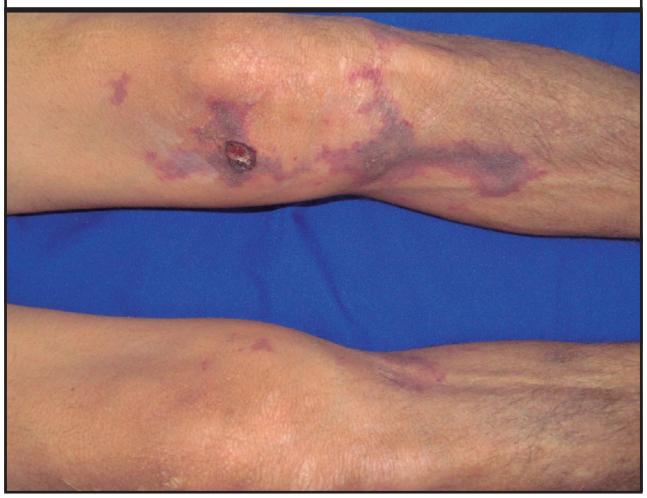
Introduction

Calciphylaxis, or calcific uremic arteriolopathy (CUA) is a rare and severe disorder characterized by the systemic medial calcification of the arterioles, leading to ischemia and subcutaneous necrosis1,2. It occurs more frequently, but not exclusively, in patients with chronic kidney disease (CKD) who are on hemodialysis therapy[1-4]. Its incidence appears to be increasing, due in part to awareness and recognition of the clinical signs and risk factors associated with calciphylaxis.

The optimal treatment of CUA is unknown. However, a multifactorial approach is the best option. We present the case of a patient with calciphylaxis associated with chronic stage 5 disease on peritoneal dialysis therapy, who was treated with sodium thiosulfate.

Figure 1.
Irregular ecchymotic macules associated with ulcers of necrotic borders located on the knees; before the start of the treatment.



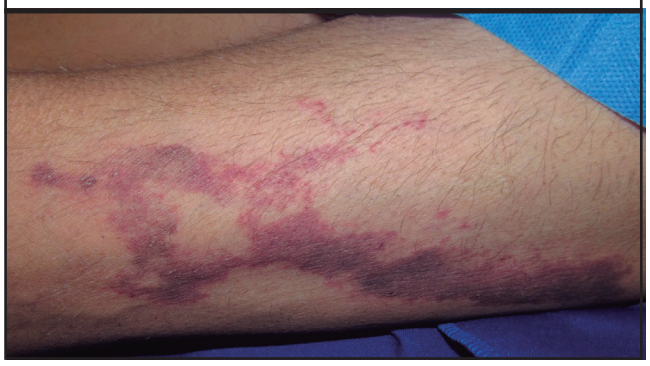
Case Description

A 37-year-old male driver who attended the Nephrology service because of a 15-day course of asthenia, adynamia, myalgias, generalized bone pain predominantly in elbows, hips and knees markedly limiting his motion, associated with the onset of burning sensation, pruritus and painful lesions on the skin, especially on the scalp, lower back and lower limbs (Figure 1, 2 and 3), for which he performed daily saline cures.

As a personal history, the patient referred arterial hypertension of 11 years of evolution, chronic renal disease secondary to focal segmental glomerulosclerosis of 4 years of evolution. This latter was under management with automated peritoneal dialysis of 14 liters, 2 bags at 2.5% each for 6000 cc for 9 hours at night, a bag at 1.5% per 2000 cc for wet abdomen at day, and manual replacement at noon for 2 liters at 1.5%, its last Kt/V was 1.77. His pharmacological treatment included sevelamer hydrochloride (2 tablets with each meal), B complex, erythropoietin, folic acid, metoprolol tartrate, minoxidil, nifedipine and prazosin. He had never received warfarin.

At the physical examination of admission, he was in normal general conditions, afebrile and hydrated, non-palpable thyroid, no heart murmurs were

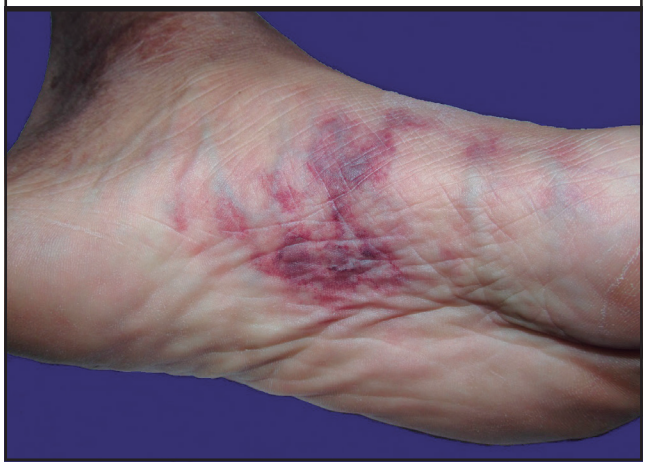
Figure 2.
Reticulate ecchymotic macules located on the left outer thigh before treatment with Sodium Thiosulfate.



auscultated at cardiac auscultation. Clean vesicular murmur, with no added noise. Soft, depressible abdomen, with no palpation pain, present peristalsis, outlet orifice and tunnel of the peritoneal dialysis catheter without alterations. Lower extremities without edema. On the scalp, lower back, lateral thigh, knee, leg, left back, and on the right lower leg he showed erythematous-violet plaques with poorly defined edges of livedoid appearance, covered by necrotic bedsores. The lesions on the knee were 1.5 cm, on the back of the left foot they were 2 cm, on

Figure 3.

Reticulate ecchymotic macula on the left internal sole area before treatment initiation.



the back and side of the right heel they were 1 and 3 cm respectively. Generalized muscle hypotrophy was also found.

The hemogram showed hemoglobin of 10.1, Hematocrit of 30.5, BUN of 88, Calcium of 9.24 mmol / L, phosphorus of 10.1 mmol / L, potassium of 3.9, PTH of 1002, ferritin of 242, transferrin saturation percentage of 15.9%, nPCR (normalized protein catabolic rate) of 1.6, indicating no adherence to the low phosphate diet, neck ultrasound without evidence of parathyroid adenomas, which was more in favor of diffuse parathyroid gland hyperplasia.

Nephrology indicated suspension of peritoneal dialysis, implantation of a central venous catheter, and transfer to hemodialysis for daily dialytic therapy without ultrafiltration for 4 hours, in order to rapidly reduce serum phosphorus levels. Dermatology, was consulted, and they opted to practice a biopsy of the ulcer covered by necrotic bedsore in the inner area of the right heel. With a clinical diagnosis of Calciphylaxis, the SES Hospital de Caldas pharmacy was contacted, requesting the attainment of Sodium Thiosulfate (Sodium Hyposulfite), which was commercially impossible to obtain, and its pharmacological preparation in bags by 100 cc at 20% was required (figure 4).The product was administered in doses of 20 grams after each hemodialysis, being well tolerated. Skin biopsy confirmed the diagnosis of Calciphylaxis (Figure 5). Twelve days later, the patient was asymptomatic, with reduction of pain and re-epithelialization of skin lesions (Figures 6, 7 and 8), serum phosphorus was reduced to 2.65, which indicated ambulatory management of the wounds (daily mechanic debridement of bedsores with SSN and covering with antibiotic ointment), exit of hemodialysis program and restart of the peritoneal dialysis. Oral Thiosulphate Sodic was prescribed at doses of 600 mg every 12 hours (figure 9), and sevelamer of 800 mg, 2 tablets with each meal. Arterial blood gas control was also requested 8 days from that moment, which was not practiced. The patient resumed feeding at home with high phosphate content, and reentered the hospital 15 days after discharge because of severe abdominal pain, diarrheal stools without mucus, or blood, underdrainage from the peritoneal catheter, although the liquid was clear. Evaluation by general surgery was requested, and they decided to perform exploratory laparotomy and removal of the catheter due to dysfunction. They found a clean abdominal cavity, clear fluid, a

Figure 4.

Sodium thiosulfate bag per 100 cc, pharmacological preparation at 20%.

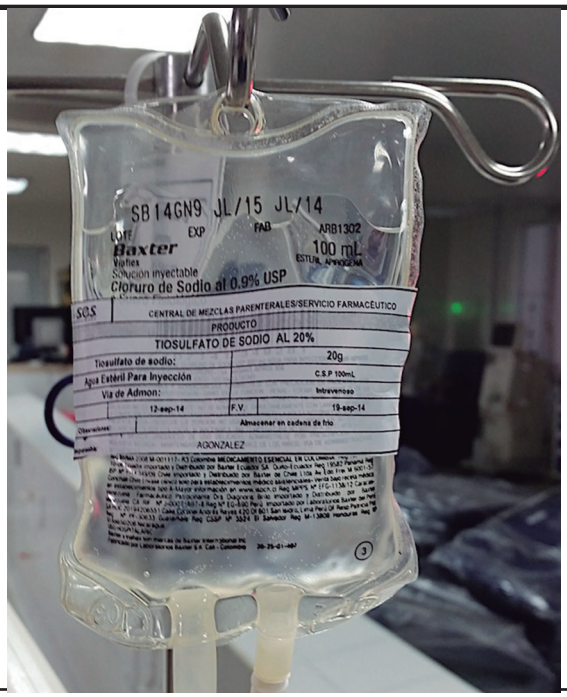


Figure 5.

Dermohipodermal interface arterioles with fine basophilic granular deposits in the medial wall (compatible with deposits of calcium crystals), with lumen occlusion by fibrocystic proliferation. Hematoxylin and eosin at 100X.

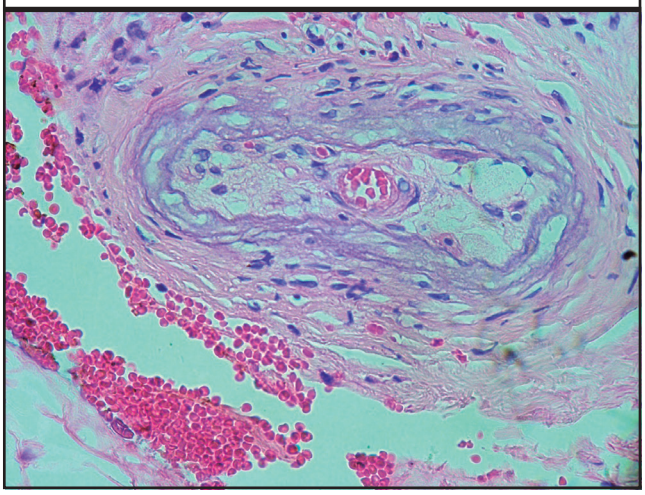


Figure 6.

Ulcers covered by necrotic bedsores and in the process of re-epithelialization, after 4 doses of Sodium Thiosulphate 20 g IV post-dialysis Monday, Wednesday and Friday.

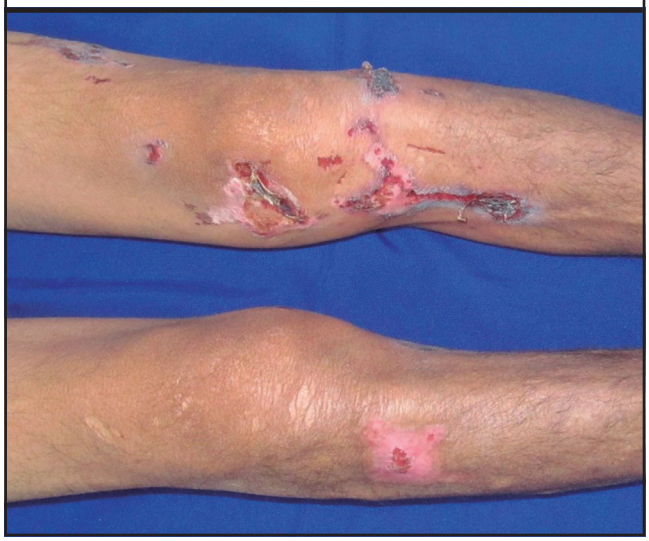


Figure 7.

Reticulate lesions covered by necrotic ulcers in the outer left thigh after 4 doses of treatment with Sodium Thiosulfate.

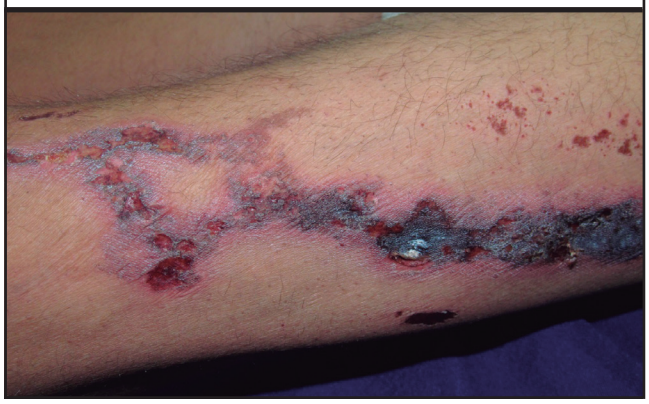
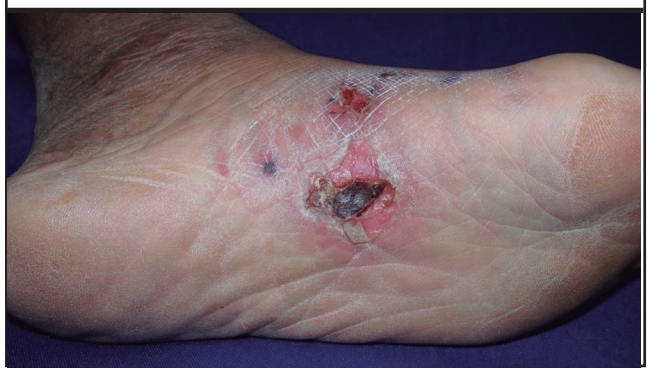


Figure 8.

Ulcer covered by necrotic bedsore located on left sole after treatment.



catheter in good conditions without fibrin, with a hemogram without leukocytosis, or neutrophilia, but a high CRP in 115. Central biliary venous catheter was implanted again, transferring the patient back to hemodialysis, and administering Vancomycin 1 g IV after each dialysis + imipenem 500 mg every 6 hours. A sample was taken for central and peripheral blood cultures.

During the following hemodialysis sessions, the patient presented episodes of hypotension, associated

Figure 9.
Sodium thiosulfate capsules per 600 mgs.

with pain and abdominal distension, with negative coprological, chest and abdomen X-ray without alterations with posterior septic shock due to peritonitis. In a second laparotomy, multiple perforations of the small intestine were identified, possibly due to Calciphylaxis, requiring vasopressor support and subsequently leading to the death of the patient. In the last days, paraclinics reported hemoglobin of 10.3, leukocytes of 42000, albumin of 2.9, calcium of 9.19, phosphorus of 2.61 and potassium of 4.3.

Discussion

Calciphylaxis is a disorder characterized by the systemic medial calcification of the arterioles that triggers ischemia and subcutaneous necrosis. Histopathological evaluation may reveal mural calcification of small vessels with or without endovascular fibrosis, extravascular calcification and ischemic vaso-occlusion, which triggers ischemic necrosis on the skin[1,2]. Calciphylaxis is a type of extra-osseous calcification (including intimal, medial and valvular calcification) that may occur more frequently in patients with advanced chronic kidney disease who are on hemodialysis or who have recently received a kidney transplant.

Regarding its prevalence, Angelis et al5 describe 10 cases of patients with calciphylaxis in a group of 242 patients on hemodialysis therapy, with a prevalence of 4.1%. The pathology was detected more frequently in young patients, with a longer time on dialysis, and with higher values of serum calcium and phosphorus.

The biopsy of the lesions constitutes the confirmatory gold standard. In our patient, we identified minimal peri-vascular infiltrates of neutrophil predominance around vessels and some arterioles of the dermo-hypodermic interface with basophilic fine granular deposits in the medial wall (compatible with deposits of calcium crystals) with lumen occlusion by fibrocystic proliferation. These findings are characteristic of calciphylaxis[1,2].

The pathogenesis of CUA is poorly understood and is possibly the result of the same process that leads to vascular and soft tissue calcification in advanced kidney disease. Clinical manifestations are caused by a reduction in arteriolar blood flow, secondary to intimal fibrosis associated with calcifications, massive calcifications of the dermo-hypodermic arterioles and the formation of thrombi within the venules. In the etiology of calciphylaxis the following are involved; Hyperparathyroidism, active vitamin D administration, hyperphosphatemia, high calcium-phosphorus product (Ca x P), low circulating levels of inhibitors of vascular calcification and chronic inflammatory states.

Several studies suggest risk factors for developing CUA in advanced stage renal disease, including; female gender6; obesity[7] (body mass index > 30) due to increasing pressure on the arterioles in the dermis and hypodermis, generating focal dystrophic calcification of the arterioles; increased phosphorus concentration6, drugs including warfarin6 (which when depleting vitamin K interfere with the activation of the Matrix gla protein that negatively regulates medial calcifications); calcium-based phosphate binders; vitamin D analogues[8], systemic glucocorticoids[9], hypercoagulability states such as deficiency in protein C and protein S; antiphospholipid syndrome and hypoalbuminemia.

CUA brings about high morbidity and mortality. The response to any therapeutic regimen appears to

be poor and is associated with high mortality, independent of efforts to treat disordered mineral metabolism. The factors of poor prognosis are advanced disease at the time of treatment, and presence of ischemic and proximal necrotic lesions in the skin and soft tissues. Digital ischemia has a better prognosis than necrosis in proximal skin. High mortality is due to superinfection (58% in one report)1, ulceration leads to mortality greater than 80%8 and the estimated survival rate at one year of CUA is about 45.8%[9].

However, the lack of evidence on the success of the treatment does not justify therapeutic nihilism. Passivity is not an option. Many aspects in the management of calciphylaxis can be used (Table 1).

The most intensely discussed therapeutic option for the management of calciphylaxis has been sodium thiosulfate (STS), which becomes a pharmacological promise because of its potential for efficacy and tolerability. The exact mechanism of action of thiosulphate is unknown, but interference with the formation of calcium phosphate crystals and its anti-inflammatory effect are among the properties that may confer therapeutic validity.

Among the adverse effects that are most frequently present due to its use are: nausea, vomiting, thrombophlebitis at the infusion site, headache and hypocalcemia, these are related to rapid infusion of the drug. It is necessary to consider the additional dose of sodium, which could stimulate thirst and volumetric overload in patients on dialysis.

The recommended schedule of application is an infusion of 20 to 25 g of the solution during the last hour of hemodialysis or shortly after each dialysis session. It can also be used through alternative routes: oral, intraperitoneal or direct topical application to the wound surface[10].

Its therapeutic success is measured by determining the parameters of quality of life, decreased pain, need for hospitalization, healing of the lesions and survival.

Zitt et al[11] report experience with this drug in 27 patients with complete remission in 52% of them, and partial remission in 19% of them, with a mortality rate of 52% at 101 days of monitoring. Nigwekar et al12 reported complete remission in 26.4%, marked

Table 1

Current modalities recommended for the management of calciphylaxis.

Intensificación de la terapia de diálisis	▪ Aumento en la duración y frecuencia de la diálisis ▪ Cambiar de hemodiálisis a hemodiafiltración ▪ Cambiar de diálisis peritoneal a hemodiálisis diaria / hemodiafiltración
Reducción del suministro e ingesta de calcio	▪ Reducir el calcio libre , evitar quelantes de fosfato basados en calcio, utilizar preferiblemente sevelamer, lantano, magnesio, hierro. ▪ Reducir dosis de vitamina D
Suspender uso de antagonistas de vitamina K	▪ Uso de anticoagulación alternativa a largo plazo: Heparina de Bajo Peso Molecular
Terapia para hiperparatiroidismo sin inducción de enfermedad ósea adinámica	▪ Aplicación de cinacalcet ▪ Paratiroidectomía ▪ Tratamiento óptimo CKD-MBD
Terapia farmacológica	▪ Tiosulfato de sodio ▪ Bifosfonatos ▪ Cinacalcet
Terapia de apoyo	▪ Manejo de heridas ▪ Tratamiento de infección local y sistémica ▪ Manejo del dolor ▪ Amputación de extremidades ▪ Atención psicológica para los pacientes y familiares

improvement in 18.9%, and some improvement in 28% of their patients, while the 1-year mortality rate was 35%.

The optimal duration of thiosulphate application is unknown, as is its safety profile. However, preliminary data indicate that bone demineralization may occur in some patients with long-term treatment. In a study13 in humans of patients with stage 5 CKD who received STS 12.5 g IV for 15 to 20 minutes after hemodialysis, twice a week for a period of at least 4 months, a significant decrease in bone mineral density of the total hip in the treated group compared to controls was observed.

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