CASE REPORT

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Successful treatment of calcific uremic arteriolopathy with pamidronate

Tratamento bem sucedido da arteriolopatia urémica calcificante com pamidronato

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ABSTRACT

Calcific uremic arteriolopathy is a rare, life-threatening obliterative small vessel vasculopathy, most commonly seen in patients with chronic renal failure. The most prominent feature of this disease is painful lesions on various areas of the skin surface. It has a complex and poorly understood pathogenesis, which limits treatment strategies. Despite all the controversies, bisphosphonates have been successfully applied in some patients. Our paper describes a case of calcific uremic arteriolopathy in a 33-year-old woman undergoing peritoneal dialysis, successfully treated with pamidronate.

Key-Words: Bisphosphonates; calcific uremic arteriolopathy; chronic kidney disease; therapy; pamidronate.

RESUMO

A arteriolopatia urémica calcificante é uma vasculopatia obliterativa de pequenos vasos, rara e potencialmente mortal, que afecta principalmente doentes com insuficiência renal crónica. A principal característica desta doença é o aparecimento de lesões dolorosas envolvendo diferentes áreas da superfície cutânea. A sua patogenia é complexa e não está completamente esclarecida, o que limita a sua abordagem terapêutica. Apesar da controvérsia, os bifosfonatos têm sido utilizados com sucesso em alguns doentes. No presente artigo, descrevemos um caso de arteriolopatia urémica calcificante numa mulher de 33 anos de idade, em diálise peritoneal, com boa resposta à terapêutica com pamidronato.

Palavras-Chave: Arteriolopatia urémica calcificante; bifosfonatos; insuficiência renal crónica; pamidronato; terapêutica.

INTRODUCTION

Calcific uremic arteriolopathy (CUA), also called calciphylaxis[1], is a rare, life-threatening disease characterized by mural calcification with intimal hyperplasia of small and medium-sized blood vessels, leading to occlusion of the vascular lumen[2].

The pathogenesis is poorly understood[3], but several risk factors have been associated with this condition, such as: end stage renal disease (ESRD), hyperparathyroidism, hypercalcaemia, hyperphosphatemia, warfarin therapy, use of vitamin D and calcium-based phosphate binders, female sex, Caucasian race, morbid obesity, recent weight loss, hypoalbuminemia and high levels of alkaline phosphatase[4,5]. Other risk factors frequently mentioned include the deficiency of vascular calcification inhibitors, such as fetuin-A and matrix Gla protein, and hypercoagulable states due to protein C and S deficiency[6].

Clinically, CUA is characterized by areas of ischaemic necrosis of the dermis and subcutaneous fat[2]. These ischaemic changes lead to livedo reticularis and/or violaceous, painful, plaque-like subcutaneous nodules that progress to ischaemic or necrotic ulcers within a few weeks[2,7].

The diagnosis of CUA is mainly based on clinical judgment and should be suspected in patients with characteristic cutaneous features and related risk factors[4]. Skin biopsy of the lesions remains the gold standard to confirm the diagnosis since there are other disorders that may mimic CUA[8].

Treatment strategies for CUA are limited by poor understanding of its pathophysiology[3]. Novel and experimental therapies have been evaluated, such as bisphosphonates and sodium thiosulfate[9]. Bisphosphonates inhibit osteoclasts and are mainly used in the treatment of resorptive bone diseases, such as osteoporosis and Paget's disease of bone[10]. A number of previous studies have shown that this class of drugs has beneficial effects on the evolution of experimental CUA[11], which has led to its use in isolated cases of this disease[9-13].

We present a case of CUA in a 33-year-old woman with end-stage renal disease requiring peritoneal dialysis, with good response to treatment with bisphosphonates.

CASE REPORT

The patient is a 33-year-old woman with congenital hydrocephaly secondary to type 2 Chiari malformation with ventricular-atrial shunt. She has been undergoing peritoneal dialysis, since June 2011, for ESRD secondary to a shunt nephritis. Her past medical history was also significant for paresis of the lower limbs and left upper limb secondary to bacterial meningitis in childhood, morbid obesity, dyslipidemia, secondary hyperparathyroidism (intact parathyroid hormone levels between 147-404 pg/mL; NR:16-87 pg/mL), stasis dermatitis of the lower limbs, pulmonary thromboembolism in 2009 and deep vein thrombosis of the lower right limb in 2006. Regarding her medication regimen, special mention is made of chronic medication with calcium carbonate (1g/day), aluminium hydroxide (1g/day), calcitriol (0.25µg/day) and warfarin. Calcitriol was administered at a dose of 0.25µg/day since 2010, after a hospitalization for severe seizures in the context of difficult to control hypocalcaemia secondary to chronic kidney disease.

In August 2011, she was admitted in the nephrology ward for volume overload and painful skin lesions, i.e., blood filled blisters, on the distal third of the right leg. She was seen by dermatology, which diagnosed pigmented purpuric dermatitis and recommended applying a moisturizer. In this admission, calcium carbonate was replaced by sevelamer carbonate.

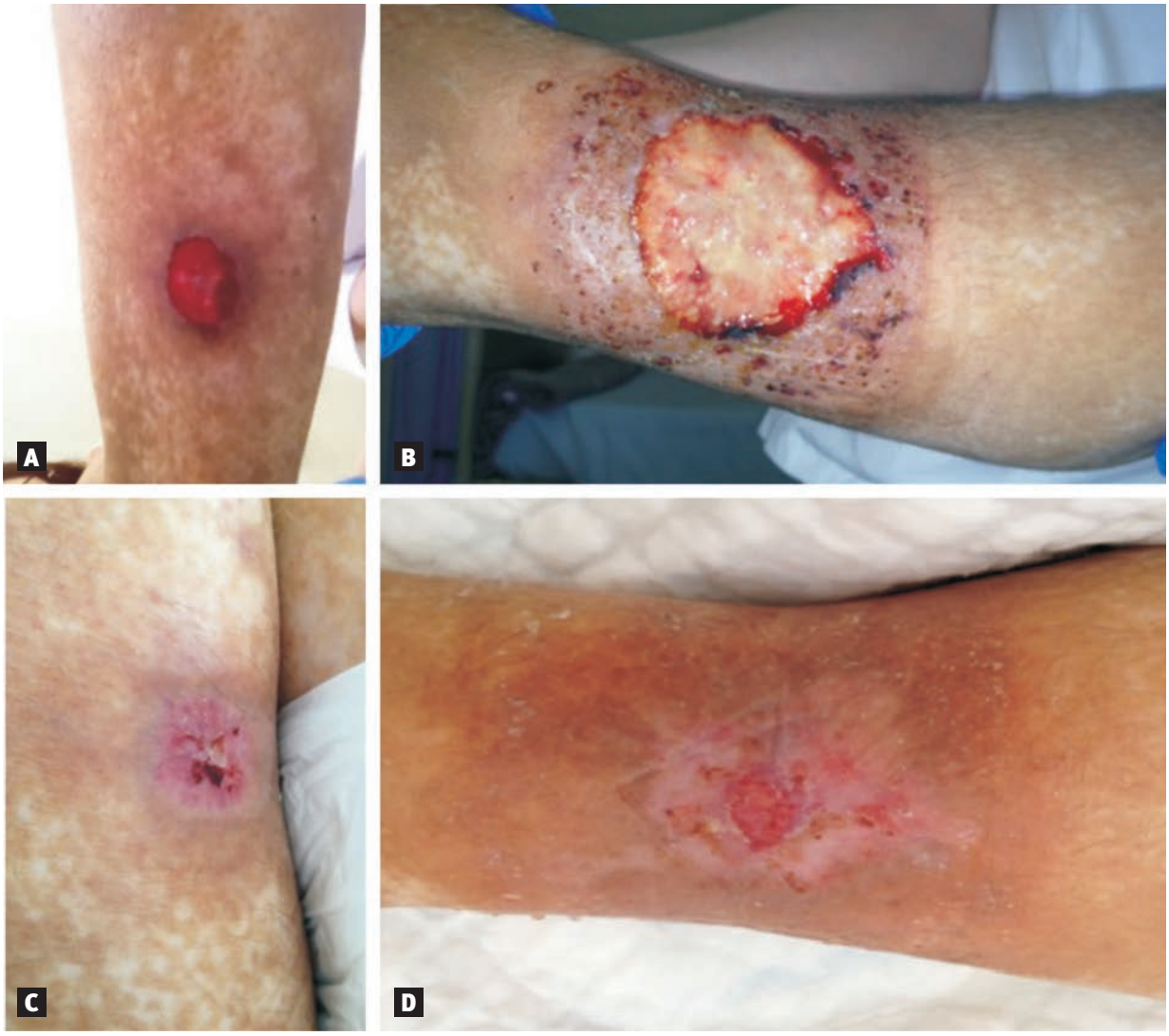
In October 2011, the calcitriol was halted due to an intact parathyroid hormone (iPTH) of 26.2 pg/mL and stable calcium blood levels (2.35 mmol/L; NR: 2.1-2.55 mmol/L). The lesions on the right leg evolved into a highly infected ulcer and were treated on an outpatient basis with antibiotic therapy and local wound care. Since the lesion proved refractory to the treatment, the patient was admitted in the nephrology ward, in November and December, to boost the local therapy. An incisional biopsy was performed in the margins of the ulcer on the right leg, which disclosed "focal loss of the epidermis covered by a superficial crust"; underlying, there was "infiltration by lymphocytes, macrophages and few neutrophils and mild dermal fibrosis"; no specific diagnosis was proposed. The skin lesions evolved slowly but favourably with local therapy. Given the non-specificity of the biopsy and the suspicion of

CUA, warfarin was replaced, in January 2012, with enoxaparin.

She was readmitted on the 9th April for worsening of the ulcer on the inner right leg. It was 6 cm in diameter with purulent exudate and necrotic edges. She presented with another ulcer on the back of the left leg measuring 2 cm in diameter, with one necrotic edge (Fig. 1). Both lesions were very painful. Skin temperature was slightly warm around the ulcer in the right leg and normal in the left leg. Both peripheral pulses were palpable. Laboratory tests showed normal leukocyte count, hypoalbuminaemia (29g/L; NR: 35-50 g/L), elevated alkaline phosphatase (226 U/L; NR: 38-126 U/L), hyperphosphatemia (2 mmol/L; NR: 0.81-1.45 mmol/L), normocalcaemia (2.19 mmol/L) and elevated C-reactive protein (12.6 mg/dL; NR: < 1 mg/dL). Further coagulation tests were normal and

Figure 1

(9 April 2012) – A) Ulcer 2 cm in diameter and necrotic edge located on the posterior aspect of the left leg. B) Ulcer 6 cm in diameter, purulent exudate and necrotic edges located on the inner aspect of the right leg. (23 May 2012) – C) Partial re-epithelialization of the lesion on the left leg. D) Complete re-epithelialization of the lesion on the right leg.

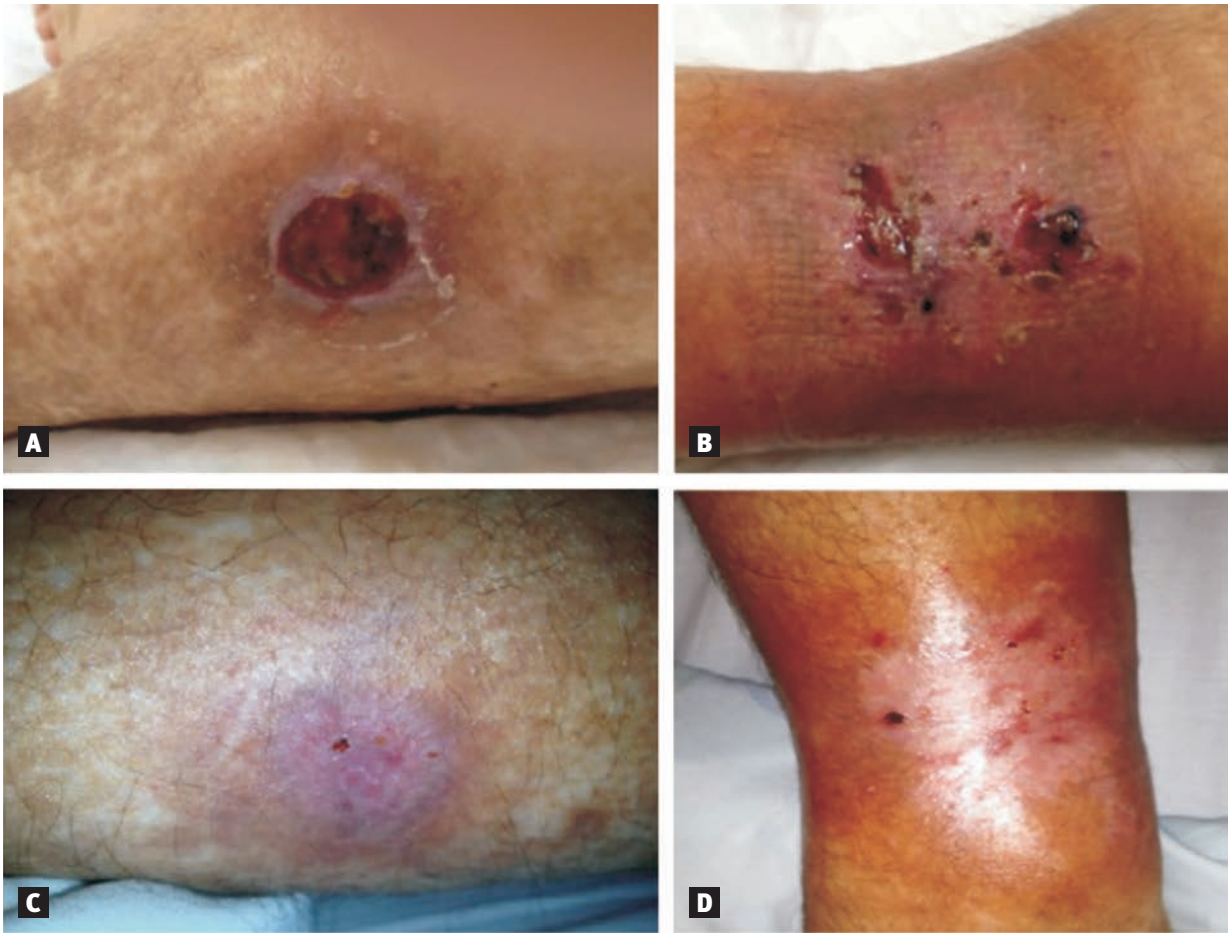


auto-immune antibodies (antinuclear antibodies, extractable nuclear antigens, antineutrophil cytoplasmic antibodies, cryoglobulins, anticardiolipin antibodies and anti β2-glycoprotein antibodies) were negative. Ciprofloxacin, buprenorphine, pamidronate (30 mg, intravenous, a total of five administrations), and local care of skin lesions were initiated. The standard calcium dialysate (1.75 mmol/L) was also replaced by a dialysate with lower calcium content (1.25 mmol/L) at the start of hospitalization. On the 15th May, iPTH of 649 pg/mL with normal phosphatemia (0.93 mmol/L) and hypocalcaemia (1.45 mmol/L), led to the reinstatement of calcitriol (0.5 ug/day) and standard calcium dialysate. She was discharged on the 23rd May, free of pain and with complete re-epithelialization of the wound on the right leg and partial re-epithelialization of the wound on the left leg (Fig. 1). Two further administrations of pamidronate were given on an outpatient basis.

The patient was readmitted on the 25th June 2012, with a 6 cm diameter ulcer on the left leg and palpable subcutaneous nodules on the right leg (Fig. 2). Laboratory tests showed normal leukocyte count, an iPTH level of 105 pg/mL, hypoalbuminemia (33 g/L), elevated alkaline phosphatase (186 U/L), hyperphosphatemia (2.52 mmol/L) and normocalcaemia (2.20 mmol/L). Bed rest and local care of skin lesions were intensified, calcitriol was stopped and pamidronate (3 administrations) and peritoneal dialysis with

Figure 2

(25 June 2012) – A) Ulcer 6 cm in diameter located on the posterior aspect of the left leg. B) Skin lesion with palpable subcutaneous nodules on the inner right leg. (23 July 2012) – C) Full re-epithelialization of the lesions on the left leg. and D) right leg.



low-calcium dialysate were restarted. Low-calcium dialysate was discontinued one week after admission due to hypocalcaemia. She was discharged on the 23rd July 2012, with complete re-epithelialization of both lesions (Fig. 2).

After 22 months' follow-up there was no further recurrence of CUA lesions, but the patient died of a non-CUA related cause.

DISCUSSION

Calcific uremic arteriolopathy has a higher incidence in patients with chronic kidney disease[14], probably due to the uremic environment, higher prevalence of mineral metabolism disorders and iatrogenic causes associated with treatment with vitamin D and calcium-based phosphate binders[5].

The histological picture of CUA is characterized by a triad: medial calcification of small and medium sized blood vessels, intima hyperplasia and necrosis of subcutaneous fat[4]. Histological evaluation may be helpful in equivocal cases of skin lesions, but a falsely negative result may occur in CUA, mainly when a single biopsy is performed[7,15-17]. In fact, the specificity and sensitivity of skin biopsies in the diagnosis of CUA have not been determined nor have definitive histologic criteria for making the diagnosis been established[7]. Besides the risk of sampling error, skin biopsy should not be routinely performed in CUA since it may inoculate or spread an infection and healing can be problematic[8]. In our case, taking into account some doubts about the diagnosis, we decided to perform the biopsy but the pattern of changes was found to be non-specific.

The current literature argues that, in cases of inconclusive histological evaluation, a presumptive diagnosis of CUA should be made and treated accordingly if other causes have been excluded and a strong clinical suspicion of CUA remains[7]. The differential diagnosis of CUA includes entities such as vasculitis, peripheral vascular disease, cryoprecipitate disorders, antiphospholipid antibody syndrome, disseminated intravascular coagulation and cholesterol embolization[3,4,7]. These diseases were considered less likely in our case attending to clinical history, physical findings and diagnostic test results – normal skin temperature, intact peripheral pulses, bilateral necrosis without other generalized skin lesions and normal coagulation and autoimmune studies. Therefore, the diagnosis of CUA was advocated based on the typical history of CUA – painful, non-healing skin lesions in the setting of a patient with ESRD with multiple risk factors (hyperparathyroidism, hyperphosphatemia, Caucasian race, female gender, obesity, treated with warfarin, vitamin D analogues and calcium-based phosphate binders)[4,6].

A multidisciplinary therapeutic approach was deemed appropriate to the presumably complex aetiology of CUA, with local wound care, adequate pain control with opiates and correction of related risk factors[6,12]. Local care of the skin wounds was based on cleansing with saline, the use of enzymatic debriding agents where there was necrotic tissue, and hydrogel dressings to stimulate granulation and epithelialization. Infection is the primary cause of mortality in CUA[7], so systemic antibiotics were given when there was suspicion of skin infection. The correction of risk factors included the suspension of warfarin and control of serum phosphorus and calcium with diet, administration of calcium-free phosphate binders, and performing peritoneal dialysis with low-calcium solutions[3]. Warfarin was discontinued because it reduces the vitamin k-dependent carboxylation of matrix Gla protein, a mineral-binding extra-cellular matrix protein that actively inhibits vascular calcification[1].

Calcific uremic arteriolopathy also calls for the replacement of vitamin D analogues with calcimimetics for the control of hyperparathyroidism[5]. In agreement with current recommendations for mineral and bone disorder in chronic kidney disease[18], we aimed to maintain iPTH levels in the range of two to nine times the upper limit for the assay. Our patient was medicated with calcitriol 0.25µg/day since a hospitalization, in 2010, for severely symptomatic hypocalcaemia secondary to chronic kidney disease. Despite hyperphosphatemia, iPTH levels were maintained within the desired goal and calcium levels were normal. In October 2011, given the low iPTH levels (26.2 pg/mL), the stabilized calcium levels and the concern of CUA, calcitriol was discontinued. However, in May 2012, it was necessary to temporarily reinstate it due to rising iPTH (649 pg/mL). At

that time, it was desirable to initiate cinacalcet but the concomitant hypocalcaemia (1.45 mmol/L), for which calcimimetics are not advisable[19], proscribed their usage.

In recent years, novel agents like sodium thiosulfate and bisphosphonates have been infrequently but successfully used off-label, in addition to previously described general measures, in the treatment of CUA[9-13,20-26]. Sodium thiosulfate acts as a potent antioxidant and increases the solubility of calcium deposits, resulting in pain relief and successful wound healing within weeks to months of initiating therapy[5]. The most commonly reported dose in dialysis patients has been 25g three times weekly until complete resolution of lesions[7]. Adverse effects to monitor include metabolic acidosis, nauseas, vomiting and headache[3]. Likewise, the use of bisphosphonates is supported by their inhibitory effect on vascular calcification[10] and their anti-inflammatory properties, resulting from inhibition of both macrophage activity and pro-inflammatory cytokines production[6]. Potential nephrotoxicity and, more especially, the risk of causing or worsening adynamic bone disease have raised questions about the safety use of bisphosphonates in chronic kidney disease[1,9]. However, some authors argue that since the bone-binding capacity of bisphosphonates is related to remodelling activity, its deposition will be reduced in the presence of adynamic bone disease[9]. In addition, the high mortality in CUA probably outweighs the concern of worsening an adynamic bone disease[1].

Since there are no randomized trials comparing bisphosphonates with sodium thiosulfate in CUA and drug approval process to use sodium thiosulfate would be time consuming and highly bureaucratic, we decided to use the former.

There is little information on the dosage of bisphosphonates in CUA, with reports of intravenous administration of pamidronate at a dose of 30 mg in 5-9 administrations, with a total treatment duration between 48 days and 3 months[3,10,11]. There are also references to success with alendronate, risendronate, etidronate and ibandronate[9,12,13]. We used intravenous pamidronate, 30 mg, in a total of 10 administrations over a period of 96 days. Response to treatment was good, with improved pain relief, full recovery of the lesions after 10 administrations and no recurrence after 24 months' follow-up. Other than a transient reduction of calcium and phosphate, no side-effect was observed.

Although there are no prospective controlled studies comparing different therapeutic strategies, which have only been evaluated in a limited number of patients, this case demonstrates the efficacy and safety of bisphosphonates in the treatment of CUA.

Conflicts of interest statement: None declared.

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