Multifaceted approach to a rare clinical case of calciphylaxis in a renal transplant recipient

Nefrologo in corsia

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ABSTRACT

Calcific uremic arteriolopathy (CUA) is a highly morbid condition usually found in ESRD patients that has rarely been reported after renal transplantation and renal function restoration. Furthermore, little is known about the optimal management of CUA in this setting. Herein, we report on the clinical case of AB, a 70-year-old woman who developed CUA after renal transplantation and renal function restoration. However, other risk factors for CUA such as diabetes and warfarin treatment, due to mechanical aortic valve implantation, were present. Thirty-eight months after renal transplantation she developed erythema and livedo reticularis in both legs and a gradually enlarging skin ulcer in the right leg. A skin biopsy of the ulcer showed features compatible with the CUA, such as sub-intimal calcification and luminal obstruction of the small dermal arterioles, tissue ischemia and signs of adipocytes degeneration. A multidisciplinary approach was adopted, including medical and non-medical treatments such as surgical debridement and vacuum-assisted closure therapy. Medical treatments included a five weeks course of once a week intravenous infusion of pamidronate and intravenous sodium thiosulfate (STS) at increasing doses. Four months after beginning the therapy with STS, a complete healing of the ulcer on the right leg and the disappearance of the livedo reticularis on the left leg was noted. In conclusion, although rare CUA may develop also in renal transplanted patients, a timely and combined therapeutic approach is essential for its resolutive treatment. Sodium thiosulfate therapy has proven to be effective and tolerated.

Key words: calcific uremic arteriolopathy, calciphylaxis, renal transplantation, sodium thiosulfate

Introduction

Calcific uremic arteriolopathy (CUA) or calciphylaxis is a rare and highly morbid condition that is found mainly in patients whit end-stage renal disease (ESRD) [1] and it has been reported only in a few clinical cases of renal transplant patients. Though largely unknown, CUA etiology is multifactorial and several elements such as hyperphosphatemia, secondary hyperparathyroidism (SHPT), use of vitamin K antagonists, diabetes mellitus, chronic inflammatory states, and female gender are thought to portend high risk of CUA [1–3]. The clinical presentation of CUA is usually characterized by skin lesions, preceded by intense pain and livedo reticularis that tend to progress to ischemic/necrotic ulcers [2]. Some histological features can be identified at skin biopsy, such as dermal arteriolar calcification, intimal hyperplasia, thrombotic occlusion and tissue necrosis [2]. At present, there is no established care of CUA aside of risk management and a multifaceted approach, rather than a single agent or treatment, is usually advocated [1, 2]. Many treatments for CUA have been proposed and, while no blinded randomized studies have taken place for any of these treatments, sodium thiosulfate (STS), either by injection or intravenous administration, is one of the most commonly utilized treatments, along with stringent wound care regimens.

In the last ten years, STS has received considerable attention and it is currently the most commonly used therapy for CUA. The beneficial effects of STS are thought to be due to its ability to promote the solubility and mobilization of calcium crystals from soft tissue calcifications [4, 5]. Furthermore, STS is known to be a powerful antioxidant agent [5]. Other lines of evidence suggest that STS may improve vascular endothelial function and promote vasodilation, reduce vascular smooth muscle cells proliferation and restore proper hepatic synthesis of albumin and fetuin-A; all these factors can contribute to reduce vascular calcification [3, 5] and may also explain the rapid improvement of pain, commonly reported by patients after initiation of STS infusion [3, 5]. Other drugs that have been used in CUA are bisphosphonate and cinacalcet, while a novel compound SNF-472 is currently under investigation [6, 7]. Although some promising results have been reported, the use of these compounds in CUA is based on case reports or case series and no randomized clinical trial (RCT) has been conducted in this domain. Several questions about the use, schedule, dosage and administration of these drugs in different patients remain unresolved, especially in renal transplant patients, in which CUA is an extremely rare condition.

Case report

In March 2012, a 70-year-old woman received renal transplantation and started taking prednisone, everolimus, and cyclosporine as immunosuppressive regimen. Nine months after renal transplantation, she underwent percutaneous mechanical aortic valve implantation and was started on warfarin. In June 2014 she developed diabetes mellitus. In January 2016, she developed extensive erythema and livedo reticularis with palpable subcutaneous painful nodules in both legs and, few weeks later, she also developed a skin ulcer in her right leg that gradually expanded (Figure 1). The ulcer was initially treated with surgical debridement and vacuum-assisted closure (VAC) therapy. At this time, the main laboratory tests showed an estimated glomerular filtration rate (eGFR; CKD-EPI) of 28 mL/min per 1.73 m^2, serum PTH levels 329 pg/mL, corrected serum calcium levels 10.4 mg/dL, serum phosphate 3.8 mg/dL, and C-reactive protein levels 110.6 mg/L (reference range, <5 mg/L). To shed light on the nature of the skin lesion, a skin biopsy was performed in March 2016, showing features compatible with CUA, such as sub-intimal calcification and luminal obstruction of the small dermal arterioles, tissue ischemia and signs of adipocytes degeneration (Figure 2). Because anti-vitamin K agents, such as warfarin, have been associated with CUA [3], the case was discussed with the cardiac surgeon and the hypothesis to replace

warfarin with direct oral anticoagulants, such as dabigatran or low-molecular weight heparin (LMWH), was evaluated. However, she was continued on warfarin because of a study conducted on patients carrying mechanical valves, showing that patients treated with dabigatran have an excess of thromboembolic and bleeding events, compared with the warfarin group [8]. Another reason was the lack of data on the chronic use of LMWH in patients with prosthetic valves, with indications for short-term anticoagulation therapy only (generally for bridging while vitamin K antagonists therapy is being initiated or temporarily discontinued) [9].

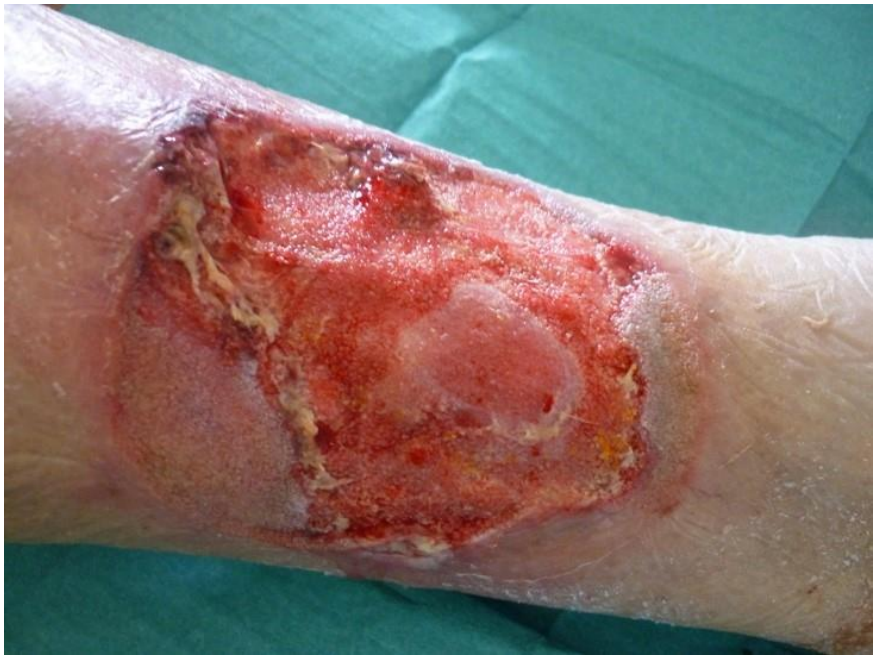

Fig. 1: Progressive ulceration of the skin and underlying sub-dermal layers

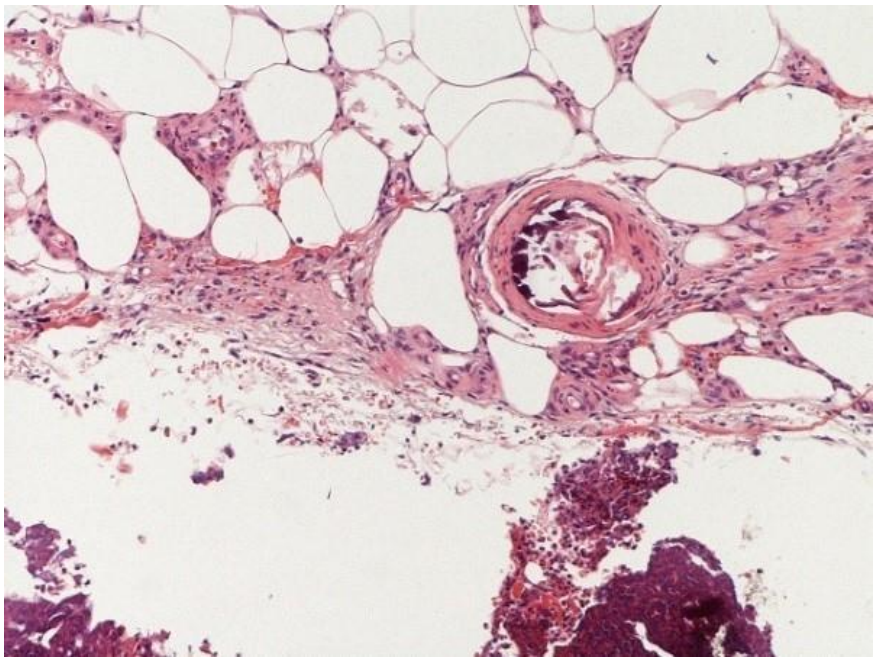

Fig. 2: H&E 100 X. Subcutaneous tissue with signs of ischemic regression. In the center a small vessel with sub-intimal calcification, partial obliteration of the lumen, and thinning of the tunica media. On the upper part adipocytes with signs of degeneration. H&E, hematoxylin-eosin

Because of the unavailability of STS at that time (off-label indication) and in consideration of the secondary hyperparathyroidism (SHPT), it was decided to start treatment with oral cinacalcet (30 mg/day) and intravenous pamidronate (Aredia® 30 mg a week for five weeks), according to what reported by the scheme of Monney et al. [10] and Floege et al. [11]. However, cinacalcet was soon discontinued due to the appearance of nausea and vomiting (common side effects of cinacalcet therapy), while treatment with pamidronate only partially reduced the pain and the extent of the ulcer. Then, in July 2016, intravenous STS treatment was started at a dose of 12.5 g two times a week, monitoring arterial blood gas and blood pressure [3]. One month after starting therapy with STS a significant reduction in pain was subjectively reported by the patient. Hence, the administration of STS was increased from two to three times a week. Four months after the beginning of the therapy with STS, a complete healing of the ulcer was documented (Figure 3).

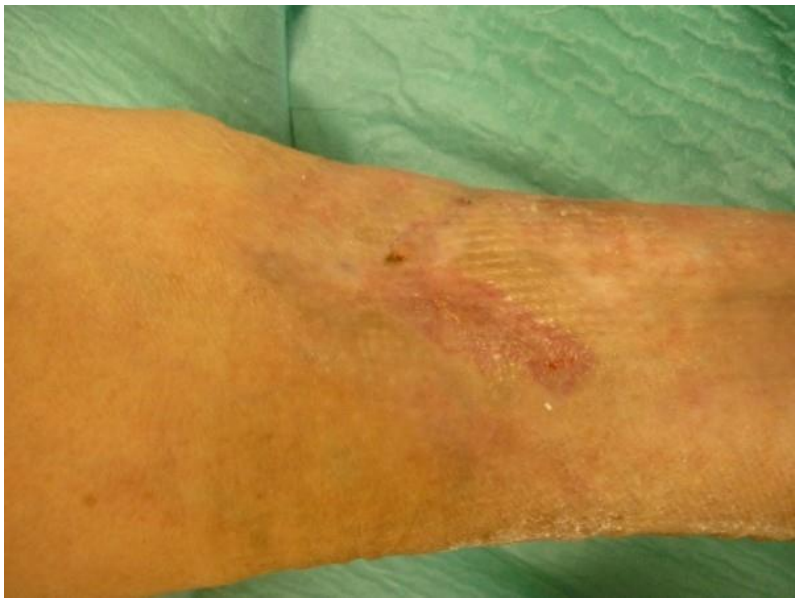

Figure 3: Complete healing of the ulceration four months later after starting treatment with STS

Notable side effects of STS were nausea, vomiting, metabolic acidosis, hypotension, hypocalcaemia, QT prolongation, and volume overload [3]. During STS treatment the main clinical and biochemical parameters did not change; in particular, the acid-base balance remained unchanged, while there was a significant reduction in both C-reactive protein levels (from 110.6 to 3.5 mg/L) and white blood cell count (from 13,600 to 7,530 per mm^3) (Table 1). During treatment with STS, blood glucose and glycated hemoglobin levels did not require special changes in the diabetes mellitus therapy. In fact, fasting plasma glucose levels were always <130 mg/dl (v. n. 60-110 mg/dl) and those of glycated hemoglobin ranged from 38-57 mmol/mol (v. n. 20-42 mmol/mol). The treatment for diabetes mellitus was based on the use of a mixture of insulin lispro solution, a rapid-acting blood glucose-lowering agent, and insulin lispro protamine suspension, an intermediate-acting blood glucose-lowering agent (Humalog® Mix 50/50™). Also, no significant electrocardiographic changes were noticed during STS therapy. Although the patient reported nausea and vomiting during the first two months of therapy, these side effects were never considered by her or by the attending physicians so severe to require STS suspension and were easily controlled with the use of antiemetics. Currently, the patient has no clinical signs of disease activity.

Parameters	Baseline	Month 1	2	3	4
serum creatinine, mg/dL	1.8	2.1	2	1.8	1.8
eGFR, mL/min/ 1.73 m^2	28	25	26	28	29
calcium, albumin-corrected, mg/dL	10.4	9.5	10.0	9.9	9.9
albumin, g/dL	3.6	3.7	3.3	3.4	3.5
serum phosphorus, mg/dL	3.8	3.3	3.2	3.8	3.6
serum potassium, mEq/L	4.0	4.1	4.2	3.8	3.8
serum PTH, pg/mL	329	220	231	258	293
C-reactive protein, mg/L	110.6	62.0	10.9	10.5	3.5
WBCs, mm^3	13.600	8.100	10.000	9.110	7.530
pH	7.42	7.40	7.42	7.43	7.46
bicarbonate (HCO_3), mEq/L	23.9	23.0	23.1	23.5	23.6
blood pressure, mmHg	140/80	142/86	130/80	150/80	140/80
nausea	marked	marked	moderate	moderate	slight
vomiting	moderate	moderate	absent	absent	absent

Table 1: Main biochemical and clinical parameters during sodium thiosulfate therapy

Discussion

Although typically associated with ESRD, the diagnosis of calciphylaxis must be considered even when treating renal transplant recipient. The early detection of CUA enabled us to treat the problem in the best possible way, including the removal of risk factors for the CUA, multimodal treatment with wound care, VAC therapy, pamidronate, and STS. In the treatment of CUA, one of the main steps is to try to correct its potential risk factors.

In our clinical case, SHPT and warfarin therapy were the 2 identified modifiable risk factor associated with CUA [3, 5]. In order to correct the SHPT without increasing the calcium and phosphate balance, we tried administering cinacalcet, that in Italy can be prescribed in renal transplanted patients with SHPT and hypercalcemia. Although CUA has been more commonly associated adynamic rather than high bone turnover disease [12], we decided to start cinacalcet therapy because, according to K/DOQI guidelines [13], our patient had markedly elevated serum parathyroid hormone and calcium, a condition that contraindicated the use of vitamin D or vitamin D analogues (which increase the risk of hypercalcemia), and because their use has been associated by some authors with CUA [3, 5]. In contrast, in a recently published post hoc analysis of the EVOLVE trial, treatment of SHPT with cinacalcet was associated with a 69-75% reduction in the risk of CUA [11]. Unfortunately, cinacalcet was stopped after a few days of treatment due to the onset of nausea and vomiting. The other modifiable factor in our patient was represented by warfarin therapy [3]. Knowing the strong association between warfarin and CUA, we investigated the hypothesis of replacing warfarin with a new oral anticoagulant such as dabigatran or low-molecular weight heparin (LMWH). However, the cardiac surgeon advised against its use because a study conducted on patients carrying mechanical valves showed that patients treated with dabigatran have an excess of thromboembolic and bleeding events as compared with the warfarin group [8]. Similarly, the replacement of warfarin with LMWH was excluded as these are only indicated in patients with prosthetic valves for short-term therapy, generally for bridging while vitamin K antagonists therapy is being initiated or temporarily discontinued [9].

Medical treatment that can be administered in cases of CUA are biphosphates and sodium thiosulphate (STS) [3, 5]. We used pamidronate as first line agent because STS was not available when the diagnosis was made. Pamidronate seems to inhibit some factors involved in vascular calcifications deposition, osteoclast activity as well as the secretion of proinflammatory cytokines by macrophages [14]. Although pamidronate has been shown to be effective in the treatment of CUA, data in the literature are scanty [10]. To date, the use of STS represents the most important advance in the treatment of CUA and its he beneficial effects are thought to be due in part to its ability to enhance solubility and mobilization of calcium crystals from the soft tissue calcifications [1, 5]. Furthermore, STS is also a powerful antioxidant agent, further corroborating the hypothesis that may exert a positive effect on vasculature [5]. Although based on case reports, data suggest that STS has a number of positive effects including improvement of vascular endothelial function and vasodilation, reduction of vascular smooth muscle cells proliferation as well as restoration of hepatic synthesis of albumin and fetuin-A [5]. Although some authors suggest a therapeutic algorithm for CUA treatment, it is still not clear what is the optimal dose of STS [3]. The dosage regimens most widely adopted in dialysis patients ranges from 20 to 25 grams three to five times per week [3] but almost no data exists on the use of STS in patients with eGFR <60 mL/min/1.73 m^2. However, as 20 to 50% of the administered dose of STS is eliminated unchanged in the urine, it seems reasonable to start therapy with a lower dose compared to dialysis patients. Hence, a reasonable approach is to start with a dose of 12.5 grams twice a week and titrate the dosage according to side effects and CUA evolution. In any case, it is preferable not to exceed 25 grams of STS three times per week in patients with eGFR <60mL/min/1.73 m^2 [3, 5]. While there is some consensus on the need to start STS as early as possible, normally at the appearance of skin ulceration [5], the optimal duration of treatment with STS is currently unknown and it seems reasonable to continue the treatment until the complete resolution of ulcerative lesions, which can take up to several months [5].

Finally, Non-medical therapy is also part of CUA management: surgical or non-surgical debridement, VAC therapy, antibiotic treatment guided by microbiological results of wound swabs, as well as pain treatment with oral opioid, are commonly employed and should be considered on case by case.

Conclusions

This clinical case demonstrates that a diagnosis of calcific uremic arteriolopathy must be considered even in renal transplant patients presenting an ulcer of unknown etiology; early diagnosis and a prompt multimodal treatment approach, in fact, may allow for the complete healing of this rare disease.

Although STS is now the most common agent used to treat CUA, there is a great need for randomized controlled trials that help determine the optimum dosage of STS and the duration of treatment. Similarly, in light of the poor prognosis of CUA, data on the safety and efficacy of novel compound currently being tested, such as SNF-472 [6], are much awaited.

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