Successful Management of Calciphylaxis in a Kidney Transplant Patient: Case Report

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Introduction. Calciphylaxis is a rare and often fatal condition mostly associated with end-stage renal disease. The pathophysiology remains elusive and treatment options are scarce. We present a rare case of severe calciphylaxis after kidney transplantation in a patient with persistent hyperparathyroidism. Case description. A 78-year-old man with a history of end-stage renal disease developed edema and ulcerations on both lower limbs 14 months after kidney transplantation while receiving an mammalian target of rapamycin inhibitor to manage polyoma virus-associated nephropathy. Skin biopsies taken from the ulcerations confirmed calciphylaxis. A multimodal treatment regimen combining medical (calcium-free phosphate binders, cinacalcet, paricalcitol, sodium thiosulfate, antibiotic treatment) and surgical treatments (debridement and autologous skin transplantation) ultimately resulted in successful wound healing. Discussion. We describe a case of severe calciphylaxis in a nonuremic patient after kidney transplantation. Rapid diagnosis by skin biopsy and an aggressive multimodal therapy regimen followed by long-term oral sodium thiosulfate treatment were crucial factors for a favorable outcome.

Calciphylaxis or calcific uremic arteriolopathy is a rare (1-4% of the population with end-stage renal disease [ESRD]) and life-threatening clinical condition with a fatal progression in the majority of cases.1 The details of the underlying pathogenesis are still poorly understood.2 Characteristic calcification of small-sized and medium-sized arterioles is considered to be the major trigger for intense septal panniculitis, thrombotic vaso-occlusion, and the subsequent pathognomonic subcutaneous necrosis. The syndrome is usually diagnosed in patients suffering from ESRD receiving renal replacement therapy.1 Established risk factors include an elevated serum phosphate levels, hyperparathyroidism (HPT), coagulopathies, the use of vitamin K antagonists, hypocalcemia, diabetes mellitus, obesity (body mass index > 30), treatment with corticosteroids and female gender.3 However, calciphylaxis can also occur in patients without ESRD, so-called nonuremic calciphylaxis.4-6 We continue to use the term calciphylaxis instead of calcific uremic arteriolopathy to also refer to the disorder in non-ESRD patients.

Recommended therapeutic approaches for calciphylaxis are heterogeneous, and there is no standardized treatment regimen. Treatment attempts mainly focus on wound and pain management, normalization of elevated calcium and phosphate levels by hemodialysis and medication, pharmacological or surgical reduction of elevated parathyroid hormone (PTH) levels, and (off-label) administration of sodium thiosulfate (STS). Sodium thiosulfate is supposed to prevent and reduce the critical calcium phosphate precipitation in small vessels.7-9 Here, we report the successful management of nonuremic calciphylaxis in a patient after kidney transplantation and present a possible blueprint for an effective therapeutic approach.

CASE DESCRIPTION

A 78-year-old man was admitted to our nephrology center with fever and painful ulcerations on both legs in December 2014, 14 months after kidney transplantation. The ulcerations developed without trauma 2 months before admission. The patient had a history of ESRD due to mesangioproliferative glomerulonephritis diagnosed in 2001. Peritoneal dialysis had been performed for 3 years preceding postmortem kidney transplantation in October 2013. There had been longstanding severe secondary HPT before transplantation.
(laboratory results 2011-2013: ionized calcium, 1.25 to 1.35 mmol/L, reference range, 1.0-1.3 mmol/l; phosphate, 1.8-2.1 mmol/L, reference range, 0.81-1.45 mmol/l; PTH, 590-740 pg/mL, reference range, 15-65 pg/mL). Furthermore, the patient was treated with vitamin K antagonists due to a heterozygous factor II mutation with venous thromboembolism. The patient was maintained on usual immunosuppressive triple therapy with tacrolimus, mycophenolate, and prednisone. Estimated glomerular filtration rate (MDRD) was 48 mL/min per 1.73 m². Because of biopsy-proven polyoma virus-associated nephropathy, the mTOR inhibitor everolimus was introduced instead of mycophenolate. Under this regimen, polyoma virus load decreased from more than 10 million copies/mL to less than 10 thousand copies/mL and estimated glomerular filtration rate (GFR) (MDRD) stabilized at around 42 mL/min per 1.73 m² with tacrolimus and everolimus trough levels of 2 to 4 ng/mL in whole blood. There was no posttransplantation diabetes mellitus.

During the course of treatment, persisting edema of the lower limbs developed and initially was considered a side effect of everolimus. Treatment with mTOR inhibitor was discontinued, leading to a dual immunosuppressive regimen with tacrolimus trough levels between 3 to 5 ng/mL and prednisone 10 mg per day. Despite discontinuation of everolimus, indurations and ulcerations of the skin formed.

Physical examination revealed extensive gangrenous ulcerations on both lower legs (Figure 1A). Wound swabs taken from the lesions grew Staphylococcus dysgalactiae, Staphylococcus aureus, Klebsiella oxytoca, and Stenotrophomonas maltophilia. Initial blood tests showed deranged serum levels of PTH (428 pg/mL), total calcium (2.29 mmol/L), ionized calcium 1.26 mmol/L, and phosphate slightly off range (1.6 mmol/L) as well as an elevation of white blood cell (27 800 cells/μL; reference range, 3500-10 500 cells/μL) and C-reactive protein (280 mg/L; reference range, <3 mg/L). There were no symptoms or signs of peripheral artery occlusive disease. Biopsies from the skin lesions were taken. The samples showed pathognomonic calcium deposits in the small dermal arterioles, confirming the diagnosis of calciphylaxis (Figures 2A-C).

We established a multimodal treatment regimen. Wounds were surgically debrided and vacuum-assisted closure therapy was applied. Antibiotic treatment was guided by clinical evaluation, microbiological results of wound swabs, and laboratory results (piperacillin/tazobactam, ceftriaxone, meropenem, piperacillin/tazobactam, levofloxacin, linezolid, and cotrimoxazole were applied sequentially over several weeks). Opioid analgesics were given according to the pain service team. Calcium-free phosphate binders (sevelamer carbonate) and cinacalcet (60-90 mg per day) were given to lower the levels of PTH below 250 pg/mL. Paricalcitol (1 μg per day) was included in the regimen having shown benefits in calciphylaxis in previous reports. The vitamin K antagonist
To dissolve calcium phosphate deposits and to prevent further deposition, off-label medication with STS has been described as beneficial in several case reports and should be considered. In this case, STS was initially given intravenously to achieve high serum levels and effectively stop ulceration growth. Intralesional STS application might also be an effective alternative for localized calciphylaxis. As a convenient maintenance therapy for our kidney transplant patient, we later switched to oral STS treatment as described above. In our case, Paricalcitol was chosen as an active vitamin D agent to circumvent cinacalcet-associated hypocalcemia and to prevent further microvascular calcification. Administration of bisphosphonates is thought to prevent arterial calcification and has been reported to be beneficial in calciphylaxis. The same could be true for denosumab. Both substances were not used in our patient because calcium levels were on the low side.

Also, administration of hyperbaric oxygen has been reported in successful treatment of calciphylaxis. Especially in patients with failure of multimodal therapy, hyperbaric oxygen treatment could be a further option with only rare serious side effects. There might even be a synergism combining STS and hyperbaric oxygen therapy.

Pathophysiologically, the calcification of the arterioles seems to trigger the subcutaneous septal panniculitis with thrombotic vaso-occlusion and subsequent necrosis, this provides the rationale for treatment with low-dose tissue plasminogen activator, which might be considered.

In conclusion, an early multidisciplinary therapeutic approach is mandatory for successful management of calciphylaxis for which our case report is suggesting a practical outline. The diverse treatment options demonstrate that the management of this rare condition should be taken over by a specialized facility. Even after kidney transplantation, and in the absence of ESRD, calciphylaxis must be considered in a given context by health care providers to allow early treatment and achieve a favorable outcome for the patient.

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