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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.

(*Transplantation Direct* 2016;2: e70; doi: 10.1097/TXD.0000000000000582. 17 March 2016.)

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, hypoalbuminemia, 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 5 years preceding postmortem kidney transplantation in October 2013. There had been longstanding severe secondary HPT before transplantation

Received 5 December 2015. Revision received 17 January 2016.

Accepted 9 February 2016.

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E.N.H. and G.W. are funded by the Deutsche Forschungsgemeinschaft (DFG).

The authors declare no conflicts of interest.

T.W. and F.A. gave equal contribution.

T.W., F.A., and A.K.Z. wrote the first draft of the article. K.T.H. performed the histological examination of the lesion. E.N.H., R.W., S.Z., and G.W. participated in patient diagnosis and treatment and critically reviewed and edited the manuscript. All authors read and approved the final article.

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000000582

(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 m^2. 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 m^2 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).

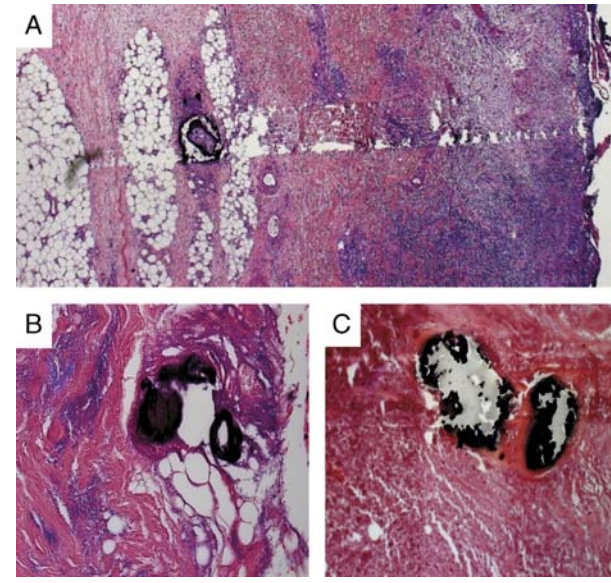

FIGURE 2. Histology of the left lower leg. A, Ischemic necrosis of skin and subcutis. B, C, Intimal proliferation of small vessels with luminal narrowing. Calcification of the media of small vessels in the panniculus with fibroplasia of the intima. A, 25 × H&E, (B) 400 × H&E, (C) 200 × von Kossa staining. H&E, hematoxylin-eosin.

We established a multimodal treatment regimen.[10] 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.[11,12] The vitamin K antagonist

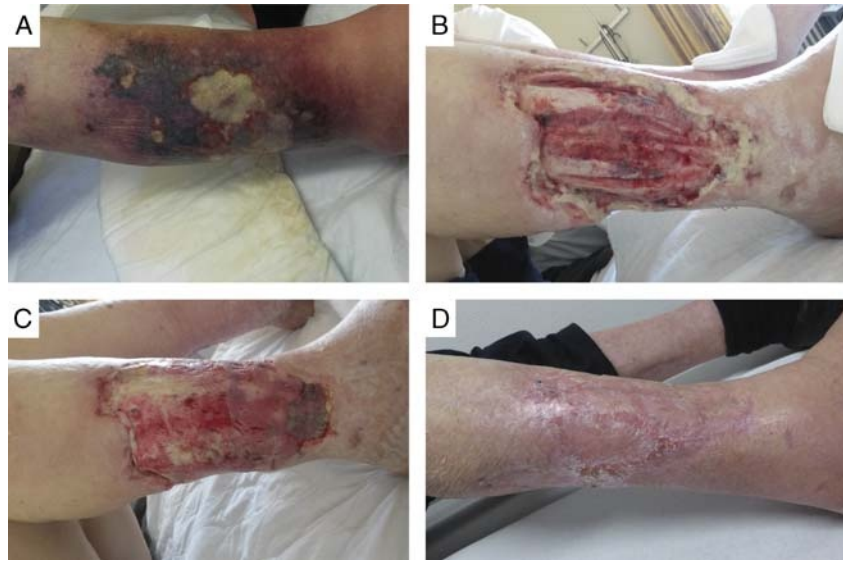

FIGURE 1. Skin manifestation of calciphylaxis on the right lower leg. At admission (A), 1 day after surgical debridement (B), 1 day after autologous skin graft transplantation (C), and 7 months after autologous skin graft transplantation (D).

(phenprocoumon) was replaced by a factor Xa antagonist (rivaroxaban) and vitamin K was supplemented regularly. To dissolve tissue calcium deposition, off-label intravenous STS was administered (GFR-adjusted dose: 12.5 g, thrice per week[12]) carefully monitoring the acid-base balance. Sodium bicarbonate was given orally to keep bicarbonate levels within normal range (measured values, 21-26 mmol/L), thus avoiding metabolic acidosis. Sodium thiosulfate treatment was well tolerated without any obvious adverse effects.

Hyperbaric oxygen therapy as a supportive treatment option for calciphylaxis was considered but dismissed by the patient due to claustrophobia.

This multimodal pharmacological approach in combination with optimal wound care and antibiotic treatment led to pain control and eventually arrested ulceration growth. To improve wound healing after debridement, plastic reconstruction with autologous skin graft transplant was performed (Figures 1B-D). Intravenous STS was administered regularly over a period of 6 months until formation of granulation tissue of the ulcer floor was achieved. Under this treatment regimen, transplant renal function deteriorated, and polyoma virus-associated nephropathy was still present on kidney biopsy. Eventually, estimated GFR (MDRD) stabilized at 30 mL/min per 1.73 m^2, with a low polyoma viral load of 500 copies/mL.

For consolidation, we switched to oral STS treatment (600 mg thrice daily[13,14]; capsules provided by our hospital pharmacy), and weekly clinical follow-ups were scheduled. Follow-up blood tests showed normalized total calcium (2.2-2.3 mmol/L), phosphate (1.0-1.2 mmol/L), and PTH levels (150-250 pg/mL). Oral STS treatment was applied for 3 additional months until complete wound healing was accomplished. Medication with cinacalcet and paricalcitol is also continued because the patient declined parathyroidectomy, the benefit of which is debatable.[3,15]

DISCUSSION

We describe the management of a case of nonuremic calciphylaxis after kidney transplantation despite normal graft function. Details of our successful multimodal regimen are highlighted, providing a possible blueprint for an effective treatment. Although typically associated with ESRD, there are some reports of calciphylaxis after kidney transplantation.[16-18] Although most case reports describe calciphylaxis either shortly or many years after kidney transplantation, implicating aftermath of ESRD or deteriorating graft function, our case illustrates that calciphylaxis must be considered even when graft function is normal.

In this case, individual risk factors included ESRD before kidney transplantation, secondary/tertiary HPT resulting in elevated calcium and phosphate levels, coagulopathy with venous thromboembolism, and anticoagulation using vitamin K antagonists.

Our case demonstrates the vital importance of both early diagnosis by skin biopsy and aggressive multimodal therapy.[3] Treatment should focus on optimal wound care (including management of peripheral artery occlusive disease if present), analgesia, antibiotic treatment if necessary, normalization of sodium, and phosphate levels as well as PTH levels by medication or surgical intervention.

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.[7,8] 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.[19] As a convenient maintenance therapy for our kidney transplant patient, we later switched to oral STS treatment as described above.[13]

In our case, Paricalcitol was chosen as an active vitamin D agent to circumvent cinacalcet-associated hypocalcemia and to prevent further microvascular calcification.[11,20]

Administration of bisphosphonates is thought to prevent arterial calcification and has been reported to be beneficial in calciphylaxis.[21-24] The same could be true for denosumab.[25] 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.[26,27] 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.[26,28]

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.[29]

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.

REFERENCES

1. Angelis M, Wong LL, Myers SA, et al. Calciphylaxis in patients on hemodialysis: a prevalence study. *Surgery*. 1997;122:1083–1090.
2. Dominguez A. Calciphylaxis: controversies in pathogenesis, diagnosis and treatment. UT Southwestern Medical Center Web site. https://cme.utsouthwestern.edu/sites/cme.utsouthwestern.edu/files/em1508d_082115_protocol_dominguez.pdf. Published August 20, 2015. (Accessed on October 1, 2015).
3. Nigwekar SU, Kroshinsky D, Nazarian RM, et al. Calciphylaxis: risk factors, diagnosis, and treatment. *Am J Kidney Dis*. 2015;66:133–146.
4. Nigwekar SU, Wolf M, Sterns RH, et al. Calciphylaxis from nonuremic causes: a systematic review. *Clin J Am Soc Nephrol*. 2008;3:1139–1143.
5. Almafragi A, Vandorpe J, Dujardin K. Calciphylaxis in a cardiac patient without renal disease. *Acta Cardiol*. 2009;64:91–93.
6. Couto FM, Chen H, Blank RD, et al. Calciphylaxis in the absence of end-stage renal disease. *Endocr Pract*. 2006;12:12406–12410.
7. Schlieper G, Brandenburg V, Ketteler M, et al. Sodium thiosulfate in the treatment of calcific uremic arteriolopathy. *Nat Rev Nephrol*. 2009;5:539–543.
8. Nigwekar SU, Brunelli SM, Meade D, et al. Sodium thiosulfate therapy for calcific uremic arteriolopathy. *Clin J Am Soc Nephrol*. 2013;8:1162–1170.
9. Cicone JS, Petronis JB, Embert CD, et al. Successful treatment of calciphylaxis with intravenous sodium thiosulfate. *Am J Kidney Dis*. 2004;43:1104–1108.
10. Baldwin C, Farah M, Leung M, et al. Multi-intervention management of calciphylaxis: a report of 7 cases. *Am J Kidney Dis*. 2011;58:988–991.

11. Kakagia D, Kriki P, Thodis E, et al. Calcific uremic arteriolopathy treated with cinacalcet, paricalcitol, and autologous growth factors. *J Cutan Med Surg*. 2011;15:121–124.
12. Santos PW, Hartle EJ, Quarles DL. Calciphylaxis (calcific uremic arteriolopathy). In: UpToDate, Goldfarb S(ED). UpToDate, Waltham, MA. (Accessed on September 23, 2015).
13. AlBugami MM, Wilson JA, Clarke JR, et al. Oral sodium thiosulfate as maintenance therapy for calcific uremic arteriolopathy: a case series. *Am J Nephrol*. 2013;37:104–109.
14. Musso CG, Enz P, Vidal F, et al. Oral sodium thiosulfate solution as a secondary preventive treatment for calciphylaxis in dialysis patients. *Saudi J Kidney Dis Transpl*. 2008;19:820–821.
15. Weenig RH, Sewell LD, Davis MD, et al. Calciphylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol*. 2007;56:569–579.
16. Alikadic N, Kovac D, Krasna M, et al. Review of calciphylaxis and treatment of a severe case after kidney transplantation with iloprost in combination with hyperbaric oxygen and cultured autologous fibrin-based skin substitutes. *Clin Transplant*. 2009;23:968–974.
17. Hanvesakul R, Silva MA, Hejmadi R, et al. Calciphylaxis following kidney transplantation: a case report. *J Med Case Rep*. 2009;3:9297.
18. Vanbelleghem H, Terryn W, Van Leuven L, et al. A dramatic case of calciphylaxis 20 years after kidney transplantation. *Nephrol Dial Transplant*. 2004;19:3183–3185.
19. Strazzula L, Nigwekar SU, Steele D, et al. Intralesional sodium thiosulfate for the treatment of calciphylaxis. *JAMA Dermatol*. 2013;149:946–949.
20. Vargemezis V, Liakopoulos V, Kriki P, et al. Pivotal role of paricalcitol in the treatment of calcific uremic arteriolopathy in the presence of a parathyroid adenoma. *Am J Kidney Dis*. 2010;55:144–147.
21. Raymond CB, Wazny LD, Sood AR. Sodium thiosulfate, bisphosphonates, and cinacalcet for calciphylaxis. *CANNT J*. 2009;19:25–27; quiz 28–29.
22. Hanafusa T, Yamaguchi Y, Tani M, et al. Intractable wounds caused by calcific uremic arteriolopathy treated with bisphosphonates. *J Am Acad Dermatol*. 2007;57:1021–1025.
23. Price PA, Faus SA, Williamson MK. Bisphosphonates alendronate and ibandronate inhibit artery calcification at doses comparable to those that inhibit bone resorption. *Arterioscler Thromb Vasc Biol*. 2001;21:817–824.
24. Torregrosa JV, Durán CE, Barros X, et al. Successful treatment of calcific uraemic arteriolopathy with bisphosphonates. *Nefrologia*. 2012;32:329–334.
25. Helas S, Goettsch C, Schoppet M, et al. Inhibition of receptor activator of NF-kappaB ligand by denosumab attenuates vascular calcium deposition in mice. *Am J Pathol*. 2009;175:473–478.
26. An J, Devaney B, Ooi KY, et al. Hyperbaric oxygen in the treatment of calciphylaxis: a case series and literature review. *Nephrology (Carlton)*. 2015;20:444–450.
27. Vassa N, Twardowski ZJ, Campbell J. Hyperbaric oxygen therapy in calciphylaxis-induced skin necrosis in a peritoneal dialysis patient. *Am J Kidney Dis*. 1994;23:878–881.
28. Rogers NM, Coates PTH. Calcific uremic arteriolopathy—the argument for hyperbaric oxygen and sodium thiosulfate. *Semin Dial*. 2010;23:38–42.
29. el-Azhary RA, Arthur AK, Davis MDP, et al. Retrospective analysis of tissue plasminogen activator as an adjuvant treatment for calciphylaxis. *JAMA Dermatol*. 2013;149:63–67.