CEN Case Reports (2020) 9:122–128
https://doi.org/10.1007/s13730-019-00439-8

CASE REPORT

Multidisciplinary management of calciphylaxis: a series of 5 patients at a single facility

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Received: 9 August 2019 / Accepted: 6 December 2019 / Published online: 17 December 2019

Abstract

Calciphylaxis is a rare and severe disease that manifests with painful skin ulceration and necrosis. Herein, we report five patients of hemodialysis patients with skin biopsy-proven calciphylaxis at a single facility. One patient had undergone parathyroidectomy (PTx) due to severe secondary hyperparathyroidism, four had been treated with vitamin D receptor activators, and two were on warfarin therapy. All patients had hyperphosphatemia, and one had hypercalcemia. The intact parathyroid hormone level at diagnosis was 2 pg/ml in the patient after PTx, while three patients were within the target range. The average period after diagnosis of calciphylaxis was 2 months. Skin lesions were present on the thighs and lower legs in two patients, and on the dorsum of the foot in one patient. In skin biopsy, calcification was found in the arteriolar media in four patients, and calcium (Ca) was deposited in the dermal lesion in one patient. All patients received local cures, surgical debridement, antibiotics to control infectious diseases, and strict control of serum Ca and phosphate. Calcimimetics were used in all patients except one who had undergone PTx one month before, sodium thiosulfate was used in 4 patients, and low Ca dialysate was used in three patients. The average follow-up period was 7.4 months. Four patients were cured, and one died due to infection. We suggest that multidisciplinary management for infectious diseases, surgical debridement, strict control of mineral and bone markers from the early stage, and elimination of risk factors may improve the course of calciphylaxis, which is a life-threatening disease.

Keywords Calciphylaxis · Calcific uremic arteriolopathy · Calcimimetics · Hyperphosphatemia · Surgical debridement

Introduction

Calciphylaxis, which is also known as calcific uremic arteriolopathy (CUA), is a rare multifactorial cutaneous vascular disease characterized by chronic, painful, non-healing wounds that occurs in patients with end-stage renal disease (ESRD) [1]. The term "calciphylaxis" was first used by Hans Selye in 1961 [2], based on laboratory experiments to induce diffuse subcutaneous soft tissue calcification in rats using preparations such as parathyroid extracts and vitamin D as sensitizing agents, in addition to trauma challenge.

The rate of calciphylaxis is 1–4% in chronic hemodialysis (HD) patients [3], and this disease has also been reported in patients without uremia [4]. The incidence of calciphylaxis has been suggested to be increasing [3], but this may be due to increased awareness of this disease. Calciphylaxis has exceptionally high morbidity and mortality. Proximal and ulcerated lesions carry the poorest prognosis, with mortality as high as 80% [5], and the most frequent cause of death is sepsis from wound infection [5]. Many patients have disturbances of mineral metabolism such as secondary hyperparathyroidism (SHPT), hyperphosphatemia, hypercalcemia, high calcium (Ca) intake, and use of vitamin D receptor activators (VDRAs) [6].

Therapy has focused on correcting abnormalities of Ca, phosphate (P) and parathyroid hormone (PTH) metabolism, in addition to supportive care with antibiotics, wound debridement and dressings, and nutritional support. Despite this management, outcomes remain poor and newer therapies such as sodium thiosulfate (STS) [7, 8], hyperbaric oxygen therapy (HBOT) [9], and calcimimetics [1, 5, 10] have been tried. Recent post hoc analyses in the framework

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of the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial suggest that cinacalcet may reduce the incidence of calciphylaxis [11]. Herein, we report five patients of calciphylaxis diagnosed by skin biopsy, and we discuss the pathogenesis and treatment of this life-threatening disease.

Case report

We conducted a retrospective review of five patients in the Department of Nephrology that were diagnosed with calciphylaxis by skin biopsy between December 2011 and April 2018. The patient characteristics are summarized in Table 1. The main sources of data were clinical records. All subjects underwent a complete medical history review, physical examination, blood tests, and a wedge biopsy of skin from the lesion margin to make an accurate diagnosis. Diagnosis of calciphylaxis was made using all clinical and histological data. The most common histological finding was ring-shaped calcification of arterioles of medium and small caliber. Calcification in capillaries is less frequent and requires von Kossa staining to be visible. Intimal hyperplasia and concentric fibrosis were observed with significant lumen reduction in four patients. Another common finding was subcutaneous fat necrosis.

All patients received local cures, surgical debridement, antibiotic medicine to control infectious diseases, rigorous control of serum Ca and P, and withdrawal of Ca-based P binders and VDRAs. Two patients underwent a partial skin graft (patients 2 and 3). Calcimimetics were used in all patients except one who had undergone parathyroidectomy (PTx) 1 month before. Two patients were treated with cinacalcet and two with etelcalcetide. Four patients received intravenous STS therapy, and only patient 4 underwent HBOT. The mean hospital stay was 60 (range 11–145) days. The average follow-up period was 7.4 months. Four patients were cured and there was one death due to sepsis caused by wound infection. The patient follow-up and outcome data are summarized in Table 2.

Patient 1

A 67-year-old female who had been on HD for 25 years due to chronic glomerulonephritis was admitted to our department because of the presence of large symmetrical ulcers on the lower limbs. She had a history of scarce compliance with treatments for control of bone mineral disorders with severe, uncontrolled SHPT with a history of percutaneous ethanol injection therapy for 12 years before. She had received long-term treatment with warfarin after aortic valve replacement surgery 18 years before. Warfarin was continued to prevent valve thrombosis and thromboembolic

Table 1 Patient demographic data and clinical characteristics

Patient	Age/Sex	ESRD cause	Dialysis modality/vintage	Obesity	Parathyroid intervention	VDRA use	Warfarin use	Maximum size of skin lesion at diagnosis	Proximal lesions	Distal lesions	At diagnosis				
											cCa (mg/dl)	P (mg/dl)	iPTH (pg/ml)	Alb (g/dl)	ALP (U/l)
1	67/F	CGN	HD/25 years	No	PEIT (12 years ago)	No	Yes (ANR)	1 × 1 cm (multiple)	Yes	Yes	8.8	8.5	130	3.4	345
2	67/F	Unknown	HD/20 year	No	No	Yes	Yes (MVR)	5 × 3 cm	No	Yes	7.4	6.1	392	3.3	312
3	48/F	CGN	Tx/8 years, HD/2 years, PD 7 years	No		Yes	No	8 × 5 cm	Yes	No	8.9	6.4	150	3.2	219
4	46/M	Unknown	HD/14 year	Yes	PTx (6 months ago)	Yes	No	20 × 9 cm	No	Yes	7.4	7	2	3.4	389
5	53/M	CGN	Tx/10 years, HD/20 year	No		Yes	No	8 × 4 cm	No	Yes	11.7	6.3	87	1.9	522

F female, *M* male, *ESRD* end-stage kidney disease, *CGN* chronic glomerulonephritis, *HD* hemodialysis, *PD* peritoneal dialysis, *Tx* transplantation, *PEIT* percutaneous ethanol injection therapy, *PTX* parathyroidectomy, *VDRA* vitamin D receptor activator, *AVR* aortic valve replacement surgery, *MVR* mitral valve replacement surgery, *cCa* corrected calcium, *P* phosphorus, *iPTH* intact parathyroid hormone, *ALP* alkaline phosphatase

Table 2 Patient treatment, follow-up and outcome data

Patient	Calcimimetic agents	Ca-free phosphate binders	Sodium thiosulfate	Dialysate Ca level (mEq/l)	Other treatments	Mean levels during the treatment			Hospital LOS (days)	Mortality
						cCa (mg/dl)	P (mg/dl)	iPTH (pg/ml)		
1	Yes (cinacalect)	Yes	Yes	2.5	Alprostadil	9.5	4.7	68	145	Death at 4 months
2	Yes(cinacalcet → etelcalcetide)	Yes	Yes	3		9.4	5.5	433	11	Alive
3	Yes (cinacalect → etelcalcetide)	Yes	No	2.5	Limaprost alfadex	8.5	4.6	101	38	Alive
4	No	Yes	Yes	3	Ca compounds	7.5	4.8	4	61	Alive
5	Yes (cinacalcet)	Yes	No	2.5	Alprostadil	10.5	4.0	158	43	Alive

cCa corrected calcium, *P* phosphorus, *iPTH* intact parathyroid hormone, *HBOT* hyperbaric oxygen therapy, *LOS* length of stay

events in patients with a prosthetic valve. Calciphylaxis was treated with intravenous STS, cinacalcet, alprostadil, and analgesia. The patient had a difficult course with severe pain and progressive lesions requiring surgical debridement, followed by poor wound healing and finally by necrosis. These conditions gradually deteriorated, and the patient died due to wound infection after 5 months.

Patient 2

A 67-year-old female who had been on HD for 19 years was hospitalized for painful subcutaneous indurations in the right lower leg. She had uncontrolled SHPT, hyperphosphatemia, and hypocalcemia. She had been treated with high dose of calcium carbonate (3000 mg/day), cinacalcet (25 mg/day), and VDRAs. Due to her poor adherence, her Ca levels were unstable. She had a history of long-term treatment with warfarin after mitral valve replacement surgery 12 years before. Warfarin was continued because of the presence of a mechanical valve. Treatment included cinacalcet and post-dialysis STS. Cinacalcet was switched to etelcalcetide because of poor adherence and digestive symptoms. The skin lesion was cured with partially scarring.

Patient 3

A 43-year-old female on continuous ambulatory peritoneal dialysis (PD) associated with chronic glomerulonephritis was hospitalized for painful skin ulcers and a reticulate pattern of erythema on both legs. On histology, the lesion showed extensive calcium deposits in the lumen of a small-sized vessel, which was pathognomonic of calciphylaxis. The patient had a history of very poor adherence to therapeutic prescriptions. Treatment was instituted with intradialytic STS along with continued cinacalcet use, switching from PD to HD, and skin transplantation. Cinacalcet was changed to etelcalcetide after 1 month for strict management of iPTH. The patient made a full recovery.

Patient 4

A 46-year-old male had been on HD for 14 years before. The etiology of his renal failure was unknown. He had received PTx for SHPT 1 month before. Three parathyroid glands were removed after a quick check of PTH intraoperatively. One month after PTx, iPTH was 6 pg/ml. He developed hungry bone syndrome following PTx, for which we prescribed a high dose of Ca compounds and VDRAs. However, he had a poor adherence to therapeutic prescriptions. Therefore, chronic hypocalcemia persisted. He had painful, erythematous skin lesions over and around the external malleolus of the left foot. In the next 2 months, these lesions necrosed and spread

to the malleolar and posterior tibial region and back of the ankle in both extremities (Fig. 1). The painful skin lesions were diagnosed as calciphylaxis (Fig. 2). The histological finding was ring-shaped calcifications of arterioles of medium and small caliber. Treatment consisted of intradialytic STS, substitution of Ca-based P binders with lanthanum carbonate hydrate, HBOT, and skin transplantation. Lesions showed slow healing over a period of 2 months.

Patient 5

A 53-year-old man who had been on HD for 19 years with IgA nephropathy was hospitalized for pain and ulcers in his left dorsal foot. Skin biopsy strongly suggested calciphylaxis, since there were some mineral deposits in the dermal lesion. He had used high-dose VDRAs to control severe bone mineral disorders. In addition to classical treatment with antibiotics, discontinuation of VDRAs, and prostaglandin, cinacalcet was administered to control SHPT. After the start of cinacalcet, CKD-MBD markers were suppressed and maintained in their target ranges. 2 months later, the ulcer on the dorsal foot showed marked improvement.

Discussion

In this series of five patients, patients on chronic dialysis were diagnosed with calciphylaxis by skin biopsy. Multidisciplinary management, including wound care, antibiotics, STS, and calcimimetics were associated with full regression of skin lesions in four patients after treatment periods of 1.5–3 months. Surviving patients had an average follow-up period of 7.4 months.

Calciphylaxis is associated with painful necrotic skin lesions that progress to ulceration over days to weeks [12]. The precise pathogenesis is unclear, but disruptions in factors that promote or inhibit vascular calcification may be involved. The key histological finding is cutaneous arteriolar medial calcification and intravascular thrombosis [13]. Vessels with calcification were observed in four patients. In the other patient, calcification of vessels was not confirmed, but extravascular calcification was observed. These histologic findings were closely associated with calciphylaxis.

Risk factors for calciphylaxis include secondary hyperparathyroidism, hyperphosphatemia, hypercalcemia, Ca-based P binders, female sex, obesity, diabetes, and warfarin use [1, 3, 5]. As such, hyperparathyroidism and high serum P are likely culprits of calciphylaxis. However, serum Ca, and iPTH levels varied widely among our patients. At

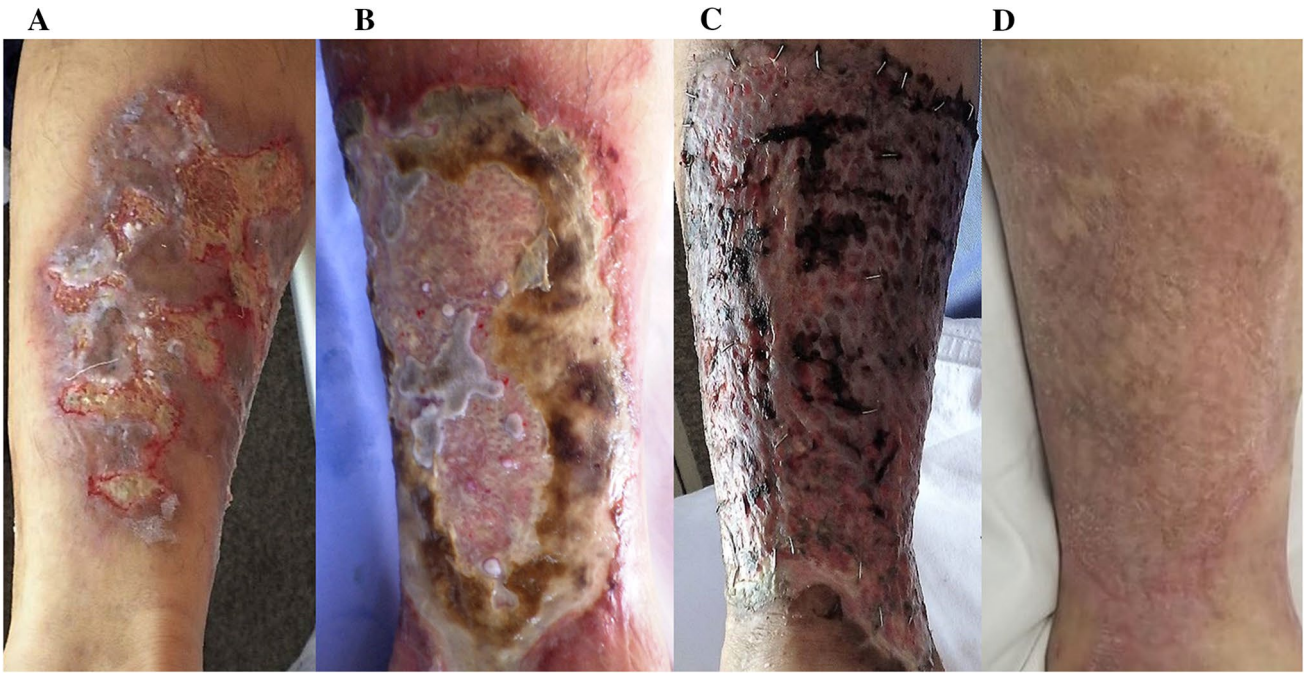

Fig. 1 Clinical presentation of calciphylaxis in patient 4. **a** Necrotic ulceration affecting the back part of the leg. A stellate-shaped ulcer with retiform purpura indicated ongoing ischemia (day 8). **b** A necrotic ulcer partially covered with a black eschar (day 20). **c** Condition after treatment with sodium thiosulfate and calcimimetics plus wound surgery of debridement and split-skin transplantation. A purplish perilesional area of the skin is apparent (day 40). **d** Skin transplantation was performed, and healing was obtained after surgery (day 300)

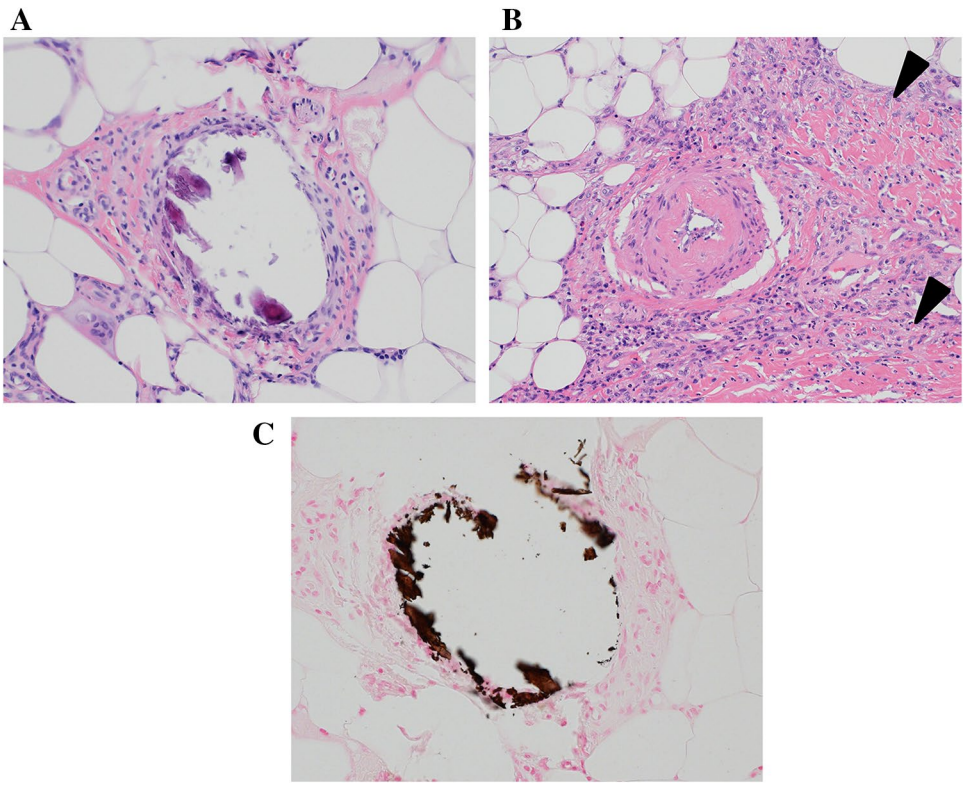

Fig. 2 Histopathologic features of calciphylaxis in a skin-biopsy section. **a**, **b** Hematoxylin and eosin staining showing ring calcification in vascular walls in subcutaneous tissue, with fibrointimal hyperplasia. Lipomembranous necrosis is observed in the panniculus (arrowheads). **c** von Kossa staining showing medial calcifications of pannicular arterioles

diagnosis, two patients had severe hypocalcemia, two had normal serum Ca levels, all had hyperphosphatemia, and one had elevated iPTH. Exacerbation of hypocalcemia was avoided by strict monitoring of medication during hospitalization, even for patients using calcimimetics. Patient 4 continued to require use of Ca compounds, but the other patients did not need to add VDRA or Ca-based binders. Previous studies have shown an increased risk of calciphylaxis in patients with hyperphosphatemia prior to diagnosis [1, 6, 14], with a threefold increase in the likelihood of developing calciphylaxis for each increment in serum P of 1 mg/dL over the 12 months prior to diagnosis [14]. Hyperphosphatemia is thought to trigger transformation of vascular smooth muscle cells (VSMCs) into osteoblast-like phenotypes through interaction with uremic toxins, reactive oxygen species, and a decrease in matrix Gla protein (MGP), a potent calcification inhibitor [10, 15]. The transdifferentiated cells secrete matrix vesicles containing Ca and P, which nucleate crystalline hydroxyapatite in the extracellular matrix. Eventually, the balance between calcification promoters (e.g., bone morphogenetic protein 2 and 4) and inhibitors (e.g., carboxylated MGP, fetuin-A, and inorganic pyrophosphate [PPi]) determines whether the arteriole will calcify. Furthermore, in areas with abundant adipose tissue, such as the thighs, mature adipocytes exposed to high phosphate levels calcify and induce calcification of VSMCs by release of vascular endothelial growth factor A [16].

VDRAs were used in four of our patients and calcimimetics were used in all patients except the one who had a history of PTx. Approximately 45% of dialysis patients with calciphylaxis have iPTH below the recommended target range [17]. We did not perform bone biopsy or bone densitometry, but there is a possibility that overuse of VDRAs can lead to iPTH oversuppression and adynamic bone, which may exacerbate extraskeletal Ca deposition [18]. Activation of MGP is dependent on vitamin K-mediated carboxylation [19]; and warfarin administration, which is common in calciphylaxis, is a potential mechanism of MGP inactivation [20]. In two patients receiving warfarin therapy, certain clinical findings led to consideration of both calciphylaxis and warfarin skin necrosis (WSN). WSN is an infrequent complication of warfarin treatment and is characterized by painful ulcerative skin lesions that appear a few days after the start of warfarin treatment. Clues were obtained from histology findings. The main histopathology findings for WSN are diffuse microthrombi and fibrin deposits within the dermal and subcutaneous capillaries, venules, and deep veins, accompanied by endothelial cell damage [21]. In contrast, the typical findings of calciphylaxis are the presence of medial calcification and intimal proliferation of small- to medium-sized arteries, primarily in dermal and subcutaneous tissues. Therefore, patients 1 and 2 were diagnosed with calciphylaxis by biopsy. It is important to differentiate between WSN and calciphylaxis in patients with painful skin lesions who are taking warfarin.

Treatment using a multimodal approach that addresses pain and wound management, risk factor elimination (e.g. warfarin discontinuation, PD), strict control of mineral metabolism, and sufficient nutrition has been described [1]. The annual incidence of calciphylaxis is 9% in PD patients [22]. Decreasing serum P by changing from PD to HD has been suggested to be beneficial in some studies. Furthermore, lactate-buffered PD fluid can cause alkalemia, which may be related to vascular calcification [23]. Hypercalcemia and hyperphosphatemia should be corrected, administration of VDRAs and Ca (including Ca-based P binders) should be discontinued, and a high Ca dialysate should be avoided. The optimal iPTH level for patients with calciphylaxis is unknown; however, extremely high and low levels are unfavorable. In the EVOLVE trial in more than 3500 patients undergoing HD, administration of cinacalcet decreased the median PTH level and the incidence of calciphylaxis [11]. This trial did not address the role of cinacalcet as a treatment option for calciphylaxis, but the possibility that calcimimetics might be useful for calciphylaxis warrants further prospective examination in prevention and treatment studies [11].

STS is regarded as a major disease-modifying agent with antioxidant and vasodilatory properties that also inhibits adipocyte calcification and blocks the ability of adipocytes to induce calcification of vascular smooth-muscle cells in calciphylaxis [24]. In a retrospective study in 53 HD patients with calciphylaxis who were treated with intravenous STS (three times per week in each dialysis session for approximately 3 months), calciphylaxis resolved in 26% of the patients. STS might improve calciphylaxis, but its efficacy and safety are unclear [25]. The typical dose is 12.5–25 g in 100 ml of solution given intravenously three times a week during the last 30–60 min of hemodialysis [24]. The optimal treatment duration is not known, but STS is commonly continued until ulcer healing is observed. Our patients received 10–12.5 g of STS three times per week. In previous case series, combined use of STS and cinacalcet was associated with complete regression of skin lesions [26], and use of cinacalcet apparently reduced the risk of mortality. Consistent with these studies, a multimodal approach with cinacalcet seemed to be successful for skin lesions in our patients. We also used etelcalcetide as an alternative for cinacalcet. Etelcalcetide is a novel intravenous calcimimetic that can be administered at the end of each HD session and has a longer elimination half-life than that of cinacalcet [27, 28]. Therefore, administration of etelcalcetide is likely to be reliable and to improve the pill burden and management of calciphylaxis [29].

In our patients, one patient had a history of PTx, but the role of PTx is controversial [1, 3, 6]. All of our patients underwent at least one surgical debridement, and two received debridement and skin grafting. A recent large case series showed that only surgical debridement led to a significant improvement in mortality [5]. Wound debridement is clearly necessary, but the wound closure strategy varies among physicians [5, 30].

In patients 2 and 4, the large ulcers were treated by staged debridement and placement of a free skin graft. Skin grafting is useful as a template for covering the wound, supporting healing and reconstruction of lost tissue. In patient 2, the patient refused split skin grafting and was treated with an artificial dermis made of a bioengineered and biocompatible polymer matrix of cellular and extracellular components such as collagen or elastin [31]. In patient 4, the skin defect was closed by an autologous split-skin graft. The donor skin was collected from the outside of the thigh. The donor site was covered with a non-adhesive foam dressing and did not show ulceration. Patients 2 and 4 achieved complete healing of transplanted ulcers and no patients developed a deep cutaneous infection or sepsis. In distal calciphylaxis, aggressive ulcer surgery with defect closure offers a marked improvement in quality of life and prevents early deep skin infections and sepsis as major causes of mortality [32].

To obtain a successful clinical course, both multidisciplinary management and close cooperation among nephrologists, surgeons, and dermatologists are required.

Conclusion

Calciphylaxis is a rare disease that is accompanied by serious complications and high mortality in patients with ESRD. For management of infectious diseases, we suggest that a combination of surgical debridement with strict control of mineral and bone markers (P in particular) from the early stage and elimination of risk factors may improve the course of the disease. Further basic and clinical studies are needed to establish optimal treatment for calciphylaxis.

References

1. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. N Engl J Med. 2018;378(18):1704–14.
2. Selye H, Gabbiani G, Strebel R. Sensitization to calciphylaxis by endogenous parathyroid hormone. Endocrinology. 1962;71:554–8.
3. Nigwekar SU, Zhao S, Wenger J, Hymes JL, Maddux FW, Thadhani RI, et al. A Nationally representative study of calcific uremic arteriolopathy risk factors. J Am Soc Nephrol. 2016;27(11):3421–9.
4. Abdalla AO, Al-Khafaji J, Taha M, Malik S. A fatal case of non-uremic calciphylaxis: a case report and literature review. Am J Case Rep. 2018;19:804–7.
5. McCarthy JT, El-Azhary RA, Patzelt MT, Weaver AL, Albright RC, Bridges AD, et al. Survival, risk factors, and effect of treatment in 101 patients with calciphylaxis. Mayo Clin Proc. 2016;91(10):1384–94.

6. Nigwekar SU, Kroshinsky D, Nazarian RM, Goverman J, Malhotra R, Jackson VA, et al. Calciphylaxis: risk factors, diagnosis, and treatment. Am J Kidney Dis. 2015;66(1):133–46.
7. Salmhofer H, Franzen M, Hitzl W, Koller J, Kreymann B, Fend F, et al. Multi-modal treatment of calciphylaxis with sodium-thiosulfate, cinacalcet and sevelamer including long-term data. Kidney Blood Press Res. 2013;37(4–5):346–59.
8. Zitt E, Konig M, Vychytil A, Auinger M, Wallner M, Lingenhel G, et al. Use of sodium thiosulphate in a multi-interventional setting for the treatment of calciphylaxis in dialysis patients. Nephrol Dial Transplant. 2013;28(5):1232–40.
9. An J, Devaney B, Ooi KY, Ford S, Frawley G, Menahem S. Hyperbaric oxygen in the treatment of calciphylaxis: a case series and literature review. Nephrology (Carlton). 2015;20(7):444–50.
10. Nigwekar SU. Calciphylaxis. Curr Opin Nephrol Hypertens. 2017;26(4):276–81.
11. Floege J, Kubo Y, Floege A, Chertow GM, Parfrey PS. The effect of cinacalcet on calcific uremic arteriolopathy events in patients receiving hemodialysis: the EVOLVE trial. Clin J Am Soc Nephrol. 2015;10(5):800–7.
12. Ghosh T, Winchester DS, Davis MDP, El-Azhary R, Comfere NI. Early clinical presentations and progression of calciphylaxis. Int J Dermatol. 2017;56(8):856–61.
13. Ellis CL, O'Neill WC. Questionable specificity of histologic findings in calcific uremic arteriolopathy. Kidney Int. 2018;94(2):390–5.
14. Mazhar AR, Johnson RJ, Gillen D, Stivelman JC, Ryan MJ, Davis CL, et al. Risk factors and mortality associated with calciphylaxis in end-stage renal disease. Kidney Int. 2001;60(1):324–32.
15. Jeong HS, Dominguez AR. Calciphylaxis: controversies in pathogenesis, diagnosis and treatment. Am J Med Sci. 2016;351(2):217–27.
16. Chen NX, O'Neill K, Akl NK, Moe SM. Adipocyte induced arterial calcification is prevented with sodium thiosulfate. Biochem Biophys Res Commun. 2014;449(1):151–6.
17. Brandenburg VM, Kramann R, Rothe H, Kaesler N, Korbiel J, Specht P, et al. Calcific uraemic arteriolopathy (calciphylaxis): data from a large nationwide registry. Nephrol Dial Transplant. 2017;32(1):126–32.
18. Mawad HW, Sawaya BP, Sarin R, Malluche HH. Calcific uremic arteriolopathy in association with low turnover uremic bone disease. Clin Nephrol. 1999;52(3):160–6.
19. Sowers KM, Hayden MR. Calcific uremic arteriolopathy: pathophysiology, reactive oxygen species and therapeutic approaches. Oxid Med Cell Longev. 2010;3(2):109–21.
20. Hayashi M, Takamatsu I, Kanno Y, Yoshida T, Abe T, Sato Y, et al. A case-control study of calciphylaxis in Japanese end-stage renal disease patients. Nephrol Dial Transplant. 2012;27(4):1580–4.
21. Nazarian RM, Van Cott EM, Zembowicz A, Duncan LM. Warfarin-induced skin necrosis. J Am Acad Dermatol. 2009;61(2):325–32.
22. Zhang Y, Corapi KM, Luongo M, Thadhani R, Nigwekar SU. Calciphylaxis in peritoneal dialysis patients: a single center cohort study. Int J Nephrol Renovasc Dis. 2016;9:235–41.
23. Udomkarnjananun S, Kongnatthasate K, Praditpornsilpa K, Eiam-Ong S, Jaber BL, Susantitaphong P. Treatment of calciphylaxis in CKD: a systematic review and meta-analysis. Kidney Int Rep. 2019;4(2):231–44.
24. Peng T, Zhuo L, Wang Y, Jun M, Li G, Wang L, et al. Systematic review of sodium thiosulfate in treating calciphylaxis in chronic kidney disease patients. Nephrology (Carlton). 2018;23(7):669–75.
25. Nigwekar SU, Brunelli SM, Meade D, Wang W, Hymes J, Lacson E Jr. Sodium thiosulfate therapy for calcific uremic arteriolopathy. Clin J Am Soc Nephrol. 2013;8(7):1162–70.
26. Baldwin C, Farah M, Leung M, Taylor P, Werb R, Kiaii M, et al. Multi-intervention management of calciphylaxis: a report of 7 cases. Am J Kidney Dis. 2011;58(6):988–91.
27. Hamano N, Komaba H, Fukagawa M. Etelcalcetide for the treatment of secondary hyperparathyroidism. Expert Opin Pharmacother. 2017;18(5):529–34.
28. Subramanian R, Zhu X, Hock MB, Sloey BJ, Wu B, Wilson SF, et al. Pharmacokinetics, biotransformation, and excretion of [(14) C]etelcalcetide (AMG 416) following a single microtracer intravenous dose in patients with chronic kidney disease on hemodialysis. Clin Pharmacokinet. 2017;56(2):179–92.
29. Mima Y, Wada Y, Shikida Y, Hamada T, Kanazawa N, Iida A, et al. Rapid regression of calciphylaxis in a hemodialysis patient after intensive management of disturbance of calcium and phosphate metabolism: a case report with literature review. Ren Replace Ther. 2019;5(1):19.
30. Vedvyas C, Winterfield LS, Vleugels RA. Calciphylaxis: a systematic review of existing and emerging therapies. J Am Acad Dermatol. 2012;67(6):e253–e260260.
31. Davison-Kotler E, Sharma V, Kang NV, Garcia-Gareta E. A universal classification system of skin substitutes inspired by factorial design. Tissue Eng Part B Rev. 2018;24(4):279–88.
32. Wollina U, Helm C, Hansel G, Koch A, Schonlebe J, Haroske G, et al. Deep ulcer shaving combined with split-skin transplantation in distal calciphylaxis. Int J Low Extrem Wounds. 2008;7(2):102–7.