Renal Replacement Therapy

CASE REPORT Open Access

Rapid regression of calciphylaxis in a hemodialysis patient after intensive management of disturbance of calcium and phosphate metabolism: a case report with literature review

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Abstract

Background: Calciphylaxis, a multifactorial cutaneous vascular disease, is a rare but therapy-resistant and life-threatening disorder that usually occurs in patients with end-stage kidney disease (ESKD). Although there have been many reports regarding calciphylaxis, its pathophysiology is not fully understood and strong evidence for its treatment is lacking.

Case presentation: A 63-year-old woman with a 20-year history of hemodialysis (HD) for ESKD of unknown etiology was admitted because of severe painful cutaneous ulcers on the right lower leg. She underwent artificial heart valve replacement surgery for infective endocarditis 13 years earlier, following which warfarin was prescribed. Laboratory findings on admission showed elevation of the calcium (Ca)-phosphorus (P) product due to hyperphosphatemia, and parathyroid hormone (PTH) levels were above the target range. Additionally, the efficiency of HD, based on Kt/V urea, was reduced because of vascular access (VA) failure. Furthermore, there was no evidence of inflammation, and the ankle-brachial index was within the normal range. Skin biopsy specimens showed thrombosis of the small vessels and marked Ca deposition in the media of the arterioles, which were compatible with a diagnosis of calciphylaxis. Hence, in addition to surgical repair of VA failure and prolongation of HD treatment time, we discontinued administration of the synthetic vitamin D3, calcitriol, and switched treatment from cinacalcet to etelcalcetide, which is a novel peptide agonist of the Ca-sensing receptor. Consequently, serum Ca, P, and Ca-P product levels decreased immediately, although her PTH levels remained high. Her painful severe skin ulcers regressed completely within 3 months.

Conclusion: In this patient, although the influence of oral warfarin therapy and secondary hyperparathyroidism, which are known risk factors for calciphylaxis, was not removed, her ulcers appeared to respond to the optimization of disturbed Ca-P metabolism. Our experience suggests that intensive management of serum Ca and P levels is essential to prevent the development of calciphylaxis. Hypercalcemia and hyperphosphatemia due to excess vitamin D receptor activators could be risk factors for calciphylaxis.

Keywords: Calciphylaxis, Calcium-phosphorus metabolism, Secondary hyperparathyroidism, Calcitriol, Etelcalcetide

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Background

Calciphylaxis, recognized as uremic small artery disease with calcification of the media and intimal hyperplasia, is a rare but therapy-resistant and life-threatening cutaneous vascular disease that usually occurs in patients with chronic kidney disease (CKD), predominantly in those with end-stage kidney disease (ESKD) who are undergoing dialysis [1–7]. Clinically, calciphylaxis is characterized by chronic, painful, and non-healing wounds [1, 3]. Its estimated annual incidence is 35 cases per 10,000 patients undergoing hemodialysis (HD) in the USA [5], 4 per 10,000 in Germany [2], and less than 1 per 10,000 in Japan [6]. Approximately 50% of patients with calciphylaxis are bedridden or wheelchair-bound, and more than 70% require hospitalization because of severe ulcers [8]. Moreover, the 1-year mortality rate is estimated as 45–80% [7].

The pathophysiology of calciphylaxis is complex, and it is believed to have several causative factors. Previous histological analysis of the skin lesions of patients with calciphylaxis revealed that calcified narrow microvessels lead to ischemia, microthrombosis, and occlusion of vessels with endothelial injury, which eventually results in extensive areas of infarction in the skin [9, 10]. Furthermore, the development of microvascular calcifications is attributed to a cell-mediated process that regulates the balance between promoters and inhibitors of calcification [10, 11]. Epidemiological studies have shown that the possible risk factors for calciphylaxis include renal insufficiency, obesity, therapy with vitamin K antagonists, calcium-based phosphate binders, vitamin D receptor activators (VDRA) and corticosteroids, secondary hyperparathyroidism (SHPT), hypercoagulable states, and female sex [7, 12, 13] (Table 1). However, crucial risk factors for the onset and progression of calciphylaxis have not been defined yet. Similarly, no definitive treatment has been established. The clinical importance of multiple interventions for the management of calciphylaxis has been proposed [12], and sodium thiosulfate (STS) with antioxidant and calcium-chelating effects has received focus as a viable first-line treatment [14]. However, the overall quality of evidence regarding its utility is poor, and there is no published data from randomized controlled trials.

Herein, we present a case of calciphylaxis in an HD patient whose severe skin ulcers drastically regressed in a short period of time, in parallel with decrease in serum calcium (Ca), phosphorus (P), and Ca-P product levels, which provides significant clues to determining the essence of pathogenesis and treatment strategies for calciphylaxis.

Table 1 Representative risk factors for calciphylaxis based on previous reports [7, 12, 13]

Renal insufficiency
Hypercalcemia
Hyperphosphatemia
Hyperparathyroidism (both primary and secondary)
Over-suppression of i-PTH with adynamic bone disease
Vitamin K deficiency
Female sex
Obesity
Diabetes mellitus
Hypoalbuminemia
Rapid weight loss
Thrombophilia (e.g., antithrombin III deficiency, protein C deficiency, protein S deficiency, or lupus anticoagulant)
Skin trauma (e.g., from subcutaneous injections)
Medications (e.g., warfarin, VDRA, calcium carbonate, corticosteroids, and recombinant PTH)

i-PTH intact parathyroid hormone, *VDRA* vitamin D receptor activators

Case presentation

A 63-year-old woman was admitted for severe painful cutaneous ulcers on her right lower leg. She had commenced HD for ESKD of unknown etiology when she was 43 years old. She underwent artificial heart valve replacement surgery for infective endocarditis at the age of 50 years, following which she was on warfarin therapy. Furthermore, she developed secondary hyperparathyroidism (SHPT) as a complication. Ultrasonography showed enlarged parathyroid glands in the neck. The major diameter of her left upper parathyroid gland, which was the maximally enlarged gland, was 17 mm. She did not have a history of alcohol consumption or smoking. Her family medical history was unremarkable. Three months prior to the current admission, cutaneous ulcers developed rapidly on the peroneal aspect of her right lower leg. The skin ulcers worsened despite supportive wound management, such as dressing, antibiotic therapy, and analgesics. At that time, her corrected serum Ca level was 9.8 mg/dL, with a P level of 8.5 mg/dL and intact parathyroid hormone (i-PTH) level of 176 pg/mL, indicating the significant elevation of Ca-P product levels. The efficiency of HD performed thrice weekly for 3 h each time, assessed as dialysate clearance of urea (Kt/V urea), was 1.61, which was within the target range for HD patients. She had been treated with calcium carbonate (3000 mg/day), the phosphate binder bixalomer (1500 mg/day), the calcimimetic cinacalcet (25 mg/day), and intermittent intravenous doses of the synthetic vitamin D3 calcitriol (1.5 μg/week). Furthermore, just before her admission, a high-pitched bruit and poor blood flow due to vessel stenosis were confirmed at her vascular access (VA) site. She was finally transferred to our institution for further evaluation and treatment.

On admission, her height was 150.7 cm, weight was 38.7 kg, and body mass index was 17.0 kg/m^2. Her temperature was 36.5 °C, pulse rate was 68 beats per minute, and blood pressure was 144/71 mmHg. Physical examination revealed a systolic heart murmur at Erb's point and painful leg ulcers (Fig. 1a–c). Laboratory tests revealed the following results: white blood cell count, 6400/mm^3; erythrocyte count, 297 × 10^4/μL; hemoglobin, 8.5 g/dL; hematocrit, 24.7%; platelet count, 16.6 × 10^4/mm^3; prothrombin time-international normalized ratio, 1.59; activated partial thromboplastin time, 35.2 s; fibrin, 384 mg/dL; D-dimer, 1.9 μg/mL; albumin, 3.3 g/dL; blood urea nitrogen, 93.8 mg/dL; creatinine, 11.0 mg/dL; adjusted-Ca, 10.1 mg/dL; P, 6.2 mg/dL; i-PTH, 392 pg/mL; alkaline phosphatase, 312 IU/L; hemoglobin A1c, 5.0%; and C-reactive protein, 0.2 mg/dL. Bone turnover markers showed the following results: undercarboxylated osteocalcin, 220.1 ng/mL (reference range < 4.5 ng/mL) and tartrate-resistant acid phosphatase type 5b, 871 mU/dL (reference range 170–590 mU/dL). Her Kt/V urea was 1.35, which was lower than her previous values. Anti-nuclear antibody, anti-cardiolipin antibody, and lupus anticoagulant were not detected. Likewise, anti-neutrophil cytoplasmic antibodies and cryoglobulin were absent. Levels of protein C and protein S were within the normal range. In addition, her ankle-brachial index was within the normal range, suggesting the absence of peripheral arterial disease. Histological examination of a hematoxylin and eosin-stained skin biopsy specimen from the relatively normal tissue around the ulcers in her right lower leg showed edematous thickening of the vessel wall and thrombosis of small vessels (Fig. 2a, b). Von Kossa staining showed marked Ca deposition in the media of the arterioles (Fig. 2c, d). X-rays of the patient's right lower leg revealed subcutaneous extravascular calcifications and a calcified artery (Fig. 3a, b). Based on these findings, the patient was diagnosed as having calciphylaxis.

The patient's clinical course is shown in Fig. 4. As part of her treatment, the VA failure was surgically repaired and HD treatment time was prolonged, which restored the Kt/V urea (1.43) and allowed for P removal. Next, we discontinued administration of intravenous calcitriol and temporally stopped prescription of calcium carbonate. Additionally, treatment with oral cinacalcet was switched to intravenous etelcalcetide (15 μg/week) in order to enhance treatment adherence. Although warfarin is a risk factor for calciphylaxis, we did not discontinue warfarin because anticoagulation therapy following artificial heart valve replacement surgery was considered essential. Administration of STS was ceased immediately because it caused severe nausea. Consequently, serum Ca, P, and Ca-P product levels decreased immediately, although PTH levels remained high (Fig. 4). With this therapy, her painful and severe skin ulcers dramatically regressed in only 3 months (Fig. 5a, c). Currently, her calciphylaxis is completely cured, and we are considering the next treatment strategy for SHPT. Surgical intervention such as parathyroidectomy was considered earlier, but such intervention was not feasible because surgery under general anesthesia was impossible due to her poor cardiac status. Restarting a low dose of calcium carbonate or VDRA, which will enable an increase in the dose of etelcacetide, will be considered as the next option.

Discussion

With reference to previous reports [7, 12, 13], the risk factors (Table 1) for calciphylaxis identified in the

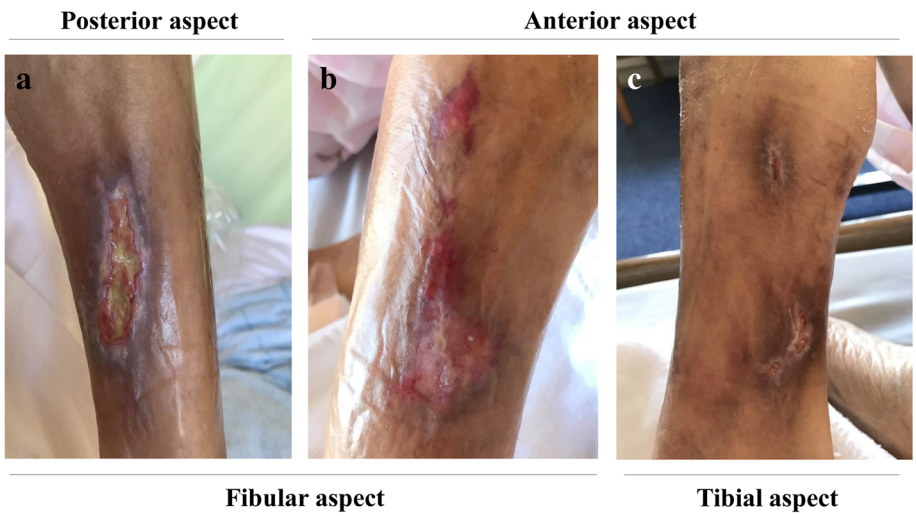

Fig. 1 Gross appearance of the cutaneous ulcers on the patient's right lower legs at admission. **a** Posterior aspect of the fibula. **b** Anterior aspect of the fibula. **c** Anterior aspect of the tibia

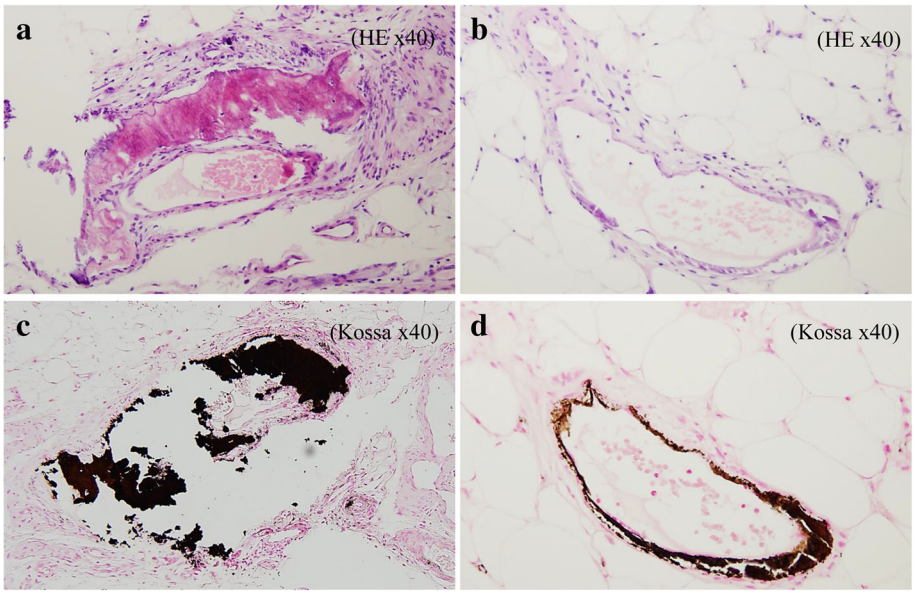

Fig. 2 Pathological findings of a skin biopsy specimen obtained from the right lower leg at admission. **a**, **b** Edematous thickening of the vessel wall and thrombosis in a small vessel were observed (hematoxylin and eosin staining, original magnification × 40). **c**, **d** Marked calcium deposition was observed in the media of the arterioles (Von Kossa staining, original magnification × 40)

present case were mainly warfarin therapy, development of SHPT as a complication, decline in Kt/V urea due to VA failure, disturbed Ca-P metabolism, use of calcium carbonate as a phosphate binder, and inappropriate administration of VDRA.

In terms of warfarin therapy, we decided not to switch warfarin to non-vitamin K-dependent oral anticoagulants (NOAC) because of the lack of a clear benefit of NOAC in patients with CKD [15]. Additionally, NOAC is a non-insurance medication for dialysis patients in Japan. Regarding the mechanism by which warfarin is a risk factor for calciphylaxis, Danziger indicated that endogenous inhibitors of vascular calcification (VC), such as matrix Gla protein (MGP), are activated by vitamin K-dependent mechanisms [16]. A recent report also implied that CKD patients on warfarin therapy may not be able to inhibit VC due to a reduction in the activation of such proteins [17]. Thus, careful assessment of the

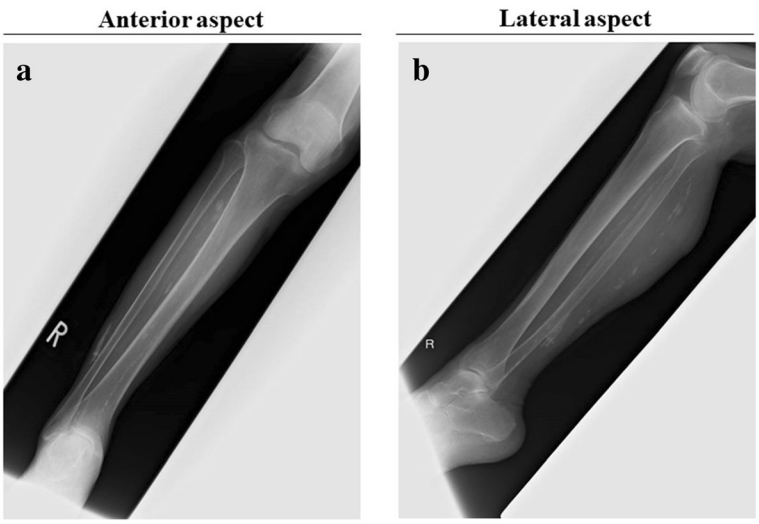

Fig. 3 Radiographic visualization of subcutaneous extravascular calcifications and a calcified artery in the patient's right lower legs at admission. **a** Anterior aspect of the leg. **b** Lateral aspect of the leg

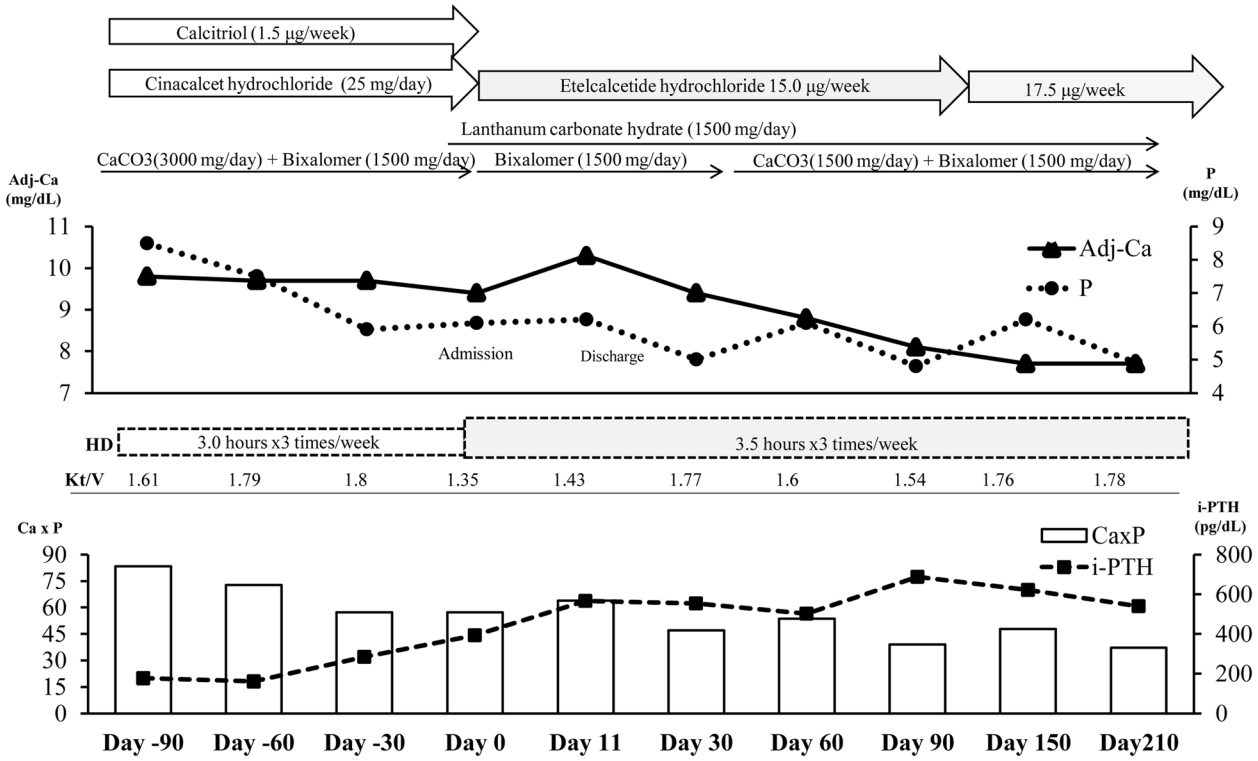

Fig. 4 Clinical course and treatment of the patient. Adj-Ca, adjusted calcium; $CaCO_3$, calcium carbonate; Ca × P, calcium-phosphorus product; P, phosphorus; i-PTH, intact parathyroid hormone

therapeutic indications for warfarin is needed in patients with CKD who have a predisposition to VC.

SHPT is known to play a pivotal role in the development of calciphylaxis [7]. However, a recent cohort study demonstrated that approximately 45% of dialysis-dependent patients with calciphylaxis have relatively low levels of i-PTH [2]. A case-control study by Hayashi et al. indicated that the elevation of i-PTH was not a significant risk factor for calciphylaxis [13]. Moreover, Karmegam et al. reported an intriguing case in which calciphylaxis developed after subtotal parathyroidectomy for severe SHPT [18]. Taken together, these previous reports temper the significance of

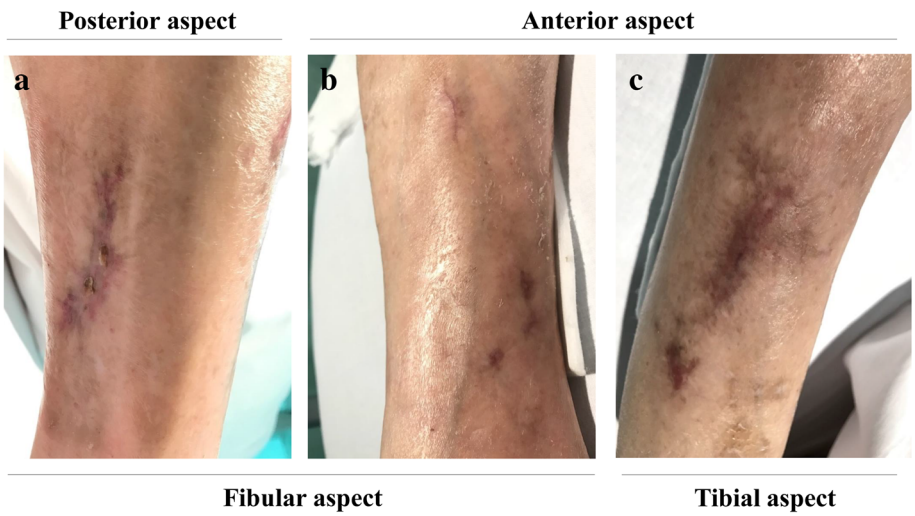

Fig. 5 Gross appearance of the cutaneous ulcers after treatment. **a–c** The patient's right lower legs on day 97 after admission. **a** Posterior aspect of the fibula. **b** Anterior aspect of the fibula. **c** Anterior aspect of the tibia

SHPT as a risk factor for the progression of calciphylaxis, which is compatible with our patient's clinical course in which calciphylaxis improved rapidly although i-PTH levels remained high. As pointed out previously [19], over-suppression of i-PTH, leading to adynamic bones (low bone turnover), can exacerbate extraskeletal Ca deposition, which may conversely aggravate calciphylaxis.

Calciphylaxis is also known by the alias calcific uremic arteriolopathy [2], since the accumulation of uremic toxins is believed to be involved in the pathogenesis of this condition [20]. Previous reports indicated that the uremic condition accelerated VC via activation of the receptor activator of NF-κB ligand [21, 22], and that intensifying dialysis by increasing its duration or frequency was critical for preventing the progression of calciphylaxis [20]. However, non-uremic calciphylaxis has recently been reported [1, 3, 7, 22], demonstrating that causative factors other than the uremic condition could be central to the development of calciphylaxis. Actually, Kt/V urea in our patient decreased just before her hospitalization, indicating that the state of under-dialysis that causes accumulation of uremic toxins was transient. Hence, we speculate that the favorable outcome in the present case could be attributable to the elimination of more crucial causative factors rather than uremic toxins.

Generally, appropriate management of Ca-P metabolism is recognized to be important in the treatment of calciphylaxis. A recent review [23] by Brandenburg et al. described that misdirected Ca-P metabolism is a key factor contributing to the development of calciphylaxis. In other words, natural mineralization methods are disturbed and pro-calcifying activities are present in the vascular walls of patients with calciphylaxis [23]. Nigwekar et al. demonstrated the rationale of this theory by detecting significant stimulation of the bone morphogenetic protein pathway in the small vessels of skin samples from patients with calciphylaxis [11]. This suggests that a treatment strategy to increase P removal and lessen the Ca burden is indispensable to prevent the progression of calciphylaxis. Indeed, in the present case, appropriate management of Ca-P metabolism led to regression of the ulcers. Immediate repair of the VA failure and prolongation of HD treatment time was effective for greater P removal. Discontinuation of intravenous calcitriol administration was also effective and reasonable to avoid hyperphosphatemia, hypercalcemia, and elevation of the Ca-P product. Furthermore, switching from oral cinacalcet to intravenous etelcalcetide, a novel peptide agonist of the Ca-sensing receptor (CaSR), might also have provided some benefit to the patient.

No definitive evidence exists regarding the influence of VDRA on VC. However, a previous report by Bas et al. showed that calcitriol treatment induced time-dependent VC in rats without renal dysfunction, with the VC regressing rapidly with decreasing aortic Ca-P deposition after the withdrawal of calcitriol [24]. In the present case, discontinuation of intravenous calcitriol administration resulted in alleviation of her ulcers in a short period of time, which indicated that induction of significant elevation of the Ca-P product by excessive VDRA administration is definitely harmful. Future studies are required to elucidate the role of VDRA in the development of calciphylaxis.

To the best of our knowledge, this is the first case of calciphylaxis in which the CaSR agonist was switched from cinacalcet to etelcalcetide in order to enhance the treatment for mineral and bone disorders (MBD). According to recent reports [25–27], etelcalcetide significantly improved treatment adherence and reduced adverse gastrointestinal effects in ESKD patients with SHPT. Furthermore, several clinical trials and observational studies have indicated that etelcalcetide is more potent than cinacalcet in reducing i-PTH levels, with the maintenance of Ca and P levels within the target range [26–28]. Thus, etelcalcetide is currently expected to be a promising agent for CKD-MBD. Unfortunately, administration of etelcalcetide did not reduce i-PTH levels in the present case, which was considered to attribute that i-PTH level just increased in response to hypocalcemia due to discontinuation of VDRA and calcium carbonate. Hence, the contribution of intravenous etelcalcetide therapy to a decrease in serum Ca and P levels appeared to be minor in this case when considering the pharmacological effects of etelcalcetide. However, we presumed that its administration might have partially contributed to the regression of calciphylaxis, as is seen in cases effectively treated with cinacalcet [29–32]. In addition, several basic studies revealed the direct therapeutic effect of calcimimetics on VC [33–35]. Mendoza et al. demonstrated the inhibitory effects of calcimimetic AMG 641 on VC in vivo and in vitro via activation of MGP [35]. These reports suggested the potential efficacy of etelcalcetide for the treatment of calciphylaxis. Actually, our patient showed poor medical adherence and resistance to increasing the dosage of cinacalcet because of nausea. Therefore, we speculate that treatment with cinacalcet alone without switching to etelcalcetide might have been slightly effective in the treatment of calciphylaxis in the present case. Accumulation of similar cases and further analysis will be necessary to elucidate the therapeutic effects of etelcalcetide on the progression of calciphylaxis.

Literature review

There are only few reported cases of calciphylaxis in which a CaSR agonist, such as cinacalcet and etelcalcetide, was administered. Table 2 shows a summary of those previously reported cases [29–32] as a literature review of five cases, including the present case.

Table 2 Clinical features of previously reported cases of calciphylaxis treated by calcium-sensing receptor agonist

Ref	Age	Sex	RRT	VDRA	CaSR agonist	Pre/post treatment			Outcome
	(year)		vintage (year)	(dosage)	(dosage)	adj Ca (mg/dL)	P (mg/dL)	i-PTH (pg/mL)	
29	45	M	PD (1)→HD (3)	Cal (unknown) i.v.→cessation	Cina (30 mg/day)	11.0/8.8	8.2/6.0	2218/115	improved
30	76	F	HD (unknown)	Alfa (0.5 μg/day) p.o.→cessation	Cina (30 mg/day)	9.9/8.1	7.9/NA	997/98	improved
31	44	M	HD (5)→RT (11)	unknown	Cina (30 mg/day)	10.2/8.4	9.9/4.7	1791/113	improved
32	50s	M	RT (10)→HD (16)	Maxa (15 μg/week) i.v.→cessation	Cina (25 mg/day)	11.7/9.0	6.3/4.5	87/405	improved
This case	63	F	HD (20)	Cal (1.5 μg/week) i.v.→cessation	Cina (25 mg/day)→Ete (15 μg/week)	10.3/8.1	6.2/4.5	392/687	improved

Ref reference, *M* male, *F* female, *RRT* renal replacement therapy, *HD* hemodialysis, *PD* Peritoneal dialysis, *RT* renal transplantation, *VDRA* vitamin D receptor activators, *Cal* calcitriol, *Alfa* alfacalcidol, *Maxa* maxacalcitol, *i.v.* intravenous, *p.o.* per os, *CaSR* Ca-sensing receptor, *Cina* cinacalcet, *Ete* etelcalcetide, *Ca* calcium, *P* phosphorus, *i-PTH* intact parathyroid hormone, *NA* not available

Almost all the cases had severe SHPT and remarkable disturbance of Ca and P metabolism. Of note, four of the five cases were receiving inappropriate VDRA therapy despite the metabolic disturbance. Eventually, all cases showed regression of calciphylaxis after optimizing hypercalcemia and hyperphosphatemia with the administration of a CaSR agonist and cessation of inappropriate VDRA therapy. Besides the present case, another case [32] also achieved a favorable outcome without suppressing i-PTH levels.

Conclusion

We successfully treated calciphylaxis by optimization of disturbed serum Ca and P levels without removing the influence of warfarin therapy or severe SHPT. Therefore, we suggest that intensive management of Ca-P metabolism is essential to prevent the development of calciphylaxis. Hypercalcemia or hyperphosphatemia due to excess VDRA therapy could be an aggravating factor for calciphylaxis in CKD patients on HD. Administration of etelcalcetide, which enhances treatment adherence might contribute to the healing of the ulcers in patients with calciphylaxis.

Abbreviations

Ca: Calcium; CaSR: Ca-sensing receptor; CKD: Chronic kidney disease; ESKD: End-stage kidney disease; HD: Hemodialysis; i-PTH: Intact parathyroid hormone; MBD: Mineral and bone disorders; MGP: Matrix Gla protein; NOAC: Non-vitamin K-dependent oral anticoagulants; P: Phosphorus; SHPT: Secondary hyperparathyroidism; STS: Sodium thiosulfate; VA: Vascular access; VC: Vascular calcification; VDRA: Vitamin D receptor activators

Acknowledgements

None applicable.

Funding

T. Shibata has received research funding from Kyowa Hakko Kirin Co., Ltd., Ono Pharmaceutical Co., Ltd. and Astellas Pharma Inc., although the funders played no role in study design and preparation of the manuscript.

Availability of data and materials

The data and materials relevant to this case presentation are all included in the published manuscript.

Authors' contributions

All the authors have approved the manuscript and agreed to the submission to this journal. YW is responsible for the manuscript. YW, YM, YS, TH, and TS participated in the study conception and design, acquisition of data, interpretation of data, drafting or revision of the manuscript, and approval of the final version of the manuscript. YM, YW, YS, TH, NK, AI, and MS provided medical care for the patient.

Ethics approval and consent to participate

According to the Ethical Guidelines for Medical and Health Research involving Human Subjects in Japan, ethics approval is not necessary for case reports.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying test results.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Received: 4 December 2018 Accepted: 18 April 2019
Published online: 10 May 2019

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