Penile calciphylaxis in a patient on combined peritoneal dialysis and hemodialysis

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Abstract

Calciphylaxis presents with painful purpura and intractable skin ulcers on the trunk and particularly the distal extremities, and it mainly occurs in patients on chronic dialysis. A 66-year-old man with renal failure due to diabetic nephropathy was on peritoneal dialysis alone for 1 year, followed by peritoneal dialysis combined with hemodialysis for 3 years. He developed calciphylaxis of the penis, which was diagnosed from the skin biopsy findings and clinical observation. To treat this condition, PD was stopped and HD was performed three times a week. In addition, warfarin therapy was discontinued and infusion of sodium thiosulfate was performed. The penile ulcers decreased in size and pain was markedly improved, so the patient was discharged from hospital. Following discharge, PD was resumed after changing the peritoneal dialysis fluid to bicarbonate-buffered dialysate. The penile ulcers eventually resolved completely. There have been very few reports about calciphylaxis in patients on combined dialysis modalities. In our patient, penile calciphylaxis progressed when lactate-buffered peritoneal dialysis fluid was used and resolved after switching to bicarbonate-buffered fluid together with cessation of warfarin therapy and infusion of sodium thiosulfate.

Keywords Calciphylaxis · Combined PD/HD therapy · Bicarbonate-buffered PD fluid

Introduction

Calciphylaxis is a potentially fatal complication that may occur in 1–4% of patients on dialysis or after renal transplantation [1]. It involves intimal calcification/fibrosis of small/medium-sized arteries and skin ulceration of the distal extremities or the penis [2–4]. Calciphylaxis is more likely to occur in patients on hemodialysis (HD) than in those on peritoneal dialysis (PD) [5].

We encountered a PD/HD patient who developed penile calciphylaxis. Calciphylaxis progressed when lactate-buffered PD fluid was used and resolved after switching to bicarbonate-buffered PD fluid.

Case description

A 66-year-old man had a history of acute myocardial infarction (age 56 years), diabetes, and renal impairment. Continuous ambulatory peritoneal dialysis (CAPD) was started at age 62, with HD being added 3 years ago due to poor fluid balance regulation and repeated exacerbation of heart failure. Penile pain developed 1 year before admission. A dermatologist diagnosed genital herpes and prescribed analgesics, but the pain persisted. Four months after its onset, he presented to the Dermatology Department at our hospital. Penile skin biopsy was performed. Analgesics were continued, but were ineffective, and HD sessions were shortened due to the pain.

Six months after the onset of penile pain, he was urgently admitted to our hospital with fluid retention and hyperkalemia.

Examination revealed ulcerated skin lesions on the head of the penis (Fig. 1). There was no leg edema. Serum levels of K, P, UA and hANP were high. CRP was negative, but the white blood cell count was elevated (Table 1). CT revealed widespread mural calcification of arteries, including the

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Fig. 1 **a** Penile findings at admission (6 months after the onset). Lactate-buffered PD fluid was being used for peritoneal dialysis. Ulcers with crusting are seen over more than 50% of the penis, especially at the tip. **b** Penile findings at 3 months after admission (9 months after the onset, 0 month after discharge). Compared with the findings at admission, the extent of penile ulceration is reduced. However,

approximately half of the penis is still covered by ulcers. **c** Penile findings at 18 months after admission (24 months after the onset, 15 months after discharge). Bicarbonate-buffered PD fluid was used from hospital month 4 and the ulcers were almost completely healed by month 18

Table 1 Laboratory results

Laboratory test	Result	Unit
TP	6.1	g/dl
Albumin	3.2	g/dl
BUN	53.5	mg/dl
Creatinine	15.47	mg/dl
UA	8.9	mg/dl
Na	137.5	mEq/l
K	6.4	mEq/l
Cl	96	mEq/l
Ca	8.9	mg/dl
P	7.0	mg/dl
Glycoalbumin	14.7	%
i-PTH	344	pg/ml
hANP	358.0	pg/ml
CRP	0.44	mg/dl
WBC	12500	/μl
RBC	561×10^4	/μl
Hemoglobin	12.8	g/dl
Hematocrit	41.4	%
Platelets	39.6×10^4	/μl
Reticulocyte	5.5	%
PT-INR	1.81	
APTT	40.4	s
Fibrinogen	462	mg/dl

TP total protein, BUN blood urea nitrogen, UA uric acid, Na sodium, K potassium, Cl chloride, Ca calcium, P phosphorus, i-PTH intact parathyroid hormone, hANP human atria natriuretic peptide, CRP C-reactive protein, WBC white bloods cell, RBC red blood cell, PT prothrombin time, INR international normalized ratio, APTT active partial thromboplastin time

dorsal artery of the penis. Parathyroid ultrasound showed nothing notable.

Biopsy of penile lesions confirmed skin ulceration, but von Kossa staining did not reveal the characteristic

vascular calcification of calciphylaxis. Degenerating collagen fibers in the ulcer base resembled the findings in perforating disorders. There were neither herpes-associated nuclear changes nor positive staining for HSV-1 or HSV-2. Penile calciphylaxis was diagnosed, because the patient had elevation of serum phosphate, calcification of the dorsal artery of the penis, and characteristic refractory penile ulcers (Fig. 1).

PD was discontinued and HD was performed three times weekly. Warfarin was discontinued, and his diet and medications were modified to improve control of calcium, phosphate, and parathyroid hormone. Pathological examination detected microabscesses in the penile ulcers and PIPC/TAZ (9 g/day) was prescribed. To control penile pain during HD, treatment was started with morphine gel, fentanyl tape (1 mg), and oral tramadol (25 mg/day). Sodium thiosulfate (10 g/dialysis) was prescribed, because efficacy for calciphylaxis has been reported. Several hypotheses have been proposed regarding the mechanisms by which sodium thiosulfate improves calciphylaxis. According to a recent report [6], sodium thiosulfate possesses antioxidant activity and improves endothelial cell function. As a result, vasodilation occurs and blood flow is increased, which promotes healing of ulceration. There have been no reports about serious side effects of sodium thiosulfate and we used it carefully according to the approved dosage in Japan. Pain improved after about 1 week and almost resolved after approximately 1 month of sodium thiosulfate administration (3 doses per week). Partial crusts formed on the penile ulcers. Because pain was well-controlled after discontinuing sodium thiosulfate, he was discharged from hospital after 3 months admission with resumption of both PD and HD. Lactate-buffered PD fluid (Dianeal) was used before admission, while bicarbonate-buffered PD fluid was used after discharge. The penile ulcers showed almost complete crusting at 6 months after discharge, with almost complete epithelialization at 15 months after that (Fig. 1).

Discussion

Patients with calciphylaxis develop skin ulceration and/or necrosis due to vascular calcification affecting the tunica media/ internal elastic lamina of small/medium-sized arteries in the dermis and subcutaneous fat, as well as edematous intimal thickening associated with concentric stenosis [2–4]. Skin biopsy may cause exacerbation of calciphylaxis, making it difficult to perform extensive biopsy. In our case, typical findings were not obtained. Even when typical features of calciphylaxis cannot be confirmed by skin biopsy, the diagnosis is often made by taking the overall clinical picture into consideration. Calciphylaxis should be suspected if refractory painful ulcers with purpura occur on the distal extremities, hips, thighs, or penis, as well as if non-ulcerated subcutaneous nodules develop [2–4].

Risk factors for calciphylaxis include hyperphosphatemia, obesity, hypoalbuminemia, hypercoagulability, low blood pressure, a history of HD, and medications (warfarin, steroids, and vitamin D preparations) [7–10]. When serum phosphate levels were assessed during 3 treatment periods (HD + PD with lactate-buffered PD fluid, HD alone, and HD + PD with bicarbonate-buffered PD fluid), no significant changes were noted (data not shown). Accordingly, it is considered that the onset of calciphylaxis in our patient was not related to poor control of serum phosphate. In our patient, risk factors for calciphylaxis other than the serum phosphate level were hypoalbuminemia and warfarin therapy for about 10 years. Treatment involves pain control, ulcer debridement and wound care, appropriate control of calcium, phosphate, and parathyroid hormone (subtotal parathyroidectomy and cinacalcet), and intravenous sodium thiosulfate [11].

Although biopsy did not reveal typical vascular calcification in our patient, penile calciphylaxis was diagnosed because of skin necrosis/ulceration and the CT findings.

Calciphylaxis has been reported in non-dialysis patients receiving warfarin [12, 13], so warfarin was discontinued in our patient.

Interestingly, calciphylaxis developed when the patient was receiving combined PD/HD. It was recently reported that the annual incidence of calciphylaxis is 9% in PD patients and its mortality rate is 71%, with prior HD being a risk factor [14]. Conversely, it was suggested that PD is only a minor risk factor for calciphylaxis or is not a risk factor [15, 16]. Therefore, it remains uncertain whether PD can be performed in patients with calciphylaxis.

Because our patient developed calciphylaxis 2 years and 8 months after initiation of combined HD/PD, prior PD or the combination of these modalities may have led to its onset.

Lactate-buffered PD fluid was used when calciphylaxis developed and progressed, while bicarbonate-buffered PD

fluid was used when calciphylaxis subsequently improved. Lactate-buffered PD fluid can cause alkalemia, which can be related to vascular calcification [17]. Data on the ionized calcium level and pH suggested that use of bicarbonate-buffered PD fluid improved alkalosis to prevent the progression of calciphylaxis. Accordingly, lactate-buffered PD fluid might aggravate calciphylaxis, but further investigation would be needed to confirm this.

Conclusion

Penile calciphylaxis developed in a patient receiving combined PD/HD. Administration of sodium thiosulfate, temporary discontinuation of PD, and use of bicarbonate-buffered dialysate after resumption of PD achieved control of this condition. Combined PD/HD and lactate-buffered PD fluid may be risk factors for calciphylaxis.

Compliance with ethical standards

Conflict of interest The authors have no financial conflicts of interest to declare.

Human rights All procedures performed in studies involving this participant was in accordance with the ethical standards of the institutional and national research committee at which the studies were conducted and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient included in this study.

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