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Case Report
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Calciphylaxis in Peritoneal Dialysis Patients: Clinical Experience and Literature Review

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Abstract

Calciphylaxis or Calcific Uremic Arteriopathy (CUA) is pathologically characterized by systemic calcification of small artery, which can lead to ischemia and subcutaneous necrosis.

The incidence rate of calciphylaxis in dialysis patients is 1% to 4%, which is a rare but severe complication. The mortality rate is as high as 80%. Calciphylaxis is often caused by poor CKD-MBD control. The high Parathyroid Hormone (PTH) and the use of high dose vitamin D will directly or indirectly cause the ectopic calcification of vessels, skin and soft tissues, decrease the elasticity of calcified tissues, and result in slow blood flow, occlusion of capillaries, insufficient blood supply, and oxygen supply to tissues, thus causing the calciphylaxis. The exact pathogenesis of the disease is still unclear, and the diagnosis and treatment methods are still limited. This paper reports the successful diagnosis and treatment of a male peritoneal dialysis patient with terminal limb calciphylaxis by low dose Sodium Thiosulfate (STS) combined with Cinacalcet and non-calcium phosphate binding agent.

Keywords: Peritoneal dialysis; Calciphylaxis; Sodium thiosulfate

Case Presentation

The patient, a 58-year-old male, Peritoneal Dialysis (PD) for 12 years, went to an outpatient clinic for "found plantar skin ulceration for more than ten days". Due to the progression of obstructive nephropathy to end-stage nephropathy, the patient underwent peritoneal dialysis catheter implantation 12 years ago. PD protocol (1.5% low-calcium PDF 2L Q4H × 3+2.5% low-calcium PDF 2L) was strictly followed. During dialysis, urine volume was about 100 mL/d, and ultrafiltration volume was 800 mL/d to 1000 mL/d. In November of 2018, there was no obvious inducement for the right plantar skin ulceration with itching, no severe pain in the wound, no fearless of cold and fever, etc. The urine volume and peritoneal dialysis ultrafiltration volume are the same as before. Outpatient service was completed with relevant tests. Blood routine: WBC 7.3 × 10^9/L, N 67.8%, HB 125 g/L. Biochemistry: Scr 1032 umol/l, ALB 26 g/L, blood calcium 2.41 mmol/L, blood phosphorus 1.67 mmol/L, iPTH 1278 pg/mL. *Staphylococcus aureus* grew in plantar secretion culture. Doppler ultrasonography of the lower limb showed the plaque formation in bilateral lower limb arterial, and the blood flow of bilateral lower limb femoral and popliteal vein was unobstructed. Paraprotein in was given to improve microcirculation, de heparin sodium was used to prevent thrombosis; Mupiroxacin ointment was used for external application for ten days. Plantar ulceration was not improved, and the patient was admitted to the hospital.

The patient has a history of hypertension for 20 years, and blood pressure can be controlled. The patient denied diabetes, coronary heart disease, atrial fibrillation, valvular heart disease, and the allergy of food and drug. The treatment of secondary hyperparathyroidism with long-term oral active vitamin D from 2006 was changed to cinacalcet in 2016. There is no special personal history, family history, or hereditary disease history. The patient underwent routine outpatient evaluation every 3 months during 12 years of peritoneal dialysis. Peritoneal dialysis adequacy assessment: Peritoneal Transport Function (PET), LA (2006-2008), HA (2008-2018), average kt/v 2.02+0.31 (/w), average Ccr 62.264 + 16.35 (l/w). The average nPCR for nutrition assessment is 0.99+0.15, SGA: A. During 12 years of dialysis, the mean blood calcium was 2.45+0.37 mmol/L, the average blood phosphorus was 1.56+0.26 mmol/L, and the median blood PTH was 554 (65 pg/mL to 1634 pg/mL).

Physical examination: H 156 cm, W 58 kg, BMI 23.8 kg/m^2, T 36.5°C, HR 80 bpm, R 20 bpm, BP 120/60 mmHg. Skin rupture was observed on the right sole of the foot, and dorsal foot artery

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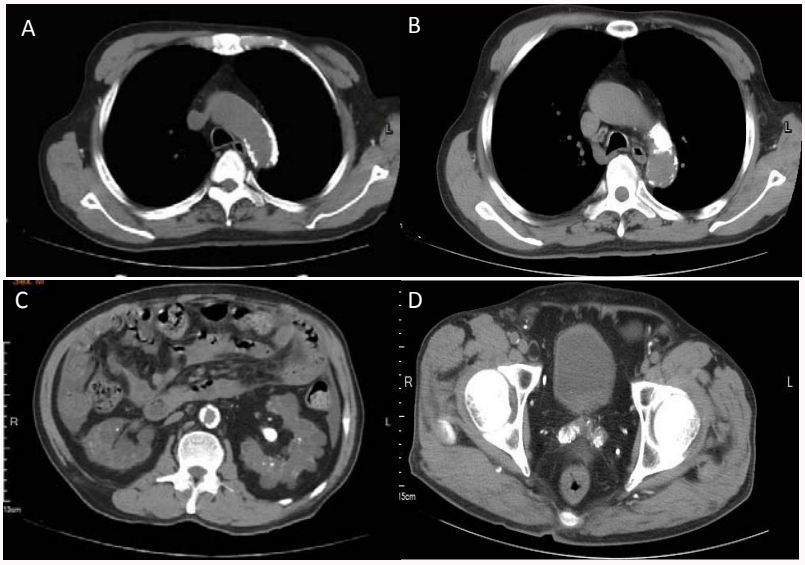

Figure 1: Chest and abdomen CT.

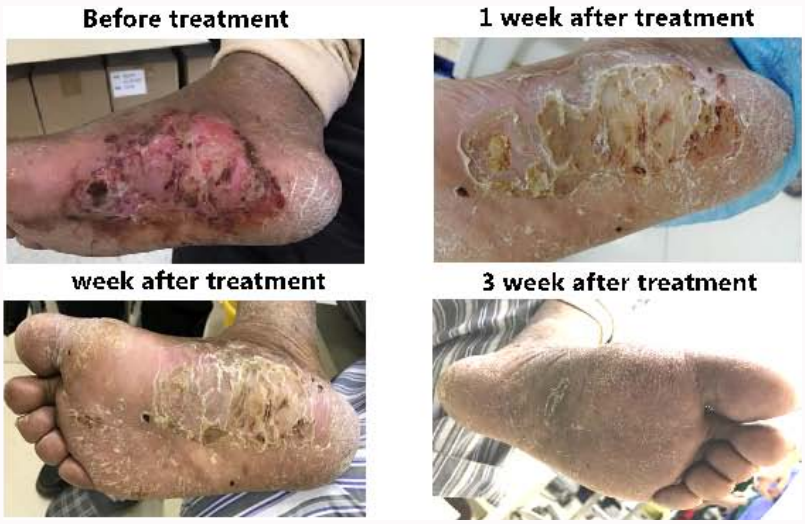

Figure 2: Plantar ulcers before and after STS therapy.

pulsation existed.

Laboratory examination: white blood cell 7.8 × 10^9/L, neutrophil percentage 79.2%, red blood cell 4.08 × 10^{12}/L, hemoglobin 125 g/L, albumin 26 g/L, urea 23.4 mmol/L, creatinine 1052 μmol/L, uric acid 359 μmol/L, calcium 2.41 mmol/L, phosphorus 1.67 mmol/L, estimated glomerular filtration rate 3.9 ml/min/1.73 m^2, triglyceride 1.03 mmol/l, total cholesterol 5.34 mmol/l, PTH1278.9 pg/ml, 25-OH-Vit D 11.80 nmol/L. Infection index: erythrocyte sedimentation rate 83 mm/h, high sensitivity CRP 65.27 mg/L, procalcitonin 1.03 ng/mL. Tumor indicators: CEA, aFP, CA199, CA125 were all negative. Immune indexes: IgA 169 mg/dl, IgG 1020 mg/dl, IgM 83 mg/dl, and ANA, ENA, ANCA, ds-DNA were all negative. DIC: APTT 27.2s, PT 11.6s, INR 0.97, Fg 5.3 g/L, D-dimer 0.41 mg/L, protein C activity 127%, protein S activity 112%. Peritoneal dialysate biochemical routine: Colorless, clear, no coagulum. Rivalta test: Negative. Microscopic examination of red blood cells: a small amount, nucleated cell counts 10.00 × 10^6/L, peritoneal dialysis fluid protein quantitative 451.47 mg/L.

Imaging examinations were shown in Figure 1. Chest CT: Sclerosis of the aortic wall and coronary artery; high-density shadow in the mitral valve area. Abdomen CT: Two kidneys atrophied, and multiple stones and cystic lesions occurred in both kidneys; calcification of the abdominal aorta and its branches; retention of peritoneal dialysis tube, peritoneal effusion, blurred omental fat space. high density shadow in the middle and lower segment of left ureter, which needed to be excluded from calculi; bladder calculus, and calcification of part of small intestine and colon wall; multiple pelvic calcification; multiple calcifications of prostate and bilateral seminal vesicles; pelvic vascular wall is extensive calcification. Ultrasonography: Bilateral thyroid nodular lesions, presumed to be TI-RADS 3. Bilateral hypoechoic masses in bilateral parathyroid regions. Isotopes of parathyroid gland: nodes at left thyroid superior posterior and inferior, nodes at right thyroid posterior, MIBI uptake positive, considering the possibility of parathyroid adenoma. Electrocardiogram: Normal. Echocardiography: Left ventricular ejection fraction: 64% and aortic valve degeneration with slight regurgitation.

Treatment and prognosis: This case was diagnosed as obstructive nephropathy, stage 5 of chronic kidney disease, mineral and bone abnormalities of Chronic Kidney Disease (CKD-MBD), calciphylaxis, secondary hyperparathyroidism, parathyroid adenoma, thyroid nodule, and hypertension. The patient was given Cinacalcet 50 mg/day, sevelamer 1.6 g/day, low-calcium peritoneal dialysis: 1.5% low-calcium dialysate 2L q4h × 3 times, 2.5% low-calcium dialysate 2L overnight, alteplase 20 μg/day to improve microvasculature, sodium thiosulfate 5,120 mg intravenous infusion three times a week, treatment for two weeks (6 times in total) for antioxidant and vasodilation. PTH decreased to 940 pg/mL after two weeks of treatment, and plantar ulcers were significantly better than before. After four weeks of treatment, plantar ulcers healed (Figure 2).

A male patient of calciphylaxis occurred at the extremity of the limb, without severe pain which is not the typical feature of calciphylaxis reported previously. Because the patient has severe disorders of calcium and phosphorus metabolic: blood calcium 2.41 mmol/L, blood phosphorus 1.67 mmol/L, 25-OH-Vit D 11.80 nmol/L, iPTH 1278.9 pg/mL. Imaging showed parathyroid adenoma, multiple vascular and soft tissue calcification. There was no history of diabetes, malignant tumor, vasculitis, cellulitis basis, long-term use of calcitriol, warfarin, long-term use of iron, and gadolinium-containing contrast agent. Improving microcirculation to prevent thrombosis was ineffective, but STS was successful. Therefore, the foot ulcers at the extremity of the limb were diagnosed as calciphylaxis. The etiology of calciphylaxis is related to 12 years of peritoneal dialysis, poor long-term control of PTH, parathyroid adenoma, and long-term history of taking vitamin D.

The incidence of calciphylaxis is low, but the prognosis is inferior. Its clinical manifestations are various and are easily overlooked by clinicians. How to prevent and treat calciphylaxis has been reviewed in a series of literatures.

Literature Review

Overview

Selye first used the word "calciphylaxis" in 1961 to describe skin calcification observed in rats, which was later used to describe the small skin and subcutaneous arteriolar calcification in the research [1]. Calciphylaxis is rare in the clinic, but its prognosis is poor. Literatures reported that the average survival time of calciphylaxis was 2.64 months, with the mortality rate of 81%. The 1-, 2- and 5-year survival rates of dialysis patients after calciphylaxis were 29%, 14.5%, and 9.1%, respectively. Most of the deaths were due to sepsis caused by secondary infection of ischemic wounds [2-4].

Pathogenesis and risk factors

The specific mechanism of calciphylaxis has not been clarified. At present, calcification is considered to be the key pathophysiological process for the occurrence and development of calciphylaxis. Vascular calcification leads to dysfunction of vascular endothelial cells. Human mesenchymal stem cells differentiate into adipocytes, osteoblasts, chondrocytes, and Vascular Smooth Muscle Cells (VSMC). In the case of chronic kidney disease, diabetes, aging, inflammation, and a variety of other toxins, VSMC can be converted into bone/chondrocyte-like cells by up-regulating transcription factors RUNX-2 and MSX2, and participate in normal bone development. Then, in participating participate in the process of bone formation, these bone/chondrocyte-like VSMC deposit collagen in vascular intima or matrix, and bind calcium and phosphorus into matrix vesicles to initiate mineralization, and further mineralize into hydroxyapatite [5]. Whether the artery calcifies depends on calcium inhibitors in circulation and artery, such as fetuin-A, (AHSG), Matrix Gla Protein (MGP), Osteopontin (OPN), and Osteoprotegerin (OPG).

According to the research results, white, woman, Warfarin, and over-weight are four risk factors for calciphylaxis [6]. Women are more prone to calciphylaxis than men, with the prevalence rate of about 2-3:1. The prevalence rate of Caucasians (white men) is higher than that of non-Caucasians [6]. Over-weight increases the pressure on dermal and subcutaneous arterioles, resulting in the focal malnutrition calcification. Warfarin can inhibit vitamin K-dependent carboxylation of MGP, which is a mineral-bound extracellular matrix and can effectively inhibit calcification of arteries and cartilage in animal models. Therefore, the use of warfarin anticoagulation may lead to CUA.

Clinical manifestations

The clinical manifestations are severe pain in the ischemic necrosis area, which usually occurs in the most fat-rich parts, including the abdomen, buttocks, and thighs [2,7,8]. Calciphylaxis is not limited to the skin and the subcutaneous adipose tissue, but also involves the skeletal muscle, intestinal tract, brain, heart, lung, eye, and mesentery [2]. The characteristic venereal disease becomes violet painful plaque-like subcutaneous nodule, which can progress to ischemic/necrotic ulcer, and the eschar with secondary infection often occurs.

Diagnosis and differential diagnosis

Typical skin damages are the main clues of diagnosis, but uremic patients do not have special skin lesions. There was no specific laboratory manifestation, and there may be an increase in PTH, blood phosphorus, calcium, and calcium-phosphorus product, but not necessarily. Other vascular diseases that cause calcified defensive skin lesions were excluded. Skin biopsy provides a pathological basis for calciphylaxis [1,9]. Typical pathological changes are the calcification of arteriole muscle layer with false appearances of cracks, and the narrowing lumen by thickening the intima. The most common pathological changes of early and late lesions are acute and chronic calcifying septal panniculitis. There may also be subcutaneous and dermal vascular thrombosis. However, the skin biopsy may lead to ulcers that are difficult to heal, malnourished calcification, and even induce infection. For patients who have not undergone the biopsy, X-ray plain film, CT, mammography, and bone scan can provide diagnostic support. The bone scan can show abnormal calcium deposition in the subcutaneous tissue of lesions, which has high value in diagnosing calciphylaxis, with the sensitivity for diagnosing calcification of up to 97%. It can also determine the accurate range of calcification disease and change, which can be used to monitor the treatment effect of patients [10]. Reticular or coarse nodular lesions can be seen on X-ray films [11].

Calciphylaxis should be distinguished from trauma, infection (such as cellulitis, diabetic gangrene), skin necrosis induced by drugs (such as warfarin, iron, and gadolinium), autoimmune diseases (such as vasculitis, scleroderma, cryoglobulinemia, and anticardiolipin antibody syndrome). Clinically, it can be excluded one by one through the careful medical history inquiry and laboratory examination.

Treatment

There is no RCT research report on calciphylaxis at present. Retrospective analysis shows that the treatment of calciphylaxis includes: (1) active wound care and pain control; (2) oxygen therapy

(10L to 15L once, for 2 h, once a day), or hyperbaric oxygen; (3) calcium-free phosphate binders, Sevelamer hydrochloride and lanthanum carbonate; (4) when the serum PTH level rises to >300 pg/mL, Cinacalcet (30 mg/d to 60 mg/d) is used for treatment; (5) dialysis is strengthened to improve dialysis adequacy; (6) low calcium dialysate, (7) drugs that can promote CUA, such as Vitamin D, calcium supplement, Warfarin, and iron, are discontinued as much as possible. (8) The occurrence of calciphylaxis is the absolute indication for parathyroidectomy, which can promote the healing calcification wounds, relieve pain, and improve survival. The survival rate of calciphylaxis patients after parathyroidectomy was 65.5%, while the survival rate without surgical treatment was only 35.1%. However, there are also reports that patients after parathyroid surgery did not improve the survival rate. (9) Sodium Thiosulfate (STS) therapy [1].

Prognosis

The prognosis of calciphylaxis is bad. One hundred one patients with calciphylaxis were included, with an average age of 60 years, female 80.2%, and obese 68.0%. There were 18.8% CKD 0-2, 18.9% CKD 3-4, and 62.4% CKD5. During the follow-up period, 75 patients died, and the six-month survival rate was 57%. The mortality of CKD-5 was 1.91 times higher than that of other CKD stages (HR: 1.91; 95% CI, 1.03-3.56; P=0.04. For CKD-5 patients, subtotal parathyroidectomy (performed only in patients with hyperparathyroidism) correlate to 6 months survival (HR: 0.12; 95% CI, 0.02-0.90; P=0.04) and overall survival (HR: 0.37; 95%CI, 0.15-0.87; P=0.02) [3].

Discussion

Calciphylaxis is a rare but severe complication of end-stage renal disease with bad prognosis. Secondary hyperparathyroidism and metabolic disorders of Vitamin D, calcium, and phosphorus are related to calciphylaxis. It is characterized by systemic calcification of the middle membrane of arterioles, which can lead to ischemia and subcutaneous necrosis. Its clinical manifestations are severe pain, ischemic necrosis, and skin ulcer. Treatment includes improvement of dialysis adequacy, correction of calcium and phosphorus metabolic disorders, wound care, parathyroidectomy, anti-infection, sodium thiosulfate, hyperbaric oxygen, etc. In addition, the treatment of calciphylaxis requires multidisciplinary cooperation of nephrology, wound surgery, dermatology, and head and neck surgery.

We report a case of male peritoneal dialysis patients with terminal limb calciphylaxis. He was treated with small dose STS combined with Cinacalcet and non-calcium phosphorus binding agent, and the wound healed completely after four weeks. There is no typical skin lesion in uremia patients as the main clue for diagnosis. The clinical missed diagnosis rate is extremely high. Although skin biopsy of the wound surface can assist in diagnosis, it will induce infections that lead to ulcers and malnourished calcification that are difficult to heal. Therefore, in dialysis patients, the manifestation is the severe calcium and phosphorus metabolic disorder, imaging shows the calcification of vessels and soft tissues, which hare highly suggested that the ulcer is caused by calciphylaxis. Literature reports STS treatment of calciphylaxis in hemodialysis patients, while only a few cases have been reported in peritoneal dialysis.

Cicone et al. [12] proposed for the first time that STS can effectively treat calciphylaxis, and thiosulfate combined with calcium to form highly soluble calcium thiosulfate salt. STS, also known as soda, is clinically used to treat skin pruritus and cyanide poisoning. Some scholars have proposed STS as the first-line drug for the treatment of calciphylaxis [9]. STS forms soluble calcium thiosulfate with free calcium *in vivo*, which promotes dissolution of calcium salt deposited on the vascular wall and reduces the deposition of calcium salt in soft tissues such as blood vessels. It can eliminate free radicals and improve vascular endothelial function through antioxidation. At the same time, glutathione and hydrogen sulfide can be produced, which are used as vasodilators with anti-inflammatory and analgesic effects [12]. Previous literatures reported that STS was used to treat calciphylaxis in hemodialysis patients. The most commonly reported dose was 25 g (diluted to 100 mL) once, and infusion started at the last hour of hemodialysis, with a duration of 30 min to 60 min [13]. There are only a few reports on peritoneal dialysis. Mataic reported that a dose of 25 g sodium thiosulfate was added to 2L low calcium PDF, and the treatment was repeated every other day for three months. Sodium thiosulfate increased calcium removal by an average of 0.65 meq/L (13 mg/L) and low calcium PDF calcium removal by 0.05 meq/L (1 mg/L) [14]. Sagar et al. treated 172 patients with calciphylaxis with sodium thiosulfate, and about 73.6% of the patients had different degrees of remission [13]. Literature reported that bone scanning after three months of STS treatment showed a significant a decrease of calcium deposition in thighs and forearms, and it showed a significant decrease in calcium deposition in the right lower leg after nine months of STS treatment [10].

In the literature, STS was combined with Cinacalcet, calcium-free phosphorus binding agent and low-dose paricalcitol to achieve the good curative effect on uremic calcified arteriopathy and reduce the side effects of STS on bones, which clinical application needed further verification. This paper reports that low dose STS combined with Cinacalcet and non-calcium phosphorus binding agent has a good effect on calciphylaxis. However, it still needs to be verified in large groups of cases.

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