Tumoral calcinosis and calciphylaxis treated with subtotal parathyroidectomy and sodium thiosulphate

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Tumoral calcinosis (TC) is a condition resulting from extensive calcium phosphate precipitation, primarily in the periarticular tissues surrounding major joints. Calciphylaxis is a fatal ischemic vasculopathy mainly affecting dermal blood vessels and subcutaneous fat. This syndrome is rare and predominantly occurs in patients with end-stage renal disease. Here, we report on a rare case involving a patient with TC complicated with calciphylaxis. Our patient was a 31-year-old man undergoing hemodialysis who presented with masses on both shoulders and necrotic cutaneous ulcers, which were associated with secondary hyperparathyroidism, on his lower legs. He underwent subtotal parathyroidectomy, and sodium thiosulfate (STS) was administered for 27 weeks. Twenty months after beginning the STS treatment course, he experienced dramatic relief of his TC and calciphylaxis.

Keywords: Tumoral calcinosis; Calciphylaxis; Parathyroidectomy; Sodium thiosulphate

INTRODUCTION

Calcinosiis cutis is characterized by the deposition of insoluble calcium salts in the skin and subcutaneous tissue. This disorder is classified according to five different subtypes: dystrophic, metastatic, idiopathic, iatrogenic calcification, and calciphylaxis, also called calcific uremic arteriolopathy. Tumoral calcinosis (TC) is a form of idiopathic calcification resulting from extensive calcium phosphate precipitation, primarily in the periarticular tissues surrounding major joints. Calciphylaxis is a fatal ischemic vasculopathy which mainly affects dermal blood vessels and subcutaneous fat [1]. TC and calciphylaxis are rare and predominantly occur in patients with end-stage renal disease (ESRD). The prevalence of TC in combination with calciphylaxis in patients on hemodialysis (HD) has been reported to range from 0.5-3%[2]. The pathomechanisms of these two disorders are poorly understood, but believed to be related to disturbances in mineral metabolism. Treatment primarily focuses on correcting disturbances of calcium, phosphorus, and parathyroid hormone (PTH) concentrations. Adjunctive therapy comprises the dissolution of tissue calcium deposits with sodium thiosulfate (STS) or bisphosphonates. In addition, several reports have described a benefit from parathyroidectomy [3-5].

Here, we report on a case involving a patient on HD suffering from refractory secondary hyperparathyroidism, who developed both extensive TC and calciphylaxis. Both lesions were almost completely resolved with the combination of subtotal parathyroidectomy and STS administration.

CASE

A 31-year-old man with ESRD secondary to hypertension (HD duration >4 years) was admitted with a protruding mass on his left shoulder and painful, nonhealing ulcerations on his right leg. The mass had become noticeable 6 months pre-
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Previously, and the ulcerations had developed without known trauma 3 months previously. After several weeks, the skin lesions became larger and black, and another lesion developed on his left leg.

The patient had a history of obesity (body mass index 34.2 kg/m²) and atrial fibrillation. However, his history did not include liver disease or connective tissue disease. He had been on HD for the past 4 years and his single-pool Kt/V was 0.77.

He had secondary hyperparathyroidism with an intact parathyroid hormone (iPTH) level of 1,513 pg/mL. At a private hospital, he had received medical management for hyperparathyroidism, which included cinacalcet, a low-phosphate diet, intensified HD, and other standard procedures. However, his markedly elevated iPTH level was poorly controlled. His medications included aluminum hydroxide, cinacalcet, aspirin, multivitamins, amlodipine, valsartan, diltiazem, minoxidil, carvedilol, rosuvastatin, furosemide, darbepoetin, oral iron, and calcium polystyrene sulfonate. He had never used warfarin. He had no history of smoking or alcohol consumption.

On physical examination, vital signs were as follows: blood pressure, 110/67 mmHg; heart rate, 60 beats per minute; respiratory rate, 18 breaths per minute; body temperature, 36.2°C. He appeared ill and in mild distress from leg pain. His lung sounds were clear. A cardiovascular examination detected an irregular rate and rhythm; however, no murmur was detected. His abdomen had normal bowel sounds and was flat and nontender. Necrotic lesions of both legs with erythematous areas were observed on his lower extremities (Fig. 1A). The surrounding erythematous areas were painful to palpation, and he had pretibial edema (grade 2+). Pedal pulses were palpable on both sides. His laboratory results were as follows: white blood cell count, 5,600/μL; segmented neutrophil count, 75.9%; hemoglobin, 7.0 g/dL; C-reactive protein, 5.2 mg/dL; blood urea nitrogen, 50 mg/dL; creatinine, 8.95 mg/dL; total calcium, 8.0 mg/dL; phosphorus, 6.5 mg/dL; albumin, 2.6 g/dL; iPTH, 1,322 pg/mL; 1,25-vitamin D3 19.6 pg/mL; and alkaline phosphatase, 245 IU/L. Plain X-rays of the shoulders and pelvis showed TC in both shoulders and hip joints (Fig. 1B).

A thyroid ultrasound showed that both parathyroid glands were enlarged with rim calcification. The left parathyroid gland measured 0.70×0.76×1.18 cm in size and the right parathyroid gland measured 1.01×0.72×1.51 cm (Fig. 2).

After admission, his necrotic skin wounds were treated with dressing, mupirocin ointment, and antibiotics for the infection. The patient underwent subtotal parathyroidectomy for refractory secondary hyperparathyroidism. His parathyroid glands showed diffuse hyperplasia. Postoperatively, he was prescribed oral calcium carbonate and oral calcitriol for the parathyroidectomy-related hypocalcemia. Intravenous (IV) administration of 25 g of STS was initiated. The STS was administered after each HD session (3 times a week) over a period of 27 weeks. After 2 months of treatment, his skin lesions had improved significantly (Fig. 3). After parathyroidectomy, his iPTH levels remained between 5 and 200 pg/mL (Fig. 4).

**Fig. 1.** (A) Skin manifestation of calciphylaxis on the patient's right leg at the time of admission. (B) Radiographs of tumoral calcinosis, showing extensive calcium deposition around both shoulders and hip joints at the time of admission.

**Fig. 2.** A thyroid ultrasound. (A) Longitudinal view of left enlarged parathyroid gland. (B) Longitudinal view of right enlarged parathyroid gland.

**Fig. 3.** Healed calciphylactic lesion after 2 months of treatment.
Fig. 4. Changes in total calcium, phosphorus, and intact parathyroid hormone levels after subtotal thyroidectomy and initiation of sodium thiosulfate administration. Serum P, serum phosphorus (mg/dL); Serum Ca, serum total calcium (mg/dL); iPTH, intact parathyroid hormone (pg/mL); PTX, parathyroidectomy; IV STS, intravenous sodium thiosulfate.

Fig. 5. (A) Completely healed calciphylactic lesion after 20 months of treatment. (B) Radiographic changes of tumoral calcinosis, showing reduced calcium deposition after 20 months of treatment.

Twenty months after the surgery and starting STS therapy, the skin lesions and other lesions compatible with calciphylaxis had completely disappeared (Fig. 5A), and the tumoral calcification of his shoulders and hip joints was significantly reduced (Fig. 5B).

DISCUSSION

The current case shows that subtotal parathyroidectomy and IV administration of STS can almost completely resolve both TC and calciphylaxis in patients suffering from secondary hyperparathyroidism. Despite incomplete understanding of the mechanisms of pathogenesis of TC and calciphylaxis, hyperphosphatemia, hypercalcemia, increased Ca-phosphate products, and secondary hyperparathyroidism are believed to be key players. Diets with high calcium and phosphate, therapies with calcium-containing phosphate binders, and vitamin D analogs may aggravate these disorders. In addition, a number of systemic and local promoters such as uremic toxins, inflammation, and decreased calcification inhibitors can promote this syndrome [6]. The related risk factors in our patient were uremia, longer dialysis vintage, low serum albumin levels, secondary hyperparathyroidism, and obesity.

The prognosis of patients suffering from this disease is generally poor. A study by Rodríguez-Villarreal et al. reported a mortality rate of 32% for patients with calciphylaxis in the lower limbs. In that study, the major causes of death were underlying comorbidities and sepsis [7].

Unfortunately, standardized management for TC and calciphylaxis has yet to be established. Effective treatment likely requires a multidisciplinary approach consisting of wound care; correction of biochemical disturbances; parathyroidectomy; and the use of phosphate-lowering therapy, steroids, cinacalcet, bisphosphonate, and STS.

Hyperparathyroidism can be treated medically or surgically. Cinacalcet is a calcimimetic agent that suppresses PTH secretion and rapidly corrects calcium and phosphate levels. For patients with ineffective responses to medical treatment and high bone turnover, parathyroidectomy has also been considered. Although the benefits of this procedure on survival have not been proven, it may promote wound healing and tissue oxygenation, particularly in patients with high PTH levels [8]. However, caution must be used when performing this procedure because the prescription of oral calcium and vitamin D analogs for post-parathyroidectomy hypocalcemia can actually promote the development of TC and calciphylaxis. In accordance with the case described by Katikaneni et al, the regimen of IV STS successfully prevented secondary calciphylaxis [5].

Interestingly, STS has been used in treatment of cyanide poisoning. Yatzidis and Agroyannis [9] also reported that STS was effective in treating TC in 5 patients over a course of 3 months. Similarly, Cicone et al. [10] reported the first successful treatment of calciphylaxis with STS. Consistent with these studies, we also observed regression of both TC and calciphylaxis after STS administration. The mechanism of action of STS is unclear, but could involve the dissolution of
calcium deposits, chelation of calcium ions, antioxidant effects, and/or vasodilatory properties. However, in previous reports, prolonged STS use was associated with multiple adverse effects including STS-induced metabolic acidosis, nausea, vomiting, headache, hypotension, and electrocardiographic abnormalities [6]. Our patient was treated with STS for 27 weeks. During this period, he did not experience any adverse effects. Since he started STS administration 1 week after parathyroidectomy, determination which treatment (parathyroidectomy versus STS administration) was more effective in improving his TC and calciphylaxis was difficult.

In conclusion, we described a case involving subtotal parathyroidectomy and STS administration that prompted TC regression and wound healing of calciphylactic skin lesions in a patient with ESRD and refractory hyperparathyroidism.

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REFERENCES