Abstract

Elevated parathyroid hormone (PTH) levels and hyperphosphatemia are thought to be associated with the development of calciphylaxis. We report a patient on hemodialysis who developed proximal calciphylaxis with consistently low PTH levels after parathyroidectomy. A 31-year-old man was admitted to our hospital because of abdominal skin ulcerations. Calciphylaxis spread to the penis, and simultaneous progressive lung calcification was evident on chest X-ray, suggestive of pulmonary calciphylaxis on \(^{99m}\)Tc-methylene disphosphonate scintigraphy. The patient died of respiratory failure despite intensive treatment including hyperbaric oxygen therapy. This is the first report of a patient on hemodialysis who developed calciphylaxis involving the penis after parathyroidectomy.


Key words: calciphylaxis, hemodialysis patient, hyperbaric oxygen therapy, low PTH, lung, penis

Introduction

Calciphylaxis is a clinical syndrome characterized by painful and pruritic skin lesions, subcutaneous nodules, skin necrosis, ulceration, and eschar formation, observed mainly in patients with end-stage renal disease (ESRD) on renal replacement therapy or after renal transplantation (1–6). This syndrome occurs in 1–4% of patients on long-term hemodialysis (HD), and is associated with high morbidity and mortality resulting primarily from local and systemic infections (2). Histopathological examination of biopsy material from such patients typically reveals a generalized involvement of small arteries in numerous organs with medial calcification and intimal proliferation with microthrombi (5, 6). Calciphylaxis has been reported in patients with severe hyperparathyroidism (7–9), but a few cases were found to have low levels of parathyroid hormone (PTH) and some had undergone parathyroidectomy (1, 10). The affected areas are usually the toes, thighs, and lower abdomen and even the breasts (11–13). However, penile involvement is rarely reported in the nephrology literature (14, 15).

Here, we describe a young adult patient who was on HD for more than 20 years who rapidly developed proximal calciphylaxis with penile involvement. The patient had undergone subtotal parathyroidectomy three years earlier for severe secondary hyperparathyroidism, which was followed by a relatively low intact PTH level even when skin lesions appeared on the abdominal wall. The etiological and physiopathological aspects of calciphylaxis are discussed.

Case Report

The patient was a 32-year-old man with ESRD on long-term HD. Based on renal biopsy examination, he was diagnosed with chronic glomerulonephritis in 1980. Despite treatment with various medications including steroids, renal function gradually deteriorated, which ultimately necessitated the use of continuous ambulatory peritoneal dialysis (CAPD) in 1987. Following failure of peritoneal ultrafiltration...
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Figure 1. A: Time courses of Ca, P, and Ca×P before and after parathyroidectomy. B: Time course of Alp before and after parathyroidectomy.

tion due to frequent peritonitis, the patient was switched to HD therapy in 1991. He gradually began to develop hypotension during HD. In 1998, he underwent parathyroidectomy secondary to severe secondary hyperparathyroidism. After parathyroidectomy, Ca, P, Ca×P and alkaline phosphatase (Alp) decreased (Fig. 1). In October 2000, the patient complained of severe pain in the left lower abdomen, which gradually increased in intensity, and was coupled with skin ulceration in the same area one month later. On January 9, 2001, the patient was transferred to our hospital for further management of acute and progressive necrotic skin ulcerations on the lower abdominal wall. The patient had a long history of morbid obesity (body mass index [BMI]=27.8 kg/m² at maximum), but marked weight loss was recognized on admission (BMI=19.7 kg/m²).

Physical examination revealed arterial blood pressure of 84/58 mmHg and pulse rate of 84 beats/min. Cardiovascular and chest examinations were unremarkable. Necrotic skin lesions were identified in the left lower abdomen, penetrating the skin to the muscular fascia. Spontaneous tenderness was noted around the right flank. Pulsation of the popliteal and dorsal pedal arteries was intact in both lower limbs, and slight edema was present in the lower extremities.

Laboratory data were consistent with those of patients with ESRD on HD, together with leukocytosis and elevated CRP levels. Intact-PTH value was 63 pg/ml, which was relatively lower than that reported in HD patients (16), although biochemical markers related to bone metabolism, such as Alp, calcium and phosphate, were almost within the normal ranges. Radiographic findings on chest-X ray were unremarkable.

The patient was treated immediately with hyperbaric oxygen (HBO) for whole body and prostaglandin E₁. Because of abscess formation on the right iliopsoas muscle and retroperitoneum, debridement, drainage and skin grafting were performed. The condition was diagnosed as proximal subcutaneous calciphylaxis based on the presence of calcification along the peripheral small artery on the X-ray and histopathological examination of skin lesions, which revealed intimal calcification and microthrombi of the small vessels (Fig. 2). Subsequently, continuous hemodiafiltration and endotoxin absorption were performed together with administration of antibiotics and catecholamines temporarily. This resulted in stabilization of blood pressure and lowering of CRP levels. On February 5, congestive heart failure developed together with pneumonia but both were successfully treated with removal of excessive water by extracorporeal ultrafiltration method and antibiotics. However, we noticed the development of progressive intense calcification of the upper lobes of both lungs on chest X-ray at June 22 (Fig. 3A). At the same time, both ⁹⁹ᵐTc-methylene disphosphonate and CT scan revealed markedly diffuse pulmonary uptake (Fig. 3B), suggesting the development of pulmonary calciphylaxis (17). During the subsequent months, calciphylaxis lesions appeared in the scapula, back and lower extremities and in the penis, glans and scrotum (Fig. 4). Skin grafting of the right flank ulcers failed to heal, and the general condition progressively deteriorated because of bacteremia. Pain was
Calciphylaxis with Penile Involvement

Discussion

We previously reported a patient on HD with systemic calciphylaxis who exhibited rapidly progressive visceral ischemia and acral gangrene (18). She rapidly developed a persistent pain and ischemic skin lesions in all appendages of the extremities, and autopsy revealed diffused medial calcification with intimal fibrous and cellular thickening partly accompanied by microthrombi (5, 6), suggestive of distal calciphylaxis. In comparison, the present case showed proximal calciphylaxis with involvement of the penis, based on the pathological findings obtained from the biopsy samples, which are comparable to those of our previous case.

Calciphylaxis is a multifactorial syndrome (19–24). In our previous case, we speculated that the administration of corticosteroids might act synergistically to cause the disease, in addition to diabetes mellitus and chronic renal failure (18). In the literature, calciphylaxis has been described in many dialysis patients with elevated serum PTH levels (5, 7, 17, 21) However, a few studies have reported calciphylaxis in patients with adynamic bone lesions (25) and in patients who underwent total or subtotal parathyroidectomy (1, 10). Recent studies suggest an increased incidence of adynamic bone disease in dialysis patients since the introduction of Ca²⁺-containing phosphate binders as therapeutic agents for severe hyperphosphatemia. It is conceivable that patients with low bone turnover (low PTH) may be at a higher risk of soft tissue calcification, including calciphylaxis (25, 26), suggesting that patients with adynamic bone lesions (6, 25), and those who had undergone parathyroidectomy (1, 10) are at risk of calciphylaxis. In the present patient, subtotal parathyroidectomy was performed earlier, and the intact PTH levels were relatively low at the time of development of calciphylaxis. It is possible that the patient also suffered from adynamic renal bone disease, although bone biopsy was not performed. Thus, relatively low PTH levels may be partly involved in the development of calciphylaxis in our case, a conclusion also based on our previous report (18) and others (1, 6). In addition, weakness of the lower abdominal wall caused by insertion and removal of CAPD catheter may have caused calciphylaxis, based on previous reports suggesting that local trauma such as subcutaneous injection of heparin or iron dextran may also be precipitating factors in the local development of calciphylaxis (14, 27).

Previous reports suggested that proximal calciphylaxis may be a distinct clinical form of distal calciphylaxis (28), and the majority of patients who died had proximal lesions (2). Several investigators indicated that obesity is one of the risk factors for proximal calciphylaxis (26, 29) and our patient was markedly obese at the time of development of calciphylaxis. The reason for the association between morbid obesity and calciphylaxis is not clear, but is likely to be related to the large amount of adipose tissue (26) and also its circulation (29, 30). In our patient, skin lesions appeared where fat tissue was most abundant; on the thighs and abdomen. It is possible that areas rich in adipose tissue are more prone to damage of small vessels, thus promoting calcifications before the cutaneous lesions and necrosis of the skin become clinically apparent. In our case, calciphylaxis occurred with similar characteristics, including obesity and a low serum albumin (29) together with a relatively low PTH, to those described in previous studies (1, 6). Furthermore, low blood pressure may be an important mediator, resulting in decreased blood flow to adipose tissue and perhaps inciting or augmenting the calciphylactic response, because the blood pressure in our patient was low (84/58 mmHg).

Proximal calciphylaxis affecting the penis and prepuce is rarely mentioned in the nephrology literature. Handa and Strzelczak (14) reported ischemic necrosis and gangrene of the penis caused by calcified changes in small arteries including anterior, dorsal and cavernous branches, which originate from the internal pudendal artery, a branch of the internal iliac artery. Recently Jacobsohn et al (15) reported a penile calciphylaxis patient with diabetes mellitus who developed signs of calciphylaxis coincident with an abrupt and marked elevation of his serum phosphorous level and his calcium×phosphorus product (15). Based on the review of the relevant published studies described in the paper, they suggested that diabetes mellitus and an elevated calcium×phosphorus product may be important precipitating factors for the development of penile calciphylaxis in hemodialyzed patients (15). Similar to the previous report reviewed (15), our patient was younger and had been receiving dialysis for a longer period. However, he had no experience of diabetes mellitus and his calcium×phosphorus product was well controlled after parathyroidectomy. Further study on the pathogenesis of this disease are required. Another notable finding in our patient was the rapid development of pulmonary...
Figure 3. A: Chest X-ray on January 7 and August 28, 2001. Calcification appeared in both sides of the lung on August 28. B: Whole-body scintigrams show markedly diffuse pulmonary uptake of $^{99m}$Tc-methylene disphosphonate.
calcification, as evident on X-ray and CT scan, and the strong $^{99}$mTc accumulation on the pulmonary scintigram. It should be noted that pulmonary calcification is not uncommon in patients on long-term dialysis. In one study (31), the prevalence of metastatic lung calcification in dialysis patients was reported to be about 20%. It is difficult to discriminate pulmonary calciphylaxis from metastatic pulmonary calcification; however, the intensity of $^{99}$mTc accumulation is usually much stronger in pulmonary calciphylaxis than in typical cases of metastatic lung calcification (17). Therefore, the pulmonary calcification in our patient represented pulmonary calciphylaxis rather than metastasis.

Calciphylaxis is associated with high morbidity and mortality resulting primarily from local and systemic infections (2, 26, 32). Several case reports have demonstrated that HBO improves cutaneous calciphylaxis in dialysis patients, suggesting the beneficial effect of HBO therapy on the progression of calciphylaxis (2, 33). In our case, HBO therapy was applied in addition to medical treatment such as prostaglandin E1 and vasodilators, but the skin lesions showed no improvement and the patient died of respiratory infection. Therefore, although the efficacy of HBO therapy was not observed in our case, it is one of the most important therapeutic options. With further accumulation of similar patients, it is important to determine the efficacy of HBO therapy for systemic calciphylaxis.

References

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