Penile Necrosis by Calciphylaxis in a Diabetic Patient with Chronic Renal Failure

Akio Ohta, Shintaro Ohomori, Tomoko Mizukami, Ryusei Obi and Yasushi Tanaka

Abstract

The patient was a 41-year-old man who had suffered from diabetes for 24 years and had been on insulin therapy for 17 years. The patient had commenced hemodialysis in 1999. Some of his toes on both feet had been amputated in 2000 due to diabetic gangrene. The patient was admitted to our hospital in early March 2005 complaining of a painful ulcer on the tip of the penis. At the time of admission, multiple ulcers and necrosis were observed on the prepuce and penis, as well as an ulcer on the left foot and gangrene of the left great toe. Imaging studies demonstrated severe arteriosclerosis with calcification of both large and small arteries. After penile amputation was performed because of severe pain, the wound became ulcerated, and a rectal ulcer as well as skin ulcers also developed in the bilateral inguinal regions. The penile necrosis, skin ulcers, and rectal ulcer were thought to have been caused by calciphylaxis. Calciphylaxis is a disorder in which necrosis occurs at sites of arterial obstruction and calcification, and the prognosis is poor. Seventeen patients with penile necrosis due to calciphylaxis, including our patient, have been reported in Japan. They all had a long history of diabetes, and 15 of the 17 patients were on dialysis.

Key words: calciphylaxis, calcific uremic arteriopathy (CUA), penile necrosis, renal failure, diabetes

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Introduction

Penile necrosis may occur with disseminated infections, such as Fournier’s gangrene, and circulatory disorders, but the penis rarely becomes ischemic because it receives blood through 3 arterial pathways, and thus necrosis is unlikely to occur. Diabetes-associated penile necrosis is a rare condition. Progressive cutaneous necrosis may be caused by arteriosclerosis that is accompanied by calcification of the small blood vessels; this is termed calciphylaxis (1, 2). Calciphylaxis is relatively common among women ranging from 40 to 60 years in age and has an incidence of 1-4% among patients with end-stage renal failure (3, 4). Progressive cutaneous necrosis most frequently affects the lower limbs, particularly the buttocks, thighs, and penis. This disorder is characterized by the development of painful skin ulceration, and it is associated with high levels of morbidity and mortality. Seventeen patients with penile necrosis due to calciphylaxis, including the present patient, have been reported in Japan. Pathological examination of our patient not only revealed arteriosclerosis accompanied by marked calcification of the penile arteries, but also showed ectopic calcification in the corpus cavernosum of the penis. Here, we report a case of penile necrosis induced by calciphylaxis associated with chronic renal failure and underlying diabetic macroangiopathy.

Case Report

A 41-year-old man complained of a painful glans penis. He had a 24-year history of type 2 diabetes. At the age of 34 years (1998), insulin therapy was started. In 1999, hemodialysis therapy was commenced to treat end-stage renal failure due to diabetic nephropathy. At the age of 36 years (2000), some of his toes were amputated on both feet due to diabetic gangrene. In February 2005, penile pain occurred and became worse, so the patient was admitted to St. Marianna University Hospital (Kawasaki, Japan) in March 2005. He had no history of smoking or alcohol intake.
Findings on admission

His height was 172 cm and weight after dialysis (dry weight) was 63.1 kg (BMI was 21.3 kg/m²). The resting supine blood pressure was 216/92 mmHg, and body temperature was 37.2°C. No vascular murmurs were heard in the cervical region or inguinal region and there were no abnormal findings in the thoracoabdominal region. The penis was pale, and multiple ulcers were noted on the glans foreskin and penis (Fig. 1). Simultaneously, gangrene was noted on the lateral left foot and the left great toe. Sensation of the bilateral lower limbs was decreased and the bilateral ankle reflexes were absent. While the right ankle brachial pressure index (APi) was 1.38, pulsation of the left pedal artery and posterior tibial artery were not palpable.

Laboratory findings (Table 1)

The white blood cell count was 13,300/µl and CRP was 1.26 mg/dl, suggesting inflammatory changes. Serum creatinine, BUN, and K⁺ levels were high because blood sampling was performed before hemodialysis (11.93, 61.3, and 5.3, respectively). Serum Ca was 9.8 mg/dl and P was 5.2 mg/dl. Despite 69 mg/dl of plasma glucose, HbA₁c value was 8.6%, showing poor glycemic control, because Hb was only 11.7 g/dl due to renal anemia by end-stage renal failure.

Serum total cholesterol and LDL-cholesterol were normal. Parathyroid hormone was also normal (18 pg/ml). Antinuclear antibody and autoantibodies related to angiitis were all negative.

Radiological findings (Fig. 2)

Abdominal contrast CT detected marked calcification of the renal artery, superior mesenteric artery, testicular artery, external iliac artery, and penile artery. CT angiography of the lower limbs detected marked calcification of the abdominal aorta, renal artery, internal and external iliac arteries, internal pudendal artery, and femoral artery, while the left internal iliac artery was completely obstructed.

Clinical course

His penile ulcers progressed despite intravenous antimicrobial therapy and prostaglandin therapy. Since the pain was very severe, penectomy was performed on the 40th hospital day. Histopathological examination of the resected penis revealed advanced arteriosclerosis (Fig. 3-A) accompanied by calcification of the tunica intima and tunica media of the penile artery with fibrin deposition, while ectopic calcification (Fig. 3-B) and inflammatory cell infiltration were noted in the corpus cavernosum. At 7 days after penectomy, ulceration had developed at the surgical wound and was accompanied by severe pain, as well as bilateral ulceration of

![Figure 1. Penile necrosis.](image-url)
the inguinal region. Skin biopsy was performed at the edge of an ulcer in the left femoral region, and von Kossa staining showed medial calcification of the small blood vessels in the skin and subcutaneous fat, suggesting typical calciphylaxis. There was also infiltration of inflammatory cells with expansion of the intima and subcutaneous fat degeneration (Fig. 4). Defecation became painful, and extensive rectal ulceration in a region extending 20 cm from the anus was detected by colonoscopy. On examination of biopsy specimens, only inflammatory and necrotic changes were noted without any signs of amyloidosis or malignancy, suggesting that the patient had ischemic ulceration of the rectum.

Calciphylaxis should be differentiated from necrotic fasciitis. In the present patient, painful skin ulcers were observed on the buttocks and thighs, which are the common sites affected by calciphylaxis. In addition, medial calcification of the small blood vessels was found in the skin and subcutaneous fat, which is the typical pattern for calciphylaxis and allowed a definitive diagnosis to be made in the presence of chronic renal failure. To relieve pain related to his skin ulcers, epidural block therapy was performed, but effective pain control could not be done. Hyperbaric oxygen therapy could not be performed, since pain-related violent move-
ments were difficult to control. Thereafter, debridement was performed to treat the skin ulcers, but there was also no improvement. The ulcers enlarged to involve the buttocks and thighs, leading to the development of a wound infection-related intravesical abscess and sepsis. The patient died in November 2005 (Fig. 5).

Discussion

Chronic renal failure may induce the progressive development of painful skin ulcers, and this is defined as calciphylaxis or calcific uremic arteriopathy (CUA) (2). Selye initially proposed the concept of calciphylaxis in 1962, and he reported skin necrosis associated with cutaneous calcium deposition in animal experiments (1). Calciphylaxis is a rare disease that develops in patients with chronic renal failure, hyperparathyroidism, and excessive intake of calcium/phosphorus regardless of the presence or absence of diabetes.

The incidence in patients on dialysis is about 1-4%, especially in those aged 40-60 years (3, 4). The most frequent sites of skin ulceration are the buttocks, thighs, and lower abdominal region, but ulceration of the penis (5-7) and digestive tract has also been reported. The histopathological characteristics of the lesions are medial calcification of cutaneous arterioles accompanied by intimal hypertrophy, thrombus formation, calcification of adipose tissue, and inflammatory cell infiltration (8). Penile necrosis due to circulatory disorders is very rare, because the penis receives an abundant blood supply from its dorsal and deep arteries and from the urethral artery. In this patient, severe arteriosclerotic stenosis accompanied by calcification was noted in all 3 arterial systems, and this led to penile necrosis. The relationship between diabetes and calciphylaxis has not been clarified, but the incidence of penile necrosis may be increased in diabetic patients with chronic renal failure. “Atherosclerosis” with diabetes widely affects the thoracic and abdominal aorta, as well as muscular arteries distal to the iliac artery, and multisegmental atherosclerotic changes are noted. In the case of arteriosclerosis developing at sites distal to the leg arteries, the state of glycemic control and the duration of diabetes are the main risk factors (9). The main pathological characteristic of vascular vessels in diabetic patients is medial calcification of the small and medium arteries, which is known as Mönckeberg’s arteriosclerosis, and its incidence is

Figure 4. Histologic examination of the specimen of ulceration in the inguinal region demonstrated vascular calcification (arrow) (von Kossa stain, ×200).

**Table 1**

<table>
<thead>
<tr>
<th></th>
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<tr>
<td>Penectomy (21/Apr.)</td>
<td>Debridement</td>
<td>Death</td>
</tr>
<tr>
<td>May</td>
<td>Antibiotics</td>
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</table>

Figure 5. Clinical course; ulcerations of the surgical wound, bilateral thighs and buttocks after penectomy.
Table 2. Penile Necrosis by Calciphylaxis in a Diabetic Patient with Chronic Renal Failure in Japan

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Duration of diabetes (yrs)</th>
<th>Dialysis</th>
<th>Treatment at penile necrosis</th>
<th>Outcome</th>
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<td>live</td>
<td>Itö</td>
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<td>Nomura</td>
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<td>17</td>
<td>41</td>
<td>17</td>
<td>HD 6yrs</td>
<td>penectomy</td>
<td>dead</td>
<td>Our case</td>
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</table>

Mean 55.6 16.7 88% on dialysis

10 times higher than in non-diabetic patients. It also occurs relatively frequently in younger diabetic individuals, and is significantly related to the duration of diabetes. This disorder is also often observed in patients on maintenance dialysis for chronic renal failure. Mönckeberg’s arteriosclerosis is usually not a clinical problem, because it is not accompanied by obstruction of the vessel lumen. However, blood flow is impaired due to decreased elasticity in advanced cases (10). Medial calcification of cutaneous arterioles in calciphylaxis may be regarded as a pathophysiological mechanism similar to Mönckeberg’s arteriosclerosis. In the present patient it was thought that the combination of calciphylaxis resulting from chronic renal failure and atherosclerosis due to type 2 diabetes synergistically induced ischemic penile necrosis. Arteriosclerosis obliterans (ASO) involves intimal atherosclerotic changes, and is frequently observed in the leg arteries. It is pathologically different from calciphylaxis. In the present patient, gangrene was observed on the lateral area of the left foot and the left great toe. However, he had severe diabetic neuropathy and arterial pulsations were not palpable in the left foot, suggesting that the gangrene was related to neuropathy and/or “atherosclerosis” rather than to calciphylaxis. This patient not only had penile necrosis, but also ulceration accompanied by severe pain occurred in the surgical wound, bilateral inguinal regions, and rectum after penectomy. These were not symptoms of diabetic obstructive arteriosclerosis alone, so calciphylaxis may have been involved.

There have been 17 cases of penile necrosis associated with diabetes, including the present case, and the duration of diabetes was always long (mean: 16.7 years) (Table 2). All of the patients had renal failure, and 88% were on dialysis, but the duration of dialysis was short in many cases and showed no correlation with calciphylaxis (11). When diabetic nephropathy progresses to end-stage renal failure, the serum phosphate level increases and this promotes arteriosclerosis. In patients on dialysis, a high serum phosphate and a decrease of calcification-inhibiting bone matrix protein (12) are factors that favour vascular calcification, and a high serum phosphate level has been reported to promote calcification and the differentiation of vascular smooth muscle cells into osteoblasts (13). A high serum phosphate also aggravates secondary hyperparathyroidism by decreasing serum calcium and inhibiting vitamin D activation. An increase of parathyroid hormone induces the releases of calcium and phosphate from bone, thus increasing the serum calcium - phosphate product. When the product is higher than 70, the risk of ectopic calcification increases and vascular calcification is promoted (8). The laboratory findings of the present patient were already under control, and although the serum P level was slightly high (5.2 mg/dl), the serum Ca and parathyroid hormone levels were normal.

Concerning the treatment of calciphylaxis, some studies have indicated that parathyroidectomy, low molecular weight heparin, and hyperbaric oxygen are useful for correcting hyperphosphatemia and hypocalemia, while local treatment includes debridement and skin grafting. However, no effective procedure has been established so far. Vitamin D therapy may increase the serum calcium - phosphate product, and thus is considered to worsen a calciphylaxis (2, 6).

The rapid development of skin ulcers and a rectal ulcer with aggravation of pain after surgery suggested that surgical stress had led to overactivation of sympathetic nerve system that promoted circulatory dysfunction. Since the survival rate of patients with diabetes and penile necrosis is low, the penectomy procedure is controversial.

Conservative treatment was reported to be superior, unless patients had severe pain or it was difficult to administer antimicrobial agents (14). Surgery was selected for the present patient, because conservative treatment with a vasodilator...
did not improve his symptoms and continuation of dialysis became difficult due to severe pain in the pudendal region. Surgical treatment should be selected with careful consideration of the risk of postoperative aggravation of the systemic condition.

In conclusion, we report the treatment of a diabetic patient on dialysis who developed penile necrosis. A long duration of diabetes and calciphylaxis associated with chronic renal failure are risk factors for penile necrosis.

References


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