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CASE REPORT

Calciphylaxis: A Report of Six Cases and Review of Literature

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Abstract

Calciphylaxis is usually a fatal condition that develops in a few chronic renal failure patients, and it is characterized by calcifications in subcutaneous arteries, infarcts in skin, and the neighboring subcutis. Calciphylaxis, once considered as a rare condition, has been reported to have an annual incidence of 1% and a prevalence of 4% in dialysis patients. We describe our clinical experience in six end-stage renal disease patients on dialysis that presented with calciphylaxis and died due to sepsis, and review the pathogenesis, epidemiology, clinical and histopathologic features, and treatment of calciphylaxis. Physicians should initially consider the possibility of calciphylaxis in case of development of skin lesions in chronic renal failure patients with impaired calcium, phosphorus, and parathyroid hormone levels. The most important cause of mortality in this condition is infection. Therefore, differential diagnosis of these lesions from systemic vasculitis in their early stages and withdrawal of immunosuppressive therapy that increases the tendency to infections are essential.

Keywords: calciphylaxis, chronic renal failure, hemodialysis, peritoneal dialysis, sepsis

INTRODUCTION

Calciphylaxis, or calcific uremic arteriolopathy, is usually a fatal condition that develops in a few chronic renal failure (CRF) patients, and it is characterized by calcifications in subcutaneous arteries, infarcts in skin, and the neighboring subcutis.[1] The term calciphylaxis was first introduced by Selye in 1962.[2]

Calciphylaxis is a small-vessel vasculopathy with intimal proliferation, endovascular fibrosis, and medial wall calcification.[3] Etiology is uncertain, which makes treatment strategies mostly empirical. There are two steps in the development of calciphylaxis. The first step is called "systemic sensitization"; there are several factors such as steroids, usage of vitamin D_3, and increment of serum phosphorus (P) levels.[4,5] Contact with a challenging factor following exposure to these factors for a certain period of time triggers calciphylaxis. Treatment with intravenous iron and other metal salts, steroids, albumin, trauma, and radiopaque contrast substances has been described as challenging.[6,7] In literature, more than 100 cases of calciphylaxis have been reported and the prevalence in hemodialysis (HD) patients has been reported as 4%.[8]

In this report, we describe our clinical experience in six end-stage renal disease (ESRD) patients on dialysis that presented with calciphylaxis and died due to sepsis.

Ethics Committee approval of Istanbul University Cerrahpasa Medical Faculty was obtained (approval no: 16062/2012). The study was in adherence with the Declaration of Helsinki.

CASE 1

A 67-year-old male was admitted to our hospital with bilateral painful dry gangrene in the distal parts of his lower extremities and around the heels in 1992. He had a history of type 2 diabetes mellitus (DM) for 36 years and ESRD for 7 years, and was being treated by HD twice weekly for 2 years. He denied the usage of vitamin D, anticoagulants, or blood products. Funduscopic examination demonstrated advanced diabetic retinopathy. Serum calcium (Ca) and P were markedly elevated

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and serum parathyroid hormone (PTH) was slightly increased. He was hypoalbuminemic. Protein C, S, and antithrombin III levels were normal (Table 1). Romatoid factor (RF), antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCAs), and serologic tests for hepatitis B and C were negative. Hence, hypercoagulability and vasculitis were excluded. Direct X-rays demonstrated metastatic calcifications along the whole vasculature of both lower extremities. Peripheral angiography of the lower extremities showed atherosclerotic wall irregularities in large vessels. Parathyroid scintigraphy was normal. Although skin biopsy showed nonspecific findings, diagnosis of calciphylaxis was based on the presence of ESRD and typical X-ray appearance after excluding the other causes of calciphylaxis. The patient was put on ceftazidime and neutramycin but died secondary to sepsis after 15 days.

CASE 2

A 74-year-old female was admitted to our hospital in July 2000 with a dry gangrenous lesion which started on the second finger of the left foot and then spread over the dorsum of the left foot. She had ESRD secondary to chronic pyelonephritis and had undergone thrice weekly HD since 1990. Her past medical history revealed the usage of active vitamin D and aluminum carbonate for a long time. On physical examination, we found a dry gangrenous lesion on the left lower extremity. The laboratory findings are shown in Table 1. Serum Ca and P were 8.8 and 9.3 mg/dL, respectively. Serum PTH was markedly elevated and serum albumin was decreased. Tests for hypercoagulability and vasculitis were normal. X-rays of lower extremity showed metastatic calcifications along the vasculature of the left foot. Parathyroid scintigraphy was normal. Lower extremity Doppler USG demonstrated widespread atherosclerotic changes in arteries of both lower extremities and hemodynamically significant stenoses at the level of the common-external iliac arteries bilaterally. The clinical findings were compatible with calciphylaxis but the skin biopsy did not demonstrate specific findings for calciphylaxis. The patient had fever and imipenem plus cilastatin therapy was initiated. However, the patient died due to sepsis on the seventh day of therapy.

CASE 3

A 72-year-old male with a 15-year history of hypertension had CRF since 1993, and HD twice a week was initiated in 1996. In accordance with his own will he was switched from HD to continuous ambulatory peritoneal dialysis (CAPD) in 1998. He had been smoking for 30 years and was using active vitamin D and aluminum hydroxide. The patient was hospitalized due to attacks of hypotension and abdominal pain 3 months after the initiation of CAPD. On physical examination,

Table 1. Clinical and laboratory findings and the outcome of the patients.

Case	Etiology of ESRD	RRT type/duration	Ca–P product (mg^2/dL^2)	PTH (pg/mL)	Serum albumin (g/dL)	Protein C, S, antithrombin III	Vascular calcification on X-ray	Therapy	Outcome
1	Diabetes mellitus	HD/2 years	90.0	88	3.0	N, N, N	+	Antibiotherapy, phosphate-binding agent	Died (sepsis)
2	Chronic interstitial nephropathy	HD/10 years	81.8	677	2.9	N, N, N	+	Antibiotherapy, phosphate-binding agent	Died (sepsis)
3	Hypertension	HD/2 years, CAPD/3 months	37.0	118	1.7	N, N, N	+	Antibiotherapy, phosphate-binding agent	Died (sepsis)
4	Diabetes mellitus	HD/2 years	70.0	682	2.1	N, N, N	+	Antibiotherapy, phosphate-binding agent	Died (sepsis)
5	Diabetes mellitus	HD/4 years	81.4	420	2.5	N, N, N	–	Pulsed steroid + cyclophosphamide, phosphate-binding agent Distal penectomy	Died (GIS bleeding + sepsis)
6	Diabetes mellitus	HD/12 years	71.3	126	3.1	N, N, N	+	Antibiotherapy, phosphate-binding agent	Died (sepsis)

Notes: ESRD, end-stage renal disease; RRT, renal replacement therapy; Ca–P product, calcium-phosphorus product; PTH, parathyroid hormone; HD, hemodialysis; N, normal; CAPD, continuous ambulatory peritoneal dialysis; GIS, gastrointestinal system; +, present; –, absent.

pretibial edema and mild abdominal tenderness were noted. The laboratory findings are shown in Table 1. Serum Ca and P were 7.4 and 5 mg/dL, respectively. Serum PTH was mildly increased and serum albumin was markedly decreased. Tests of hypercoagulability and vasculitis did not yield any abnormalities. Peritoneal fluid examination revealed a white cell count of 4600/mm^3. The patient was diagnosed as peritonitis, and intraperitoneal vancomycin was started at a dose of 2 g per week. Since peritoneal fluid cultures yielded *Candida albicans,* he was switched to intraperitoneal fluconazole. On the third week of therapy, erythema was noted on the first and second fingers of the right foot, on the distal part of the fourth finger of the left hand, and on the third, fourth, and fifth fingers of the right hand. During follow-up, all lesions advanced progressively and necrotizing dry gangrene developed. The patient's skin biopsy was non-diagnostic; however, diagnosis of calciphylaxis was made based on clinical findings and history of ESRD. A phosphorus-binding agent (calcium acetate) was added to the therapy for his hyperparathyroidism. The patient died due to sepsis 7 days after the development of necrosis.

CASE 4

A 57-year-old male suffering from deterioration in consciousness and progressive gangrenous lesions which had started on the third finger of the left foot and on the left heel four weeks ago was admitted to our hospital in April 2001. He had type 2 DM for 14 years and had developed CRF in 1998, and was being treated with HD thrice a week since 1999. Physical examination revealed dry gangrenous lesions on the heel and fingers of the left foot and on the distal parts of the fingers of his hands. Peripheral arteries were palpable. The laboratory findings are shown in Table 1. Serum Ca and P were 7 and 10 mg/dL, respectively. Serum PTH was markedly elevated. He was hypoalbuminemic. Tests for hypercoagulability and vasculitis were normal. Hand and foot X-rays showed diffuse medial calcification along the vessels and calciphylaxis was considered. Skin biopsy was not performed. Aluminum hydroxide was administered to decrease serum P levels. *Escherichia coli* and *Enterococcus* spp. were cultured from the swab cultures of the gangrenous lesions. Antibiotherapy was started; however, the patient died due to sepsis.

CASE 5

A 48-year-old male who had type 2 DM since 1987 developed CRF in 1990 and started to undergo HD thrice a week in 1991. In 1995, painful cyanosis was observed on the middle finger of the right hand and as the lesion progressed the finger was amputated spontaneously. Subsequently, he developed progressive gangrene of his hand, foot fingers, and penis. On physical examination, the pulse rate was found to be 140/min and blood pressure was 90/60 mmHg. There were painful dry gangrene on the second, third, and fifth fingers of the left hand, middle finger of the left foot and second finger of the right foot, and necrosis spreading from the penis to the scrotum. The laboratory findings are shown in Table 1. Serum Ca and P were 7.4 and 11 mg/dL, respectively. RF, ANA, anti-DNA, anticardiolipin antibody, cryoglobulin, HBsAg, and anti-HCV were negative. C3 and C4 complement levels were within the normal ranges. The patient was considered to have a systemic vasculitis in the absence of laboratory findings because of the rapid progression of the lesions, and was put on pulse steroid and cyclophosphamide therapy. Distal penectomy was performed. However, pathological examination of the penectomy material revealed fibrous intimal proliferation and a dense medial calcification causing luminal constriction with no evidence of vasculitis. The patient was diagnosed with calciphylaxis and immunosuppressive drugs were withheld. He died after the development of gastrointestinal hemorrhage and *Staphylococcus aureus* sepsis. Postmortem examination demonstrated significant medial calcification and fibrous intimal proliferation of the medium-sized vessels of the heart, the pancreas, the kidney, and the lungs. This case has been previously published as a case report.[9]

CASE 6

A 42-year-old female had been diagnosed with type 1 DM when she was 11. She was found to have proteinuria and hypertension when she was 18, and an increment in creatinine (1.6 mg/dL) was observed when she was 20. She had laser treatment for retinopathy in the same year, and she started to undergo HD for ESRD when she was 30. On her admission to our hospital in May 2006, she was suffering from a dry skin lesion on her left heel. On physical examination, the body temperature was found to be 38.2°C and blood pressure was 160/100 mmHg. Peripheral pulses in the lower extremity were hardly palpable and a lesion on the left heel was noted. Funduscopic examination revealed diabetic proliferative retinopathy and laser spots. The laboratory findings are shown in Table 1. Serum Ca and P were 9.9 and 7.2 mg/dL, respectively. Serum PTH was slightly elevated. RF, ANA, p- and c-ANCAs, hepatitis B, C and HIV serologies, anticardiolipin antibody, and cryoglobulin were negative. Protein C, S, and antithrombin III levels were normal. Telecardiography showed cardiomegaly and a blunted right sinus. Echocardiography revealed systolic and diastolic dysfunction. Metastatic calcification along the vasculature was detected on direct X-rays of the lower extremities. Parathyroid scintigraphy was normal. Although tissue cultures obtained from the lesion over the heel remained sterile, blood cultures yielded gram-positive and gram-negative cocci and *Staphylococcus epidermidis*. Tuberculosis culture was negative. Doppler

USG demonstrated an atherosclerotic plaque causing 30–40% stenosis in the left femoral artery, which was hemodynamically nonsignificant. Vancomycin and neutramycin were administered to the patient with severe sepsis. She was transferred to the intensive care unit as her clinical situation worsened, and died on the 14th day of follow-up.

DISCUSSION

Calciphylaxis, once considered as a rare condition, has been reported to have an annual incidence of 1% and a prevalence of 4% in dialysis patients.[8,10,11] Its incidence has increased significantly in the last decade, with estimates ranging up to 5% of dialysis-dependent patients.[12] It occurs mainly in patients with ESRD on dialysis but can be observed predialysis and after transplantation.[13–17] Although calciphylaxis is almost specific for ESRD, some subjects with normal renal function have been also reported.[18,19]

Calciphylaxis is characterized by small-vessel calcification and cutaneous necrosis.[20,21] Skin and subcutaneous tissues are the most common sites affected. However, skeletal and heart muscle, joint, lung, eye, penis, breast, pancreas, and intestinal tissue involvements have also been reported.[22–32] Lesions begin characteristically as a livedo reticularis pattern of mottling with violaceous, superficial, tender nodules with palpable subcutaneous deposits of Ca or thickened blood vessels.[5,12,33,34] Lesions progress to ulceration and become hemorrhagic with dry necrosis.[5,10,33,35] The most distinctive characteristic of calciphylaxis is severe pain, which is not usually responsive to standard analgesics. Weenig et al. reported that 63 of their 64 (98%) patients complained having severe pain.[15] Although ulcerations are hallmark for calciphylaxis, patients presenting with nonulcerating lesions have been reported by Fine et al.[10] The same authors reported approximately twofold increase in mortality when ulcerations develop. Calciphylaxis may develop in an acral pattern or may involve proximal parts of the extremities such as thighs or buttocks. In general, distal lesions appear to have a better survival rate.[12] Lesions are frequently symmetric. It has a tendency toward involving adipose-rich sites of the body.

Disseminated intravascular coagulation, clotting disorders such as protein C, protein S, and antithrombin III deficiency, systemic vasculitis, antiphospholipid syndrome, marantic endocarditis, myxoma, cryoprecipitate disorders, infections, atheroemboli and cholesterol emboli take place in the differential diagnosis of cutaneous lesions associated with calciphylaxis.[36] We excluded all above-mentioned diseases in our cases. All of our patients were undergoing chronic HD or CAPD. Case 6 presented with penil lesions, which is a rare involvement site for calciphylaxis. Heart, pancreas, lung, and kidney involvements were also demonstrated in the same patient.

There are no serological or hematological tests that confirm diagnosis of calciphylaxis. Imaging techniques are neither specific nor sensitive for calciphylaxis. Vascular calcification may be detected as an abnormal uptake on bone scan imaging, which is a noninvasive way to diagnose and monitor.[35] Bone scan has been reported as a very sensitive method in some reports.[10]

Biopsy may not be performed in all cases since it may lead to nonhealing ulcers and may be hazardous.[10] A single biopsy may be negative for calciphylaxis. Histological findings are not pathognomonic but are helpful.[37] However, some authors suggest that diagnosis of calciphylaxis must be based on pathological findings.[3,16] Since similar findings might be encountered in metastatic calcification, the diagnosis of calciphylaxis is reached by a combination of clinical features, skin examination and the histologic features. Painful and pruritic skin lesions localized on the lower extremities are almost characteristic of calciphylaxis. The histopathological findings were typical for calciphylaxis in only one of our patients. In the remaining five patients, calciphylaxis was diagnosed depending on the clinical features and skin examination. In addition, the direct X-rays of the lower extremity revealed "pipe-stem" calcification in five of our cases. However, this finding is quite nonspecific and is seen in most patients with ESRD.[7]

This disease occurs more frequently in women than in men with a 3-to-1 ratio. The range in ages is reported as 6 months to 83 years with a mean age of 48 [or -] 16 years.[38] Obesity has also been reported as a risk factor.[39] High body mass index, low serum albumin level, and white race were found as risk factors in one study.[39]

The prognosis of advanced calciphylaxis is quite poor and the mortality is about 60–80%.[15] Mortality is mainly associated with secondary infection of the ulcerated lesions as a result of disturbed skin barrier.[15,40] All of our patients died due to sepsis; and in one patient gastrointestinal hemorrhage was another factor contributing to mortality. In patients with nonulcerative plaques, a better prognosis may be expected and steroids may be beneficial in this subgroup of patients.[10]

The definite pathophysiologic mechanism of calciphylaxis is unknown. The most characteristic lesion is intimal proliferation and endovascular fibrosis, which primarily involves small arterioles and venules associated with cutaneous necrosis.[6] Medial calcification is a common finding. Pathologic specimens characteristically show Ca deposition in the walls of the small-medium-sized vessels. Electron microscopic analyses revealed only Ca and P deposition but no evidence of other salts such as aluminum, magnesium, or iron.[21]

Elevated Ca, P, and PTH levels, a high Ca–P product are quite important risk factors for calciphylaxis.[1] Inconsistent findings have been reported in a recent review, which suggested that hyperphosphatemia but not hypercalcemia or hyperparathyroidism was a risk factor for calciphylaxis.[41] A few studies have reported calciphylaxis in patients with adynamic bone lesions.[42]

A patient on HD who developed calciphylaxis after parathyroidectomy has been reported as well.[26] These findings suggest other possible unidentified factors in the pathogenesis of calciphylaxis. Both hyperparathyroidism and adynamic bone disease in patients with relative or absolute hypoparathyroidism may cause elemental derangement in mineral metabolism predisposing for development of calciphylaxis. The presence of concomitant diabetes also increases the risk of calciphylaxis and the development of acral gangrene.[27,43] Nevertheless, recent data claim that calciphylaxis might develop in the absence of these changes.[44,45] Other suggested risk factors for calciphylaxis are obesity, Caucasian race, middle age, female gender, liver disease, and low albumin level.[1,15,21,39] Increased serum alkaline phosphatase has been demonstrated to be a risk factor; however, it is probably related to it being a bone turnover marker and it is synthesized by vascular smooth muscle cells.[12,15] Interestingly, most of our patients were males (four of six patients). The Ca–P product and PTH levels were elevated in five of six patients, and hypoalbuminemia was present in all six patients. Four patients had diabetes.

Vessel calcification has been hypothesized to result from the dysregulation of vascular Ca deposition, which was triggered by the impairment of endogenous calcification inhibitors such as osteoprotegerin, matrix γ-carboxyglutamic acid protein (MGP), and alpha-2-Heremans–Schmid glycoprotein (fetuin-A).[35,46] MGP, which is a major calcification inhibitor, requires vitamin K–dependent γ-carboxylation for activation. Warfarin has been suggested to be an important cofactor through the inhibition of vitamin K–dependent γ-carboxylation of MGP.[15] Fetuin-A is probably the most potent circulating calcification inhibitor and represents a major proportion of the α-2 band of serum electrophoresis. Fetuin-A is a negative-phase protein and tissue levels may decrease significantly in situations of acute and chronic inflammation. Dialysis patients show low fetuin-A levels, and low fetuin-A level is associated with increased cardiovascular mortality in dialysis patients.[47] Bone-specific proteins, collagen I, bone morphogenic protein 2 and 4, osteopontin, osteocalcin, osteonectin, bone sialoprotein, MGP, and alkaline phosphatase have all been shown to be expressed in human atherosclerotic plaques.[48] These proteins have been suggested to play a role in the pathogenesis of calciphylaxis.[49] Increased osteopontin and decreased alpha-actin, a marker of smooth muscle cell differentiation within the arterial media, have been demonstrated in the biopsies of calcified vessels obtained from patients with calciphylaxis.[50] Although small-vessel calcification is a common finding in CRF, these lesions do not usually result in ischemia and necrosis. It has been suggested that a secondary factor is required for the development of calciphylaxis. Hypoalbuminemia, trauma (local injection), systemic hypotension, sepsis, intravenous iron, corticosteroids, subcutaneous insulin, blood products, immunosuppressants, heparin, and warfarin have been proposed to precipitate in the development of calciphylaxis.[21,35,51,52] Uremia is a proinflammatory state in which interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) levels are elevated. Proinflammatory cytokines promote endothelial dysfunction, vascular calcification, and atherosclerosis. HD itself triggers IL-6 and TNF-α production. Induction of proinflammatory cytokines may have a role in the development of calciphylaxis.[53–55] One study found a relation between calciphylaxis and increased serum aluminum levels in dialysis patients.[15] It has been shown that aluminum activates calpain, a protein that degrades nuclear factor κ B (NFκB) inhibitory protein which consequently could increase bone resorption and differentiation of vascular smooth muscle cells into osteoclasts.[12,56] Alkaline media induce Ca deposition and tissue calcification in the presence of high serum Ca and P levels. HD increases pH and results in a relative alkaline pH, which may contribute to the formation of tissue calcification.[31]

Female preponderance may be related to increased fat mass in which blood supply is less than other tissues. This hypothesis may explain the tendency toward adipose-rich tissue involvement. Diabetes, which is a vascular disease, may contribute to ischemia.

Therapy for calciphylaxis is largely supportive. Local care of the wound is essential for the prevention of secondary infections. Once progressive ulceration and necrosis develop, adequate antibiotic regimen should be initiated promptly. In order to normalize Ca and P levels, diet, phosphorus-binding agents, reduction of Ca exposure, reduction or withdrawal of vitamin D therapy, low-calcium dialysis, and parathyroidectomy might be utilized.[57] Parathyroidectomy might be performed as an emergency procedure.[1] Dramatic results have been achieved with parathyroidectomy,[57–59] but the results are generally controversial and its use in patients with mildly elevated or normal PTH levels is a matter of debate.[1] Local injections to adipose-rich areas should be avoided.

Wound dressing, surgical debridement, and, in some cases, even amputation may be indicated. Patients undergoing surgical debridement appear to have improved survival.[15] On the other hand, underlying vasculopathy may prevent the formation of granulation tissue after surgery and may worsen the prognosis.

Intravenous sodium thiosulfate treatment has been reported to be beneficial in a few cases.[3,12,60] It has been successfully administered either by intravenous infusion or by intraperitoneal infusion.[60–62] It has been reported that empiric hyperbaric oxygen therapy might be useful in some calciphylaxis patients.[63–65] Steroid treatment and administration of prostaglandin E1 and vasodilators demonstrated no beneficial effect.[26] Improvement of calciphylaxis after intravenous pamidronate therapy has been recently reported as a new alternative therapy.[12,66] Adynamic bone disease should be

excluded before starting bisphosphonate therapy. Cinacalcet has been recently reported to be associated with improved pain control and ulcer healing.[12,67,68]

In calciphylaxis patients on warfarin treatment, warfarin withdrawal and switch to heparin should be considered. Steroid treatment is not recommended since it is an etiological factor. However, it has been reported that patients with nonulcerating plaques may be the early form of the disease and may respond to steroids.[10] Our patients were all administered palliative therapy; none underwent surgery. The most likely explanation for this was that the patients were admitted to our center at later stages of their diseases and their general conditions on admission were not adequate for surgery.

In conclusion, physicians should initially consider the possibility of calciphylaxis in case of development of skin lesions in CRF patients with impaired Ca, P, and PTH levels. The most important cause of mortality in this condition is infection. Therefore, the differential diagnosis of these lesions from systemic vasculitis in their early stages and the withdrawal of immunosuppressive therapy which increases the tendency to infections are essential. Since an increasing number of patients are on chronic dialysis and on Ca and vitamin D therapy, calciphylaxis will be encountered more frequently than in the past. Awareness of physicians and early recognition is mandatory for a better prognosis.

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