Calciphylaxis in Chronic Renal Failure

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ABSTRACT

Calciphylaxis is a rare and life-threatening complication that is estimated to occur in 1% of patients with ESRD each year. Typically, extensive microvascular calcification and occlusion/thrombosis leads to violaceous skin lesions, which progress to nonhealing ulcers and sepsis. Secondary infection of skin lesions is common, often leading to sepsis and death. The lower extremities are predominantly involved (roughly 90% of patients). Patients with skin involvement over the trunk or proximal extremities have a poorer prognosis. Although most calciphylaxis patients have abnormalities of the calcium:phosphate axis or elevated levels of parathyroid hormone, these abnormalities do not appear to be fundamental to the pathophysiology of the disorder, and the etiology of calciphylaxis remains unclear. Recently, functional protein C deficiency has been hypothesized to cause a hypercoagulable state that could induce thrombosis in small vessels, with resulting skin ischemia, necrosis, and gangrene. The lack of understanding of the pathophysiology of the disease results in treatments that are equally unsatisfactory. Patients who undergo parathyroidectomy have a tendency to improve, but the prognosis for the disease is poor and mortality remains high.

Calciphylaxis is a rare but serious complication in patients with ESRD. The disease is manifested by painful skin lesions that become necrotic (Figure 1), leading to nonhealing ulcers and/or gangrene that
Figure 1. Skin lesions on the lower extremity in a patient with calciphylaxis.

may require amputation. Despite treatment, infection usually supervenes, resulting in septicemia and death. In this report, we present a case of calciphylaxis with an acquired coagulation abnormality. We also reviewed 46 published cases of calciphylaxis that we could identify in the English literature to define some common features of this unusual disorder.

CASE PRESENTATION

A 20-year-old black man with ESRD attributed to focal segmental glomerulosclerosis was hospitalized for leg pain, altered coagulation tests, and skin lesions. Peritoneal dialysis had been initiated 31 months before this hospital admission. Historically, the patient's compliance with medication and his dialysis regimen had been extremely poor. Multiple episodes of peritonitis were documented. A kidney transplant failed 1 month after transplantation some 20 months before admission. Three weeks before admission, the patient developed constant pain in both legs, accompanied by bilateral calf swelling. He had anemia associated with prolonged prothrombin time and partial thromboplastin time with no history of bleeding, liver disease, or anticoagulant treatment. At the time of admission to our hospital, the patient's physical examination was remarkable for two 6 x 7-cm black indurated plaquelike lesions on the inner surface of both calves and violaceous patches over the lower back, flanks, thighs, and penis. His peripheral pulses were symmetrically full. Laboratory data showed white blood cell count, 16.4/mm³; hemoglobin, 7.3 g/dL; hematocrit, 22.4%; calcium, 7.0 mg/dL; albumin, 2.5 mg/dL; phosphorus, 6.8 mg/dL; BUN, 109 mg/dL; creatinine, 11.6 mg/dL; alkaline phosphatase, 316 IU/l (normal, 40 to 170 IU/l); iron, 20 mcg/dL; total iron binding capacity, 176 mcg/dL; ferritin, 338 ng/mL; prothrombin time, 36.3 s; partial thromboplastin time, 112.8 s; fibrinogen, 812 mg/dL; D-dimer, 0.5 to 1.0 UG/mL (normal, less than 0.5 UG/mL). On the second hospital day, the patient's condition deteriorated, with development of hypotension, confusion, lethargy, and acute respiratory failure that necessitated tracheal intubation, ventilatory support, and support for low blood pressure. Tests for lupus anticoagulants were reported positive with borderline positive immunoglobulin M antiphospholipid antibodies. Antinuclear antibodies were positive in a titre of 1:80 (homogenous pattern), with negative anti-DNA and normal levels for C3 and C4 complement. Coagulation profile revealed (all values are expressed in U/dL; normal values are shown in brackets): protein C antigen, 21.0 (77 to 124); factor X antigen, 23.1 (50 to 150); ratio of protein C/factor X, 0.909 (0.605 to 1.477); protein C functional activity, less than 26.3 (65 to 145); protein S antigen level, 26.7 (57.9 to 137.7); free protein S, less than 18.7 (33.5 to 68.5). N-terminal parathyroid hormone (PTH) was 128 pg/mL (normal, 8 to 24 pg/mL) and C-terminal (midmolecule) PTH was 3001 pg/mL (normal, 50 to 330 pg/mL). A radiologic examination of the extremities and a chest x-ray revealed metastatic soft tissue calcifications, Mönckeberg's calcifying sclerosis, and alveolar calcinosis. No skeletal changes suggesting secondary hyperparathyroidism were evident. Cultures of skin lesions grew Escherichia coli, Pseudomonas aeruginosa, coagulase-negative Staphylococcus, and Enterococcus. The patient was treated with intensive hemodialysis, intravenous antibiotics, and aggressive local wound care. Despite treatment, the patient's skin lesions progressed to multiple deep ulcerations on the back and lower extremities. Multiple violaceous nodules, some with ulceration, developed in the right axilla, anterior chest wall, and proximal right arm (photomicrographs of an axillary lesion biopsy is shown in Figures 2 and 3). On the 38th hospital day, the patient became hypercalcemic with a serum calcium level as high as 13.9 mg/dL in the absence of exposure to calcium or vitamin D. On the 60th hospital day, the patient underwent subtotal parathyroidectomy. After parathyroidectomy, the patient's N-terminal PTH level decreased to 46 pg/mL and the C-terminal PTH (mid-molecule) level decreased to 190 pg/mL, falling as low as 102 pg/mL, but his serum calcium level remained elevated. Necrotic skin lesions with eschars remained on the trunk and upper legs. The patient died 44 days after parathyroid surgery.

CLINICAL PRESENTATION

Calciphylaxis is estimated to occur in approximately 1% of dialysis patients each year (1). Our review of 47 patients with calciphylaxis who were reported in the literature suggests a female preponderance of approximately 3:1. The classical presentation described (2–4) starts with painful, purplish (violaceous) mottled skin lesions that may become plaquelike or nodular. The lesions often progress to nonhealing ulcers with wound infection and eschar formation, and usually develop gangrene (Table 1). Infected ulcers are a frequent source of sepsis, which is ultimately the cause.
of death in the majority of patients. Involvement of the lower extremities is almost universal; in our review only 10% of the patients did not have lesions on the lower extremities. Overall, 68% of the patients had proximal involvement with skin lesions (lesions on the trunk or above the knees or elbows), whereas 32% of the patients exhibited only distal involvement of skin (lesions distal to the knees or elbows).

In early stages of the disease, calciphylaxis lesions can resemble those seen in vasculitis, systemic lupus erythematosus, cryoglobulinemia, scleroderma/CREST syndrome, disseminated intravascular coagulation, cholesterol emboli, or bacterial endocarditis (5-7). Calciphylaxis should be distinguished from the acral ulcerations or gangrene that accompany atherosclerotic peripheral vascular disease, resulting in distal necrosis and gangrene. Preserved peripheral pulses favor the diagnosis of calciphylaxis (8).

For the patient group we reviewed, the time period for the onset of symptoms of calciphylaxis ranged from less than 1 month to as long as 12 yr after the onset of ESRD (median, 2 yr 9 months). Three patients presented with symptoms of calciphylaxis before the onset of ESRD and six patients had functioning kidney transplants.

Histologic examination of skin lesions in calciphylaxis reveals microvascular calcification with ischemic epidermolysis (9). Small arteries generally show calcification in the intima and, to a lesser extent, in the media. Small veins exhibit transmural involvement. The lumen of vasculature is narrowed, some totally occluded, although some have signs of recanalization through thrombi. Although not pathognomonic, the presence of small vessel calcification and recanalized thrombi are highly suggestive for calciphylaxis.

PATHOGENESIS

The pathogenesis of calciphylaxis (Table 2) remains unclear. Abnormalities of calcium, phosphorus, and PTH are common, but their pathogenic significance continues to be controversial. Two-thirds of the pa-
TABLE 1. Frequency of various symptoms and signs at presentation in calciphylaxis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>Hyperphosphatemia(^a)</td>
<td>68%</td>
</tr>
<tr>
<td>Hypercalcemia(^a)</td>
<td>20%</td>
</tr>
<tr>
<td>Increased Calcium × Phosphorus Product(^a)</td>
<td>33%</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>82%</td>
</tr>
<tr>
<td>Skin Lesions on Upper Extremities</td>
<td>42%</td>
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<tr>
<td>Skin Lesions on Lower Extremities</td>
<td>90%</td>
</tr>
<tr>
<td>Skin Lesions on Trunk</td>
<td>30%</td>
</tr>
<tr>
<td>Location of Skin Lesions on Extremities</td>
<td></td>
</tr>
<tr>
<td>Proximal Involvement</td>
<td>68%</td>
</tr>
<tr>
<td>Distal Involvement</td>
<td>32%</td>
</tr>
<tr>
<td>History of Corticosteroid Treatment</td>
<td>49%</td>
</tr>
<tr>
<td>History of Kidney Transplant</td>
<td>38%</td>
</tr>
</tbody>
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\(^a\) Phosphorus > 5 mg/dL.  
\(^b\) Calcium > 10.5 mg/dL.  
\(^c\) Calcium × phosphorus > 70 mg/dL.

TABLE 2. Factors proposed as etiologic in the pathophysiology of calciphylaxis\(^a\)

Sensitizing Agents
- Hyperphosphatemia
- Hypercalcemia
- Increased calcium × phosphorus product levels
- Increased parathyroid hormone levels
- Vitamin D activity

Challenging Agents
- Blood products (proteins)
- Metallic salts (iron salts and others)
- Glucocorticosteroids
- Cytotoxic/immunosuppressive drugs
- Local trauma

Protein C Deficiency

\(^a\) Modified from Selye (10).

Patients we reviewed had serum phosphorus levels greater than 5 mg/dL. Twenty percent exhibited serum calcium levels greater than 10.5 mg/dL. Only one-third had calcium × phosphorus product levels greater than 70 mg/dL, suggesting that this abnormality may have less significance in calciphylaxis than in metastatic calcification. Of the 40 patients for whom data were available, seven did not have increased PTH levels, two of these as a result of prior parathyroidectomy.

On the basis of experiments in rats, Selye (10) defined calciphylaxis as a condition of hypersensitivity in which after sensitization by a systemic calcifying factor such as vitamin D or PTH, topical (or systemic) treatment with certain challengers (e.g., proteins, metallic salts, local trauma, corticosteroids) results in local (or systemic) calcification. Albumin, blood products, iron overload, immunosuppressive/cytotoxic agents, or glucocorticoids have been suggested as challengers of the disease (4,7,8,11,12) (see Table 2). Of the 47 cases we reviewed, one-half had a history of treatment with glucocorticoids and 41% had a history of treatment with immunosuppressive or cytotoxic drugs. Eighteen patients had received one or more kidney transplants. Six of these grafts were functioning at the time that the symptoms of calciphylaxis developed. In the remaining 12 patients, the interval between transplant failure and symptom development ranged from 2 weeks to 6 yr (median, 4 months).

Several investigators have noted the association of calciphylaxis with diabetes mellitus and diabetic kidney disease (2,13). However, our review indicated that only 30% of the 47 cases had a history of diabetic disease, a number not impressively different from that of the population at large. Recently, functional protein C deficiency has been implicated in the pathogenesis of systemic calciphylaxis (14). It has been hypothesized that a hypercoagulable state caused by protein C deficiency could induce thrombosis in small vessels, resulting in skin ischemia, necrosis, and gangrene. We identified ten patients with systemic calciphylaxis in whom protein C was measured, and eight of them reportedly exhibited decreased levels. Although attractive, these cases present insufficient data to clearly implicate protein C deficiency in the pathogenesis of systemic calciphylaxis at the present time. However, these interesting observations deserve further evaluation.

TREATMENT AND OUTCOME

The failure to understand the pathogenesis of this disease results in treatment that is generally unsatisfactory. Systemic calciphylaxis is rare, and controlled studies that could demonstrate the advantages of a particular therapeutic option (Table 3) will be difficult or impossible to perform. Normalization of altered calcium and phosphorus levels is the first logical step to prevent or treat the disease. Some authors have advocated the use of aluminum phosphate binders over calcium-containing phosphate binders without convincing evidence to support the primacy of hypercalcemia in the disease (2,15). It is possible that substitution of calcium-containing phosphate-binding agents for aluminum-containing binders, or the increasing use of calcitriol might contribute to an increased incidence of calciphylaxis. However, it is not apparent from the literature that calcium-containing agents or vitamin D have resulted in an increased incidence of calciphylaxis. A prospective study will be necessary to resolve this issue. Aggressive wound care, debridement of necrotic tissue, and judicious

TABLE 3. Treatment options proposed for calciphylaxis

<table>
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<th>Treatment Option</th>
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<tr>
<td>Normalization of Serum Calcium and Phosphorus</td>
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<tr>
<td>Parathyroidectomy</td>
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<tr>
<td>Aggressive Treatment of Infection</td>
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<tr>
<td>Removal of Sensitizing/Challenging Agents</td>
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<tr>
<td>Sympathectomy</td>
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<tr>
<td>Diphosphonate</td>
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<td>Hyperbaric Oxygen</td>
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use of antibiotics are extremely important steps in preventing sepsis.

Parathyroidec tomy is considered by many as a crucial element of therapy (2,4,7,8). Of the 47 patients we reviewed, 31 had a parathyroidec tomy performed after development of calciphylaxis. Fifty-seven percent of these patients died within a median period of 9 wk (range, 1 to 32 wk) after the procedure. The interval between the onset of systemic calciphylaxis and parathyroidec tomy ranged from 3 wk to 6 months (median, 9 wk for those who died and 13 wk for survivors).

Seven patients had parathyroidec tomy before the development of calciphylaxis. Follow-up studies showed that one-third ultimately died. It is not clear if parathyroidec tomy was performed in 9 patients and only 25% of those survived.

The association of the alleged challengers with the pathogenesis of systemic calciphylaxis remains speculative. Furthermore, the need to use agents such as iron, cytotoxic drugs, glucocorticoids, and blood products is sometimes dictated by critical clinical conditions and is thus unavoidable. Cervical or lumbar sympathectomy in an attempt to relieve possible vasospasm has not been found to be helpful (4,8). Diphosphonates were shown to be capable of preventing the induction of experimental calciphylaxis but did not have any effect on the disease once it had become established (16). Too few patients have been treated to allow any viable conclusion regarding the efficacy of this treatment (4). A recent anecdotal report suggests that hyperbaric oxygen had favorable results on the skin lesions in one patient, but the patient ultimately died (17).

The prognosis for calciphylaxis remains poor. Sixty percent of the 47 patients we reviewed ultimately died. Many of the survivors were severely disabled and incapacitated as a consequence of limb amputations and reconstructive surgeries. Obviously, much better insight into the disease’s pathogenic mechanisms is necessary before major improvements in treatment can be achieved.

Finally, after analysis of published data 10 yr ago, Chan et al. (18) found that the outcome of calciphylaxis was influenced more by the localization of the lesions than by treatment. Involvement of proximal areas (i.e., lesions on the trunk and above the knees and elbows) was shown to dictate a poorer prognosis than involvement that was limited to distal areas (lesions below the knees or elbows). Our review of 47 cases lends support to the observation that proximal involvement carries a poor prognosis, in that 72% of patients with proximal lesions died in contrast to 42% of patients with distal lesions.

**SUMMARY**

Calciphylaxis is a rare and life-threatening complication in patients with ESRD. Clinical presentation consists of violaceous skin lesions that progress to nonhealing ulcers and/or eschar formation. Secondary infection of skin lesions is common, often leading to sepsis. The lower extremities are predominantly involved. Patients with skin involvement of the trunk or proximal extremities have a worse prognosis. The etiology of calciphylaxis is unclear. In the majority of patients, PTH levels are elevated but yet do not appear to be fundamental to the pathophysiology of the disorder. Current treatments for calciphylaxis are unsatisfactory. Patients who undergo parathyroidec tomy have a tendency to improve, but overall mortality remains high.

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**REFERENCES**