A Case of Calciphylaxis and Chronic Myelomonocytic Leukemia

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A 70-year-old woman presented for evaluation of symmetric necrotic ulcers of the lower extremities. Biopsy results revealed changes consistent with calciphylaxis. The predisposing factors in this patient included calcium supplementation, obesity, female gender, viscous blood, renal failure, and diabetes mellitus. To our knowledge, this is the first report of calciphylaxis occurring in the setting of chronic myelomonocytic leukemia. We discuss the history, clinical presentation, diagnosis, and treatment of calciphylaxis.

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Calciphylaxis involves a pathologic calcification of nonosseous tissue for which neither hypercalcemia nor hyperphosphatemia is necessary. The condition results in calcification of subcutaneous arterioles and infarctions of subcutaneous adipose tissue. Although the etiology of calciphylaxis is unclear, many predisposing factors have been identified.[1-3]

Selye[4] reproduced metastatic calcification in rat models in 1962. His model included 2 stages. In the first stage, a sustained absolute or relative hypercalcemia acted as a sensitizer. This stage was followed by exposure to a challenger substance, such as an injection of metallic salts, steroids, or albumin, which induced pathophysiologic derangements.[4] In humans, sensitizers that have been identified include hyperparathyroidism, high serum levels of vitamin D, calcium supplementation, and metastatic breast cancer.[5] Several reports have implicated systemic administration of steroids, intravenous injection of albumin, iron supplementation, and tissue trauma as physiologic challengers in calciphylaxis in humans as well.[5-7]

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Case Report

A woman came to our hospital for a second opinion regarding symmetric necrotic ulcers with central leathery eschar and surrounding violaceous erythema and bullae on the inferior and posterior aspects of both lower extremities; these lesions had begun developing 3 weeks earlier (Figure 1). According to the patient's history, the lesions were initially painful, hard, lumpy areas, which eventually proceeded to break down into small individual violaceous papules with central ischemic ulceration; the papules gradually eroded from about 1 cm to larger than 10 cm in diameter.

The patient also had risk factors for calciphylaxis, including calcium supplementation, obesity, female gender, viscous blood, renal failure, and diabetes mellitus. In addition, the patient had a history of chronic myelomonocytic leukemia, hypothyroidism, and recent colon cancer resection. The cancer surgery included administration of blood products followed by diuresis. The diuretics were administered during an earlier hospital stay and continued on an outpatient basis, leading to a relatively protracted period of impaired renal function.

Initial laboratory values included low plasma potassium levels (2.2 mEq/L; reference range, 3.5–5 mEq/L), increased serum creatinine levels (2.6 mg/dL; reference range, 0.7–1.4 mg/dL), increased serum blood urea nitrogen levels (31 mg/dL; reference range, 6–23 mg/dL), and low serum calcium levels (6.9 mg/dL; reference range, 8.6–10.3 mg/dL). The serum phosphorus level was slightly elevated at 6.1 mg/dL (reference range, 2.2–4.3 mg/dL), and the level of thyroid-stimulating hormone was elevated to 39.13 mIU/mL (reference range, 0.35–5.50 mIU/mL). Results of a complete blood count demonstrated a leukocyte count of 49.4×10^9/L (reference range, $4.8–10.8\times10^9$/L) with 32% neutrophils, 8% bands, 5% atypical lymphocytes, 1% metamyelocytes, and 1% myelocytes. The hematocrit value was 33.1%

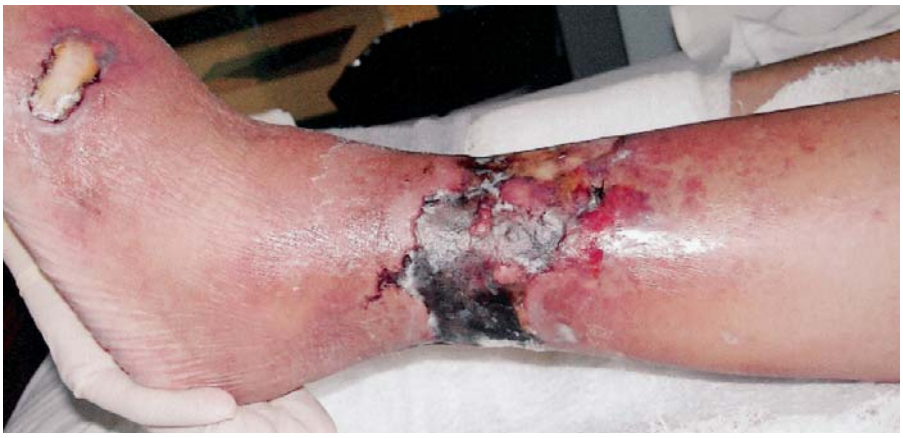

Figure 1. Necrotic ulceration with surrounding violaceous erythema and bulla formation on the distal lateral aspect of left lower extremity.

(reference range, 36%–46%), mean corpuscular volume was 99.7 fL (reference range, 80–98 fL), and the red cell distribution width was 8.1% (reference range, 12.6%–15.7%). The platelet count was 300×10^9/L (reference range, $130–400\times10^9$/L), and serum levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were low.

The patient's primary care physician provided the results of laboratory studies conducted just prior the development of skin lesions according to the history given by the patient. These results showed a serum calcium level of 8.8 mg/dL and a serum creatinine level of 2.1 mg/dL; serum phosphate levels had not been determined at that time. Results of biopsies performed prior to the time of presentation were interpreted by our hospital's dermatopathology service as consistent with a diagnosis of calciphylaxis (Figure 2).

Comment

Most cases of calciphylaxis described in the literature are associated with chronic renal failure requiring dialysis.[3,6-9] However, cases of calciphylaxis during episodes of acute renal failure in patients with normal serum calcium levels have been reported.[2,10] Most patients with this condition are women, and there is a significant association with hypercalcemic states such as secondary hyperparathyroidism, autonomous hyperparathyroidism, and metastatic breast cancer.[5,6] In addition, obesity and diabetes mellitus are commonly seen in patients in whom this condition develops.[11-12] Other studies show that serum levels of parathyroid hormone, calcium, and phosphate are not statistically higher in patients with calciphylaxis and chronic renal failure than they are in control subjects with chronic renal failure alone.[12]

The role of "challengers" as classically described by Selye[4] (ie, insults that occur in a patient predisposed to the development of calciphylaxis) is equally important. Results of a study by Wilmer et al[12] revealed a positive correlation between decreased percutaneous oxygen tension and the development of calciphylaxis. Decreased percutaneous oxygen tension also was seen more commonly in patients with obesity; this correlation may help explain why obese body habitus is a risk factor for calciphylaxis.[12]

One study focused on the role of matrix protein expression by vascular smooth muscle cells in tissue calcification.[11] It has been demonstrated that smooth muscle cells in vitro can dedifferentiate into osteoblastlike cells and produce bone matrix proteins such as osteopontin, which has been found at the base of calcium aggregates in calcified vessels of patients with calciphylaxis. It is postulated that mechanisms of cellular injury, such as ischemia, may be causative factors leading to vascular smooth muscle cell dedifferentiation and calcification.[11] In the case of our patient, diabetes and obesity were likely contributing factors to a physiologic milieu that led to poor tissue perfusion and vascular endothelial damage. In addition, chronic myelomonocytic leukemia may have enhanced her risk of developing calciphylaxis by furthering ischemia in small vessels. This supposition is based on the demonstration that larger, more rigid blast cells occurring in leukemias can impede the flow of erythrocytes in the microcirculation.[13]

Histologic features of calciphylaxis include microcalcifications of small and medium vessels in the dermis and subcutaneous fat.[14] In addition to microvascular calcifications, one of the most consistent histologic features of calciphylaxis is acute

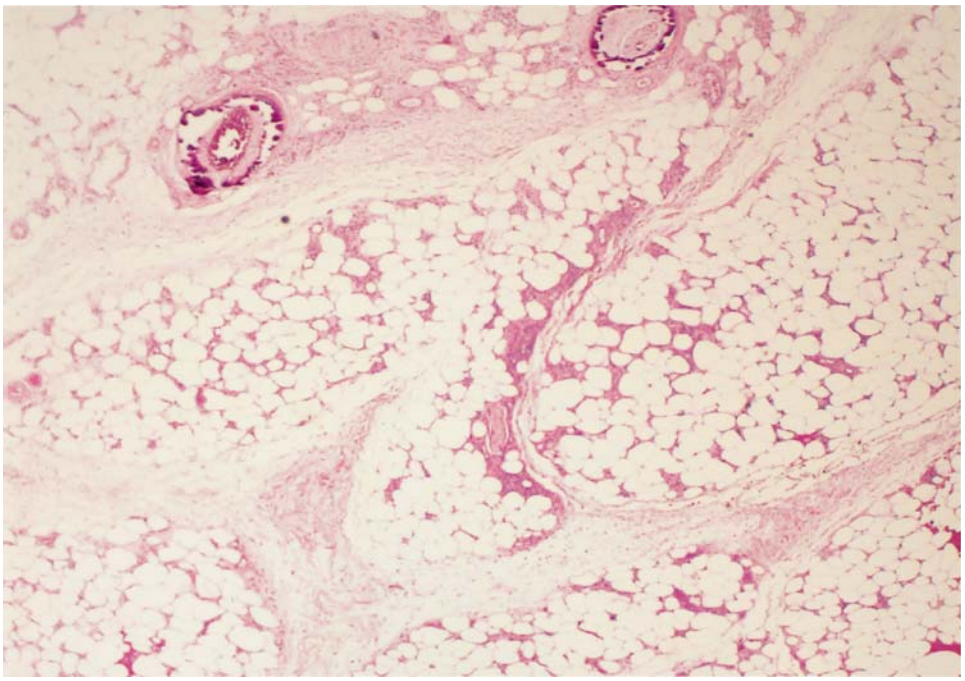

Figure 2. Subcutaneous fat with calcifications of the small to medium vessels in a biopsy sample taken from left lower extremity (H&E, original magnification ×20).

and chronic panniculitis with a predominant septal pattern.[15] A case study indicates that these microscopic findings develop slowly and silently over a period of months to years prior to the onset of clinical manifestations.[16] For this reason, some authors feel the lesions associated with calciphylaxis in humans represent 2 stages: primary lesions that involve microvascular calcifications and secondary lesions that include the gross manifestations of this disease, including infarcts of the superficial fascia and skin that often follow a livedo reticularis pattern.[1,6,14,15]

The treatment of calciphylaxis focuses on removing the inciting factors. Because the results of parathyroidectomy have been mixed, its use should be reserved for cases in which elevated parathyroid hormone level is believed to be a causative agent.[7,17,18] Patients taking calcium carbonate supplements should stop and consider substituting aluminum hydroxide gel or other phosphate binders. Because sepsis is the most common cause of death, every attempt should be made to thwart infection, including diligent wound care, hyperbaric oxygen therapy, and judicious use of antibiotics.[3,14] The mortality rate associated with calciphylaxis is very high, and death is usually due to overwhelming septicemia.

This case is unique because of the concurrent presence of chronic myelomonocytic leukemia and calciphylaxis. The literature does not support a single, clear, pathophysiologic milieu that leads to calciphylaxis, but the reports reinforce the concept that development of this condition is a complicated physiologic process that can result from multiple, concomitant physical states and insults. Further research may help identify additional factors associated with calciphylaxis prior to its development in at-risk patients, thereby targeting aspects amenable to intervention to prevent the occurrence of secondary skin lesions.

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