Protracted Calciphylaxis, Part I

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Calciphylaxis is a serious and often lethal condition that mostly affects patients with renal disease. Patients with calciphylaxis typically have variable degrees of cutaneous necrosis on initial presentation. An unusual, protracted course of calciphylaxis without cutaneous ulcerations has been encountered in the case of a 46-year-old woman. Thirteen additional cases with similar presentation will be discussed in part II of this article. Calciphylaxis may include several clinical presentations, ranging from an acute, rapidly fatal course to an indolent, more benign variant.

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Calciphylaxis is a serious and often lethal condition that mostly affects patients with renal disease. It is characterized by the rapid progression of tender subcutaneous nodules or cutaneous plaques to epidermal necrosis. We report a case of calciphylaxis in a 46-year-old woman in whom subcutaneous nodules on the lower extremities persisted for approximately 6 months without developing cutaneous ulcerations. We believe this case represents an unusual, protracted course of calciphylaxis.

Case Report

A 46-year-old woman with a history of end-stage renal disease and a kidney transplant in 1984 presented in October 1999 with an approximate 6-month history of subcutaneous nodules on her lower extremities. The nodules became increasingly painful in the 2 months prior to presentation. The overlying epidermis showed some erythema and livedoid changes (Figure 1). Biopsy results demonstrated scattered calcifications with surrounding fibrosis and inflammatory reaction in the lowermost dermis and subcutaneous fat (Figure 2). A few small vessels showed calcifications within their walls, while others demonstrated intimal proliferation. Foci of fat necrosis were seen in a patchy distribution. Vascular thrombi were not identified. X-ray films of the lower extremities demonstrated extensive vascular calcification and multiple soft tissue lucencies in the areas corresponding to subcutaneous nodules. Results of laboratory tests revealed an elevated parathyroid hormone level of 1240 pg/mL, a phosphate level of 7.5 mg/dL, and a calcium phosphate product of 79.5. The calcium level was high normal at 10.6 mg/dL. Within 3 months after a subtotal parathyroidectomy, the patient's lesions completely cleared.

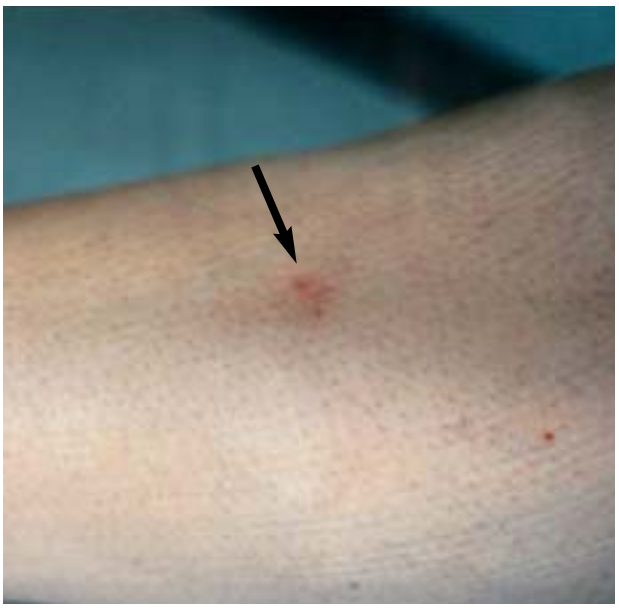

Figure 1. Erythematous patch overlying a subcutaneous nodule on the leg.

Surgical pathology demonstrated hyperplasia of all the patient's parathyroid glands. She never developed cutaneous ulcerations in affected areas. The patient is alive with good functional capacity one year after the initial presentation.

Comment

The pathogenesis of calciphylaxis is unknown. The concept guiding our understanding of this interesting

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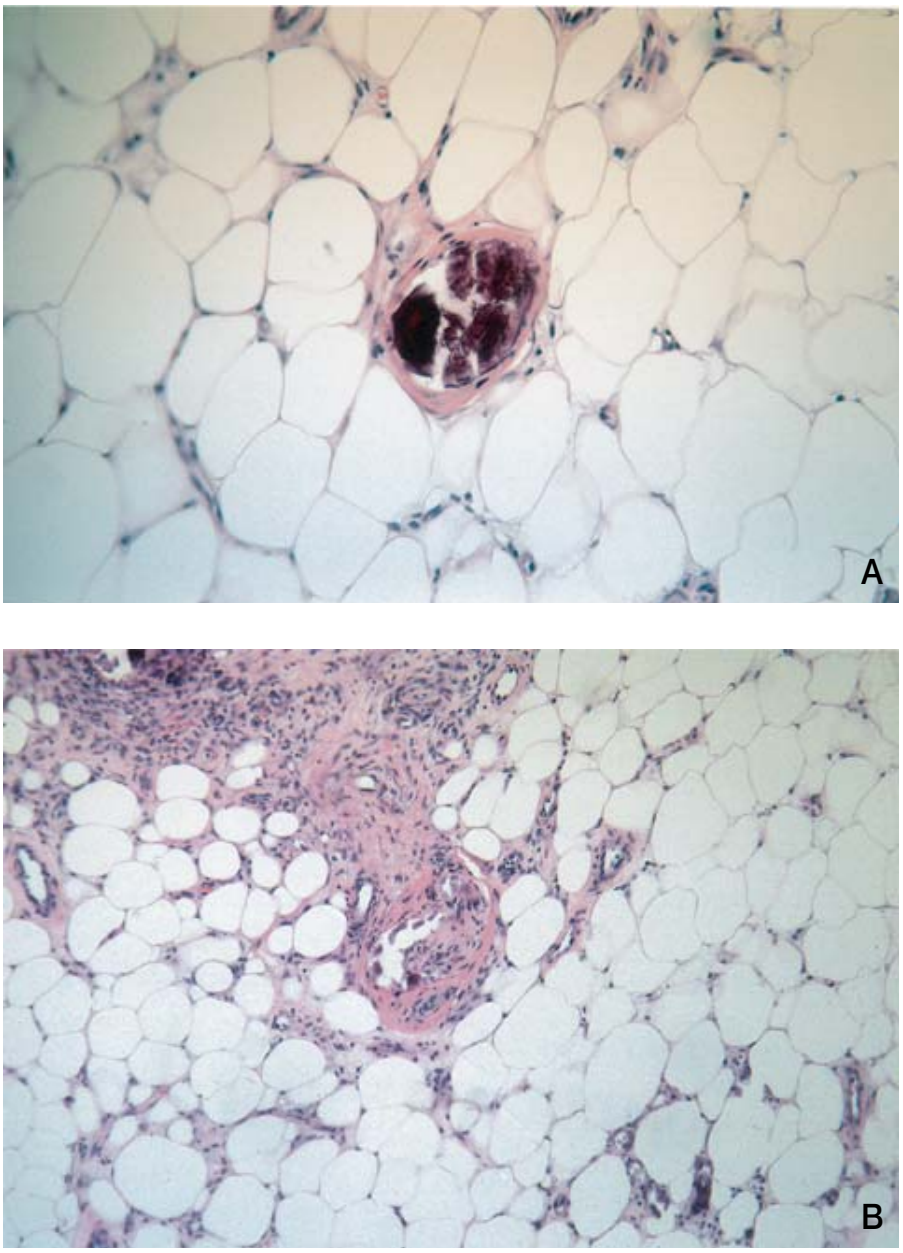

Figure 2. Calcifications within walls of a small vessel (A)(H&E, original magnification ×40). Fibrosis of lowermost dermis and subcutaneous fat, foci of fat necrosis, and calcifications of small blood vessels (B)(H&E, original magnification ×10).

phenomenon came from animal experiments performed in the 1960s by Selye.[1] In these experiments, rats received a "sensitizer" such as parathyroid hormone or vitamin-D derivative. After a short critical period, the rats were "challenged" either locally or systemically by various agents. The animals subsequently developed calcinosis and sclerosis of multiple organs, including the skin.[1]

The concept of calciphylaxis is similar to the one of anaphylaxis. In anaphylaxis, the patient is exposed to the same antigen twice before reaction occurs. In calciphylaxis, the exposure occurs to 2 different antigens. Calciphylaxis implies a sensitivity phenomenon, rather than simply a precipitation reaction when calcium and phosphorus levels reach a critical point.

Multiple reports of calcium deposition and cutaneous necrosis in a subset of patients with renal disease have appeared in the literature in the past 40 years. The similarity to Selye's experiments has been evident. Most reported patients had elevated parathyroid hormone levels, and some of them received vitamin-D supplementation. As noted above, parathyroid hormone and vitamin D were used as "sensitizers" in Selye's experiments. In addition, patients were the subjects of various

"challengers," such as local trauma from injections. Though significant differences exist between animal experiments and human disease, Selye's concept of sensitizers and challengers has proven useful in explaining calciphylaxis. To highlight the differences between Selye's[1] animal model and human disease, the terms *calcific uremic arteriolopathy*[2] and *uremic small-artery disease with medial calcification and intimal hyperplasia*[3] have been proposed to describe this nosological entity. Yet, the term *calciphylaxis* seems to be deeply entrenched in the literature.

Calciphylaxis is rare, with only 208 cases reported in the literature to our knowledge. It presents as tender purpuric patches and plaques in a reticulate pattern with focal central necrosis. It evolves into dusky plaques with woody induration and irregular ulcers covered by thick eschars on the abdomen, thighs, buttocks, and lower extremities.[4] The histology of calciphylaxis is characterized by calcium deposition in the walls of small vessels. Wedge-shaped ulcers extend to the subcutis. Calcium is deposited as fine granules in the dermis and large irregular masses in the subcutis. Calcium deposits are surrounded by foreign body reaction, inflammation, and fibrosis.[5]

The slowly evolving course of calciphylaxis in our case was dissimilar to the rapid occurrence of cutaneous ulcerations seen in most published reports. In Selye's original experiments, sensitization and challenge did not result in skin necrosis, but the onset of internal and cutaneous calcification was quite rapid, occurring within 2 days of the challenge.[1] Our patient had a near-normal blood calcium level. This was not unusual for patients with calciphylaxis, of whom only 20% were reported to have had elevated calcium levels.[6] The high serum phosphate and parathyroid hormone levels seen in the present case also were typical of the levels seen in calciphylaxis cases.[6] Although calcification of small blood vessels, characteristic of calciphylaxis, was seen in our patient's biopsy results, the wedge-shaped necrosis was not observed.

To find out if patients with a protracted course of calciphylaxis have been previously reported in the literature, we decided to look for cases similar to ours. The literature review identified 13 additional reports on calciphylaxis in which cutaneous necrosis was delayed until 4 weeks to 2 years after the initial presentation. The review of these cases will follow in part II of this article.

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