

# Protracted Calciphylaxis, Part II

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*An unusual protracted course of calciphylaxis without cutaneous ulcerations has been encountered in 14 cases. Calciphylaxis may include several clinical presentations ranging from an acute, rapidly fatal course to an indolent, more benign variant. Calciphylaxis should be included in the differential diagnosis for patients with kidney disease presenting with a clinical picture of panniculitis. Patients with renal disease with a characteristic clinical presentation with or without cutaneous ulcerations should undergo an urgent biopsy to confirm the diagnosis.*

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This is the second of a 2-part series on an unusual, slowly evolving course of calciphylaxis. After encountering an atypical case of calciphylaxis in a 46-year-old woman, we undertook a search for similar cases. Literature review identified 13 additional reports on calciphylaxis in which cutaneous necrosis was delayed 4 weeks to 2 years after the initial presentation.

## Methods

A MEDLINE and secondary literature search by 2 independent reviewers identified 208 calciphylaxis cases<sup>1-93</sup> reported in English from 1962 (the year of publication of Selye's<sup>94</sup> experiments on calciphylaxis) to the present. Patients with calciphylaxis typically had a variable degree of cutaneous necrosis on the initial presentation or had skin ulcerations that developed shortly thereafter. Reports demonstrating a 4-week or more duration of clinical disease (tender subcutaneous nodules or cutaneous plaques without skin necrosis) before the onset of cutaneous ulcerations were believed to have a protracted course and were selected for our review. Sixteen cases satisfying this criterion were found.<sup>83-93</sup> Thirteen patients had biopsy-confirmed

calciphylaxis, and 3 patients did not have histopathologic evaluation and therefore were excluded from the study.

## Case Report

Calciphylaxis with a prolonged course has been a feature in 14 cases identified in our literature review,<sup>83-93</sup> including Part I of our report<sup>95</sup> (*Cutis.* 2003;71:473-475)(Table). All patients had some form of kidney disorder ranging from mild renal insufficiency to end-stage renal disease. Most of the patients were middle-aged women who developed tender subcutaneous nodules and/or erythematous plaques on their legs and thighs. Involvement of the buttocks was seen in 2 patients,<sup>86,87</sup> and the abdominal wall,<sup>84</sup> heel,<sup>90</sup> axilla,<sup>86</sup> and popliteal fossa<sup>86</sup> were affected in one patient each. An elevated phosphate level was seen in 7 of the 14 patients (50%), and all but one patient<sup>91</sup> had an elevated parathyroid hormone level. No parathyroid hormone measurement was reported in one case.<sup>85</sup> Calcium levels were normal in 11 of 14 patients (79%), and in 3 cases the levels ranged from low<sup>90,92</sup> to high.<sup>87</sup> The onset of cutaneous ulcerations after the appearance of initial clinical symptoms ranged from 4 weeks to 2 years, with an average of approximately 4 months.

Only one of the 7 patients with proximal involvement (abdomen, trunk, buttocks, and thighs) died (14% mortality rate). Multiple complications, including sepsis, pneumothorax, gastrointestinal bleeding, electrolyte abnormalities, and cardiac instability, were listed as this patient's cause of death.<sup>88</sup> One death that occurred among 7 patients with distal localization of lesions (calves, lower legs) cannot be attributed to calciphylaxis<sup>92</sup>; rather, this outcome resulted from sepsis that occurred 3 months after the patient's parathyroidectomy.

## Comment

The protracted course of calciphylaxis in the 14 cases presented herein is dissimilar to the rapid occurrence of cutaneous ulcerations seen in the majority of published reports.

In our review, all but one patient (93%) with a slowly evolving course of calciphylaxis had elevated parathyroid hormone levels. Half of the patients

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## Patients With a Protracted Course of Calciphylaxis\*

Case No.	Author	Age/ Sex	Location	Presentation	Duration Before Ulceration	Para- thyroidectomy/ Outcome	Follow-up
1	Blumberg et al, 1977 <sup>83</sup>	52/M	Lower legs	Tender, red patches	1 mo	Yes/healed	None given
2	Grob et al, 1989 <sup>84</sup>	53/F	Abdominal wall	Tender nodules	3 mo	No/alive	10 mo
3	Lugo-Somolinas et al, 1990 <sup>85</sup>	48/F	Legs	Tender erythema	3 mo	No/survived initially	Died 1 y later
4	Wenzel-Seifert et al, 1991 <sup>86</sup>	50/F	Buttocks, axilla, popliteal fossa	Tender, platelike subcutaneous calcifications	Never ulcerated	Yes/alive	1 y
5	Yoong et al, 1991 <sup>87</sup>	60/F	Buttocks, thighs, lower legs	Tender nodules	3 mo	No <sup>†</sup> /alive	5 mo
6	Lowry et al, 1993 <sup>88</sup>	50/F	Thighs	Tender nodules and plaques	2 mo	Yes/died	NA
7	Van Hamersvelt et al, 1994 <sup>89</sup>	60/F	Legs	Tender nodules	2 y	Yes/alive	14 mo
8	Dahl et al, 1995 <sup>90</sup>	44/F	Thighs, heel	Tender erythema	4 wk	No/healed	None given
9	Dahl et al, 1995 <sup>90</sup>	46/F	Thighs, legs	Tender nodules	3 mo	Yes/healed	None given
10	Dahl et al, 1995 <sup>90</sup>	67/M	Thighs, legs	Tender nodules	6 mo	Not reported	None given
11	Fine et al, 1995 <sup>91</sup>	73/F	Calves	Tender subcutaneous plaques	Never ulcerated	Yes/alive	10 mo
12	Lue et al, 1996 <sup>92</sup>	36/F	Legs	Tender plaques	4 mo	Yes/survived initially	Died 3 mo later
13	Rudwaleit et al, 1996 <sup>93</sup>	50/F	Legs	Tender patches	5 wk	Yes/alive	Several mo
14	Doctoroff et al, 2003 <sup>95</sup>	46/F	Legs	Tender nodules	Never ulcerated	Yes/alive	10 mo

\*M indicates male; F, female; NA, not applicable.

<sup>†</sup>Lesions healed with medical therapy. Parathyroidectomy was performed 5 months after initial presentation.

had elevated phosphate levels, and 78% had normal calcium levels. These laboratory findings seen in the setting of mild to severe renal disease did not differ significantly from those of a typical patient with a rapid progression of calciphylaxis. According to a review by Budisavljevic et al,<sup>43</sup> elevated parathyroid hormone levels were seen in 82% of patients, hyperphosphatemia in 68% of patients, and hypercalcemia in only 20% of patients with a typical, rapid course of calciphylaxis. An elevated level of parathyroid hormone serves as a “sensitizing” setup for calcification precipitated by one of multiple “challengers.” According to this theory, no elevated calcium or phosphorus levels are needed to initiate calcification. In contrast, metastatic calcification requires a high calcium phosphate product for it to occur.

No additional factors, such as the use of a specific medication, recent kidney transplant, or initiation of dialysis, which would distinguish patients with a prolonged course of calciphylaxis, were identified in our literature review. Overall, it is not clear why the progression of lesions to necrosis was prolonged in this subset of patients.

A histopathologic review of 13 cases by Essary and Wick<sup>96</sup> subclassified calciphylaxis cases as “early” or “late,” based on whether the patients did or did not exhibit necrosis. Fully evolved disease demonstrated patchy, relatively “clean” necrosis with scant acute and chronic inflammation and a background of calcified small- and medium-sized blood vessels in the dermis and subcutis. In lesions of calciphylaxis devoid of necrosis, collagenous degeneration, mild septal panniculitis, and calcified vessels may be seen. It is entirely possible that histologic differentiation between protracted and rapid courses of calciphylaxis can be achieved when more cases are reviewed. The format of reporting histologic findings differed greatly among reviewed cases. Therefore, it was not possible to extract similarities related to histopathology. In our case,<sup>95</sup> only a few vessels showed calcified walls, which are typical for calciphylaxis.

Hafner et al<sup>97</sup> reported a 63% mortality rate for patients with a proximal location of skin necrosis and a 23% rate for patients with a distal location. Our review shows a more benign course for patients with proximal lesions (14% mortality rate) and no mortality attributable to calciphylaxis for patients with distal localization of lesions. The large meta-analysis by Hafner et al<sup>97</sup> includes cases dating back to the 1930s, when parathyroidectomy was not in wide use for patients with calciphylaxis, and even the entity of calciphylaxis was not characterized. Therefore, lower mortality rates for patients treated with

more advanced therapies are justifiably expected. Also, patients with protracted calciphylaxis might have a course that is more benign than that of patients with rapid development of the disease.

Although still a subject of some controversy, parathyroidectomy seems to be the treatment of choice for patients with calciphylaxis and elevated parathyroid hormone levels. Recent meta-analysis of all case reports of calciphylaxis from 1936 to 1996 revealed that 70% of patients who were parathyroidectomized survived compared with 43% of those who did not receive the operation.<sup>97</sup> This meta-analysis did not stratify patients into those with and without hyperparathyroidism. In our review, 8 of 9 (89%) patients who received a parathyroidectomy survived, as did all 5 patients who did not undergo parathyroidectomy. Currently, parathyroidectomy seems to be indicated only for patients with elevated parathyroid hormone levels. Patients with normal parathyroid hormone levels could benefit from conservative treatment, such as normalization of calcium and phosphate levels, monitoring for infection, debridement of necrotic tissue, and aggressive wound care.

In summary, we reviewed a group of patients with a slowly evolving, possibly more benign, course of calciphylaxis. A prolonged course of calciphylaxis might provide a window for therapeutic intervention aimed at halting the progression of this devastating disease. A lack of cutaneous necrosis may preclude the diagnosis of calciphylaxis. Our review indicated the possibility of indolent disease without skin ulcerations in some patients with calciphylaxis. Therefore, it is prudent to include calciphylaxis in a differential diagnosis of patients with kidney disease presenting with a clinical picture of panniculitis. We recommend urgent biopsy for patients with renal disease who present with tender subcutaneous nodules or cutaneous plaques on the lower extremities, buttocks, and abdomen. In histologically confirmed cases of calciphylaxis, treatment should begin immediately, even in the absence of cutaneous ulcerations.

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