Cutaneous Calciphylaxis

An Underrecognized Clinicopathologic Entity

Lydia R. Essary, MD,1 and Mark R. Wick, MD2*

Key Words: Calciphylaxis; Vascular calcification–cutaneous necrosis syndrome; Metastatic calcification; Microangiopathies

Abstract

Calciphylaxis (CPX), an uncommon syndrome characterized, in part, by progressive cutaneous vascular calcification, is seen principally in the setting of renal failure–associated hyperparathyroidism and is difficult to distinguish histologically from other microvasculopathies. We assessed histologic specimens from 13 cases of clinicopathologically classic CPX of the skin and reviewed documented histologic findings in the literature. Our series included 7 “early” and 6 “late” lesions (absence or presence of tissue necrosis, respectively). Histologically, early lesions were subtle and almost inapparent microscopically. Late lesions were easier to recognize because of obvious epidermal ulceration, dermal necrosis, and easily seen mural vascular calcification. The most common finding in both groups was acute and chronic calcifying septal panniculitis. Endovascular fibroblastic proliferation was more common in advanced lesions. Necrosis of dermal collagen was identified in only a few early lesions. Frank luminal vascular thrombosis was infrequent in both groups. The cited histologic findings largely were mirrored by those in the literature. Although they are relatively nonspecific when considered in isolation, the cited histopathologic features of cutaneous CPX allow for the diagnosis of this potentially lethal disorder when they are seen in combination with one another, particularly if detailed clinical data also are available.

Calciphylaxis (CPX) of the skin is a rare and potentially life-threatening syndrome characterized by progressive microvascular and superficial soft tissue calcification. It is usually, but not invariably, seen in the setting of secondary hyperparathyroidism and chronic renal failure with elevation of the serum CaPO4 product1-4 and also is known as the “vascular calcification–cutaneous necrosis syndrome.”5 This condition develops in approximately 1% of patients with end-stage renal disease each year6 and, as such, generally is known to nephrologists. However, other physicians—including many pathologists—still are not acquainted with all of its attributes.

CPX usually manifests with painful violaceous skin lesions that typically progress to nonhealing ulcers with underlying tissue necrosis. Potential complications include digital gangrene, supervening sepsis, pancreatitis, and multisystem organ failure, among others, with an overall mortality of more than 60%.2-7-10 Clinically, CPX also may simulate other conditions, such as connective tissue diseases,11-13 and, conversely, may itself be mimicked by other disorders, such as atheroembolization, antiphospholipid syndrome, and isolated acquired protein S or C deficiencies.14,15

Given the multiplicity of disorders that can be associated with spontaneous cutaneous necrosis, many of the histopathologic features of CPX are, as expected, nonspecific. Also, they are clinicopathologically variable and largely dependent on the stage of the process at which skin lesions are sampled and the amount of tissue that is obtained for microscopic evaluation. Furthermore, in view of the complicated pathogenesis of the disease in question and the possibility of other concomitant pathologic conditions in the patient population at risk, it is important to
recognize the histopathologic features that would facilitate early recognition of CPX. Accordingly, we present the spectrum of microscopic observations that was observed in an institutional analysis of 13 cases involving the skin (the most commonly biopsied site in this disorder), seen during a decade, as well as those reported in the pertinent literature.

Materials and Methods

Cases featuring “nonspecific” ulceration of the skin and superficial soft tissue were retrieved from the archival files of the Lauren V. Ackerman Laboratory of surgical pathology at Washington University Medical Center, St Louis, MO, as accessioned during the period November 1988 through December 1998. In addition, biopsy specimens from patients with an outright clinical or pathologic diagnosis of CPX also were reviewed. Clinical data for these cases were obtained from hospital records, referring physicians, and written contact with the patients or their families. H&E-stained sections were examined by both of us and correlated with clinical findings in all cases. Minimal clinicopathologic criteria for the diagnosis of CPX in this series were represented by the presence of livedo reticularis, nodular violaceous cutaneous lesions, or ulceration of the skin; an elevated serum calcium-phosphate coefficient; and skin biopsy specimens demonstrating abnormalities of cutaneous blood vessels with or without dermal inflammation and necrosis, accompanied by positive labeling of small vessels with the histochemical von Kossa stain. The lesions additionally were subclassified as “early” or “late” CPX based on whether they did or did not exhibit necrosis, respectively; this decision was made because clinical ulceration historically tends to appear only after the cutaneous changes of CPX have been present for some time.9

For the specimens that met the aforementioned criteria, detailed notes were taken on the histologic appearance of the epidermis, dermis, and subcutis, with particular attention to small blood vessels in the latter 2 compartments. Results of treatment (if any had been given) and the overall clinical outcome were recorded and correlated with microscopic findings. Finally, recorded histologic descriptions of CPX in previous publications were reviewed in detail (using the PubMed Internet database at http://www.ncbi.nlm.nih.gov/PubMed/), and variations thereof were tallied and compared with the results of the present analysis.

Results

Thirteen institutional cases that were reviewed met the aforementioned criteria for a diagnosis of CPX, whereas other examples of clinically and pathologically similar lesions could be attributed retrospectively to other causes (septic embolization, atheroembolization, disseminated intravascular coagulation, and other coagulopathies). Patient ages ranged from 40 to 82 years (median, 53 years). The female/male ratio was 10:3. Clinical appearances of CPX lesions were heterogeneous; they were variably described as livedo reticularis, superficial “blisters,” nonblanching purpuric maculae or nodules, painful subcutaneous masses, and necrotic ulcers. Table 1. Predominant anatomic sites of development were the lower extremities and the skin over the pelvic girdle, including the buttocks. Two patients, however, had large abdominal wall ulcers. All of the patients had known renal insufficiency (with a variety of pathogeneses) and had been given dialysis-based therapy. Two patients recently had undergone successful allogeneic renal transplantation for end-stage native renal disease. No patient in the present study had undergone quantitative or functional assessments of hematologic coagulation factors, and we could not perform those studies because of the retrospective nature of the assessment.

Microcalcifications in small to medium-sized venules were evident in all 13 cases, in the dermis (5 cases) and subcutis (12 cases). These were obvious on routine microscopy in all but 1 case in which fine granular stippling of the vascular media was seen on H&E stains, and results of the von Kossa stain were needed for definitive interpretation. There was no apparent relationship between the size or density of calcium deposits and the clinical status of the lesions. In addition to microvascular calcification, the most consistent microscopic feature of CPX was that of acute and chronic panniculitis, with a predominantly septal pattern. This was seen in 11 (85%) of cases overall (6 in the late CPX phase, 5 in early CPX) Table 2. Typically, the subcutaneous inflammation was slight to moderate and consisted of a dispersed infiltrate comprising neutrophils, lymphocytes, and rare eosinophils. The septal component of late CPX lesions was somewhat more dense than that seen in early CPX. Five early-phase cases showed scant infiltrates of neutrophils and lymphocytes in the dermis as well, with a tendency for the inflammation to be centered around superficial and deep blood vessels. Two of 7 early CPX lesions were completely devoid of inflammation, and the only recognizable abnormality in the biopsy specimens was calcification of small venules Image 1. Degeneration of collagen was seen only in early CPX, in 3 cases (23%), in the deep corium or subcutaneous septa Image 2; none of the lesions assumed the histologic image of pseudoxanthoma elasticum, as reported by other authors.16

Endovascular endothelial proliferation and intimal fibrosis in cutaneous blood vessels were seen more commonly in late CPX lesions, but, overall, these findings
were represented in only 6 cases (46%) and had no relationship to the presence or degree of vascular microcalcification in the same blood vessels [Image 3]. Similarly, no association was seen between endothelial abnormalities and obliteration or recanalization of blood vessels or the presence of tissue necrosis. Venular and arteriolar microthrombi were present in both phases of CPX, in 23% of cases [Image 4].

Two of the 3 cases featuring thrombosis were early CPX lesions, 1 of which also showed marked endovascular proliferation with luminal occlusion and partial recanalization. Of the lesions, 2 (15%) showed dermoeipidermal separation and epidermal devitalization; both were cases of early CPX. Uncommonly, erythrocytic extravasation was present as well in early-phase lesions, both in the corium and subcutis. Advanced late CPX cases (4 [31%]) showed ulceration and contiguous areas of dermal or dermal and subcutaneous necrosis with mixed acute and chronic inflammation.

Review of the existing literature on the histopathology of CPX revealed descriptions of mural calcifications of small vessels in the dermis and subcutis (Table 1).

<table>
<thead>
<tr>
<th>Case No./ Sex/Age (y)</th>
<th>Clinical Data*</th>
<th>Septal Subcutaneous Inflammation/Ulceration</th>
<th>Calcified Dermal Vessels/Calcified Subcutaneous Vessels</th>
<th>Size of Calcified Vessels</th>
<th>Thrombi</th>
<th>Necrosis/ Dermal Inflammation</th>
<th>Other Vascular Abnormalities</th>
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<tbody>
<tr>
<td>1/M/40</td>
<td>Ulcer on leg</td>
<td>+/+</td>
<td>+/+</td>
<td>Small and medium vessels</td>
<td>+</td>
<td>+/0</td>
<td>Endovascular fibrosis</td>
</tr>
<tr>
<td>2/F/82</td>
<td>Painful nodules on hip</td>
<td>+/0</td>
<td>+/+</td>
<td>Small and medium vessels</td>
<td>0</td>
<td>0/0</td>
<td>Endovascular fibrosis</td>
</tr>
<tr>
<td>3/F/45</td>
<td>Livedo reticularis on leg</td>
<td>0/0</td>
<td>0/+</td>
<td>Small</td>
<td>0</td>
<td>0/0</td>
<td>None</td>
</tr>
<tr>
<td>4/F/51</td>
<td>Purpuric lesions on leg</td>
<td>0/0</td>
<td>0/+</td>
<td>Small</td>
<td>0</td>
<td>0/0</td>
<td>None</td>
</tr>
<tr>
<td>5/M/55</td>
<td>Ulcer on leg</td>
<td>0/+</td>
<td>0/+</td>
<td>Small</td>
<td>0</td>
<td>0/0</td>
<td>RBC</td>
</tr>
<tr>
<td>6/F/56</td>
<td>Abdominal wall ulcer</td>
<td>+/+</td>
<td>+/+</td>
<td>Small and medium vessels</td>
<td>0</td>
<td>+/0</td>
<td>Endovascular fibrosis</td>
</tr>
<tr>
<td>7/F/60</td>
<td>Necrotic ulcers on abdomen and buttocks</td>
<td>+</td>
<td>+/+</td>
<td>Small and medium vessels</td>
<td>+</td>
<td>+/0</td>
<td>Endovascular fibrosis</td>
</tr>
<tr>
<td>8/F/53</td>
<td>Painful nodules and bullae on leg</td>
<td>+</td>
<td>+/0</td>
<td>Small</td>
<td>0</td>
<td>0/0</td>
<td>None</td>
</tr>
<tr>
<td>9/F/60</td>
<td>Painful nodules and bullae on leg</td>
<td>+</td>
<td>+/0</td>
<td>Small and medium vessels</td>
<td>0</td>
<td>+/0</td>
<td>Endovascular fibrosis</td>
</tr>
<tr>
<td>10/M/45</td>
<td>Painful plaques, nodules, and ulcers on legs</td>
<td>+</td>
<td>0/+</td>
<td>Small and medium vessels</td>
<td>+</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td>11/F/73</td>
<td>Painful plaques and nodules on leg</td>
<td>+</td>
<td>0/+</td>
<td>Small</td>
<td>0</td>
<td>0/0</td>
<td>None</td>
</tr>
<tr>
<td>12/F/44</td>
<td>Livedo reticularis on leg</td>
<td>+</td>
<td>0/+</td>
<td>Small</td>
<td>0</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td>13/F/49</td>
<td>Ulcers on leg</td>
<td>+</td>
<td>0/+</td>
<td>Small and medium vessels</td>
<td>0</td>
<td>+</td>
<td>None</td>
</tr>
</tbody>
</table>

+, present; 0, absent.
* All patients had renal failure.

<table>
<thead>
<tr>
<th>Lesional Category/Histologic Features</th>
<th>No. (%) of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Early&quot; (nonulcerated) lesions (n = 7)</td>
<td></td>
</tr>
<tr>
<td>Calcification of small and medium vessels</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Dermal and subcutaneous inflammation</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Dermal collagenous degeneration</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Dermoeipidermal separation</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Microthrombi in dermis, subcutis, or both</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Endovascular fibroplastic proliferation</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Erythrocyte extravasation in soft tissue</td>
<td>1 (8)</td>
</tr>
<tr>
<td>&quot;Late&quot; (necrotic) lesions (n = 6)</td>
<td></td>
</tr>
<tr>
<td>Necrosis</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Dermal and subcutaneous inflammation</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Calcification of small and medium vessels</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Endovascular fibroplastic proliferation</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Ulceration</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Microthrombi in dermis, subcutis, or both</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>
represent venules, arterioles, or both); extravascular soft tissue calcification, usually in the subcutaneous lobules; ischemic necrosis of the skin and superficial soft tissue; microvascular thrombi and endovascular fibroblastic proliferation; and mixed inflammatory infiltrates of the dermis and subcutis, with the latter site predominating. The relative proportions of cases demonstrating such abnormalities varied from series to series, but, in general, they paralleled the results obtained in the present evaluation.

Discussion

The general phenomenon known as calciphylaxis initially was defined conceptually by Selye as a condition of hypersensitivity that resulted in “metastatic” calcification in various organs. In addition to the vascular calcification–cutaneous necrosis syndrome, other systemic manifestations of CPX include calcification of the lungs, stomach, kidneys, and adrenals in the setting of hyperparathyroidism, as well as calcifying pancreatitis in selected patients with hypercalcemia. Some, but not all, of these syndromic elements are known to pathologists; in particular, the dermatopathologic and soft tissue manifestations of CPX are unfamiliar to many practitioners. For example, an informal poll taken of 10 of the authors’ academic colleagues, all of whom are general surgical pathologists, showed that 40% were not conversant with the findings seen in this disorder in the skin and subcutis.

The cause of CPX undoubtedly is multifactorial, but its precise mechanisms are unclear. Selye hypothesized that hyperparathyroidism (or other causes of sustained, relative, or absolute hypercalcemia) served as a “sensitizing” event, and other pathophysiologic derangements or iatrogenic factors served as “challengers.” The interaction of such elements then was postulated to produce the clinicopathologic entity of CPX. In the most common setting for this disorder, that of end-stage renal disease, secondary hyperparathyroidism, hyperphosphatemia, and a high calcium-phosphate product may be considered as components of the sensitizing “arm,” and the use of various medications or

![Image 1](image1.png) Skin lesion of the leg in a patient with chronic renal failure. Clinically, the lesion was a nonblanching purpuric macula. The principal abnormality is that of calcification of small blood vessels. The dermal and subcutaneous architecture are preserved, and there is no inflammation or necrosis (H&E, ×100).

![Image 2A](image2a.png) A, Early changes of calciphylaxis, including collagenous degeneration with erythrocytic extravasation. Adjacent areas show mild septal subcutaneous inflammation. No overt necrosis or obvious calcium deposits are noticeable on conventionally stained sections (H&E, ×250). B, A von Kossa stain of the same case highlights calcium deposits in soft tissue and within the walls of small vessels (H&E, ×250).
**Image 3** A, Low-magnification microscopic image of septal panniculitis associated with calciphylaxis with focally overt necrosis (H&E, ×250). B, The same case shows recanalized thrombi with calcification of blood vessel walls. The small vessel at the lower right exhibits a mild degree of endovascular proliferation as well (H&E, ×250). C, The vessel in the center of the photograph shows mild endovascular fibrosis, whereas another contiguous small vessel shows fibrinoid mural necrosis with early thrombosis (H&E, ×250).

**Image 4** A, Calcification of small and medium-sized vessels is readily recognizable in calciphylaxis, with a relatively “clean” (noninflammatory) background (H&E, ×100). B, At higher magnification, septal subcutaneous necrosis containing minute calcium deposits and nuclear debris is readily apparent (H&E, ×200).
alterations in biochemical constituents of the blood are potential challengers.9,64 In particular, previous studies have suggested that hypercoagulability due to functional protein C abnormalities34 or protein S deficiency27,36,65 is a seminal cause of ischemia in patients who are otherwise susceptible to developing CPX. One case report of a patient with well-documented CPX (in the setting of longstanding regional enteritis complicated by short-bowel syndrome and minimal renal dysfunction)66 suggested that end-stage kidney disease and secondary hyperparathyroidism are likewise not absolutely requisite factors. In the final analysis, a current synopsis of the causation(s) of this enigmatic disease process must acknowledge that the issue remains unsettled and incompletely understood.

At a histologic level, a constant finding in all reported cases of CPX has been the presence of intravascular calcium deposits, chiefly within small and medium-sized venules and arterioles. They also may be observed in the extravascular soft tissues and viscera. Such deposits may be associated with endovascular fibroblastic-intimal proliferation, luminal thrombosis, or calcific obliteration of the affected vessels.1,67,68 Confirmation of their chemical identity in tissue sections can be accomplished with the von Kossa method, which yields a black reaction product.47 It should be noted that the majority of all patients who have undergone long-term hemodialysis develop intravascular microcalcification of the type just described,9 and yet only a very small minority eventually manifest the clinicopathologic syndrome of CPX. Thus, it is clear that this histologic abnormality is necessary for development of the latter disorder but not sufficient for it, in and of itself.

Endovascular fibrosis previously was thought to be the proximate cause of ischemic tissue damage in CPX.1 The results of our study are at variance with that postulate, because fibrotic changes in small vessels were not a ubiquitous observation. Another hypothesis relating to the cause(s) of ischemia in this disease is that patients with CPX develop microthrombosis, which is associated with acquired coagulopathies.1,27,34 Although the findings presented in some analyses of this association27,34 have been rather compelling, we found microthrombi in only one fourth of our cases. This result may simply reflect a sampling bias, but it also may be true that acquired coagulopathies help to define a subset of CPX cases rather than the entire patient group with this disorder.

In general, the microscopic observations reported herein and those in the literature suggest that although the features of CPX are not specific or pathognomonic, they are reproducible. In combination with one another or with persuasive clinical information, they should prompt the pathologist to consider CPX as a strong diagnostic possibility. As described, the classic histologic appearance of the fully evolved disease features 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. When CPX lesions are devoid of necrosis, the presence of collagenous degeneration, mild septal panniculitis, and calcified vessels serves as a similar cue. Obviously, clinical data are crucial as well. The lesions of CPX typically are painful; they begin as livedo reticularis–like or purpuric areas with relatively rapid progression to ulceration9,28,30,31 and have an overwhelming predilection to arise in patients with elevated serum calcium-phosphate products. An association with HIV infection also may be present in some instances,32 and rare examples of CPX may show epidermal or hair follicle calcification.37

A number of other conditions may imitate CPX histopathologically, and the differential diagnosis between those disorders again depends on careful integration of clinical and microscopic findings. As outlined by Barnhill15 and others,11,12,25,69,70 the diseases that can simulate CPX histologically include atherosclerotic peripheral vascular disease, atheroembolus syndrome, septic embolism, dermatomyositis, mixed connective tissue disease, oxalosis, protein C or S deficiencies, “Coumadin necrosis,” lupus anticoagulant/antiphospholipid syndrome, disseminated intravascular coagulation, cryoglobulinemia, cryofibrinogenemia, livedoid vasculitis, pyoderma gangrenosum, lipodermatosclerosis, infection-related panniculitis, and other calcifying panniculitides. Because of shared pathogeneses, several of these conditions may complicate end-stage renal disease,6 adding an additional degree of difficulty to the task of distinguishing them from CPX and from one another. Hence, to reiterate, detailed clinical information and attention to laboratory coagulation parameters, immunologic assessments, and biochemical data are essential to this process. Levin et al71 developed an interesting model for the prediction of the likelihood of CPX in patients with chronic renal failure. Although it was based on a limited number of cases, the mathematical expression of (2 × [CaPO4

\[
\text{coefficient} – 5] × \text{serum alkaline phosphatase level} × \text{parathormone ratio}) 
\]

seemed to separate patients at high risk for CPX in comparison with other patients receiving long-term hemodialysis. Whether there is a need to perform von Kossa stains in all clinically suspected cases of CPX is debatable. Many biopsy specimens will demonstrate such overt vascular, soft tissue, and visceral microcalcification that H&E examination is wholly sufficient, but we indeed encountered cases in the present study in which histochemistry was necessary to confirm a tentative diagnostic impression of that process. Ultimately, the application of “special” stains in CPX cases is a decision that depends on the judgment of the pathologist, as is true of this issue in virtually all facets of surgical pathology.

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As stated previously, the prognosis for patients with CPX is unfavorable. More than 60% of cases progress to death in a relatively short time after initial presentation. Treatments for this syndrome have been varied and, to some extent, must be chosen on an individual basis. Parathyroidectomy has been used with some success, as has the administration of hyperbaric oxygen therapy, exogenous corticosteroids, and H₂ histamine-blocking medications. Ultimately, the effectiveness of therapeutic interventions and the prevention of complications depend on a timely diagnosis of CPX by clinical physicians and pathologists alike.

From the 1Department of Pathology, University of Alabama at Birmingham Medical Center, and the 2Lauren V. Ackerman Laboratory of Surgical Pathology, Department of Pathology, Washington University Medical Center, St Louis, MO.
*Dr Wick is presently at the University of Virginia Health Sciences Center, Charlottesville.

Address reprint requests to Dr Wick: Fechner Laboratory of Surgical Pathology, Room 3882 Old Medical School, University of Virginia Health Sciences Center, Jefferson Park Ave, Box 214, Charlottesville, VA 22908.

References