Pathogenesis of calciphylaxis: Hans Selye to nuclear factor κ-B

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The clinical syndrome of calciphylaxis is characterized by arteriolar medial calcification, thrombotic cutaneous ischemia, necrotic skin ulceration, and a high mortality rate. This review integrates calciphylaxis risk factors with the molecular processes governing osseous and extraosseous mineralization. As the pathogenesis of calciphylaxis is better understood, targeted therapies aimed at disease prevention and reversal will follow. (J Am Acad Dermatol 2008;58:458-71.)

The syndrome known as calciphylaxis is well conceptualized as the skin equivalent of a myocardial infarction. Cutaneous arterioles, narrowed by medial calcification and subintimal fibrosis, are predisposed to thrombotic occlusion that eventuates in ischemic skin necrosis (Fig 1). Calciphylaxis is recognized clinically by painful ischemic purpura and necrotic ulceration (Fig 2). More than 50% of patients with calciphylaxis die within 1 year of receiving the diagnosis, and sepsis is the leading cause of death.[1]

Approximately 45 years ago, Hans Selye[2] published *Calciphylaxis*, which described induction of soft-tissue calcification in rodents. Soon thereafter, reports of calciphylaxis in human beings were published. Despite commonalities between Selye's rodents and human cases with so-called sensitization factors (eg, hyperparathyroidism, hypervitaminosis D) and challenging factors (eg, trauma, metallic salt exposure), the contrasting histopathologic findings of extravascular calcification in Selye's rodents and vascular calcification in human beings led to numerous alternative designations for the latter. However, the term "calciphylaxis" still is used widely to describe the human disease.

Today, the combined contributions from the fields of endocrinology, vascular medicine, nephrology, and bone science have been used to identify many molecular regulators of skeletal and extraskeletal mineralization. In the context of modern understanding, Selye's definition of calciphylaxis ("a condition of induced systemic hypersensitivity in which tissues respond to appropriate challenging agents with a precipitous, though sometimes evanescent, local calcification"[2]) closely approximates the description of vascular calcification that occurs in human calciphylaxis. However, medial arteriolar calcification in human calciphylaxis typically does not occur as precipitously as it did in Selye's experiments, which showed soft-tissue calcium deposition in 3 to 5 days. Furthermore, vascular calcification in human calciphylaxis is insufficient to produce acute cutaneous ischemia by itself. Notably, ischemic skin necrosis was not observed in Selye's experiments.

Modern dermatology textbooks[3,4] describe calciphylaxis under the heading of "Metastatic Calcification" and indicate that calcium-phosphate crystals form when calcium and phosphate concentrations are increased. However, extensive research indicates that vascular calcification is the result of an active cellular process, not passive mineral precipitation. Furthermore, observation of de novo bone formation (inappropriate osteogenesis) adjacent to calcium deposits in cutaneous

Abbreviations used:

BMP:	bone morphogenic protein
Cbfa:	core-binding factor α
CPP:	calcium-phosphate product
ET:	endothelin
IL:	interleukin
MGP:	matrix Gla protein
NFκB:	nuclear factor κ-B
OPG:	osteoprotegerin
PTH:	parathyroid hormone
RANK:	receptor activator of nuclear factor κ-B
RANKL:	ligand of receptor activator of nuclear factor κ-B
TNF:	tumor necrosis factor

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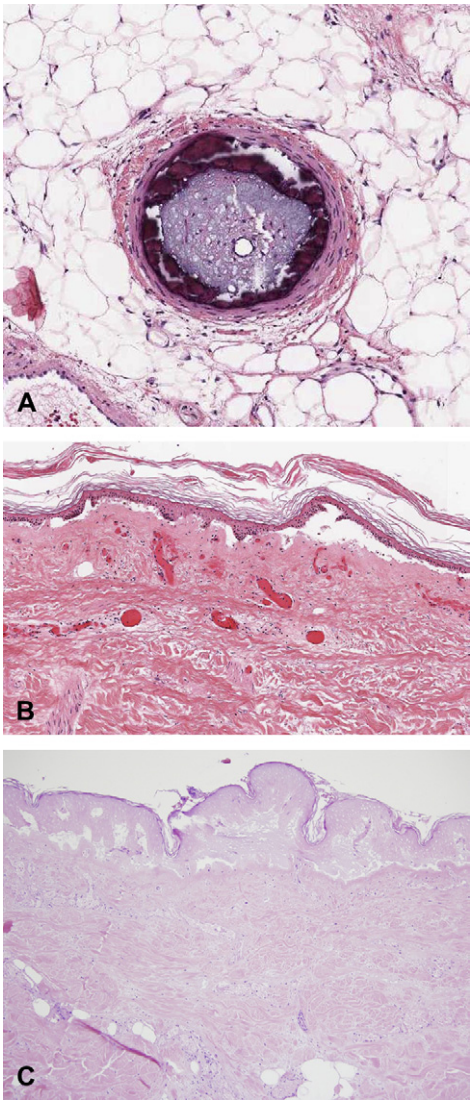

Fig 1. Photomicrographs of biopsy specimens taken from skin affected by calciphylaxis. **A**, Medial calcification and subintimal fibroplasia of pannicular arteriole. **B**, Thrombotic occlusion of numerous papillary dermal vessels. **C**, Pancutaneous ischemic (coagulative) necrosis. (**A** to **C**, Hematoxylin-eosin stain; original magnifications: **A**, ×80; **B** and **C**, ×100.)

arterioles challenges the theory of passive calcium deposition in the pathogenesis of calciphylaxis (Weenig RH, unpublished data) (Fig 3). However, this finding likely is rare because it was observed in only two of greater than 70 biopsy specimens taken from skin affected by calciphylaxis (Weenig RH, unpublished data).

Cutaneous arteriolar stenosis and vascular (thrombotic) occlusion are both required to produce the clinical lesion of calciphylaxis. However, vascular stenosis and vascular thrombosis in calciphylaxis are chronologically, clinically, and etiologically distinct.

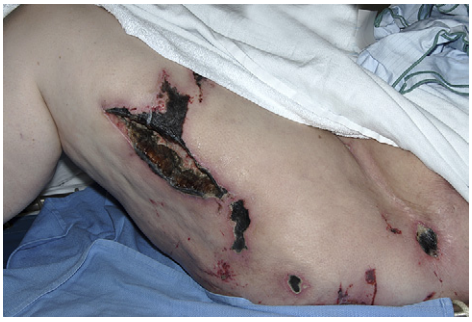

Fig 2. Photograph of clinical findings of calciphylaxis shows multiple areas of ischemic purpura, necrosis, and ulceration of thigh, hip, and abdomen.

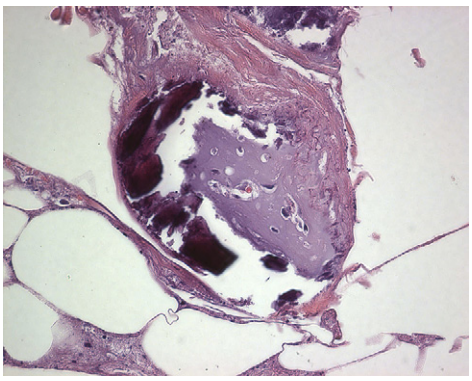

Fig 3. Photomicrograph of biopsy specimen taken from skin affected by calciphylaxis shows medial calcification and adjacent osteoid formation in pannicular arteriole. (Hematoxylin-eosin stain; original magnification: ×400.)

Vascular stenosis occurs via medial arteriolar calcification and subintimal fibrosis, which progresses insidiously and usually without clinical recognition. In contrast, vascular thrombosis develops acutely and is characterized clinically by painful ischemic purpura. Recognition of the differences between vascular calcification and thrombosis is essential when determining appropriate interventions for the prevention and treatment of calciphylaxis.

The aim of this review is to construct a pathway that illustrates the pathogenesis of vascular calcification in calciphylaxis. This includes a description of recently characterized regulatory receptors and ligands that affect bone mineralization and resorption and how these may be affected by risk factors associated with calciphylaxis. Mechanisms that lead to vascular occlusion and ischemic cutaneous necrosis will also be discussed.

HISTOPATHOLOGIC DIAGNOSIS

Biopsy specimens taken from skin affected by calciphylaxis may show medial calcification and subintimal fibroplasia of pannicular arterioles;