Epidermal and follicular calciphylaxis

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A patient with secondary hyperparathyroidism due to chronic
renal failure developed epidermal and follicular calcification
without concomitant dermal calcification in the lesions of toxic
epidermal necrolysis. We propose that the combination of
keratinocyte necrosis and an elevated serum calcium-phosphorus
product resulted in epidermal calciphylaxis.

**A. R. Solomon,[1] S. L. Comite,[2]
J. T. Headington[3]**

Departments of [1]Dermatology and Pathology
University of Texas Medical Branch, Galveston,
[2]Dermatology New York University School of
Medicine, [3]Pathology and Dermatology, The
University of Michigan Medical Center, Ann
Arbor, U.S.A.

Alvin R. Solomon, M.D., Department of
Dermatology, University of Texas Medical
Branch, Galveston, TX 77550, U.S.A.

Although calcification of the dermis and subcutis
takes several different histological forms, calcifica-
tion of the epidermis and follicular infundibula
alone has not, to our knowledge, been previously
reported in other than an experimental setting
(1, 2). We herein report a patient with secondary
hyperparathyroidism due to chronic renal failure
who developed epidermal and follicular calcification
without concomitant dermal calcification in the le-
sions of toxic epidermal necrolysis.

Case report

A 40-year-old white male with a long history of
systemic lupus erythematosus and chronic renal
failure was admitted for evaluation of fever and oral
mucosal ulcers.

The patient initially developed proteinuria 15
years prior to admission and he had required dialy-
sis 2 years prior to admission. For 2 years prior to
admission he was noted to have secondary hyper-
parathyroidism and numerous determinations of se-
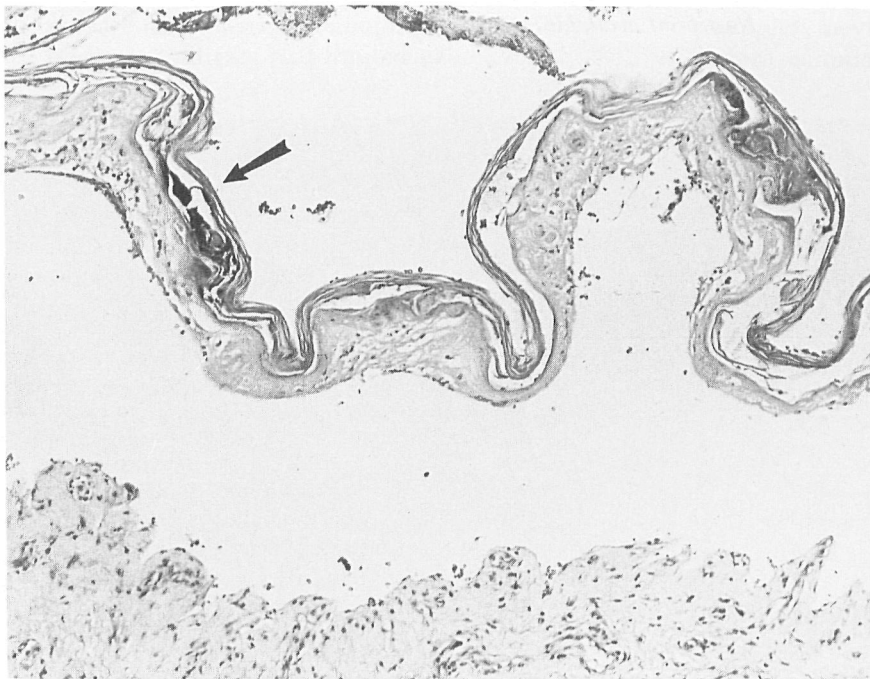rum levels of calcium and phosphorus exceeded a

Fig. 1. The epidermis is com-
pletely necrotic and separated
from the dermis at the level of the
epidermal-dermal junction. The
arrow points to basophilic gran-
ular material beneath the stratum
corneum and in the stratum
granulosum (H&E, ×63).

Fig. 2. Linear granular calcium deposits within the stratum granulosum (von Kossa, ×200).
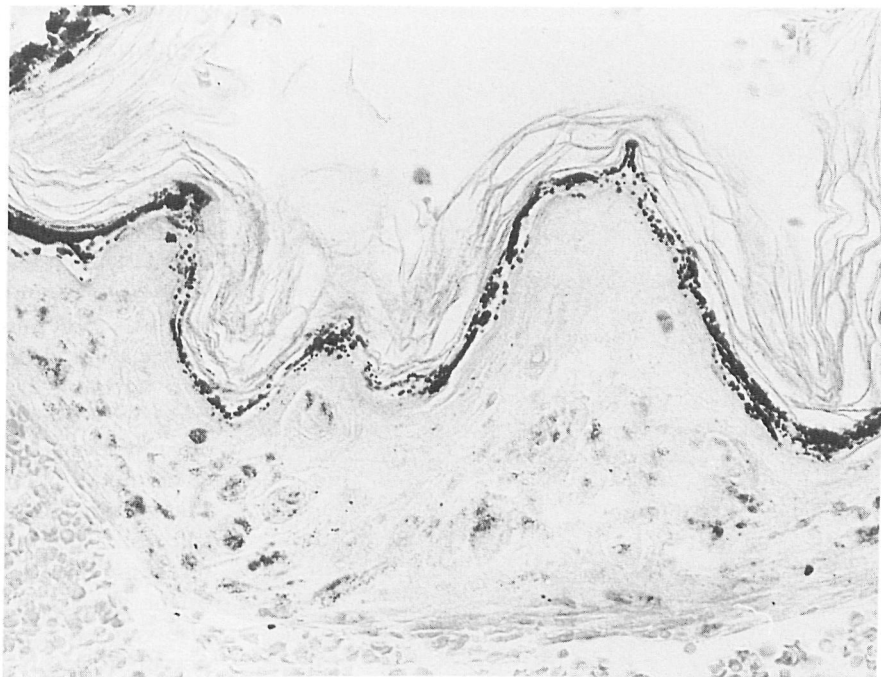
calcium-phosphorus product of 70. Four months before admission erythema multiforme was diagnosed and thought to be secondary to one of his medications which included minoxidil, propranolol, aluminum hydroxide gel, and cephalexin.

On physical examination the patient was noted to be cachectic and febrile. Numerous 5–10 mm in diameter ulcers were present on the lips and buccal mucosa bilaterally. The serum urea nitrogen (BUN) was 104 mg/100 ml (normal = 8–20), serum creatinine 17.9 mg/100 ml (normal = 0.6–1.3), serum calcium 7.4 mg/100 ml (normal = 8.5–10.5), serum phosphorus 11.5 mg/100 ml (normal = 2.5–4.5) and the serum albumin was 2.7 mg/100 ml (normal = 3.5–5.5).

The patient was treated with 60 mg of prednisone per day for a presumed flare of his lupus erythematosus. Phenytoin sodium was added because of an observed seizure. Four days after starting this latter medication, the skin was noted to be sloughing in large sheets from his back. Nikolsky's sign was positive. A clinical diagnosis of toxic epidermal necrolysis presumably secondary to phenytoin sodium was made and a biopsy was taken from the back. The phenytoin sodium was discontinued and replaced by carbamazepine. Prednisone was continued at the same dose since the clinical diagnosis was lupus cerebritis. Complete exfoliation of the skin on the patient's back, as well as smaller isolated areas of exfoliation on the chest and arms, were present. Topical treatment consisted of only saline soaks. Within several days, the denuded areas began to heal. The patient then refused further treatment and left the hospital.

At the time of biopsy, clinical examination of the areas of skin exfoliation did not reveal any evidence of gross calcification. The skin was soft and pliable. Histologically the epidermis was separated from the underlying dermis. Full-thickness necrosis of the epidermis and follicular infundibula was present along with scant lymphocytic infiltrates in the underlying dermis (Fig. 1). The histologic diagnosis was toxic epidermal necrolysis. Aggregates of dark blue granules were present beneath the stratum corneum and within the stratum granulosum with routine hematoxylin and eosin staining (Fig. 1, arrow). These aggregates stained black with the von Kossa stain. In addition, linear finely granular von Kossa positive material was present in the stratum granulosum throughout the specimen (Fig. 2). Basophilic aggregates similar to those in the epidermis were seen in the necrotic follicular infundibula (Fig. 3). No von Kossa positive staining was noted in the dermis.

Discussion

Calcium deposition in soft tissues is perhaps best divided into four types based on the presence or absence of abnormally elevated serum calcium or phosphorous levels. In dystrophic calcification, calcium salts are deposited in sites of disease or injury within soft tissues but the serum levels of calcium
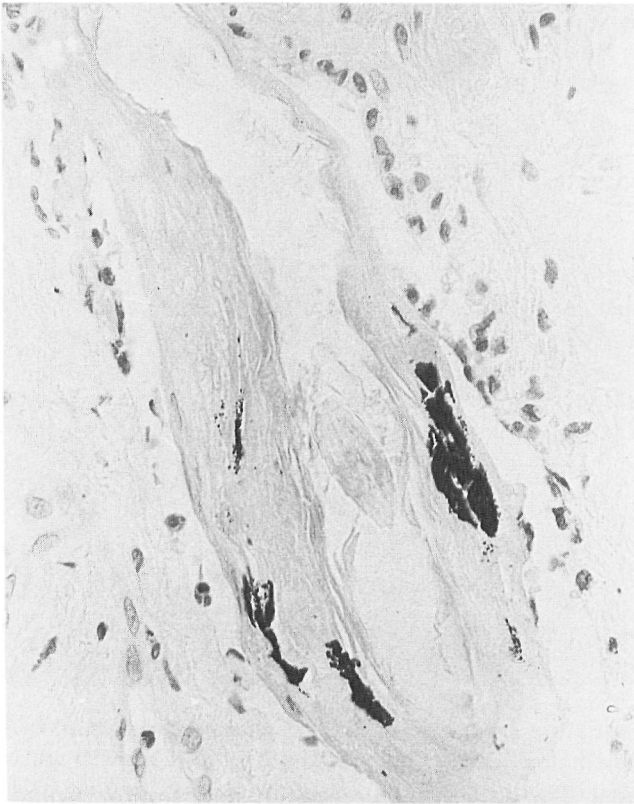
Fig. 3. Aggregates of calcified material present within a necrotic follicular infundibulum (von Kossa, ×400).

and phosphorous are normal (1). Calcification in an acne cyst is an example of dystrophic calcification. Metastatic calcification is characterized by the deposition of calcium salts within normal soft tissues (1). In this type of pathologic calcification, the serum levels of either calcium or phosphorous or both are elevated. These elevated levels result in a calcium-phosphorous product (the level of the serum calcium multiplied by the level of the serum phosphorous) greater than 70 (3). It is believed that this abnormally high calcium-phosphorous product, possibly in association with other metabolic abnormalities such as acidosis, is responsible for the deposition of calcium salts within otherwise normal soft tissues. Metastatic calcification has frequently been reported in association with secondary hyperparathyroidism due to chronic renal failure. However, the calcium deposition has been limited to the dermis and subcutis (4–6). A third type of calcium salt deposition is idiopathic calcification. This form of soft tissue calcification is associated with normal serum levels of calcium and phosphorous and is characterized by massive deposition of calcium salts in previously normal soft tissues (1). Tumoral calcinosis and idiopathic scrotal calcinosis are the prototype diseases of this type of calcification. The fourth type of soft tissue calcification has been termed cal-

ciphylaxis (2). The concept of calciphylaxis was popularized by Selye in the early 1960's (2). Selye defined calciphylaxis as "a condition of induced systemic hypersensitivity in which tissues respond to appropriate challenging agents with precipitous, though sometimes evanescent local calcification" (2). Two forms of calciphylaxis, topical and systemic, were described. Topical calciphylaxis was induced by contact of a substance called a *direct challenger* with the target tissue. The experimental animal was previously sensitized systemically with a calcification promoter called the *calcifer*. Parathyroid hormone is a potent naturally occurring calcifer. Selye experimented primarily with subcutaneous injections of the direct challenger. He primarily used metal salts as a direct challenger but found that certain organic compounds such as egg white or egg yolk could also act in a similar manner. Interestingly, he found that mild mechanical trauma of the skin such as epilation or skin pinching was also very effective in inducing local calcification. In one photograph (Plate I–F) from his 1962 text, *Calciphylaxis*, he shows calcification in the follicular epithelium after simple epilation in a rat previously sensitized with dihydrotachysterol, a potent calcifer (2). Our patient had secondary hyperparathyroidism due to chronic renal failure. Although the epidermal calcification may have simply been the result of the elevated serum calcium-phosphorous product, many patients in chronic renal failure suffer this pertubation. We propose that the additional stimulus of epidermal necrosis secondary to toxic epidermal necrolysis acted as a direct challenger as conceived and described by Selye with the end result being local epidermal calcification. In essence, epidermal calciphylaxis is possibly a combination of metastatic calcification (hyperparathyroidism with a high calcium-phosphorous product) and dystrophic calcification (local tissue injury).

It is interesting that the calcium deposits were localized to the upper granular layer of the epidermis. Menon et al. have elegantly demonstrated that in mouse epidermis the highest concentration of both intracellular and extracellular calcium ions is found in the upper granular layer (7). With the altered calcium metabolism that occurred in our patient, the zone of the epidermis with the highest concentration of calcium ions would be a likely site for precipitation of calcium salts.

The von Kossa staining reaction is not specific for calcium (8). In this reaction, silver nitrate which is in the von Kossa solution reacts with the calcium anion complex. The anions, usually phosphate or carbonate are then precipitated as an insoluble black silver-anion complex (8). However, in a patient in chronic renal failure with secondary hyperparathyroidism, calcium salts are present in such a

high concentration that the stain is virtually specific for calcium salt deposits.

In conclusion, we report the striking histologic finding of epidermal calcification following toxic epidermal necrolysis in a man with secondary hyperparathyroidism due to chronic renal failure. We propose that the epidermal calcification was due to epidermal calciphylaxis resulting from the specific injury of toxic epidermal necrolysis in conjunction with a high serum calcium-phosphorous product.

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