The Koebner phenomenon may contribute to the development of calciphylaxis: A case series

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Et al.
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**Key words:** calciphylaxis; Koebner phenomenon; Koebnerization; pathogenesis; risk factors; trauma.

**INTRODUCTION**
Calciphylaxis is characterized by calcific occlusion of vessels and subsequent tissue ischemia due to thrombosis.1,2 The precise pathogenetic mechanism behind calciphylaxis remains unclear. In the original experiment by Hans Selye and colleagues,3-7 soft-tissue calcification was induced in rats by applying a sensitizing agent, followed by a “challenger” agent after a specific time period. Trauma may represent one of these “challenger” agents, serving as an inducer of endothelial dysfunction and subsequent thrombosis, leading from tissue calcification to calciphylaxis.

Koebnerization, a term used to describe the appearance of isomorphic lesions in areas of trauma,8 has been postulated to be a feature of calciphylaxis.9 This hypothesis arose from reports of patients who developed calciphylaxis following mild skin trauma, such as that caused by chronic resting of elbows on thighs, placement of ice packs, and injections involving various medications such as iron dextran, tobramycin, and especially insulin.10,11

Rigorous studies demonstrating the relationship between calciphylaxis and Koebnerization and an underlying mechanism are limited. To better understand this association, this study retrospectively identified characteristics of patients who presented with calciphylaxis in areas of trauma, suggesting the presence of Koebnerization.

**METHODS**
A retrospective chart review was performed of patients with a diagnosis of calciphylaxis at Massachusetts General Hospital and Brigham and Women’s Hospital between January 2006 and December 2018. Patients with calciphylaxis were identified from the Partners Research Patient Data Registry, an electronic medical record database, using the diagnosis code **International Classification of Diagnosis, Tenth Revision** (ICD-10) E83.59 and ICD-9 275.49, and a word search for “calciphylaxis” in the hospital discharge and/or outpatient clinic notes.

Each record was examined to determine whether the clinical findings and/or biopsy supported a diagnosis of calciphylaxis, recorded either by a dermatologist or a nephrologist with expertise in calciphylaxis. In total, 145 patients with calciphylaxis were identified. Chart review was conducted of the initial consultation with dermatology as well as progress notes to assess the presence of calciphylaxis lesions in sites of prior trauma. Patients were included if clinical documentation stated that a lesion had appeared in a site of trauma. Twenty-two patients meeting this definition were identified. The study was...
approved by the Partners Health Institutional Review Board (approval number: 2008P001589).

From each patient’s chart, age at presentation, sex, race, and comorbidities before presentation were abstracted. Warfarin exposure was defined by continuous use of warfarin for at least 6 months before development of calciphylaxis. Thromboembolic events were defined as deep venous thrombosis or pulmonary embolism. Each chart was also reviewed to record the date of onset of calciphylaxis, the date of diagnosis, and the circumstances around development of lesions in sites of trauma, if applicable. All patients were followed for at least 1 year. Categorical variables are reported as percentages, and continuous variables as medians and interquartile ranges (IQR).

RESULTS
Baseline characteristics

Table I summarizes the patient characteristics. The incidence of calciphylaxis lesions appearing in sites of trauma in this cohort was 22/145 (15.2%). The median age at diagnosis was 62.0 years (IQR, 53.5-65.5 years). There were 11 female patients, comprising 50.0% of the study population; 17 patients (77.3%) were Caucasian, and 1 patient (4.5%) was Hispanic or Latino.

Among the patients studied, 20 (90.9%) had chronic kidney disease and 15 (68.2%) had end-stage renal disease. Other comorbidities included diabetes (81.8%), obesity (50.0%), hyperparathyroidism (36.4%), autoimmune diseases (systemic lupus erythematosus or antiphospholipid antibody syndrome) (13.6%), past or current malignancy (9.1%), and thromboembolic events (4.5%). Prior medication use included vitamin D (50.0%), warfarin (31.8%), and systemic corticosteroids (22.7%). One patient (4.5%) was receiving nonwarfarin anticoagulation treatment at the time of calciphylaxis diagnosis. The median number of years on dialysis at the time of diagnosis was 3.0 (IQR, 0.5-4.0).

Development of Koebner phenomenon
The circumstances in which calciphylaxis developed in patients were evaluated (Table II). In 1 patient, Koebnerization developed twice, and these incidents are listed twice in the table. In 14 patients (60.9%), calciphylaxis lesions appeared in sites of noniatrogenic accidental trauma. These inciting events included hitting a body part on an object (wheelchair, dishwasher) (4 patients), abrasion (3 patients), mechanical fall (3 patients), unknown minor trauma at home (2 patients), toe clipping (1 patient), and stubbed toe (1 patient). In 9 patients (39.1%), lesions appeared in sites of iatrogenic trauma, including insulin injections (3 patients), surgical interventions (3 patients), biopsy site (1 patient), catheter placement (1 patient), and removal of peritoneal dialysis catheter (1 patient). The details of patients who had surgical interventions are as follows: In 1 patient, active calciphylaxis developed after surgical debridement of a chronic sacral decubitus ulcer previously not affected by calciphylaxis; in 1 patient, calciphylaxis developed in a sternotomy wound after a coronary artery bypass graft; and in 1 patient, calciphylaxis developed in previously uninvolved areas of the lower extremity after a below-the-knee amputation. The patient who underwent a biopsy had multiple other lesions, which remained stable in the immediate and longitudinal perioperative time frame, whereas the affected lesion had drastic expansion of purpura, which subsequently broke down into ulceration.

In 17 patients (77.3%), trauma-induced calciphylaxis was the first presentation of the disease, and in 5 patients (22.7%), new calciphylaxis lesions appeared...
in patients already diagnosed with calciphylaxis. In 5 patients (21.7%), new calciphylaxis lesions appeared in sites of trauma while active calciphylaxis lesions were also present elsewhere on the body. In all these patients, existing disease did not worsen in parallel with the lesions in areas of trauma.

In 15 patients (65.2%), lesions developed on the lower extremities. Lesions developed over a median of 14.0 days (IQR, 5.0-30.0) after the inciting insult. The precise timing of lesion development could be assessed in 15 instances (65.2%). Sufficient documentation was not available for the other 8 patients. Fig 1 depicts examples of calciphylaxis lesions associated with trauma.

**DISCUSSION**

This case series suggests that trauma may be associated with the development of calciphylaxis, representing both the first cutaneous manifestations of the disease and the spreading of disease in patients with a pre-existing diagnosis of calciphylaxis.

In true Koebnerization, the development of isomorphic lesions is reproducible by multiple insults. Other subtypes include “pseudo-Koebnerization,” where the phenomenon is produced by infectious seeding to surrounding tissue (ie, molluscum contagiosum), “occasional lesions” (ie, erythema multiforme), and “questionable trauma-induced processes” (ie, bullous pemphigoid). The cases discussed in this cohort likely represent true Koebnerization because of the multiple different insults described, from abrasions and subcutaneous insulin injections to full-thickness epidermal, dermal, and subcutaneous tissue disruption from surgical procedures. One alternative hypothesis is that these patients could have already been on a trajectory to spread of disease, and thus the development of calciphylaxis in sites of trauma might represent natural disease progression. However, the high proportion of patients in this cohort whose first calciphylaxis lesions developed in an area of trauma, as well as the fact that the majority of patients with existing active disease did not have parallel spreading of their disease into other, nontraumatic areas, argues that these cases represented true Koebnerization.

The mechanism of the Koebner phenomenon in calciphylaxis remains unclear. A previous study of calciphylaxis in sites of insulin injection hypothesized multiple mechanisms: local generation of immune mediators leading to a procoagulable state, the local anabolic effect of insulin disrupting local tissue and vasculature, or introduction of infectious agents into a previously sensitized area of arterial calcification with compromised blood flow. Another study demonstrating a dose-response relationship between the odds of developing calciphylaxis lesions and insulin injections suggests that insulin may play a role in triggering dermal arteriolar endothelial damage due to an immune reaction to insulin.

There may have been other contributing factors to the development of calciphylaxis in our population, because the inciting trauma was not limited to insulin injection. We postulate that physical trauma may lead to endothelial damage and subsequent activation of the coagulation cascade leading to thrombosis. Trauma may be the “challenger” agent in individuals previously sensitized to development of this disorder. Even though Seyle’s model does not recapitulate human calciphylaxis, the trauma as a challenger may be important for initiating the thrombotic process (Fig 2). Only 1 patient in this cohort had a history of thromboembolic events, which would further support the contribution of trauma, rather than a predisposing thrombophilia, to the development of calciphylaxis.

The limitations of this case series include its retrospective nature. Information regarding each patient’s presentation was limited to review of provider notes, and it is possible that there was reporting bias regarding preceding trauma leading to

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**Table II. Inciting events associated with development of calciphylaxis lesion in a cohort of calciphylaxis patients**

<table>
<thead>
<tr>
<th>Event</th>
<th>Total (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noniatrogenic accidental trauma, n (%)</td>
<td></td>
</tr>
<tr>
<td>Direct trauma with object (wheelchair, dishwasher)</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>Abrasion</td>
<td>3 (13.0)</td>
</tr>
<tr>
<td>Mechanical fall</td>
<td>3 (13.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Toe clipping</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Stubbed toe</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Iatrogenic trauma, n (%)</td>
<td></td>
</tr>
<tr>
<td>Insulin injection</td>
<td>3 (13.0)</td>
</tr>
<tr>
<td>Biopsy</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Below-the-knee amputation</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Sternotomy</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Catheter placement</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Surgical debridement</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Peritoneal dialysis catheter removal</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Affected location, n (%)</td>
<td></td>
</tr>
<tr>
<td>Lower extremity</td>
<td>15 (65.2)</td>
</tr>
<tr>
<td>Trunk</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>Buttocks</td>
<td>2 (8.7)</td>
</tr>
</tbody>
</table>
development in calciphylaxis lesions. Additionally, provider interpretation was relied on in identifying lesions. In a retrospective study such as this, a definite causal relationship between the traumatic event and the subsequent lesion cannot necessarily be confirmed. In the future, a prospective study will
be needed to deepen our understanding of this phenomenon.

In conclusion, this report suggests that the Koebner phenomenon may be associated with calciphylaxis. The authors propose considering these findings when caring for patients with active disease in order not to worsen their condition and informing patients of this occurrence before unavoidable skin injury. Additionally, the authors suggest close monitoring of possible lesion formation or propagation after trauma. Prospective studies are needed to further explore this phenomenon and assess whether ongoing treatment may mitigate this outcome.

Conflicts of interest

Dr Nigwekar has received grant support from Hope Pharmaceuticals. Authors Gabel and Chakrala and Drs Dobry, Garza-Mayers, Ko, Nguyen, Shah, St. John, and Kroshinsky have no conflicts of interest to declare.

REFERENCES