

# Calciophylaxis in Patients With Normal Renal Function: A Case Series and Systematic Review

Richa Bajaj, MBBS; Marie Courbebaisse, MD, PhD; Daniela Kroshinsky, MD, MPH; Ravi I. Thadhani, MD, MPH; and Sagar U. Nigwekar, MD, MMSc

## Abstract

**Objective:** To define concomitant risk factors, treatment, and outcomes for patients with nonnephrogenic calciophylaxis (NNC).

**Patients and Methods:** A retrospective review of Massachusetts General Hospital (MGH) medical records (January 1, 2014, through February 29, 2016) and a systematic literature review of PubMed, Google Scholar, EMBASE, MEDLINE, and CENTRAL (August 1, 1970, through July 31, 2016) were performed. Demographic characteristics and concomitant features were summarized and compared between patients with different lesion characteristics. Outcomes (lesion improvement and mortality) and their predictors were analyzed.

**Results:** Nine patients (median age, 72 years [interquartile range (IQR), 44-82 years]; 78% women; 89% white race) were identified through MGH records. The literature review identified 107 patients (median age, 60 years [IQR, 49-72 years]; 77% women; 86% white race). Vitamin K antagonism and obesity were the most common concomitant factors. In the literature review, lower age ( $P < .001$ ) and higher body mass index ( $P = .03$ ) were associated with the central location of lesions, whereas vitamin K antagonism was associated with the peripheral location ( $P = .009$ ). In the MGH series, median survival was 24.0 months (95% CI, 7.8-36.0 months), and 33% (95% CI, 14%-60%) had lesion improvement by 6 months. In the literature review, median survival was 4.2 months (95% CI, 1.9-5.9 months), median time to lesion improvement was 5.9 months (95% CI, 3.9-8.9 months), and none of the treatments were associated with lesion improvement or survival.

**Conclusion:** This description of concomitant traits may augment an earlier recognition of NNC. Future research is needed to investigate NNC pathogenesis and treatments.

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Calciophylaxis is a condition with reported 1-year mortality of 60% to 80%.<sup>1,2</sup> It is predominantly seen in patients with end-stage renal disease (ESRD). Patients with calciophylaxis present with painful skin lesions that progress to ulceration. This rare disease is characterized histologically by calcification of small and medium-sized dermal and subcutaneous vessels. The incidence of calciophylaxis is on the rise in patients with ESRD,<sup>2</sup> and now there are registries and clinical trials in place to investigate the pathogenesis and develop novel treatments for calciophylaxis in patients with ESRD.

Mineral bone abnormalities (eg, hyperphosphatemia and hyperparathyroidism) and their treatments (eg, calcium-based phosphorus

binders and vitamin D) are frequently implicated in the origin of calciophylaxis in patients with ESRD. However, calciophylaxis also affects patients with normal renal function, referred to herein as *nonnephrogenic calciophylaxis* (NNC); the risk factors, pathogenesis, outcomes, and treatments for NNC are unclear. We conducted the present study to define the concomitant factors and presenting features of NNC. We also aimed to examine the treatments and outcomes in patients with NNC.

## PATIENTS AND METHODS

The criteria for NNC were skin manifestations consistent with calciophylaxis, histopathologic evidence of dermal or subcutaneous microvascular calcification, and normal renal function

From the Department of Medicine, Division of Nephrology (R.B., R.I.T., S.U.N.), and Department of Dermatology (D.K.), Massachusetts General Hospital, Boston, MA; Khorana Scholar 2016, Khorana Program for Scholars, INDO-US Science and Technology Forum, New Delhi, India (R.B.); Division of Bone and Mineral Research, Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, Boston, MA (M.C.); Faculty of Medicine, Paris Descartes University,

*Affiliations continued at the end of this article.*

at the time of calciphylaxis diagnosis. An institutional medical records database was used to identify patients with NNC managed at Massachusetts General Hospital (MGH) from January 1, 2014, through February 29, 2016. Patients were identified using *International Classification of Diseases, Ninth Revision*, code 275.49, "Other Disorders of Calcium Metabolism"; *International Classification of Diseases, Tenth Revision*, code E83.59; and skin biopsy procedure codes. Medical records were reviewed for clinical manifestations, histologic descriptions, and renal function. Normal renal function was defined as an estimated glomerular filtration rate (eGFR) greater than 60 mL/min/1.73 m<sup>2</sup>.

We also conducted a systematic review of the literature for NNC reported from August 1, 1970, through July 31, 2016. We searched the PubMed, Google Scholar, MEDLINE, CENTRAL, and EMBASE databases independently and in duplicate using the Medical Subject Headings terms *calciphylaxis*, *calciphylaxis not kidney disease*, and *nonuremic calciphylaxis* as the primary search. The bibliographies of the retrieved articles were reviewed. Normal renal function in the systematic review was defined as an eGFR greater than 60 mL/min/1.73 m<sup>2</sup> or normal as reported by the authors of the original reports. There were no language restrictions. We followed the guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.<sup>3</sup>

Data regarding demographic characteristics, concomitant factors, laboratory parameters, and skin lesion characteristics at the time of NNC diagnosis were abstracted by 2 authors (R.B. and S.U.N.). Data regarding NNC treatment and outcomes (lesion improvement and mortality) were also extracted. Missing data elements were summarized.

### STATISTICAL ANALYSES

Categorical variables are reported as percentages and continuous variables as medians and interquartile ranges (IQRs). The demographic and concomitant factors were compared between lesions involving body areas proximal to the knees and elbows (central) vs lesions restricted to areas distal to the knees and elbows (peripheral). Categorical variables were compared using a Fisher exact test and continuous variables using a

Wilcoxon rank sum test. The Kaplan-Meier method was used to estimate all-cause mortality and lesion improvement and their corresponding 95% CIs. Unadjusted and adjusted (for the demographic variables of age, sex, and race) analyses were planned to examine the hazards (hazard ratio [HR] and 95% CI) for mortality and lesion improvement by Cox proportional hazards analyses with concomitant factors and NNC treatments as predictor variables. The treatments were examined individually and as combinations of different medical and surgical interventions (multimodal treatment). Statistical significance was set at a 2-sided  $P < .05$ . Analyses were performed using SAS software, version 9.4 (SAS Institute Inc).

## RESULTS

### MGH Case Series

Thirty-six patients with skin manifestations consistent with calciphylaxis and histopathologic evidence of dermal or subcutaneous microvascular calcification were identified in the institutional database. Of these, 9 patients (78% women (n=7); 89% white race (n=8); median age, 72 years [IQR, 44-82 years]) had normal renal function at the time of calciphylaxis diagnosis and were included in the MGH case series (Table 1). These patients had the following concomitant conditions: vitamin K antagonism by warfarin (78%; n=7), obesity (67%; n=6), liver disease (44%; n=4), malignancy (44%; n=4), autoimmune disorder (44%; n=4), diabetes mellitus (33%; n=3), and nephrolithiasis (33%; n=3). All the patients had more than 1 concomitant condition. Median serum levels of calcium (9.1 mg/dL [IQR, 9.0-9.4 mg/dL] [to convert to mmol/L, multiply by 0.25]), phosphorus (3.2 mg/dL [IQR, 2.4-3.9 mg/dL] [to convert to mmol/L, multiply by 0.323]), and 25-hydroxyvitamin D (35 ng/mL [IQR, 30-45 ng/mL] [to convert to nmol/L, multiply by 2.496]) were overall unremarkable for all the patients. Eight patients exhibited normal parathyroid hormone (PTH) levels and 1 had an elevated PTH level. Median serum albumin level was 3.5 g/dL (IQR, 3.1-3.7 g/dL) (to convert to g/L, multiply by 10) and hemoglobin level was 8.9 g/dL (IQR, 8.2-10.6 g/dL) (to convert

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