MAYO CLINIC

Calciphylaxis in Patients With Preserved Renal Function: **W**orrisome **W**ounds

See also page 1202

Calciphylaxis has historically been understood as an issue of soft tissue and vascular calcium deposition associated with advanced renal failure. In other words, historically, renal failure was *necessary* for the diagnosis of calciphylaxis and coupled with renal bone mineralization disorders, *sufficient* to lead to calciphylaxis. Traditionally, therefore, therapy involved correction of these abnormalities of calcium/phosphorus and parathyroid hormone (PTH)/vitamin D metabolism and management of the "uremic milieu."[1,2]

Much has been learned over the decades since this condition was initially recognized, including information provided by isolated case reports and small series of cases of calciphylaxis not associated with renal failure; such literature emphasized the association of this condition with the use of warfarin.[3] However, despite tremendous efforts to change practice with respect to appropriate management of vitamin D, PTH levels, with close attention to avoidance of calcium overload and concomitant phosphorus management, reports of calciphylaxis have not lessened over time.[1,2] Indeed, in recent years, despite national trends of improved management of bone mineral disorders associated with chronic kidney disease, reports of this devastating condition nonetheless continue to increase.[1-3] This situation calls into question whether our current understanding of calciphylaxis is complete.

Alternative explanations for this condition have hence been proposed, and the article in this issue of *Mayo Clinic Proceedings* by Bajaj et al[4] emphasizes our need to begin more systematic investigation of the pathophysiology of calciphylaxis. This work clearly documents a substantial number of cases of calciphylaxis involving patients without renal failure in the case records of the Massachusetts General Hospital (MGH) and in the literature. Essentially, in our historic paradigm, "uremia" was thought *necessary* to the diagnosis, although not necessarily *sufficient* to cause calciphylaxis. The work by Bajaj et al[4] suggests that another paradigm shift needs to be entertained and that uremia is neither necessary nor sufficient to lead to this devastating condition.

Bajaj et al undertook a retrospective investigation of individuals who had lesions consistent with calciphylaxis and normal renal function, or nonnephrogenic calciphylaxis (NNC). The study combined 2 groups, one culled from the records of MGH and the other based on a survey of the world literature. Patients from the MGH cohort included 9 patients seen from January 1, 2014, through February 29, 2016. The vast majority of these patients were female (78%) and white (89%). These individuals were identified through a combination of *International Classification of Diseases, Ninth and Tenth Revisions* codes and the pathology database. Inclusion required preserved renal function with an estimated glomerular filtration rate (GFR) greater than 60 mL/min per per 1.73 m^2. The cohort obtained from review of the world literature identified 107 patients reported from August 1, 1970, through July 31, 2016. This cohort also identified the vast majority of patients as female (77%) and white (86%). Again, normal renal function in the systematic review was defined as a GFR greater than 60 mL/min per per 1.73 m^2. Interestingly, in the current work, a marked increase in the reporting of NNC occurred after 2010, with 61% of the cases being reported since 2011.[4]

Among the MGH cohort of patients with NNC, no less than 78% of this group were treated with vitamin K antagonists, specifically warfarin. Other concomitant/associated conditions included obesity, liver disease, malignancy, autoimmune disorders, diabetes, and nephrolithiasis, with most patients having more than one condition. Emphasizing the nonnephrogenic nature of this cohort, serum calcium, phosphorus, vitamin D, and PTH levels (with one exception of an elevated PTH

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level) were all within normal limits. Among the small, but well-defined, MGH cohort, follow-up duration was approximately 28 months, during which the median survival was only 24 months with mortality occurring in 4 of the 9 patients. All of the patients in the MGH cohort received sodium thiosulfate, analgesics, direct wound care, and withdrawal of vitamin K antagonists (warfarin). The causes of death, not unexpectedly, were primarily infectious and cardiovascular in origin. Somewhat encouragingly, 3 of the 9 patients had lesion improvement at 6-month follow-up.

The cohort of patients in the systematic literature review included 83 case reports in 12 case series. Again, Bajaj et al[4] identified vitamin K antagonism, obesity, and diabetes mellitus as the most common associated/concomitant factors identified along with NNC. Also consistently, 89% of the patients in the literature cohort had at least 2 of the contributing associated/concomitant factors and normal markers of bone metabolism. Management varied and was not uniform in the literature cohort, with less than half of the patients in this cohort receiving sodium thiosulfate.

Bajaj et al acknowledged several caveats, including the inability to accurately assess the true incidence or prevalence of NNC from this work. Case findings, essential in the literature cohort, are hampered by publication bias and by the vagaries of *International Classification of Diseases, Ninth and Tenth Revisions* coding factors in database searches. Additionally, reliance on GFR reports can be problematic in literature review studies because correction factors for weight and other important clinical circumstances are often not available with medical record–reviewed creatinine or GFR reports. Finally, the inherent difficulty in assessing the histopathology of the lesion in the literature cohort may lead to overreporting of lesions similar in appearance to calciphylaxis.

How does this article help clinicians? The data provided highlight the concomitant/associated factors of white race (**W**hite), female gender (**W**omen), vitamin K antagonism (**W**arfarin), and obesity (over-**W**eight). These "Four Ws" provide a very useful anchoring concept for clinicians when NNC is suspected and diagnosed.

The striking associations of white race, female sex, use of vitamin K antagonists, and obesity with these devastating skin lesions are absolutely consistent across both subgroups of patients with calciphylaxis, namely, those with renal failure, as described in the current literature, and those with preserved renal function, as described in the present study. The mortality risk calciphylaxis imposes on patients with either renal failure or preserved renal function is striking. This article highlights not only a tremendous need for devoted attention to understanding the true pathophysiology of calciphylaxis but also the need for all disciplines to become aware of this condition, particularly in light of the increasing incidence of obesity and diabetes across the globe. Effective therapeutic strategies for calciphylaxis, however, do exist. Namely, withdrawal of inciting factors including vitamin K antagonists, utilization of sodium thiosulfate, potential use of non–vitamin K antagonist anticoagulation therapy, hyperbaric oxygen treatment, and tissue plasminogen activator all offer clinicians a road map for managing these very difficult lesions.[1-3,5]

The authors propose a biologically plausible mechanism for the soft tissue and vascular calcification based on the fact that matrix GlA protein, an inhibitor of soft tissue calcification, is in fact stimulated by vitamin K.[6,7] Therefore, abnormalities in vitamin K metabolism, highlighted by the authors to occur not only with the use of warfarin but also in patients with obesity, malignancy, liver disease, and malnutrition, may provide a common pathogenetic pathway in these devastating lesions; this hypothesis merits further examination. A recent review highlights the involvement of another vitamin K–dependent protein, Gla-rich protein or unique cartilage matrix–associated protein, in regulating soft tissue and vascular calcification.[8]

We are still left with several unanswered questions as practicing clinicians. Should all proximal violaceous painful nodular lesions be biopsied? Should malignancies and connective tissue disorders be exhaustively evaluated in all patients with stereotypic-appearing calciphylaxis lesions? Is it is safe to provide sodium thiosulfate to all patients, and what is the

duration of therapy for this agent? As vitamin K antagonists are stopped, are the direct thrombin inhibitors safe? Would weight loss make a difference, particularly for prevention of, or recurrence of, these lesions? Should vitamin K be supplemented when appropriate?

Bajaj et al[4] are to be congratulated for their thorough gathering and analysis of data regarding a rarely reported and likely underrecognized occurrence of NNC. This work importantly highlights that the standard of therapy—the administration of intravenous sodium thiosulfate and withdrawal of vitamin K antagonists—offers enhanced survival and chances for wound healing and the pressing need for a central registry of definitive cases of calciphylaxis in patients with renal failure and those with preserved renal function. Such a multisite registry would facilitate a standardized approach in therapeutic trials for this condition.

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