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A CASE OF CALCIPHYLAXIS IN A PATIENT WITH HYPOPARATHYROIDISM AND NORMAL RENAL FUNCTION

Blake L. Erdel, M.D.[1], **Rattan Juneja, M.D.**[1], and **Carmella Evans-Molina, M.D. Ph.D.**[1,2,3,4]

[1]Department of Medicine, Indiana University School of Medicine, Indianapolis IN, USA

[2]Department of Cellular and Integrative Physiology, Indiana University School of Medicine, Indianapolis IN, USA

[3]Department of Biochemistry, Indiana University School of Medicine, Indianapolis IN, USA

[4]Department of Herman B Wells Center for Pediatric Research, Indiana University School of Medicine, Indianapolis IN, USA.

Abstract

Objective—To present the case of a patient with a history of thyroid cancer, post-surgical hypoparathyroidism, chronic calcitriol use, and normal renal function who presented with painful skin lesions secondary to calciphylaxis.

Methods—We describe the history, biochemistry, histopathology, evaluation, and management of this patient.

Results—A 47 year-old female with hypoparathyroidism, chronically treated with calcitriol and calcium, presented with exquisitely painful skin ulcerations. Four months prior to the onset of symptoms, she had initiated warfarin therapy for atrial fibrillation. Review of laboratory data from the past year revealed elevated calcium and phosphorus levels. A diagnosis of calciphylaxis was made based upon pathologic evaluation of a skin biopsy. Management included titration of calcitriol and calcium to maintain serum calcium and phosphate levels in the low normal range. Sodium thiosulfate was administered at a dose of 25 mg IV three times a week with some resolution in the patient's pain. Unfortunately, the patient battled recurrent bacteremia and sepsis, presumably related to her calciphylaxis wounds, and ultimately succumbed to complications from sepsis.

Conclusion—While calciphylaxis is typically associated with renal insufficiency and secondary hyperparathyroidism, we highlight the case of a patient with normal renal function and hypoparathyroidism. Patients treated with chronic calcitriol should have serum calcium and phosphorus monitored closely and may benefit from non-calcium based phosphate binders if

Correspondence address: Blake Erdel or Carmella Evans-Molina, Indiana University School of Medicine, 635 Barnhill Drive, MS2031A, Indianapolis, IN 46202, cevansmo@iu.edu or blakeerdel@gmail.com.

hyperphosphatemia becomes unavoidable. This is especially important in the presence of other risk factors for calciphylaxis including warfarin use.

Keywords

Hypoparathyroidism; Calciphylaxis; Phosphorus; Hyperphosphatemia; Calitriol; Calcium Phosphate product

INTRODUCTION

Calciphylaxis, or calcific uremic arteriolopathy, is a rare condition involving calcification and fibrosis of small and medium sized arterioles that results in painful, necrotic skin lesions (1). Histologic findings include “clean” necrosis with inflammation over a background of small and medium sized blood vessel calcification (2). While the prognosis of calciphylaxis remains guarded given potential complications of digital gangrene, sepsis, pancreatitis, and multisystem organ failure (2), treatment with sodium thiosulfate has led to successful resolution in a number of cases. Calciphylaxis has its strongest association with end stage renal disease; however, a number of other predisposing factors have been identified (Table 1). Moreover, while renal insufficiency was previously felt to be a prerequisite for the development of calciphylaxis, an increasing number of cases have been reported in persons with normal renal function (3). There is literature to suggest that primary hyperparathyroidism as well as treatment with vitamin D analogues, such as calcitriol, in hypoparathyroidism are associated with calciphylaxis (1, 4-7). New insights into the molecular pathways that normally act to inhibit tissue calcification have provided an enhanced understanding of the pathophysiology of how calciphylaxis occurs. Most notably, protein inhibitors of calcification, such as matrix Gla protein require vitamin K for optimal activity, providing a molecular explanation for a clinical association with warfarin.

CASE REPORT

We present the case of a 47 year-old female who was transferred from an outside hospital for management of painful, necrotic, skin lesions. She had a remote history of a complete thyroidectomy for thyroid cancer resulting in chronic hypoparathyroidism. The patient required calcitriol and calcium supplementation since her initial surgery > 5 years ago. Additional evaluation revealed normal renal function, but a BMI of 37 m/kg^2, indicating morbid obesity. Approximately four months prior to presentation, warfarin therapy was initiated for atrial fibrillation. Biochemical data describing serum calcium and phosphorus levels were somewhat incomplete due to treatment at different facilities (Table 2). However, the general trend revealed a rising phosphorus level with serum concentrations as high as 7.4 mg/dL and serum calcium levels as high as 9.5 mg/dL, indicating a calcium phosphate product of nearly 70.

Based on the clinical history and physical examination, the differential diagnosis included calciphylaxis, warfarin-induced skin necrosis, antiphospholipid syndrome, cellulitis, pyoderma gangrenosa, vasculitis, embolic phenomenon, disseminated intravascular coagulation, connective tissue disease, and peripheral vascular disease (8). To obtain a definitive diagnosis, the patient went to the operating suite for surgical debridement of her

abdominal wounds at the outside hospital (Figure 1A-C). The pathology from these specimens indicated findings consistent with calciphylaxis (Fig 1D-E). Upon transfer to our facility and because of the recent initiation of warfarin, specimens were obtained from the outside hospital. Review by a second set of pathologists again indicated a diagnosis of calciphylaxis, which was based on evidence of soft tissue and focal small vessel calcification (Fig 1D-E).

Despite surgical debridement, the patient continued to have severe and unrelenting pain associated with her wounds. In consultation with Nephrology, the patient was started on sodium thiosulfate at the standard dose of 25 g IV three times a week. While she continued to have pain, there was some improvement with this intervention. In terms of her calcium management, an attempt was made to keep her calcium in the range of 7-8 mg/dL and phosphorus in the range of 3-4 mg/dL. Unfortunately, the patient battled recurrent bacteremia and sepsis, presumably related to her calciphylaxis wounds, and later succumbed to complications from sepsis.

DISCUSSION

Calciphylaxis is a profoundly painful, debilitating and sometimes deadly condition that typically affects patients with chronic kidney disease. The mortality of calciphylaxis approaches 45-50% and is generally associated with the development of sepsis (1, 3). We present a case of calciphylaxis in a patient with normal kidney function but other risk factors including an elevated serum phosphorus related to chronic calcitriol use, warfarin anticoagulation, obesity, and Caucasian race. Levels of serum calcium and phosphate are important determinants of calcification, and a calcium phosphate product >70 significantly increases the risk of developing calciphylaxis (1). However, there is emerging data that elevations in serum phosphorus play a more central role in the development of calciphylaxis (4). This may explain why individuals maintained on chronic calcitriol, where hyperphosphatemia can occur during dose titration, would be prone to the development of calciphylaxis in the right clinical setting. Nephrologists commonly use phosphate binders to control phosphate levels in CKD. To our knowledge, phosphate binders are used less frequently in hypoparathyroid patients with normal renal function. A literature review revealed only two other cases of calciphylaxis in the setting of hypoparathyroidism, one of which was associated with preserved renal function and the other with end stage renal disease (9, 10). Admittedly, this appears to be a rare complication in hypoparathyroid individuals, however findings from cases such as ours suggest that Endocrinologists should be aware of this potential complication of calcitriol.

An important risk factor in this patient was the initiation of warfarin anticoagulation. The mechanism through which warfarin contributes to the development of calciphylaxis is thought to be related to its interaction with matrix Gla protein (MGP). While MGP normally inhibits bone morphogenic protein-2 from causing arteriole mineralization, warfarin inhibits carboxylation of the MGP, leading to its inactivation (5, 11). Additional studies have also identified a role for α2-Heremans-Schmid glycoprotein (Ahsg) in the inhibition of calcification. Deficiencies in Ahsg, as is seen in chronic kidney disease and other inflammatory states, may further contribute to the risk of developing calciphylaxis (12, 13).

The diagnosis of calciphylaxis is based largely on histologic findings, but there are reports that three phase bone scan might have diagnostic utility and be useful in monitoring progression (14). Severe pain is a hallmark of calciphylaxis, and it is historically very difficult to treat. Several modalities have been reported to improve pain and contribute to resolution of this condition. Sodium thiosulfate has now been widely used and is thought to work via multiple mechanisms. First, it may act as antioxidant with resulting vasodilation in the peripheral vasculature leading to reductions in necrosis and inflammation. More notably, the administration of sodium thiosulfate results in the production of calcium thiosulfate, which is thought to pull calcium out of the arterioles and peripheral tissue and allow it to be eliminated via urinary excretion or dialysis. Up to 2 months of treatment may be required to see improvement, and it is important to note that the literature supporting the use of sodium thiosulfate consists of case series and case reports (6, 7, 14, 15). No randomized controlled studies have been performed. There have also been case reports of resolution of calciphylaxis with the use of bisphosphonates and cinacalcet (15, 16). The obvious limitation in the widespread use of bisphosphonates is that many patients with calciphylaxis also have decreased renal function. Diligent wound care is a must, and hyperbaric oxygen used alone or in combination with sodium thiosulfate is also thought aid in resolution (6, 15).

CONCLUSION

We present this case for the benefit of the Endocrinology community. Much of the existing literature describing calciphylaxis has been published in Nephrology and Dermatology journals. However, the calcitriol label explicitly contains a warning for an elevated calcium phosphate product as well as the possibility of vascular and soft tissue calcification (17). Patients treated with chronic calcitriol should have serum calcium and phosphorus monitored closely and may benefit from the use of non-calcium based phosphate binders if hyperphosphatemia becomes unavoidable. Also of relevance to Endocrinologists is data to suggest that primary hyperparathyroidism is the most common non-uremic condition associated with the development of calciphylaxis (1, 4). These associations are especially important in our Endocrine patients with other risk factors for calciphylaxis including CKD, obesity, or warfarin use. Given that calciphylaxis is still very difficult to treat and associated with high mortality, preventing the development of this condition should be considered imperative.

Acknowledgments

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Abbreviations

Ahsg	α2-Heremans-Schmid glycoprotein
CKD	chronic kidney disease
OR	operating room
DIC	disseminated intravascular coagulation

GFR	glomerular filtration rate
Ca	Calcium
Phos	Phosphorus
Ca × Phos	calcium phosphorus product
MGP	Matrix G1a protein
PTH	parathyroid hormone
RANK	receptor activator of nuclear factor-κB

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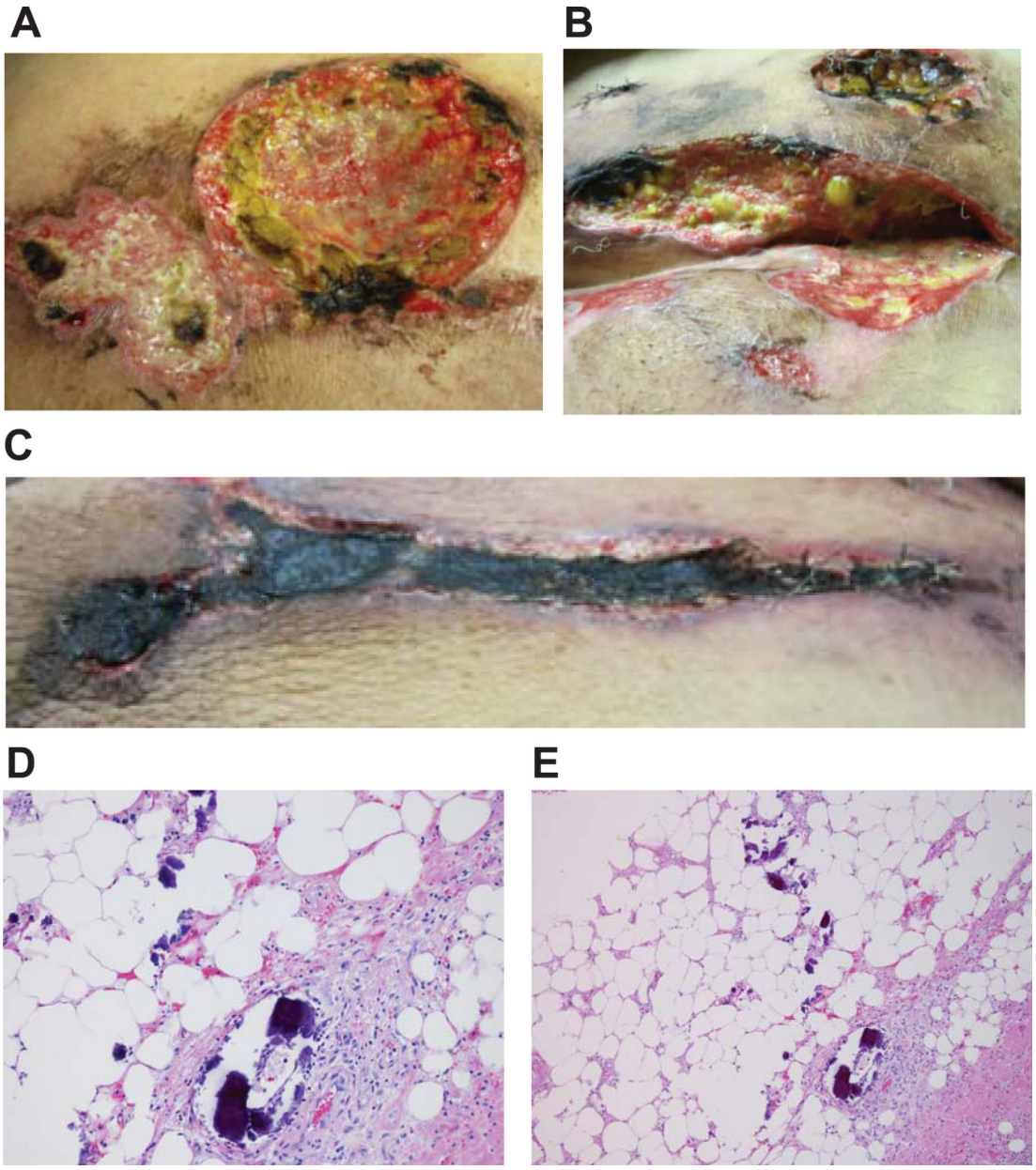

Fig 1.

A-C, Photographs of the patient's abdomen showing violaceous skin with nonhealing ulcers and underlying tissue necrosis consistent with a calciphylaxis lesion. D-E, High and low power magnification of biopsy of lesions showing obvious calcification of a blood vessel and subcutaneous tissue indicative of calciphylaxis (2).

Table 1

Risk Factors in Developing Calciphylaxis (7)

1. End Stage Renal Disease	5. Caucasian race
2. Hyperparathyroidism	6. Calcium containing phosphate binders
3. Hyperphosphatemia	7. Vitamin D therapy
4. Elevated calcium x phosphate product (>70)	8. Warfarin use

Table 2

Timeline of presentation including known biochemical values

Date	Notes	Serum Ca	Serum Phos	Ca x Phos
7/10/2010		7.6 mg/dL	5.8 mg/dL	44.08
5/16/2012		7.3 mg/dL	4.7 mg/dL	34.31
5/21/2012	Initiation of warfarin			
7/30/2012		unknown	6.7 mg/dL	Unable to calculate
8/2/2012		unknown	7.4 mg/dL	Unable to calculate
8/17/2012	Skin lesions develop			
10/2/2012		9.6 mg/dL	unknown	Unable to calculate
11/24/2012		8.0 mg/dL	5.5 mg/dL	44 mg/dL