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Non-uremic calciphylaxis in alcoholic hepatitis

Talal Alnabelsi, Ramzi Mulki, Corrado Minimo, Janani Rangaswami

ABSTRACT

Introduction: Calciphylaxis is a rare vasculopathic disorder associated with high morbidity and mortality. Its pathogenesis is poorly understood but likely involves a complex cascade of metabolic interactions culminating in abnormal calcium deposition in vascular and extravascular structures. Calciphylaxis is well documented in the uremic population. Some cases in literature are reported in non-uremic patients, six of which are in patients with alcoholic cirrhosis. Our case demonstrates calciphylaxis successfully treated with bisphosphonates in a patient with alcoholic hepatitis without cirrhosis or kidney disease. Case Report: A 37-year-old Caucasian female was, recently hospitalized for alcoholic hepatitis, presented with a painful rash on the thighs. The patient underwent extensive evaluation which revealed an elevated calcium-phosphorus product and slightly abnormal liver function tests. She underwent a biopsy of the rash which revealed evidence of calciphylaxis. The patient underwent topical wound care along with an aggressive pain regimen. She also received intravenous bisphosphonate therapy. The patient was subsequently discharged and on a follow-up visit demonstrated almost complete resolution of her symptoms. Conclusion: Calciphylaxis is a rare and life-threatening disorder of subcutaneous vascular calcification and necrosis. While reported in patients with chronic kidney disease, only few cases describe the occurrence of calciphylaxis in the presence of liver disease. The patient had evidence of alcoholic liver disease which was likely a culprit in the pathogenesis of this condition. Our case reports on a rare entity occurring in an unusual setting and illustrates the importance of perusing a tissue diagnosis.

Keywords: Alcoholic liver disease, Calciphylaxis, Hepatitis, Non-uremic

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INTRODUCTION

Calciphylaxis is a life-threatening condition characterized by medial calcification of cutaneous arterial vessels associated with painful cutaneous lesions [1]. This disorder has been almost exclusively described in patients with advanced chronic kidney disease (CKD) or end stage kidney disease (ESKD), especially those on dialysis with uncontrolled secondary or tertiary hyperparathyroidism

[2]. Rarely, calciphylaxis occurs sporadically outside the context of kidney injury such as malignancy, chronic inflammatory disorders and liver cirrhosis. We hereby report a case of calciphylaxis occurring in the setting of alcoholic hepatitis in the absence of cirrhosis or kidney disease.

CASE REPORT

Our patient is a 37-year-old Caucasian female who presented with a history of bariatric surgery 10 years ago, and a history of heavy alcohol use. Two months prior to her presentation, she was hospitalized with abdominal pain, diarrhea and fatigue. She was noted to have deranged liver function tests consistent with an alcoholic hepatitis pattern. There was no evidence of viral or autoimmune hepatitis on laboratory analysis and imaging revealed steatohepatitis with no evidence of cirrhosis. She was treated with steroids for her alcoholic hepatitis and antibiotics for Clostridium difficile colitis. No liver biopsy was performed at that time because her liver function tests were improving and there was no suspicion for an alternative diagnosis. Her current presentation consisted of a month long history of a painful rash on her thighs and buttocks. They started as small subcutaneous nodules on the legs that have become painful and were associated with overlying skin changes. The patient denied any history of trauma or intravenous drug use. She reported no symptoms similar to this in the past and was not complaining of any constitutional symptoms, joint pain or swelling.

The patient had been abstinent from alcohol since her last discharge and denied illicit drug or tobacco use. She was not sexually active. The patient was on daily multivitamin supplements and acetaminophen as needed for the pain.

The patient was afebrile with normal vital signs. Examination of the rash on the thighs and buttocks revealed subcutaneous pea-sized nodules with overlying ecchymosis and evidence of black eschar (Figure 1). On abdominal examination the patient had mild non-tender hepatomegaly but no ascites or stigmata of chronic liver disease. A detailed musculoskeletal examination revealed no joint deformities or effusions.

Laboratory data revealed a mildly elevated phosphorus level 5.5 mg/dl (3.0–4.5 mg/dl), normal corrected calcium levels 9.8 mg/dl (9–10.5 mg/dl), albumin of 2.5 g/dl (3.5–5.0 g/dl), alkaline phosphatase 217 IU/L (40–150 IU/L), alanine transaminase 58 IU/L (0–55 IU/L), aspartate transaminase 201 IU/L (5–34 IU/L), total bilirubin 2.4 mg/dL (0.2–1.2 mg/dL) and an intact PTH 19.2 pg/ml (9–73 pg/ml). Serum cryoglobulins were negative. CRP was mildly elevated at 5.1 mg/L (0–5.0 mg/L) and an ESR was elevated to 98 mm/hr. The patient's creatinine clearance was normal; 100 mL/min/1.73 m^2. Screening serologies for an autoimmune process, including antinuclear antibodies/double-stranded/ antineutrophil cytoplasmic antibody/ extractable nuclear antigen were all negative. Anticardiolipin antibodies, lupus anticoagulant and anti β_2-glycoprotein I antibodies were all negative. Coagulation parameters showed an INR of 1.4 (0.8–1.2) and an elevated prothrombin time of 16.1 s (10.0–13.0 s). Fibrinogen, thromboplastin time and D-dimer levels were all normal.

Histopathology of the rash revealed thrombotic vasculopathy and subcutaneous fat necrosis with focal calcification suggestive of calciphylaxis (Figures 2–4). Curvilinear lacelike calcifications within the subcutaneous blood vessels were seen on plain X-ray films of the involved areas.

An important diagnostic consideration is a cutaneous vasculitis secondary to a connective tissue disorder, infection or adverse drug reaction. The patient had no systemic features of a rheumatologic disorder, did not receive any new medication recently and did not have any constitutional symptoms. The negative serum cryoglobulin levels and autoimmune panel makes this diagnosis unlikely. Another mimic of calciphylaxis is antiphospholipid syndrome. However, our patient did not have a history of venous or arterial thrombi and the serological tests for antiphospholipid syndrome were all negative.

The patient received aggressive topical wound care and opiate pain medication. A non-calcium containing phosphate binder was started for her elevated phosphorus levels, and intravenous pamidronate was administered. At the time of discharge her liver function tests had returned to normal and a dedicated MRI of the liver revealed hepatomegaly with no evidence of cirrhosis. The patient was then discharged to a rehabilitation facility and a follow-up appointment six months later revealed almost complete resolution of the rash.

DISCUSSION

Calciphylaxis is a rare disorder characterized by subcutaneous vascular calcification and cutaneous necrosis. Reported mortality rates for this disease are as high as 60-80% usually as a result of severe sepsis secondary to superinfection of the skin lesions and multi-organ failure [1]. It is most often seen in patients with CKD, especially those on dialysis with uncontrolled secondary or tertiary hyperparathyroidism. A few cases have been reported in non-CKD patients and only 6 cases have been described in patients with liver disease [2].

The precise mechanism of the disease is complex and likely multifactorial (Figure 5). The current accepted model of vascular calcification begins with differentiation of vascular smooth muscle cells (VSMC) into osteoblast-like cells [3, 4]. Mechanisms involved in this process include the loss of calcification inhibitors, the overproduction of reactive oxygen species (ROS) or the elevation in the calcium-phosphorus product [5]. ROS have been implicated at various stages of the cycle

that eventually lead to calciphylaxis. Uremia, acute and chronic inflammatory states are amongst the causes of excess ROS production. The overproduction of ROS activates the nuclear factor kappa B (NFkB) pathway resulting in inflammatory cytokine surges [5]. ROS also induce VSMC apoptosis, endothelial cell dysfunction and reduce the levels of nitric oxide (NO) [5]. Together these processes lead to vascular calcification, which often precedes the development of skin changes and ulcers associated with calciphylaxis. In the presence of an inflammatory burden, the calcified lesions worsen along with the formation of obliterative endovascular fibrosis and subsequent skin necrosis [5].

Another possible contributing mechanism to the calcification of VSMC is the reduction in local vascular calcification inhibitors. Two endogenous vascular calcification inhibitors are recognized; Matrix Gla protein (MGP) and Fetuin-A (α 2-Heremans-Schmid glycoprotein) [6]. MGP is a Vitamin-K dependent protein produced by VSMC and chondrocytes and acts as a potent inhibitor of vascular calcification. Similarly, Fetuin-A is a circulating protein synthesized in the liver and is regarded as the most potent circulating inhibitor of calcification [7]. Studies have shown that levels of MPG and Fetuin-A are reduced in patients with ESKD and chronic inflammatory states, including alcoholic steatohepatitis, increasing the risk of vascular calcification and calciphylaxis [5].

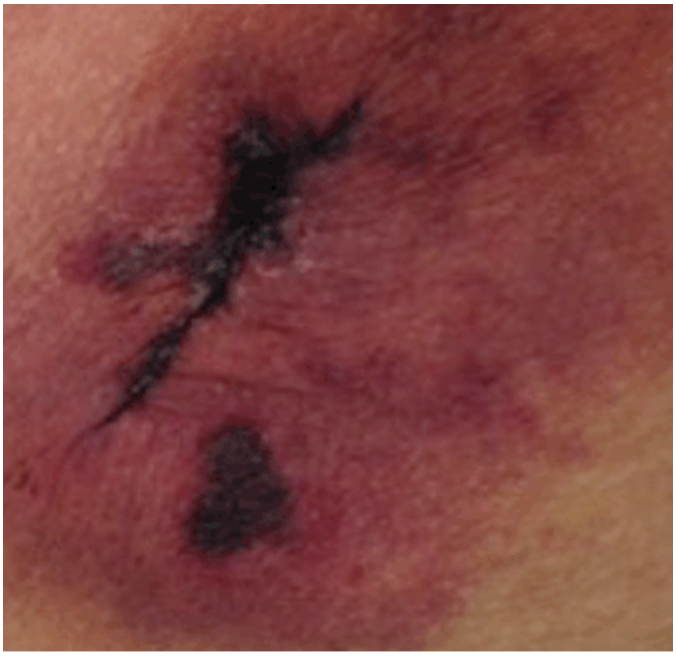

Figure 1: Lesion on medial thigh. Note the violaceous skin rash and black eschar.

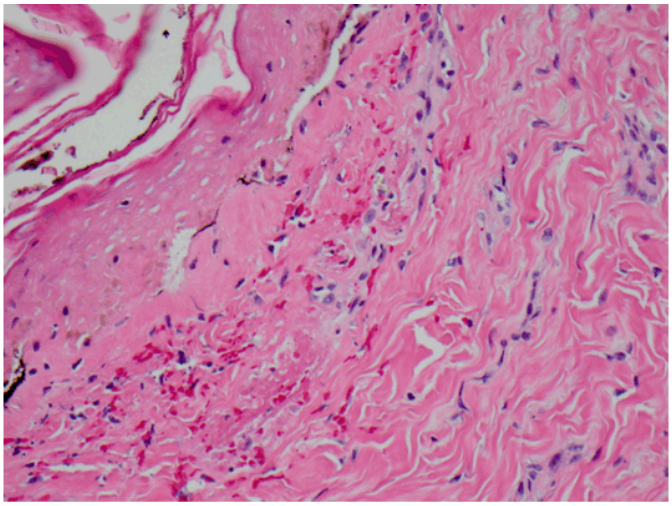

Figure 2: Histopathology showing evidence of epidermal necrosis with detachment from the papillary dermis and dermal extravasation of red blood cells (H&E stain, x40)

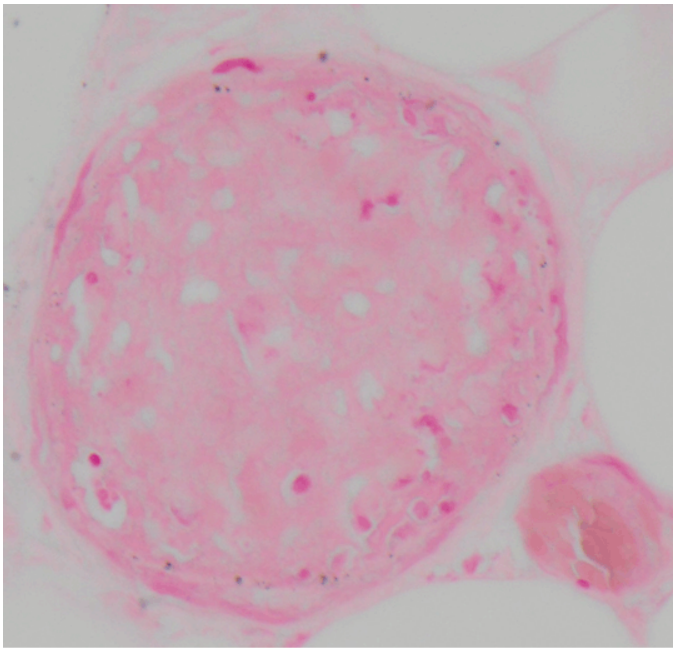

Figure 3: Histopathology showing thrombotic vasculopathy. Note microthrombus within the capillary and fine granular basophilic deposits in the vessel wall which have stained black for calcium using the histochemical Von-Kossa stain (magnification: x60).

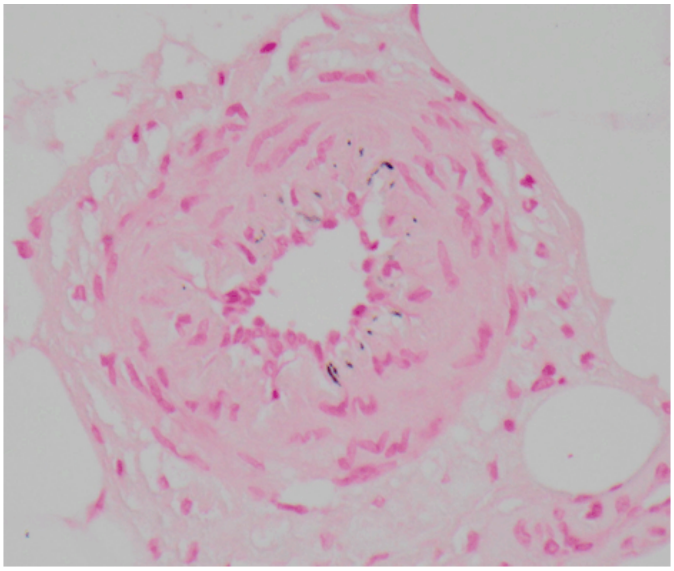

Figure 4: Coarser deposition of calcium in an arteriole (Von-Kossa stain, x60).

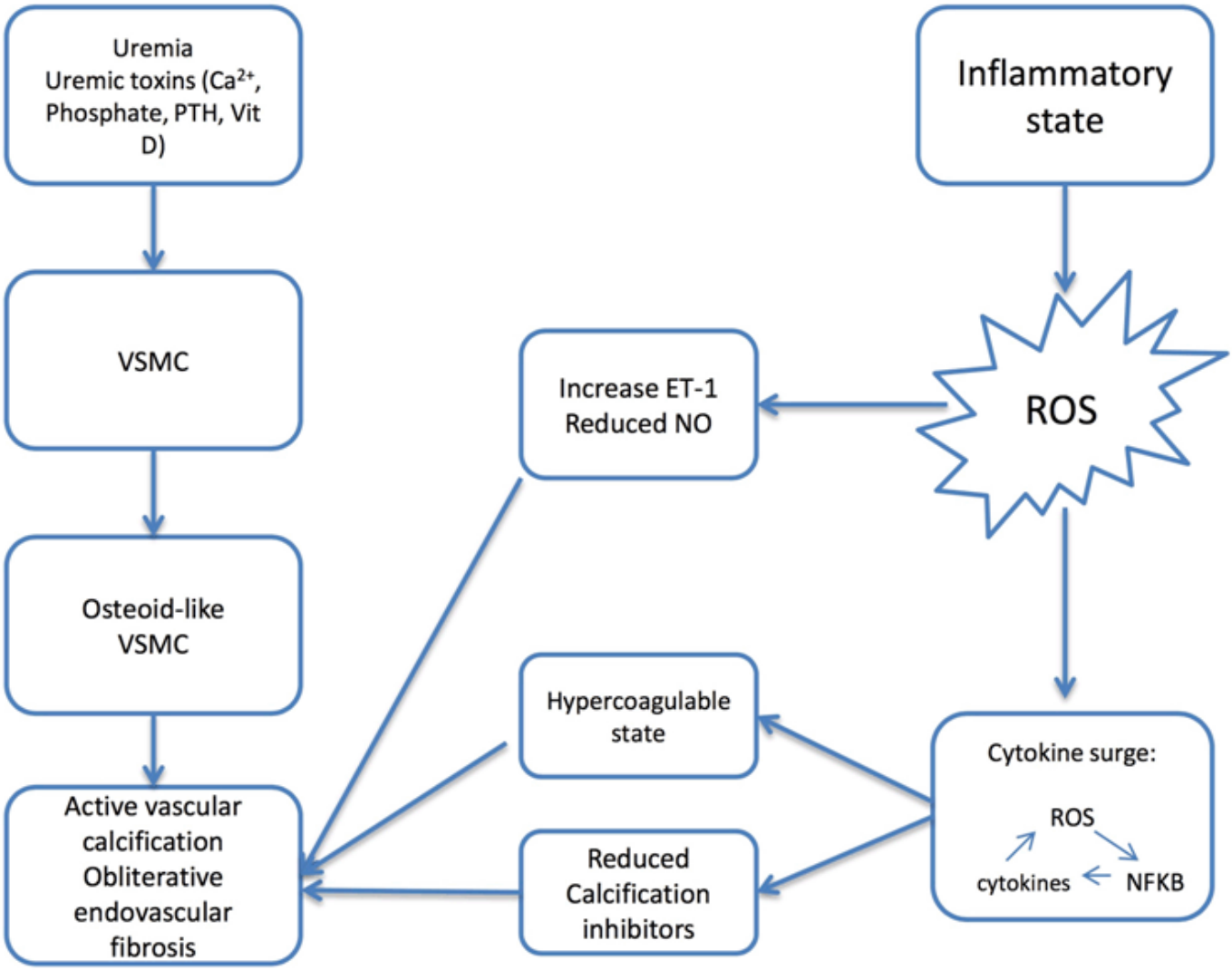

Figure 5: Proposed mechanisms involved in vascular calcification and calciphylaxis [5].
Uremic toxins such as calcium, phosphorus, PTH, and vitamin D along with ROS contribute to VSMC differentiation into osteoid-like cells. Phosphate absorption into these cells results in an osteogenic switch. On the other side, an inflammatory state contributes to the production of ROS which in turn results in a multitude of effects. A cytokine surge ensues due to the activation of the NFkB pathway resulting in the release of inflammatory cytokines including TNF-alpha, IL-1 and IL-6 leading to more ROS production. This in turn results in the down regulation of two calcification inhibitors (Fetuin-A & MGP). All these processes eventually lead to active vascular calcification of the arteriole media. On the other hand, ROS also induce excess release of ET-1 and cause reduced levels of NO. This along with a hypercoagulable state induced by the inflammatory cytokine surge promotes a proinflammatory, proconstrictive and a prothrombotic endothelium. Eventually this leads to obliterative endovascular fibrosis.
Abbreviations used: PTH-parathyroid hormone, ROS-reactive oxygen species, VSMC-vascular smooth muscle cells, NFkB-nuclear factor kappa B, MGP-matrix Gla protein, ET 1-endothelin 1, NO-nitric oxide.

Identified risk factors for the development of calciphylaxis include: hyperphosphetemia, ESR > 30 mm/1hr, reduced serum albumin and a calcium-phosphorus product > 70 mg^2/dl^2 [1]. Medications including heparin, vitamin K antagonists and calcium based phosphate binders are further risk factors [1]. Other associated disorders include autoimmune conditions, hyperparathyroidism and protein C or S deficiency [2]. Nevertheless, ESKD remains the single most important risk factor for the development of calciphylaxis [1].

Treatment of the condition is mainly supportive. Wound care is essential including debridement of necrotic tissue periodically and the early use of tailored antibiotics if signs of infection arise. Efforts should be made to control the calcium-phosphorus product with the use of non-calcium based phosphate binders. The use of albumin, steroids and blood transfusions should be eliminated if possible as they may have a causal though unproven effect [1]. The role of parathyroidectomy remains controversial but it has been reported to be helpful in cases of calciphylaxis in the setting of primary and tertiary hyperparathyroidism [8]. Sodium thiosulfate has been used particularly in ESKD, possibly secondary

to its calcium chelating properties [4]. Additionally, bisphosphonates showed some success likely due to their antiresorptive effects [4].

The prior reported cases of non-uremic calciphylaxis in alcoholic liver disease occurred in patients with cirrhosis, raising the possibility of protein C and S deficiency contributing to the pathogenesis of calciphylaxis [9, 10]. Our patient had no evidence of alcoholic cirrhosis. The rash appeared one month following her hospitalization for an episode of alcoholic hepatitis where she received steroids and albumin. While we cannot rule out a transient protein C and S deficiency contributing to the patient's presentation, the absence of cirrhosis and the negative thrombophilia workup makes this a less likely possibility. We speculate that the presence of hyperphosphatemia and an inflammatory state (alcoholic hepatitis) lead to excess ROS formation, up-regulation of the NFkB pathway and down regulation of the calcification inhibitor proteins eventually resulting in calciphylaxis. The patient was successfully managed with supportive measures in addition to bisphosphonate therapy which is encouraging given the high morbidity and mortality of the disease.

CONCLUSION

In conclusion, we present an unusual case of calciphylaxis occurring in the absence of cirrhosis and chronic kidney disease. The high morbidity and mortality of the disease emphasizes early detection and our case highlights the importance of obtaining a tissue diagnosis. To our knowledge this is the first reported case of calciphylaxis in alcoholic hepatitis in the absence of cirrhosis, and alerts clinicians to the morbidity of this unusual but important presentation.

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Author Contributions

Talal Alnabelsi – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Ramzi Mulki – Substantial contributions to conception and design, Critical revision of the article, Final approval of the version to be published

Corrado Minimo – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Janani Rangaswami – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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