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Nonuremic calciphylaxis in a post renal transplant patient

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ABSTRACT

Background: Calciphylaxis is a potentially fatal condition previously observed in patients with poor renal function. We present a case of atypical presentation in a patient with good renal function after transplantation.

Case Presentation: A-68-year old African American female with history of end-stage renal disease (ESRD) secondary to type II diabetes mellitus on hemodialysis for ten years, status post living related donor kidney transplant from her son three years prior to this presentation, parathyroidectomy, and atrial fibrillation on warfarin presented to our institution with progressively worsening, severely tender bilateral thigh lesions that were diagnosed as calciphylaxis. She was treated with sodium thiosulfate infusions for six months and continues to do well.

Conclusions: Calciphylaxis, also known as calcific uremic arteriolopathy (CUA), has traditionally been associated with ESRD patients on maintenance dialysis, however several nonuremic cases of CUA have been reported in recent years. Multiple pathophysiologic mechanisms for CUA development have been proposed expanding the scope of known risk factors and possible triggers. CUA can be a life-threatening condition that is important for clinicians to recognize and treat as soon as possible.

Implication for health policy/practice/research/medical education:
Clinicians need to be aware that CUA can occur in patients with good renal function, such as post transplantation, when other risk factors such as obesity and warfarin treatment exist.

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Case Report

1. Background

Calciphylaxis also known as calcific uremic arteriolopathy (CUA) is a life threatening syndrome of microvascular calcification in dermis and subcutaneous adipose tissue that may manifest in a continuum starting as tender nonulcerated violaceous skin patches with a reticulate pattern of erythema and/or tender palpable subcutaneous nodules with overlying erythema progressing to very tender indurated dusky colored skin lesions, and finally extremely painful necrotic ulcers covered with a black eschar. It has historically been thought of as a phenomenon occurring in end-stage renal disease patients who are dialysis dependent. However, a few cases of post-transplant calciphylaxis have been reported (1,2). Nigwekar et al identified several nonuremic causes of the condition in their 2008 review article, including primary hyperparathyroidism, connective tissue diseases, and malignancies (1-3). As a result calciphylaxis can now be classified as uremic or nonuremic (i.e., patients with normal renal function or in earlier stages of chronic kidney disease). Thus, the terminology calciphylaxis may be preferred over CUA. Calciphylaxis lesions can be distributed centrally involving abdomen, breast or thighs where there is more subcutaneous adipose tissue, or may be distributed peripherally (legs, feet, digits and penis) with limited adipose tissue. In the end-stage renal disease (ESRD) patients 70%-80% of the lesions are distributed centrally, in contrast to approximately 50% in the nonuremic cases. Nonuremic and peripheral lesions have a better prognosis with less mortality. Centrally distributed lesions are more in females and obese patients, and carry a worse prognosis with up to 80% 1-year mortality. For an excellent review one may refer to a recent publication by Nigwekar et al (4).

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Herein we present a case of calciphylaxis in a post-renal transplant obese female patient with sufficient renal function who was receiving warfarin for atrial fibrillation.

2. Case Presentation

A-68-year old African American female with past medical history of ESRD secondary to type II diabetes mellitus on maintenance hemodialysis for ten years, status post living related donor kidney transplant from her son three years prior to this admission, presented to our institution with progressively worsening, severely tender bilateral thigh lesions. The patient had chronic atrial fibrillation and was on warfarin therapy. The patient also had history of tertiary hyperparathyroidism and had undergone subtotal parathyroidectomy three months prior to this admission.

On presentation, her vital signs included blood pressure of 148/92 mm Hg, heart rate 109 beats/min, and body mass index (BMI) of 37.4 kg/m^2. The patient had an ulcerated and indurated lesion measuring ~7×5 cm on her left buttock that was extremely tender to palpation (Figure 1). Laboratory testing revealed a corrected calcium level of 10.0 mg/dL when adjusted for hypoalbuminemia, serum albumin 2.6 g/dL, phosphorus 3.3 mg/dL, international normalized ratio (INR) of 6.2, creatinine of 1.6 mg/dL with estimated glomerular filtration rate (eGFR); 39 ml/min, and PTH 174 pg/mL.

The patient was clinically diagnosed as calciphylaxis and was started on treatment with intravenous sodium thiosulfate (STS) 25 g three times weekly post each hemodialysis session for the next 6 months. A punch biopsy of the lesion was non-diagnostic, however, Klebsiella grew out of wound biopsy that showed microabscesses. She was treated with a 14-day course of ceftriaxone.

The patient's course was complicated by the development of sudden severe right foot pain a few days after initiation of STS treatment. Physical exam was concerning for vascular compromise and CT angiography revealed severe calcific plaques throughout the right posterior tibial artery. She underwent angioplasty and right anterior tibial endarterectomy without complication. She continued to receive STS infusions for 6 months following initiation of treatment. She tolerated the infusions well and her ulcer completely healed.

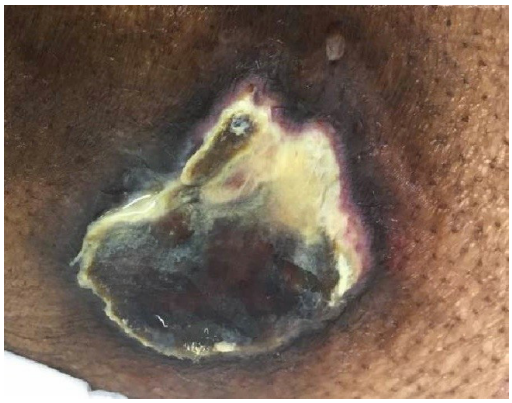

Figure 1. An ulcerated and indurated lesion measuring ~7x5 cm on her left buttock that was extremely tender to palpation. The patient was clinically diagnosed calciphylaxis and was treated with a six-month course of sodium thiosulfate.

3. Discussion

Well-established risk factors for calciphylaxis include ESRD on dialysis for more than 2 years, adynamic bone disease (low-bone turnover) with over suppressed PTH levels due to excessive vitamin D and calcium supplementation in ESRD patients, primary or secondary hyperparathyroidism, active calcium/vitamin D supplementation, hyperphosphatemia and elevated calcium phosphate product, as well as, female gender, increased BMI, warfarin use, chronic immunosuppression, diabetes mellitus, and hypoalbuminemia (4-6). Our female patient had a recent history of tertiary hyperparathyroidism and was status post subtotal parathyroidectomy presenting with PTH 174 pg/mL, had a high BMI, was on warfarin therapy, was chronically immunosuppressed, and had diabetes mellitus and hypoalbuminemia. However, she was only CKD stage 3, and had normal serum calcium and phosphate levels, and a normal range calcium phosphate product.

The mechanism of calciphylaxis in the setting of a high calcium-phosphate product in ESRD patients requiring dialysis is often driven by hyperparathyroidism and they generally respond well to emergency parathyroidectomy. However, the mechanism of developing calciphylaxis in nonuremic patients, e.g., post-kidney transplantation, is not well-known. In light of increasing incidence of these cases, more theories about the pathophysiology of calciphylaxis have emerged. While serum level of fibroblast growth factor 23 (FGF-23), a phosphaturic hormone, is elevated in ESRD patients with calciphylaxis, its role in vascular calcification and in nonuremic patients is not clear yet (4).

Fetuin-A and matrix-gla protein (MGP), both vascular calcification inhibitors, have been suspected as major players in the development of calciphylaxis. MGP is activated via vitamin K-dependent carboxylation and has been shown to prevent arterial calcification. Mice who lack MGP have been shown to develop overwhelming arterial calcification (7). A recent study by Nigewaker et al, compared patients on hemodialysis with and without calciphylaxis. Patients in the calciphylaxis arm were found to have higher concentrations of MGP but a lower fraction of carboxylated MGP (cMGP). Similarly, patients who were taking warfarin also had a lower fraction of cMGP, suggesting that plasma concentrations of cMGP may

have a significant role in the pathogenesis of the disease (6,8,9). Additionally, warfarin is a known inhibitor of the vitamin-K dependent natural anticoagulant Proteins C and S. Moreover, Yu et al, speculated that warfarin disrupts the normal microenvironment of endothelial cells in a way that preferentially favors coagulation (10).

Vanbelleghem et al have proposed that perhaps some patients are genetically predisposed to calciphylaxis due to low α2-Heremans-Schmid (Ahsg), a serum protein that acts to inhibit ectopic calcification (11).

Diagnosis of calciphylaxis is predominantly based on clinical suspicion. Skin biopsy has been the standard method to confirm diagnosis in suspicious cases, however, it can provoke new non-healing ulcers and infection. Moreover, while histopathologic finding of a combination of arteriolar medial calcification and thrombosis is a hallmark of CUA, its specificity has recently been questioned, and many of the histopathologic findings that were historically attributed to CUA can also be found in biopsy specimens of unaffected ESRD patients (12). Thus, biopsy is not needed in an ESRD patient with classic presentation. Moreover, a punch biopsy is safer than an excisional biopsy, however, its limited depth may make it non-diagnostic. A double punch biopsy (a second biopsy through the center of the first biopsy) would obtain deeper subcutaneous tissue and a better chance of showing classic histopathologic changes (4). Additionally, biopsy if attempted should be from the margin of affected lesion rather than its necrotic center (4).

Possible treatments for calciphylaxis include STS, hyperbaric oxygen and parathyroidectomy, however there is no prospective trial data available for any of these modalities. Urgent parathyroidectomy was considered the modality of choice in ESRD patients with severe secondary hyperparathyroidism and high calcium-phosphate product. However, in recent years, many cases of calciphylaxis without elevated PTH levels or high calcium-phosphate product have been described. STS was shown to be of some benefit in a multicenter retrospective cohort study performed by Nigwekar et al, though the investigators acknowledge significant bias in their study and conclude that the true efficacy of the treatment remains unclear (13).

4. Conclusions

Calciphylaxis can be a quickly devastating condition. It is important that clinicians be aware of the signs and symptoms of the disease, pertinent risk factors (particularly obesity and use of warfarin, or nutritional vitamin K deficiency), and possible treatments in order to best serve their patients. STS has been used in many cases described in the literature, however no large-scale clinical trials have been done to study the efficacy of therapy. Other treatment options include administration of bisphosphonates and denosumab to prevent arterial calcification, and hyperbaric oxygen. Use of systemic corticosteroids has also been tried but has been associated with a high risk of mortality (14). Still, prompt diagnosis and early intervention are critical to survival and decreased morbidity.

Authors' contribution

Both authors had equal contribution in data collection, review of the literature, and preparation of the case report.

Conflicts of interest

The authors report no conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. The patient has given her informed consent regarding publication of this case report.

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