CASE REPORT

Curious case of calciphylaxis leading to acute mitral regurgitation

Grant Gardner Gallimore,¹ Blair Curtis,¹ Andria Smith,¹ Michael Benca²

¹Department of Internal Medicine, Keesler Medical Center, Biloxi, Mississippi, USA
²Department of Cardiology, San Antonio Military Medical Center, San Antonio, Texas, USA

Correspondence to
 Dr Grant Gardner Gallimore,
 grantillius1@gmail.com

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SUMMARY

Calciphylaxis is uncommon and typically seen in patients with end-stage renal disease. It has been defined as a vasculopathic disorder characterised by cutaneous ischaemia and necrosis due to calcification, intimal fibroplasia and thrombosis of pannicular arterioles. We present the case of a 74-year-old woman with chronic kidney disease stage III who developed calciphylaxis leading to mitral valve calcification, chordae tendineae rupture and acute mitral regurgitation. Although an alternative explanation can typically be found for non-uraemic calciphylaxis, her evaluation did not reveal any usual non-uraemic causes including elevated calcium–phosphorus product, hyperparathyroidism, or evidence of connective tissue disease. Her wounds improved with sodium thiosulfate, pamidronate, penicillin and hyperbaric oxygen therapies but she ultimately decompensated with the onset of acute mitral regurgitation attributed to rupture of a previously calcified chordae tendineae. This case highlights an unusual case of calciphylaxis without clear precipitant as well as a novel manifestation of the disease.

BACKGROUND

Calciphylaxis is a multifactorial disorder usually seen in end-stage renal disease (ESRD) with limited therapeutic options and a high mortality rate.¹ When non-uraemic calciphylaxis is found, alternative causes often include hyperparathyroidism, malignancy, connective tissue disease and corticosteroid use.² A multi-intervention approach is generally accepted due to the various possible contributors to the disease and lack of clinical trials to support one particular modality.³

Our case emphasises that evaluation for non-uraemic calciphylaxis will not always reveal a clear precipitant for the disease. It also reviews the multiple therapies currently accepted for the disease and the high mortality seen even with maximal medical therapy. Finally, this patient also suffered a previously undescribed complication of the disease related to chordae tendineae rupture thought to be secondary to calcification of the valve apparatus.

CASE PRESENTATION

A 74-year-old woman with chronic kidney disease stage III, remote history of diffuse large B-cell lymphoma (DLBCL), diabetes, chronic atrial fibrillation treated with warfarin and rate control, mitral regurgitation and obesity was seen in clinic for a 1-month history of dark lesions on the medial aspect of her right leg and lateral aspect of her left leg. These were gradually progressive and quite

painful, but were not associated with significant oozing, purulence or spreading erythema. Initial differential included warfarin-induced skin necrosis, cellulitis, vasculitis and cholesterol emboli.

She was referred to dermatology for biopsy of the lesions. When pathology reported calciphylaxis, she was admitted to the hospital to expedite further evaluation for possible aetiology and therapy. Physical examination was remarkable only for three violaceous, leathery plaques on proximal thighs with induration but without fluctuance (figure 1). She was afebrile and haemodynamically stable with mild leucocytosis of $12.2 \times 10^3/\mu\text{L}$.

A CT of the chest, abdomen and pelvis did not suggest recurrence of her DLBCL (2002) from which she was thought to be in remission. She had stable stage III chronic kidney disease with creatinine 1.2 mg/dL. Serological evaluation was most notable for normal calcium–phosphorus product, parathyroid hormone (PTH) and vitamin D level. Evaluation for autoimmune aetiology was similarly unrevealing as detailed below.

INVESTIGATIONS

Mineral metabolism: vitamin D 37 ng/mL (30–100), PTH 39.5 pg/mL (15–65), phosphate 4.8 mg/dL (2.7–4.5), calcium 9 mg/dL (8.4–10.2), calcium–phosphorus product 43.2.

Immunological: antinuclear and anti-Smith antibodies were negative. Other negative antibody evaluations included Sjogren's syndrome A antibody (SSA) and Sjogren's syndrome B antibody (SSB), anti-U1 ribonucleoprotein (U1-RNP), Scl-70, anti-mitochondrial antibody (AMA), anti-Jo-1. Rheumatoid factor was 12 IU/mL (<14), C3 was 154 mg/dL (90–180) and C4 31 mg/dL (16–47). Antiphospholipid antibody panel, including

Figure 1 Left thigh lesion.

CrossMark

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cardiolipin IgG/A/M, β_2 glycoprotein I, was also negative. HIV ELISA was non-reactive.

Punch biopsy of right medial thigh and left lateral thigh were notable for calciphylaxis (figure 2).

DIFFERENTIAL DIAGNOSIS

Usual causes of non-uraemic calciphylaxis in the differential diagnosis for our patient included primary hyperparathyroidism, malignancy, alcoholic liver disease, connective tissue disease, diabetes, chemotherapy-induced protein C and S deficiency, Crohn's disease, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome, vitamin D deficiency and chronic kidney disease.²

TREATMENT

On initial presentation, warfarin was held as this is a known risk factor in susceptible patients; stroke prophylaxis for atrial fibrillation was transitioned to aspirin and clopidogrel. A peripherally inserted central catheter line was placed and sodium thiosulfate (25 g) infusion was initiated on three times weekly basis. Pamidronate (90 mg) was administered intravenously monthly and benzathine penicillin G (2.4 million units) was injected intramuscularly monthly. Hyperbaric oxygen therapy was given on each weekday.

OUTCOME AND FOLLOW-UP

The patient reported moderate improvement in her pain and had some objective improvement in her wounds with therapy. Penicillin depot injections were discontinued due to a serum sickness-like reaction with a diffuse maculopapular rash; this resolved with discontinuation and a brief course of prednisone. She eventually self-discontinued hyperbaric oxygen therapy as well due primarily to the significant time commitment.

Four months after initial therapy and moderate wound improvement, the patient presented with severe shortness of breath at rest, markedly changed from her baseline dyspnoea on exertion. Although she did have a history of moderate mitral regurgitation, repeat echocardiogram demonstrated dramatic worsening and severe mitral regurgitation. A calcified lesion of the chordae tendineae had ruptured since her previous study (figure 3). Afterload reduction was obtained with angiotensin receptor blocker and

Figure 3 Echocardiogram image demonstrating calcification of chordae tendineae.

hydralazine therapy and dyspnoea improved significantly with intravenous furosemide therapy over a 5-day hospital course. After cardiology consultation, she was not referred for valve replacement due to comorbidities, likelihood of poor wound healing after valve surgery with calciphylaxis, and high 1-year mortality of calciphylaxis. Unfortunately, she succumbed to her severe heart failure over the following months.

DISCUSSION

Calciphylaxis is an often devastating disease involving calcification of subcutaneous arterioles leading to infarctions of subcutaneous adipose tissue and skin. It is most often seen in haemodialysis patients with a prevalence of 4.1% in one study of 242 haemodialysis patients; it is rare in non-ESRD patients.⁴ The 1-year survival rate has been estimated at near 46%,¹ and skin ulceration seems to be a major prognostic factor.⁵

Histopathology is characterised by the deposition of calcium salts in the media of arterioles followed by the thickening of the vessel intima by loose connective tissue and finally thrombosis.⁶ The pathogenesis is not fully understood but there are several known associations including increased phosphorus levels, female gender, high alkaline phosphatase and low albumin.⁷ Medications implicated as risk factors include warfarin,⁸ corticosteroids,¹ calcium-based phosphorus binders and vitamin D.⁵ Connective tissue diseases and hypercoagulable states² are known associations as well. Our patient's most important risk factors were warfarin use, obesity and chronic kidney disease.

The contribution of warfarin to calciphylaxis may be related to decreased vitamin K-mediated carboxylation of the γ -carboxyglutamic acid protein, an inhibitor of extraosseous calcification in vessels and cartilage.⁹ Multiple case reports have noted an association with calciphylaxis after warfarin initiation even in the absence of ESRD.^{10 11} One case highlighted onset of calciphylaxis and metastatic pulmonary calcification temporally related to warfarin use.¹² The underlying mechanism for development of these lesions remains theoretical with several known associations clinically and biochemically. Interestingly, a broadly applicable risk factor may be decreased fetuin A levels as seen in chronic inflammation.^{13 14}

Diverse interventions have been attempted with variable efficacy including parathyroidectomy,¹⁵ cinacalcet,¹⁶ sodium thiosulfate,^{17 18} phosphorus binders, wound management, intensified haemodialysis, hyperbaric oxygen^{3 19} and bisphosphonate therapy.^{20 21} Broadly, these therapies are aimed at

Figure 2 There is calcification of small-to-medium-sized blood vessels and focal fat necrosis along with a few thrombosed vessels. In addition, there is thickening of fibrous septae in the subcutis which contain fragmented eosinophilic granular debris, similar to that seen in pseudoxanthoma elasticum. This debris stains positively with Verhoeff-Van Gieson (elastic) and Von Kossa (calcium) stains. Periodic acid Schiff-F and Grocott's methenamine silver stains are negative for fungus.

decreasing PTH and phosphorus levels, increasing calcium-phosphorus solubility, and anti-inflammatory effects.

Although mitral annular calcification is often seen in chronic renal failure (10%),²² to the best of our knowledge mitral calcification, chordae tendineae calcification and valve rupture have not been reported as a complication in non-uraemic calciphylaxis. One case report described mitral valve calciphylaxis in a man with diabetic renal failure but this was reported as secondary to nanobacteria acting as a nidus for carbonate apatite formation (calcium phosphate).²³

Learning points

- Calciphylaxis is typically associated with end-stage renal disease and an increased calcium-phosphorus product.
- When non-uraemic calciphylaxis is discovered, evaluation for known alternative aetiologies should be initiated.
- Despite a multi-interventional approach for calciphylaxis, the disease remains associated with a high morbidity and mortality.
- This case serves to highlight a novel complication of non-uraemic calciphylaxis; to the best of our knowledge, acute severe mitral regurgitation has not been reported in this setting.

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