CASE REPORT

The calcium invasion: Calciphylaxis in Lupus

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Abstract

Calciphylaxis is a poorly understood and highly morbid syndrome of vascular calcification and skin necrosis. We describe the case of a 52-year old woman with systemic lupus erythematosus (SLE), inappropriately treated with oral steroids for 18-years who developed renal impairment followed by skin necrosis and gangrene of right hand. She had subcutaneous calcium deposition with bilateral renal stones and widespread vascular calcifications. She was diagnosed with calciphylaxis and in spite of treatment died of a myocardial infarction.

Keywords: Calciphylaxis, Lupus, Skin necrosis, Chronic renal failure.

Introduction

Calciphylaxis is described as a syndrome primarily seen in uraemic patients characterized on histopathology by small-vessel mural calcification, extravascular calcification, and thrombosis leading to ischaemia with skin and soft tissue necrosis and high mortality. It is an uncommon condition that affects up to 4% of the population with ESRD.[1] In SLE chronic inflammation is the likely trigger. Prolonged steroid use is also a known cause.[2]

Case Report

A 52-year old woman presented to the emergency room at Liaquat National Hospital in September 2013 with complaints of a painful bluish right hand since two weeks and sudden onset of chest heaviness of few hours duration. Chest pain was diagnosed as angina and responded to conservative treatment with nitrates, aspirin and beta-blockers. Further inquiry revealed that she was diagnosed with SLE 18-years ago on the basis of polyarthralgias, facial rash, oral ulcers, alopecia, bicytopenias, positive anti-nuclear antibody (ANA) and anti-dsDNA antibody. She had been on variable doses of steroids since then and had never received any other immunosuppressant medication. Her previous investigations also revealed that she had renal impairment for 18-months which was treated conservatively.

Her examination showed thin papery skin and purplish stria with multiple palpable subcutaneous bead-like nodules scattered over abdomen and limbs. There were multiple areas of cutaneous necrosis on the torso and limbs (Figure-1). Right radial and brachial pulses were weak and right hand was cold and gangrenous. Systemic examination was otherwise unremarkable.

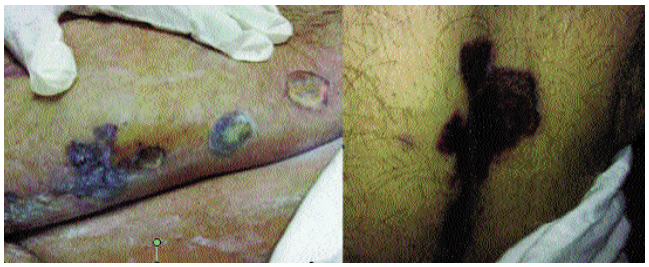

Figure-1: Cutaneous necrosis over abdomen and thigh.

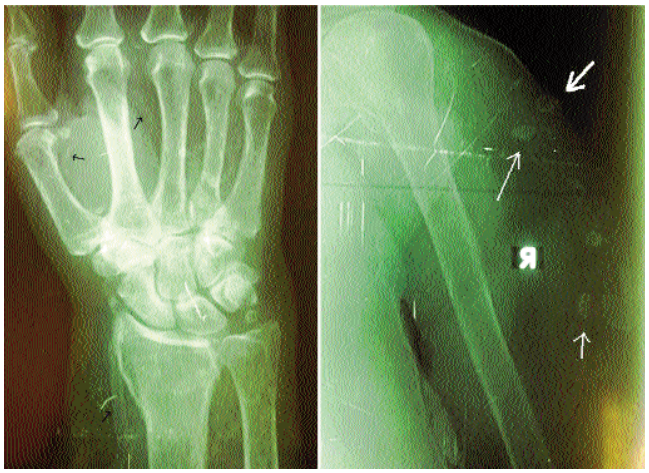

Figure-2: Calcified vessel walls and subcutaneous tissue (arrows).

Her laboratory findings showed high serum calcium (13.4 mg/dl) and phosphate levels (9.2 mg/dl) with raised serum urea (244 mg/dl) and creatinine (9.1 mg/dl). Her WBC count was elevated (26,400 cells/ml) and urine had multiple leukocytes. Her X-rays showed numerous renal stones. There were foci of calcification in pelvis, subcutaneous tissues of arms and legs and the walls of radial and inter digital arteries (Figure-2). Her skin punch biopsy revealed focal areas of epidermal necrosis with infarction of superficial dermis with focal areas of calcifications in dermal vessel walls. She was diagnosed with

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calciphylaxis and started with daily haemodialysis, oral phosphate binder, Sevelamer and oral sodium thiosulphate (2.6g daily). Antibiotics were added prophylactically.

Patient was discharged home after one week when her urine infection was controlled and uraemia improved. However, she was readmitted after a month with urosepsis and worsening limb ischaemia. She was again managed conservatively with antibiotics, regular haemodialysis and analgesics and continued to receive oral sodium thiosulphate. She underwent thrice weekly haemodialysis but approximately three months after the diagnosis of calciphylaxis she died of an acute myocardial infarction.

Discussion

Calciphylaxis is a rare, life-threatening condition characterized by progressive cutaneous necrosis and ulceration secondary to small- and medium-sized vessel calcification.[3] It is also known as the 'vascular calcification-cutaneous necrosis syndrome'. This calcification is thought to result from imbalance between bone deposition and resorption.[4,5] Various bone-regulating proteins are involved in the process of vascular calcification.[4,5] RANKL (receptor activator of nuclear factor-κB (NF-κB) ligand) and its antagonist, osteoprotegerin (OPG), play a critical role in bone remodeling.[4,5] The activation of RANK-mediated NF-κB pathway causes osseous mineral loss and extra-osseous, such as vascular, mineral deposition.

Besides uraemia, other causes identified include hyperparathyroidism, malignancy, chronic liver disease, diabetes and rheumatic diseases.[1] Systemic lupus erythematosus (SLE) results from chronic and recurrent activation of the immune system, with production of antibodies and other protein products contributing to inflammation and tissue damage. The pathogenic link between calciphylaxis and SLE appears to be chronic inflammation. Several pro-inflammatory cytokines, including interleukin-1 and tumour necrosis factor-α, promote vascular calcification by activating RANK-mediated NF-κB pathway.[4] Corticosteroids, as well as parathyroid hormone (PTH), are known to activate RANK-mediated NF-κB pathway and inhibit OPG.[4] Thus, long-term corticosteroid administration as in this case, is likely to promote osseous mineral loss and vascular calcification. Given the relative rarity of the condition and uncertain etiology, treatment strategies are not well delineated and based on case reports and series.

In general, medications that may initiate or potentiate the condition should be stopped, particularly warfarin and calcium-containing phosphate binders, as well as vitamin D analogues.[6] In order to optimize calcium and phosphate balance, non-calcium containing phosphate binders are employed, the frequency of haemodialysis is increased and a low calcium or calcium-free dialysate is used.[7] Hyperparathyroidism is another treatment target. Urgent parathyroidectomy has been used with some success. Sodium Thiosulphate (STS) has been used in calciphylaxis successfully.[6,8] The mechanisms of its action remains unclear, however it may lower the calcium-phosphate product by binding to calcium to form calcium thiosulfate, a highly soluble calcium salt.[9] Cessation of new lesion formation along with complete or partial wound healing and reduction in the size of subcutaneous plaques have been reported with the use of STS.[9] There is no clear guidance about the appropriate duration of therapy, but most suggest continuing it until lesions have healed completely, and the course is often extended for several weeks or months thereafter in an effort to prevent recurrence.[8] The swift and often complete relief of otherwise intractable pain achieved with STS treatment, along with its favourable side effect profile, appears reason enough to justify its use even when the extent and severity of calciphylaxis lesions and the overall condition of the patient make the situation apparently unsalvageable.[9]

In conclusion, calciphylaxis is a multifactorial and usually fatal condition. There are few case reports of this rare syndrome in SLE.[10] Awareness of this morbid syndrome will likely lead to prevention, early diagnosis and appropriate treatment.

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