

Case Report

Calcinosis cutis in systemic sclerosis: a conundrum

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ABSTRACT

Calcinosis cutis (CC) is an autoimmune disorder that presents with a wide range of systemic manifestations. Respiratory and gastrointestinal tracts along with skin are affected. Skin manifestations can progress to significant deformities, causing discomfort to patients severely affecting quality of life. Management of patients with Scleroderma requires a multidisciplinary approach in order to attain the best possible outcomes. Wound care is not yet standardized and multiple approaches exist with varying degrees of success. Surgical approaches vary based on anatomical location along with the depth and area of the wound. It is imperative to provide continuity of care with this patient population. If there is not adequate communication with regards to expectations, the disease burden may progress and ultimately prolong patient treatment. We presented the case of a 65 year old female with scleroderma that is followed within our wound care clinic for long term care of cutaneous lesions. Wound healing varied throughout the duration of treatment with moderate success seen with the use of wound vac therapy.

Keywords: Calcinosis cutis, Scleroderma, Wound care

INTRODUCTION

Scleroderma is a connective tissue disorder with a complex and largely unclear pathogenesis. Diffuse forms develop systemic sclerosis with systemic manifestations, internal organ involvement and increased mortality. limited cutaneous systemic sclerosis (LCSSc), previously known as CREST syndrome, is a constellation of symptoms including cutaneous manifestation such as CC, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia. CC affects at least one quarter of patients with scleroderma and is associated with digital ulcers, acro-osteolysis, positive anticentromere antibody, positive anti-PM/Scl antibody and dysregulation of bone matrix proteins as potential mechanisms.¹ CC itself has been classified as dystrophic, metastatic, iatrogenic and idiopathic. Treatment of CC focuses on the use of anti-rheumatic drugs that limit the immune-mediated inflammatory response of the system affected, and the surgical management presents a unique challenge due to the lack of standardized approaches. In a

cross-sectional study, comparing clinical characteristics of SSc patients with (SSc-calcinosis) and without calcinosis (SSc-control), limited cutaneous scleroderma was more common (54%) in the calcinosis group. Longer disease duration and osteoporosis remained independently associated with calcinosis.² Treatment modalities depend on anatomical location and can range from surgical debulking and wound care for lower extremities, to flap reconstruction and carbon dioxide laser use in cases with severe hand pathology. Our case report highlighted the lack of standardized approach in LCSSc, the limitations of pharmacotherapy and surgical management for improved and sustained outcomes.

CASE REPORT

A 65 year old Hispanic female with a 10 year history of scleroderma and past surgical history significant for right index distal phalanx amputation, presented at the wound clinic in January 2013 with two painful right anterior leg ulcers of three months duration (Figure 1). The wound

measured 2 cm by 0.5 cm, length and width respectively, notably containing calcium deposits. The patient's serum calcium and phosphorus levels were within normal limits as well as her renal function, likely suggestive of dystrophic calcification. Initial imaging studies, bone biopsy and wound culture were negative. She underwent weekly debridements, removal of calcium deposits, topical agents were used and colchicine was added to her treatment regimen of nifedipine, nexium and reglan. Patient showed significant worsening of right proximal tibial lesion at the one year mark despite multiple attempts at debridement (Figure 2). The patient subsequently developed localized wound infections and a left elbow ulcer over the following year. After 23 months her wounds healed and she remained ulcer free for the following two years. In 2016, new systemic manifestations of scleroderma included weight loss, dysphagia and pulmonary insufficiency with required supplemental oxygen therapy. She returned to the wound clinic with four new bilateral lower extremity ulcers, containing calcium deposits, with delayed healing. Despite multiple surgical debridements, increased colchicine dosing and additional medications such as prednisone, sildenafil, zocor, topol and letairis, her clinical condition worsened. She developed multiple systemic sequelae of scleroderma including pulmonary hypertension, congestive heart failure, severe dysphagia. Her last clinic visit in April 2018 showed marked improvement in right tibial ulceration (Figure 3) yet she was ultimately lost to follow up in May 2018.



Figure 1: First clinic encounter 30 January 2012.



Figure 2: 18 March 2013.



Figure 3: Last clinic encounter 16 April 2018.

DISCUSSION

CC is a rare disease. It is distinct from osteoma cutis (OC) or cutaneous osteoma, a benign condition defined as the eruption of an osseous structure in the skin, arising from membranous ossification without cartilage as a precursor.³

The formation of calcified deposits is based on the presence of initial tissue insult and serum levels of calcium and phosphorus. In dystrophic CC, tissue damage leads to the release of phosphate-binding proteins by dying cells. Binding of phosphate leads to calcification, chronic inflammation and vascular hypoxia. Autoimmune connective tissue disorders (ACTDs) such as systemic sclerosis, dermatomyositis and systemic lupus sclerosis are associated with dystrophic CC located most commonly in the lower extremities.

This differs from metastatic calcification in which salt deposits form in the presence of elevated calcium and phosphorus. These salts precipitate when calcium phosphate exceeds $70 \text{ mg}^2/\text{dl}^2$. The most common cause of was chronic kidney failure. Other less common sources were sarcoidosis, milk-alkali syndrome and malignancy.

Idiopathic CC resulted from calcium salt deposition without any underlying tissue injury, while calcium and phosphorus levels were also normal. Iatrogenic CC was seen in patients that received calcium or phosphate containing substances such as IV calcium gluconate, calcium chloride and para-aminosalicylic acid during the treatment of pulmonary tuberculosis. Other causes include tumor lysis syndrome and calcinosis cutis after transplant surgery. Iatrogenic CC had also been described.

Iatrogenic CC had been described at the site of placement of calcium-containing electrode compounds for electromyographic or electroencephalographic examination and at the location of extravasated peripheral infusion of intravenous calcium-containing solution. Typically extravasations led to abrupt symptoms of

erythema, tenderness, induration and edema, however, subclinical extravasations may lack these initial symptoms and still present with calcinosis. It developed within two weeks as yellow-white papules, plaques or nodules with possible tissue necrosis or ulceration.⁴

Some classified calciphylaxis as the fifth subtype of calcinosis.⁵ Also called calcific uremic arteriopathy, it was found in patients with renal failure as a net-like or mesh-like network of small vessel calcification affecting the dermis or subcutaneous fat.⁶

The pathophysiology of calcinosis cutis remained poorly understood. There was some consensus around vascular hypoxia and chronic inflammation being seen as a nidus for dystrophic calcification.⁷⁻⁹ Ultimately, these calcific deposits can erode through the dermis resulting in the exudation of chalky deposits through patient's skin, increasing the risk for infection.⁶

The presence of calcium within the wound bed served to upregulate the presence of inflammatory markers, leading to infection, increased wound exudate and impaired healing.¹² The presence of localized alkaline phosphatase (ALP) elevations led to hydrolysis of extracellular pyrophosphates, which usually inhibited calcium deposition.¹³ Further analysis of patients with ACTDs suggested that phosphate bound to necrotic injured cells can serve as a nidus for dystrophic calcification.¹⁴ Inflammatory markers also played some role. IL-1 was seen to be elevated within juvenile dermatomyositis patients with calcinosis. Whereas IL-6, IL-8 and TNF-alpha were elevated within calcium laden fluid collections characteristic within juvenile dermatomyositis patients. These findings supported the role that macrophages play in the proliferation of this disorder.¹⁵

Plain radiography had been shown to be very sensitive in detecting calcinosis. It was recommended as the initial imaging modality in patients with ACTD.¹⁶ A novel scoring system had been developed in patients with hand manifestations of systemic sclerosis. This system scored the burden affecting the hands taking into the area covered, density, number and anatomic locations of calcinosis lesions.¹³ Increased enhancement was observed after the administration of intravenous gadolinium contrast on the MR scan believed to be due to increased vascularity derived from an inflammatory foreign body type reaction.⁶ Cytological findings can help make the diagnosis of CC. An FNA can identify whitish granular material, Papanicolaou and hematoxylin and eosin-stained smears showed pauci-cellularity and crystalloid background with occasional multinucleated cells and a few histiocytes. Alcohol-fixed smears subjected to von Kossa silver stain confirm the presence of calcium deposits.¹⁷

Treatment of calcinosis cutis of systemic sclerosis was challenging and authors suggested that pharmacotherapy should be continued for months to years. No randomized

clinical trial had provided guidelines, the evidence-based literature has relied mostly on case reports, hence a wide variety of agents have been used. CC can be treated with pharmacotherapy, surgical or combined therapy based on the clinical characteristics. Response to therapy was categorized as complete in case of total resolution of the lesion with no recurrence of the healed lesion, partial response in case of regression or recurrence of the healed lesion and no response in case of persistence or progression of the lesions.⁵

Robert et al in their retrospective review of 34 cases of CC over 13 years of experience, recommended calcium channel blockers namely diltiazem as the first line with surgical excision of solitary, painful lesion as they worked by decreasing intracellular calcium influx in affected tissues along with local macrophage infiltration, reducing the formation and crystallization of a calcium nidus. Bisphosphonates also worked by altering macrophage function.⁵ They inhibited macrophage proinflammatory cytokine production, reduced bone resorption and decreased circulating relative serum calcium levels. Vitamin K was also known to impact the calcium-binding process and calcinosis when abnormally elevated and the use of warfarin may help in the management of small, calcified deposits. Monoclonal antibodies have also shown some promise with the use of infliximab (anti TNF-alpha) and rituximab (anti CD-20) therapies.

Targeting the inflammatory process with colchicine, minocycline, probenecid, ceftriaxone and intravenous immunoglobulin (IVIG) have been used with clinical improvements cited in case reports. Aluminum hydroxide decreases phosphate levels and reduces the size and symptoms of calcified lesions. Intra-lesional corticosteroids have also alleviated the symptoms of inflamed calcified lesions. Sodium thiosulfate in zinc oxide has been administered topically with success in dystrophic calcinosis, likely due to its vasodilatory, anti-inflammatory effects and increases solubility of calcium hydroxide.

Considering the side effects of pharmacotherapy, surgical therapy may also be applied for early, solitary lesions. Extracorporeal shock-wave lithotripsy for pain control, and some success has been found using carbon dioxide laser therapy and myocutaneous flaps for hand lesions. Reports exist in the literature of wide *en bloc* surgical excision with primary closure or negative pressure wound therapy for lower extremity lesions.^{10,11} In our patient, the location of the CC over the anterior leg limited the area of excision and she underwent bimonthly surgical debridement with removal of the calcium deposits.

CONCLUSION

The management of LCSSc, formerly known as CREST syndrome, is medical in nature but patients must be informed early on about the potential development of CC

and subsequent skin ulcers, which may require surgical intervention. More research is needed to highlight triggers to subsequent inflammatory processes and calcification deposits. Despite combined pharmacologic and surgical therapy, worsening episodes and recurrences of CC can often parallel the progression of the systemic disease, representing an additional hurdle to an already heavy burden of disease. Ultimately, a patient-tailored approach is needed in order to provide longer disease-free intervals and improve patients' quality of life.

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