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Resolution of SLE-related soft-tissue calcification following haematopoietic stem cell transplantation

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Abstract

Background. Calciphylaxis and calcinosis can both cause severe morbidity and mortality in patients with systemic lupus erythematosus (SLE). Haematopoietic stem cell transplantation (HSCT) has been successfully used to treat patients with refractory SLE. It was hypothesized that in calciphylaxis and calcinosis, ongoing inflammatory activity contributes to the calcium deposition in the media of small arteries, as well as perivascular and periarticular tissues. We report three patients whose soft-tissue calcification syndromes dramatically resolved after undergoing HSCT.

Methods. Three patients referred for refractory SLE underwent HSCT at a tertiary care medical center. SLE serologies and clinical features before and after HSCT were recorded.

Results. Despite receiving >6 months of intravenous cyclophosphamide (CYC), three SLE patients showed signs of persistent lupus activity, including severe soft-tissue calcification. The first patient was on haemodialysis and developed severe calciphylaxis with large ulcers and tissue necrosis. The second patient had calcinosis, with palpable crystals extruding from ulcers. The third patient had calcinosis characterized by subcutaneous nodules and plaques. Because prior conventional therapies had failed, the three were treated with high-dose CYC, anti-thymocyte globulin and HSCT. They have been followed post-HSCT for 26–38 months, with excellent clinical responses, including sustained resolution of skin abnormalities.

Conclusions. The successful treatment of advanced calcium deposition by aggressive immune ablation underscores the contribution of SLE-mediated inflammation to soft-tissue calcification syndromes.

Keywords: calcinosis; calciphylaxis; haematopoietic stem cell transplantation; systemic lupus erythematosis

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Introduction

Deposition of calcium and phosphate salts in extra-skeletal locations is associated with a number of metabolic and inflammatory disorders [1]. The types of soft-tissue calcification that occur most commonly are calciphylaxis and calcinosis. Both conditions are difficult to treat, and are associated with significant morbidity and mortality.

Calciphylaxis is a disorder that predominantly occurs in end-stage renal disease (ESRD). The incidence of calciphylaxis in haemodialysis patients has been reported as ∼4% [2]. Patients develop painful skin lesions with ulceration and necrosis [3]. Histologically, the medial elastic lamina of small arteries becomes calcified, resulting in ischaemia [4,5]. The lesions begin as painful, bland or violaceous areas in the extremities, then enlarge, ulcerate and necrose. These lesions are associated with high morbidity and mortality due to infection [3].

The term 'calciphylaxis' was coined to describe an experimental animal model of soft-tissue calcification, thus implying a systemic immune-mediated mechanism underlying the mineral deposition [6]. The term calciphylaxis was applied to humans on dialysis with arterial calcification, in part because chronic inflammation is often present. However, the animal model is not ideal, since the animals do not develop the arterial calcification that is characteristic of the human disorder. As a result, some have suggested that a better term for calciphylaxis would be calcific uraemic arteriopathy [7]. Despite its limitations, calciphylaxis is the term we use in this report because its use is so widespread.

Calcinosis, also known as dystrophic calcification, is a distinct type of extra-skeletal calcification, which has been described in inflammatory connective-tissue diseases, including SLE, scleroderma and dermatomyositis [8]. In contrast to calciphylaxis, calcinosis is usually not associated with calcium and phosphorus abnormalities or an ischeaemic process. Calcinosis typically occurs in the extremities, and may range from limited, small subcutaneous nodules to widespread deeper deposits that are often

Table 1. Summary data of three SLE patients with soft-tissue calcification. All laboratory results were taken at the time of HSCT

Patient	Duration of SLE[a]	Location of calcification	Renal function	Type of calcification	Indications for HSCT	Ca/P (mg/dl)	C3/C4 (mg/dl)	PTH (pg/ml)
Patient 1	6 years	Bilateral proximal and distal upper and lower extremities	ESRD	Calciphylaxis	Calciphylaxis	9.0/4.7	63/11	230
Patient 2	7 years	Bilateral calves, upper arms and shoulders	GN WHO III GFR >100	Calcinosis	Cutaneous vasculitis and cerebritis	8.6/4.1	60/15	31
Patient 3	13 years	Bilateral arms, legs, buttocks, and thighs	GN–GFR >100	Calcinosis	Cutaneous vasculitis	9.4/3.8	166/34	Not available

[a]Years between diagnosis and HSCT.

periarticular [8]. While there is a temporal correlation between the chronic inflammatory state and soft-tissue calcification in SLE, it is not known why some SLE patients develop calcinosis and others do not.

In treating patients with severe and refractory manifestations of manifestations of SLE with HSCT at Northwestern University [9–11], we included one patient with calciphylaxis and two with calcinosis (Table 1). All three patients were previously treated with intravenous CYC and prednisone with some clinical improvement, but had persistent and severe soft-tissue calcification, as well as active lupus in other organ systems. Despite standard measures such as controlling serum calcium, phosphorus and PTH, the calciphylaxis lesions on the first patient did not improve. Given the large areas of soft-tissue calcifications in all three patients, surgical resection was not an option.

HSCT has been successfully used to treat refractory SLE [9–11]. Aggressive leukocyte depletion and infusion of autologous haematopoietic stem cells allow repopulation of the bone marrow with naïve stem cells, and subsequent expansion of normal lymphocyte clonal diversity and remission of lupus in a majority of patients [10]. Since calcinosis in the setting of lupus appears to be promoted and maintained by a leukocyte-mediated inflammatory state, we hypothesized that controlling the activity of underlying SLE would help arrest or reverse the tissue calcification. We report here that each of the three SLE patients with disabling and life-threatening calcifications had successful resolution of these lesions after HSCT.

Methods

Three patients with soft-tissue calcification fulfilled the following inclusion criteria prior to HSCT [9,10]: (1) at least 4 of 11 American College of Rheumatology (ACR) criteria for SLE; (2) failure to sustain SLE remission after monthly IV pulse CYC and corticosteroids; (3) failure of IV CYC to control CNS, pulmonary, cardiac or mucocutaneous manifestations. Each patient signed a Food and Drug Administration (FDA) and Investigational Review Board (IRB)-approved consent form in order to enter this single-arm Phase II trial. During the haematopoietic stem cell procurement phase, the peripheral blood stem cells were mobilized with CYC and subcutaneous G-CSF. Following the successful harvest of peripheral stem cells, the patients were admitted to the transplant unit and CYC 50 mg/kg/day × 4 days and ATG 30 mg/day × 3 days were then infused as the conditioning regimen. All patients

received prophylactic antibacterial, antiviral and antifungal therapy during and after HSCT. The details of the protocol have been previously published [9].

Results

Patient 1

Patient 1 presented with inflammatory polyarthritis at age 15. She was diagnosed with SLE and treated with prednisone and hydroxychloroquine. The following year she developed diffuse proliferative lupus nephritis. This prompted initiation of monthly IV CYC, which was continued for 18 months. When CYC was discontinued, it was followed by four additional months of mycophenolate mofetil (MMF). Despite appropriate therapy including MMF, in the third year of disease her lupus flared and renal function declined. She received two additional months of IV CYC without significant effect. The patient was admitted to hospital with a dilated cardiomyopathy, a left ventricular ejection fraction of 15%, fluid overload and pulmonary hypertension. An echocardiogram showed a large thrombus in the left ventricle. Blood testing revealed the presence of antiphospholipid antibodies. The patient initiated both warfarin therapy and haemodialysis during this admission. Her cardiomyopathy improved over time with medical management, and the thrombus resolved on warfarin. Six months later she began peritoneal dialysis. Poor compliance with phosphate binders and relatively poor clearance resulted in hyperphosphataemia and severe hyperparathyroidism. After 3 months of peritoneal dialysis, she returned to haemodialysis.

On haemodialysis, calcium, phosphorous and PTH of Patient 1 markedly improved. Nevertheless, 5 months later, she developed severe burning pain in both thighs and these areas became violaceous. Despite early initiation of wound care and antibiotics, over several weeks her legs developed large and deep ulcerations with central necrosis. A punch biopsy of a thigh lesion revealed panniculitis with associated calcification of small and medium sized arteries, consistent with calciphylaxis (Figure 1). These ulcerative lesions caused recurrent fevers and required prolonged hospitalizations. Despite discontinuation of warfarin and initiation of hyperbaric oxygen treatment, the ulcerations continued to widen and deepen, causing escalating IV narcotic requirements over the ensuing 8 weeks. She was referred for hospice care.

Because standard therapies failed, the patient's nephrologist referred her for HSCT and she had an excellent clinical
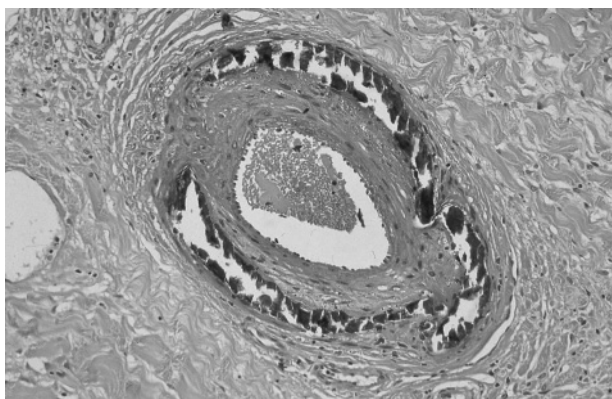
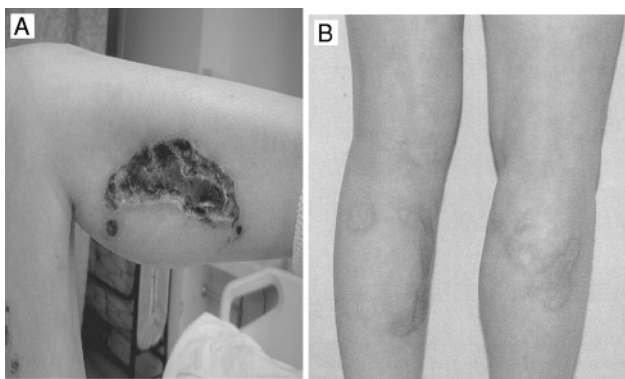**Fig. 1.** Biopsy of Patient 1 revealing medial calcium deposition.

Fig. 2. Patient 1 before (**A**) and 18 months after (**B**) stem cell transplant.

Fig. 3. SLE serologies before and after HSCT. (**A**) Anti-dsDNA titer of Patient 1. (**B**) Anti-dsDNA titer of Patient 2. (**C**) ANA titer of Patient 3 (anti-dsDNA undetectable at all time points).

and serological response. Photographs of her leg lesions before and 18 months after stem cell transplant are shown in Figure 2. Patient 1's dsDNA titers before and after HSCT are shown in Figure 3A. She was discharged from the hospital on a tapering dose of prednisone and continued wound care, and she came off prednisone entirely after 8 months. Twelve months after HSCT, she underwent kidney transplantation from a sibling donor. Two years later, her only immunosuppression is tacrolimus. She has residual scars, but no ulcerations or wounds at the sites of prior calciphylaxis. She requires no narcotic analgesia and has a normal performance status.

Patient 2

Patient 2 presented at age 35 with a decline in neurocognitive function, profound fatigue, myalgias and progressive exercise intolerance. Serological testing confirmed SLE. She was managed with hydroxychloroquine, glucocorticoids and azathioprine. Despite these therapies, over the following 4 years she experienced recurrent fevers, musculo-skeletal pain and fluctuations in mental status, leading to disability. The following year she developed acute pneumonitis and increasing proteinuria. She next developed diffuse ulcerations on both of her calves, associated with painful crystal deposition within the ulcerations. She became confused and lethargic and was hospitalized with nephrotic r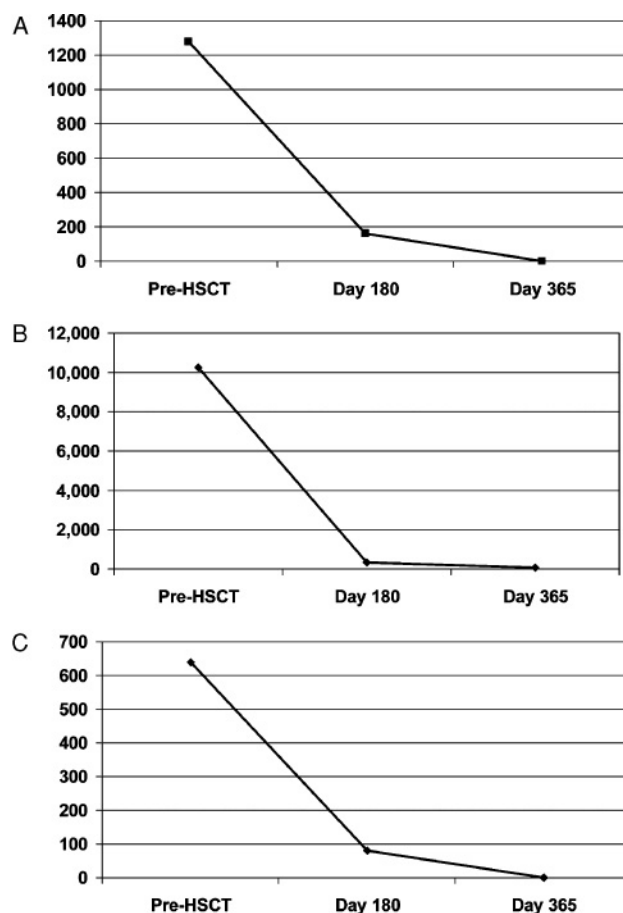ange proteinuria. She was started on monthly intravenous CYC, and over the next 6 months her mental status improved, but the areas of skin ulceration remained open and exudative. Over the next several months, she experienced worsening proteinuria (8.1 g/24 h). A kidney biopsy revealed diffuse proliferative glomerulonephritis and ultrasound revealed renal calculi.

She was self-referred for stem cell transplantation. The ulcerative calcinosis was treated for 4 weeks with topical medications and whirlpool baths, to facilitate removal of crystals from the ulcers. The crystals in her wounds were found to be 100% calcium phosphate with no nidus. Wounds were culture negative. In anticipation of undergoing HSCT, she received a mobilization dose of CYC (2 g/m^2). Despite developing neutropaenia, her wounds improved and granulated. On Day 20 following HSCT, she was discharged. She was tapered off prednisone over the following 10 months. Photographs of her wounds at the time of diagnosis, and 1 year post-HSCT are shown in Figure 4. Patient 2's dsDNA titers in response to HSCT are shown in Figure 3B.

Patient 3

Patient 3 presented at age 17 with cutaneous lupus vasculitis, cerebritis and myocarditis. Initially, she was treated with glucocorticoids, hydroxychloroquine and azathioprine. Her
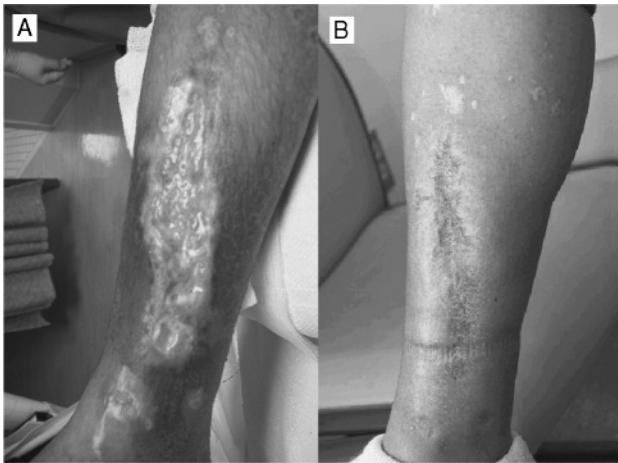
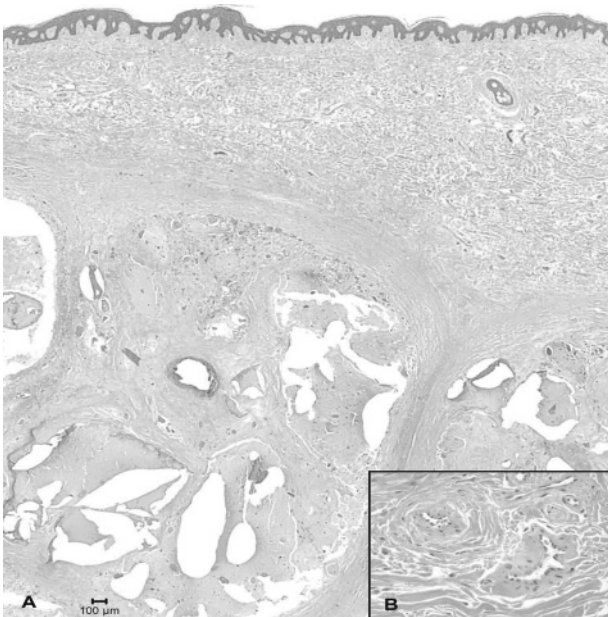**Fig. 4.** Patient 2's right medial calf before (**A**) and 1 year after (**B**) HSCT.

Fig. 5. Patient 3's biopsy of calcinosis universalis, showing dermal calcium deposition (**A**), without vessel deposition (inset **B**).

symptoms progressed, however, and she began to take daily oral CYC. Her myalgias and cutaneous vasculitis were resistant to therapy. By age 25, despite taking 1 mg/kg of prednisone and oral CYC daily, she developed large, coalescent areas of subcutaneous calcium deposition. Calcifications were mostly bilateral, on the thighs, arms and flanks. She began monthly intravenous CYC, and after 6 months, the calcinosis improved dramatically. However, within 1 year of discontinuing IV CYC, the cutaneous disease again worsened. Many of the areas of calcification were ∼1 cm in size, and when exposed dermis healed, hyperpigmented scars remained. However, larger calcium deposits were 12–16 cm in diameter, and were painful and disfiguring. Periarticular nodules ranging from 1 to 5 cm emerged along the upper arms, lower legs, buttocks and thighs. SLE34 was self-referred for HSCT therapy. A biopsy of her tumoural calcinosis is shown in Figure 5.

The patient experienced a marked improvement in several areas of calcinosis after receiving the mobilization dose of CYC (2 g/m^2). A large area of indurated calcium deposition measuring 10 × 12 cm at the right flank completely resolved over the following 4 weeks. She completed her conditioning regimen and HSCT without bacteraemia or significant toxicity. Figure 6 shows her right arm before and 1 year after HSCT. Patient 3's ANA titers in response to HSCT are shown in Figure 3C. She has been tapered off all immune suppressive medications 1 year post-HSCT. She underwent surgical resection of the only large, remaining area of calcium deposition and has remained free of any new depositions in the post-transplant period.

Discussion

SLE patients have multi-organ involvement related to their chronic inflammatory, autoimmune disease. Calciphylaxis and calcinosis are manifestations of SLE that may be associated with significant morbidity and mortality. Features that distinguish calciphylaxis include the violaceous, painful presentation of lesions, skin necrosis, the presence of intact distal pulses and the characteristic arteriolar medial calcification [4,5]. Risk factors for the development of calciphylaxis include hyperparathyroidism, hyperphosphataemia, high calcium–phosphate product, hypoalbuminaemia and obesity [3,12,13]. In contrast, calcinosis

Fig. 6. Patient 3: right arm with calcinosis universalis before (**A**), and 1 year after (**B**) HSCT. Discoloration persisted, but many tumoural calcinoses resorbed and no new lesions developed.

occurs in the absence of altered mineral metabolism, in areas of cutaneous inflammation or damaged tissues, and histologically shows calcium deposits with dermal infiltration of lymphocytes [14,15]. Calcinosis is disfiguring and painful, but it is not associated with tissue ischaemia or gangrene.

Despite differences in clinical presentation and histology between calciphylaxis and calcinosis, abnormalities in the regulation of tissue mineralization have been implicated in both conditions. Patients with calciphylaxis commonly have an elevated calcium–phosphate product and some degree of uraemia [16,17]. In response to elevated calcium and phosphate levels, vascular smooth muscles cells (VSMC) undergo phenotypic changes that promote matrix mineralization. In response to uraemia, VSMCs secrete the osteoblast differentiation factor Cbfa1 as well as alkaline phosphatase, type I collagen and osteopontin [18]. Thus, VSMCs transform into osteoblast-like cells and increase the mineralization of tissues and vessels. Matrix gamma carboxyglutamic acid protein (Gla protein), also synthesized by VSMCs, is a major local inhibitor of vascular calcification [19,20]. Since matrix Gla protein requires vitamin K-dependent gamma carboxylation for biological activity, inhibition of vitamin K by warfarin can shift the balance toward calcification. This effect is markedly enhanced by vitamin D experimentally [21]. Clinically, warfarin has been implicated in the development of calciphylaxis [22], as may have been the case for Patient 1.

Less is known about the pathophysiology of calcinosis. Most calcinosis described in SLE patients occurred at sites of prior cutaneous inflammation [23]. Tissue injury, inflammation and diuretic use may produce an alkaline environment, allowing calcium precipitation and the activation of alkaline phosphatase, which both contribute to the pathogenesis [10,15,24]. Tissue damage is often followed by deposition of type I collagen matrix, which can serve as a site for further calcium precipitation [25–27]. Administration of vitamin D may worsen ectopic calcification in SLE patients and may overburden matrix Gla protein inhibitory activity [28–30].

Some of the extensive data demonstrating the role of inflammation in producing atherosclerosis in the general population and in SLE may also be relevant to understanding calcinosis and calciphylaxis [31,32]. Production of cytokines such as IL-6 and TNF-α can be atherogenic [33]. Subsequent vascular damage activates osteogenic cells, particularly osteoblasts, osteoclasts and chondrocytes, which can also be atherogenic [34]. In addition, pooled B lymphocytes from SLE patients have been shown to induce bone reabsorptive activity. This bone reabsorptive activity is enhanced with IL-1 and is inhibited by antibody to IL-1, suggesting that regional demineralization of bone may be an important consequence of inflammation [35]. The calcium release from bones leads to the formation of basic calcium–phosphate product, which may also contribute to calcification. Fetuin A (alpha 2 Schmid Heremans glycoprotein), a systemic inhibitor of vascular calcification, facilitates the formation of soluble calciprotein particles and limits the formation and expansion of hydroxyapatite crystals [36]. Fetuin A is downregulated during an inflammatory process [37]. The persistent systemic inflammatory response observed in ESRD patients correlates with low Fetuin A levels and associated atherosclerosis [38,39].

Conventional therapeutic options for the treatment of calciphylaxis include lowering the calcium–phosphorus product with non-calcium-based phosphate binders [40], parathyroidectomy [41], cinacalcet [42] and aggressive dialysis clearance [43]. There are some case reports of successful resolution of calciphylaxis with sodium thiosulfate [44] and hyperbaric oxygen therapy [45]. Treatment options for calcinosis are even more anecdotal [8]. Therapies for both calcification syndromes are limited by the lack of controlled clinical trials.

Clinical and experimental models of calcification syndromes and atherosclerosis suggest a number of potential mechanisms by which inflammation might contribute to both calciphylaxis and calcinosis. A single prior report documents resolution of calcinosis in a child with autoimmune disease treated with autologous stem cell transplantation [46]. Although our three patients did not undergo HSCT primarily to treat their calcifications, these mechanisms provide plausible explanations for why their skin lesions responded so dramatically along with remission of systemic lupus activity.

Despite the many reports of potential treatments for soft-tissue calcification syndromes, none have high success rates. Our data are preliminary and HSCT has too much potential toxicity to be routinely recommended for therapy of calciphylaxis or calcinosis. However, the high morbidity and mortality of these SLE-related calcification syndromes justify a continued search for improved therapies. The efficacy of steroids has been questionable, possibly because of adverse effects on wound healing and mineral metabolism, and possibly because the immunosuppressive effects are not sufficiently strong. However, the striking benefits of HSCT in three patients with calcification syndromes are consistent with an important role for inflammation in their pathogenesis. Our results suggest that immunosuppressive strategies may hold promise for future therapy.

Conflict of interest statement. None declared.

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