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Calcinosis Cutis Related to Sclerodermatous Chronic Graft Versus Host Disease

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We present the case of a 54-year-old woman who had calcinosis cutis related to sclerodermatous chronic graft versus host disease. Graft versus host disease had developed following stem cell transplantation for acute myelogenous leukemia 14 years earlier, but was shown by skin biopsy to have resolved by the time of presentation. Radiographs showed extensive cutaneous calcifications in the lower extremities.

Introduction

Calcinosis cutis, or calcification of the skin, is a radiologic finding that is associated with a variety of conditions. We present a case of calcinosis cutis that was related to sclerodermatous chronic graft versus host disease (GVHD).

Case Report

A 54-year-old woman presented with bilateral foot pain. Fourteen years earlier, at age 40, she was treated for acute myelogenous leukemia by myeloablative peripheral stem cell transplant from her HLA-matched sister. Two years later, at age 42, she was diagnosed with GVHD involving multiple organs, including the joints, liver, mouth, vagina, eyes, lungs and skin. She was initially treated with prednisone and cyclosporine for immunosuppression, but these were discontinued within the year due to depression and adequate control of her GVHD. One year later, at age 43, she was noted to have a reprisal of her GVHD manifested by tightening and thickening of the skin over her arms, hands, legs, and feet. A diagnosis of sclerodermatous GVHD was confirmed by skin biopsy. Immunosuppressive therapy was re-started with tacrolimus. Cellcept was later added due to progression of her scleroderma with new onset of joint contractures. These medications were discontinued due to lack of subjective improvement and azathioprine was started at age 46. Azathioprine was discontinued three years later, at age 49, and subsequent skin biopsies have not shown evidence of GVHD, though her sclerodermatous skin changes have not resolved.

The patient stated that, over the past year, she had had pain in her feet from a progressive loss of the fat pads of her soles. She also noted a loss of fat in her calves and thighs. Review of her past medical history included insulin dependent diabetes mellitus, neuropathy

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Abbreviations: GVHD, graft versus host disease

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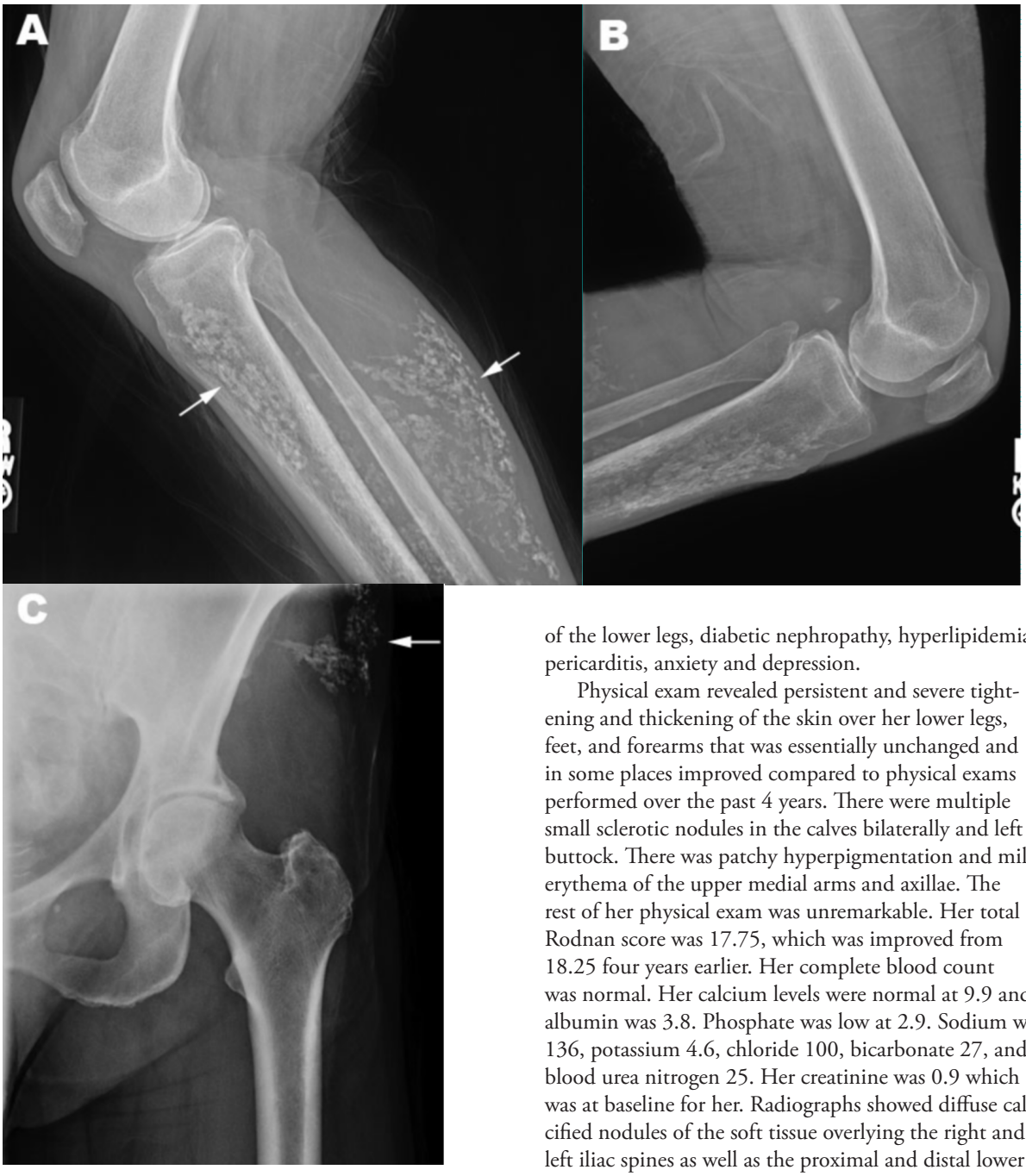

Figure 1. 54-year-old woman with calcinosis cutis and sclerodermatous graft versus host disease. Radiographs of the right lower leg (A), left lower leg (B), and left hip (C) show calcifications in the skin (arrows), some of which overlie the bones.

of the lower legs, diabetic nephropathy, hyperlipidemia, pericarditis, anxiety and depression.

Physical exam revealed persistent and severe tightening and thickening of the skin over her lower legs, feet, and forearms that was essentially unchanged and in some places improved compared to physical exams performed over the past 4 years. There were multiple small sclerotic nodules in the calves bilaterally and left buttock. There was patchy hyperpigmentation and mild erythema of the upper medial arms and axillae. The rest of her physical exam was unremarkable. Her total Rodnan score was 17.75, which was improved from 18.25 four years earlier. Her complete blood count was normal. Her calcium levels were normal at 9.9 and albumin was 3.8. Phosphate was low at 2.9. Sodium was 136, potassium 4.6, chloride 100, bicarbonate 27, and blood urea nitrogen 25. Her creatinine was 0.9 which was at baseline for her. Radiographs showed diffuse calcified nodules of the soft tissue overlying the right and left iliac spines as well as the proximal and distal lower legs (Fig. 1). Biopsies of the skin from her thigh, arm, and buttock were performed shortly after the current visit and showed fibrosis and calcifications, indicative of calcinosis cutis, but no evidence of active GVHD.

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Discussion

Calcinosis cutis is a condition characterized by calcium deposits in the dermis or hypodermis [1]. There are four types of calcinosis cutis based on etiology: dystrophic, metastatic, idiopathic, and iatrogenic. Dystrophic calcinosis cutis is the most common form and occurs in abnormal tissue with normal serum calcium and phosphate levels. The exact mechanism of calcification is unknown. Dystrophic calcinosis is associated with connective tissue disease such as systemic lupus erythematosis, dermatomyositis, and systemic sclerosis as well as devitalized tissue from trauma or infection.

Metastatic calcinosis is characterized by elevated serum calcium and phosphorous levels in the presence of normal, undamaged tissue. Diseases associated with metastatic calcinosis include malignancy, hypervitaminosis D, hyperparathyroidism, milk-alkali syndrome, paraneoplastic hypercalcemia, sarcoidosis, chronic renal failure, and destructive bone disease [2]. Idiopathic calcinosis occurs in the setting of normal tissue and normal serum and phosphorous levels. This type of calcinosis has been observed in childhood disorders like Down syndrome, idiopathic calcinosis of the scrotum, and subepidermal calcified nodule of Winer [3]. Iatrogenic calcinosis typically occurs secondary to intravenous calcium chloride or calcium gluconate therapy for hypocalcemia [4].

There are a number of diseases that can affect the skin post allogenic bone marrow transplant. The most common is acute graft vs. host disease, which occurs in 50-80% of bone marrow transplant patients. The incidence of chronic graft vs. host disease, defined as GVHD that persists beyond or begins 40 days after bone marrow transplant, is 30-50%. Skin involvement in chronic GVHD is reported to occur 90-100% of the time [4]. Other common skin problems post-bone marrow transplant include infections related to immunosuppression with bacteria, fungi, protozoa, or viruses such as human papilloma virus (molluscum contagiosum, and verruca vulgaris). Medication side effects can cause allergic rashes, skin pigmentation, and petechiae. Immunosupppressed patients are also at increased risk of malignancy [5].

The most common skin manifestations of acute GVHD include erythema, hyperpigmentation, and desquamation of the axillae and groin, which occurs in about 55% of patients who have acute GVHD with skin involvement. Erythematous maculopapular eruptions occur in about 29% of these patients. Chronically, lichenoid GVHD is the most common skin lesion. It is characterized by plaques that are purple or violet in color, which can be difficult to differentiate from lichen planus. Sclerodermoid GVHD is characterized by skin sclerosis and fibrosis. It has been reported to occur in about 11% of allogenic bone marrow transplant patients at a median time of 15 months after transplant. While sclerodermatous GVHD shares many of the same features of systemic sclerosis, Raynaud's phenomenon, calcinosis, and Scl-70 and anti-centromere antibodies are virtually always absent [6-7].

As mentioned above, dystrophic calcification is most commonly found in patients with rheumatic diseases, such as scleroderma, dermatomyositis, and systemic lupus erythematosus as well as tissue damaged by infection or trauma. Furthermore, it is often discovered incidentally and has a predilection for the extremities and buttocks. While the mechanism of dystrophic calcification is unknown, several theories have been postulated for its development, including an imbalance between promoters and inhibitors of calcium deposition as a result of high alkaline phosphatase or acid levels in devitalized tissue, the influx of calcium into cells with damaged cell membranes, the precipitation of calcium caused by phosphate bound to denatured proteins, high mitochondrial calcium and phosphate cytosolic levels, and local tissue ischemia from tissue damage or steroid use [8]. Although calcinosis cutis is well known to be associated with systemic sclerosis and CREST syndrome, our literature search failed to locate previous reports of calcinosis cutis related to GVHD. There is, however, one reported case of calcinosis cutis post allogenic bone marrow transplant [5]. In this case, skin biopsy demonstrated no evidence of GVHD. In the absence of other identifiable causes of calcinosis, it was thought that the calcinosis was secondary to allogenic bone marrow transplant.

In the present case, normal calcium and only mildly decreased phosphorous levels make metastatic calcinosis unlikely. Moreover, while the patient had diabetic nephropathy with microalbuminuria, her baseline creatinine levels were within normal range and she showed no evidence of primary or secondary hyperparathyroidism, though her parathyroid hormone levels were not

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checked. Post-bone marrow transplant reactivation of viruses, such as HTLV1 virus, is also a potential etiology of dystrophic skin calcinosis [5]. Unfortunately, no viral work up was done. It is unlikely that acute myelogenous leukemia was responsible for the calcification as the patient had been in remission since her stem cell transplant. Idiopathic development of skin calcinosis cannot be excluded. Medication side effects from previous steroid use, chemotherapy, or antibiotic use could also have caused or contributed to the development of calcinosis. However, given the presence of calcinosis cutis in tissues affected by sclerodermatous changes, we believe this case to be secondary to tissue damage related to chronic GVHD. This may represent the first radiologically and histologically documented case of calcinosis cutis secondary to sclerodermatous chronic GVHD.

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