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Cutaneous dystrophic calcification following high-dose radiotherapy for a liposarcoma

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Abstract

Cutaneous dystrophic calcification as a late change of radiation therapy is a rarely reported finding. Initially, it was almost exclusively described as occurring on the chest wall in breast cancer patients but has since been described in several other malignancies. We describe the first reported case of radiotherapy-induced calcinosis cutis occurring at the site of a previous liposarcoma. Review of the literature including risk factors, similar cases, pathophysiology, and management is also explored.

Keywords: calcinosis cutis, liposarcoma, radiotherapy

Introduction

Cutaneous dystrophic calcinosis as a late manifestation of radiation therapy is a rarely reported change, though awareness has increased in the last 20 years following the first documentation of this phenomenon in the literature. The most commonly reported site is the chest wall, typically following radiotherapy for breast cancer. Several other anatomic sites in association with a variety of different malignant neoplasms have since been shown to exhibit this change. A thorough review of the current literature uncovered 30 reported cases. Herein, we describe the first reported case, to the best of our knowledge, concerning post-radiotherapy cutaneous calcification at the site of a previous liposarcoma of the leg.

Case Synopsis

An 80-year-old woman with a history of rheumatoid arthritis and liposarcoma on her left thigh twenty-five years prior, status-post resection with multiple rounds of radiotherapy (40Gy over 15 fractions) presented with a linear scar on her left lateral thigh associated with multiple firm erythematous nodules, one of which was ulcerated near the distal aspect of the scar (**Figure 1**). This new lesion appeared on the same site as her previously resected liposarcoma and had been present for five months prior to her appointment in the dermatology clinic. Initially, it had been diagnosed and treated by other providers as cellulitis with multiple antibiotics including cephalexin, trimethoprim sulfamethoxazole, and doxycycline, none of which helped. When the wound



Figure 1. Left lateral thigh with multiple firm nodules and prominent ulceration surrounded by erythema.



Figure 2. Extensive cutaneous calcifications are evident in this left femur x-ray image.

did not heal, imaging was obtained including a femur X-ray (**Figure 2**) and MRI showing extensive subcutaneous dystrophic calcifications and edema. Based on her presentation and imaging findings, a presumptive diagnosis of calcinosis cutis secondary to radiation therapy was made.

A punch biopsy was obtained and histopathologic examination demonstrated ulceration with dermal calcification and fibrosis, confirming the diagnosis (**Figure 3**). She subsequently underwent excisional debridement of larger calcified nodules and was started on a daily application of 10% sodium thiosulfate compounded in an oil in water emulsion, with noticeable improvement in both the external appearance of the wound and associated subcutaneous calcifications.

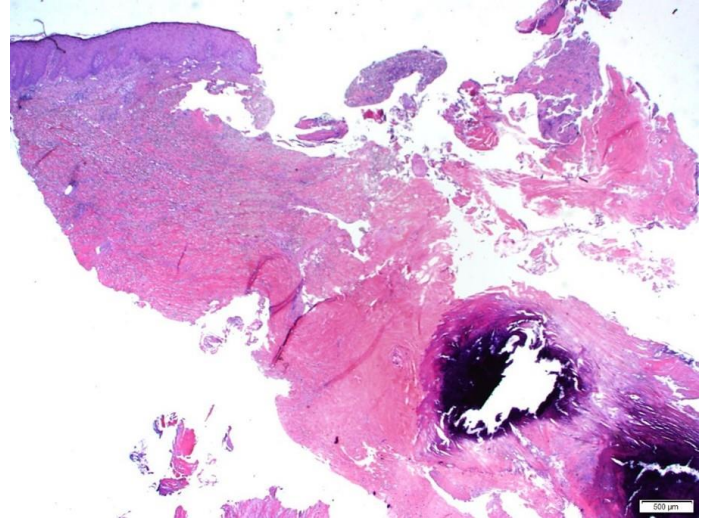


Figure 3. Dystrophic calcinosis cutis. H&E-stained punch biopsy demonstrating intradermal calcium deposits.

Case Discussion

Calcinosis cutis comes in five main subtypes: dystrophic, metastatic, idiopathic, iatrogenic, and calciphylaxis. The dystrophic subtype is most common and frequently occurs in association with connective tissue diseases, certain cutaneous neoplasms (pilomatrixoma, pilar cyst, basal cell carcinoma), and trauma (burns, surgery, keloid scars), [1,2]. Rarely, dystrophic calcification may also occur following high dose radiotherapy, usually in doses exceeding 40Gy [3-9], as a late complication; in one series it occurred an average of 19 years following radiation treatment [8]. More frequent and well-known late cutaneous complications of radiotherapy include dyspigmentation, telangiectasias, fibrosis, atrophy, ulceration, and more rarely, necrosis. Many factors have been identified as contributing to a higher risk of developing late dystrophic calcification. These include higher overall dose, higher dose per fraction, and overlapping radiation fields which deliver a larger dose to tissue caught in both areas [5]. In this case, the most significant etiologic contributor to calcinosis cutis is likely high-dose radiotherapy, although other causes, such as late post-surgical and rheumatoid arthritis-associated dystrophic calcification, could be involved as well.

The vast majority of the literature reporting on this rare phenomenon is described in breast cancer

patients who underwent high-dose radiation therapy. The first report of dystrophic calcification following radiotherapy was published in 1999 by Cowie et al. regarding a patient with breast cancer exposed to all three of the above risk factors (40Gy in 10 fractions with overlapping glancing and anterior fields). Since then, numerous additional publications have described this in association with other malignancies, including head and neck cancer [6], Hodgkin lymphoma [7], seminoma, cervical cancer, bladder cancer, endometrial carcinoma, and anal carcinoma [9]. Carl et al. also briefly mentioned an example of a 37-year-old treated with 16Gy of neutron radiation therapy to a lower extremity sarcoma but did not specify the type of sarcoma. Hence, this is the first report in the literature to focus on and fully describe a case of calcinosis cutis following radiation to a lower extremity liposarcoma. Our patient received 40Gy of radiation in relatively large fractions (>2Gy/fraction).

The pathophysiologic process of radiation-induced dystrophic calcification is poorly understood but thought to involve vascular damage, hypoxia, and cell necrosis with extrusion of calcium phosphate/hydroxyapatite deposits. Specifically, the effects of radiation directly lead to vessel wall thickening with intimal and subintimal cell proliferation, eventually resulting in fibrosis which induces local hypoxia. Local failure of cellular respiration results in calcium influx with intracellular calcium phosphate deposition. With subsequent tissue necrosis, these deposits are extruded into the extracellular environment. The local necrotic, alkaline environment, promoted by low metabolic activity, low carbon dioxide concentration, and release of alkaline phosphatase, also facilitates the precipitation of calcium phosphate crystals [2].

Treatment of calcinosis cutis can be difficult and many of these modalities are poorly studied and typically only modestly effective. Surgical excision at an early stage prior to extensive ulceration may offer

an effective option, though patients exposed to radiation may not heal appropriately with poor cosmetic outcomes. Other pharmaceutical options include the calcium channel blocker diltiazem, anti-inflammatory medications such as colchicine, minocycline, and intralesional corticosteroids [1], and topical medications such as sodium thiosulfate [10], as used in our patient. These medications have largely been studied in connective tissue disease-associated dystrophic calcinosis. Ours is the first reported use of topical sodium thiosulfate to treat radiation-induced calcinosis, which has demonstrated objective improvement in this case.

Conclusion

An awareness of acute and chronic radiotherapy changes is important for properly managing these increasingly common patients. Many of the more typical chronic changes are easily recognizable. Although heterotopic calcification remains a rarely reported late change, more recent reports over the last 10-15 years have demonstrated that a multitude of malignancies and anatomic locations may manifest this feature. Post-radiation dystrophic calcification, often associated with other worrisome features such as ulceration, may be mistaken for either cancer recurrence or a secondary malignancy. Properly distinguishing between benign and malignant skin changes can be difficult but remains a critical task. A history of extensive radiation often precludes effective wound healing when invasive biopsy and surgical management are considered. In these patients with significant past radiation exposure who may experience poor surgical outcomes and are proven to have benign cutaneous calcinosis, a trial of topical sodium thiosulfate may be an appropriate new treatment option.

Potential conflicts of interest

The authors declare no conflicts of interest.

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