

Subcutaneous Calcification as a Delayed Complication of Radiotherapy: A Case Report and Review of the Literature

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Received: 4 April 2008 / Accepted: 26 April 2008 / Published online: 28 August 2008
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Abstract Subcutaneous calcification following radiotherapy is a very rare late complication. Here we report a case of radiotherapy for Hodgkin's disease in a patient with ichthyosis. Our review of the literature revealed that subcutaneous calcifications occurred in previously normal skin following irradiation. In our case the calcification developed in abnormal skin after telecobalt radiotherapy for mediastinal Hodgkin's disease. Ichthyosis is a systemic cutaneous disease and may increase the risk of late radiation complications.

Keywords Ichthyosis · Hodgkin's disease · Radiotherapy · Subcutaneous calcification

Introduction

Necrosis, ulceration and fibrosis are well known end-points of therapeutic irradiation, and some patients with nonmalignant systemic disease have greater risk of complications [1]. Subcutaneous calcification following irradiation is a very rare sequel. So far only 24 cases have been reported in the literature [2–6]. To date, there have not been any reported cases of post-irradiation subcutaneous calcification occurring in people with previously abnormal skin. Here we report on a long-term radiotherapy survivor with subcutaneous calcification in pre-existing ichthyotic skin, and relevant literature is reviewed.

Case Report

Clinical History

A 32-year-old man was presented with mediastinal Hodgkin's disease. The patient's past medical history was notable for ichthyosis vulgaris, which began soon after birth. This inherited skin disease was found in his brother as well. In January 1976, 40 Gy (2 Gy/fraction at 11 cm depth, 10 Gy/week) telecobalt irradiation (source-to-skin distance: 50 cm) was given using two paravertebral oblique fields (one field /day; field size: 10 × 15 cm; gantry angle: 20 degrees). The maximum of total dose at 0.5 cm depth was 41 Gy in each field. Follow-up at 1 month showed brisk erythema on treated skin. At one year after treatment, skin became atrophic, fibrotic, and hyperpigmented in the irradiated area. Chest radiography showed no evidence of mediastinal tumor. Following this patient remained well until December 2001, when a 2 cm subcutaneous solid mass was found in the right irradiated region. A wide

All authors substantially contributed to this work and have all read and approved the final manuscript. There are no direct or indirect commercial or financial incentives associated with publishing this article. This manuscript or portions of thereof are not under consideration by any other journal

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excision removed the lesion en block with the overlying skin. After surgery the wound healing was delayed (Fig. 1). He then remained well until December 2006, when died of myocardial infarct.

Pathologic Findings

The surgical specimen was examined histologically. Representative samples were routinely fixed in 10 % buffered formalin solution, dehydrated in graded alcohol solution, and embedded in paraffin. Slices were cut at 5-micromilimeter sections and stained with hematoxylin–eosin. Histologic sections of the skin showed hyperkeratosis, absent granular layer, pigment deposition in the keratinocytes, mononuclear cells in the dermis and dense fibrotic–collagenous tissue (Fig. 2). Of note, abnormalities in the granular layer is characteristic of ichthyosis. Histologic analysis of the removed subcutaneous solid mass showed calcification without organized parts (Fig. 3).

Discussion

Hyperpigmentation, telangiectasia, atrophic dermatitis, fibrosis, necrosis, and ulcer are well known late complications of radiation therapy. However, calcification is not included in the morbidity scoring system. Subcutaneous calcification as a late radiation damage occurs infrequently. To our knowledge, only 24 cases have been published in the literature (Table 1), and all developed in previously normal subcutaneous tissue after irradiation for cancer diseases. Post-irradiation subcutaneous calcification is described first by Cowie et al. [2]. In their case, calcification developed following 40 Gy dose post-mastectomy telecobalt radiotherapy to the left chest wall and supraclavicular/axillary region for breast cancer. Calcification was due to the overlap



Fig. 1 Late postoperative photograph (six months after excision) shows scaling in- and outside of the irradiated skin, infield atrophic dermis, hyperpigmentation (more prominent right side), and delayed wound healing

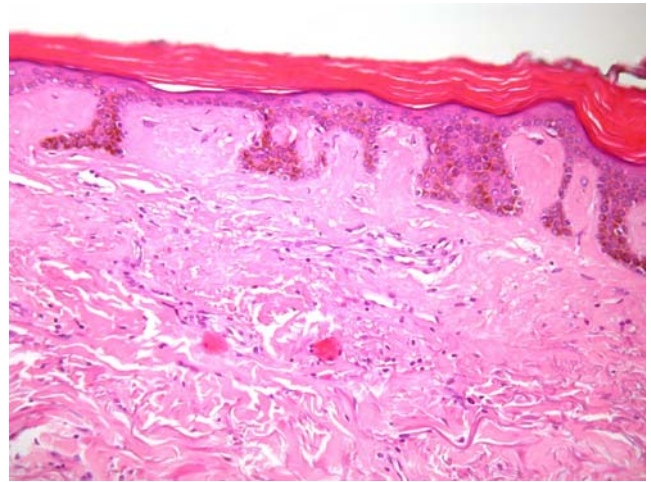


Fig. 2 Photomicrograph of skin specimen: hyperkeratosis, absent granular layer, pigment deposition in keratinocytes, dense fibrotic–collagenous tissue with mononuclear infiltrate (hematoxylin and eosin, original magnification $\times 200$)

between tangential glancing chest wall and anterior supraclavicular fields and the large fraction size (4 Gy/day), resulting in an area receiving higher dose than intended. In the six cases of Amin et al. [4] subcutaneous calcification also occurred following chest wall or breast telecobalt irradiation for breast cancer (total dose 40–45 Gy, fraction size 2.25 to 4 Gy). Calcification appeared to lie in the mach plane of fields. Carl et al. [5] reported 15 cases with post-irradiation heterotopic calcifications linked to other radiation sequel, e. g. ulceration, nerve damage and fibrosis. Their patient received doses in excess of 40 Gy for breast, gynecological, rectal cancer, seminoma and lower limb sarcoma. The fraction size was 2 to 4 Gy, and overlap of adjacent fields played a role in some cases. Of note, very different beam qualities were used (cobalt, cesium, 200 kV

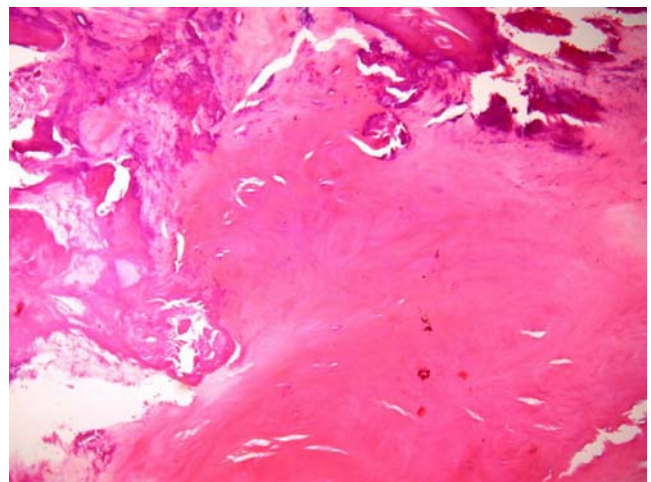


Fig. 3 Specimen of removed subcutaneous solid mass shows calcification throughout, without organized part (hematoxylin and eosin, original magnification $\times 200$)

Table 1 Summary of published cases of radiotherapy induced subcutaneous calcification

Cases	Authors	RT dose/FS (Gy)	Overlap ^a	Skin damage	Time to calcification (yr)
15	Carl UM et al. 2002 [5]	40–90/2–4	Yes (five cases)	Telangiectasia, fibrosis, ulceration	19 (median)
6	Amin R et al. 2002 [4]	40–45/2.25–4	Yes (six cases)	Fibrosis, stiffness of the shoulder, rib fracture	11 (mean)
1	Cowie F et al. 1999 [2]	40/4	Yes	Telangiectasia Fibrosis	NA
1	Steinert M et al. 2001 [3]	NA	NA	Fibrosis	32
1	Lewis VJ et al. 2004 [6]	50/2	No	Fibrosis, ulceration	8
1	Present study	40/2	No	Skin atrophy, fibrosis	25

RT radiotherapy, FS fraction size, NA not applicable, yr years

^aOverlap of adjacent fields

X-ray, neutrons, low dose rate brachytherapy). Ulceration of the skin was the most frequent co-existing radiation damage in 11 of 15 patients. In the case of Steinert et al. [3] a female patient was hospitalized because of a deep abscess in the radiation-exposed area on the sacrum. As a secondary finding, subcutaneous calcification was diagnosed, developed 32 years after postoperative combined radiotherapy for cervical carcinoma. In the case of Lewis et al. [6] a female patient was irradiated with 50 Gy (2 Gy/day) for bladder cancer. Subcutaneous calcification became clinically apparent 8 years after the initial radiotherapy.

In the aforesaid studies subcutaneous post-irradiation calcification occurred in previously normal skin following irradiation for cancer disease. In all cases subcutaneous calcification was linked to other late radiation complications, e. g. ulceration, telangiectasia and fibrosis (Table 1). In our case the irradiation was given via two separated paravertebral fields, and the total dose/field was 41 Gy (4.1 Gy/fraction). The patient suffered from ichthyosis vulgaris, and dermal atrophy, hyperpigmentation, dense subcutaneous fibrosis and subcutaneous calcification were developed in the treated area. Some hereditary and collagen vascular diseases increase the risk of late toxicity from therapeutic irradiation, but ichthyosis was not earlier described as a contributing factor to exaggerated radiation response [1,7,8]. Patients with ichthyosis may have decreased survival of skin fibroblast lines after UVB exposure, granular layer abnormalities, a decrease in skin moisture, a reduction of skin lipids, and a defect in enzyme steroid sulfatase [9–12]. These abnormalities may modify cellular radiosensitivity, but the exact mechanism that leads to an increase in late injuries is unclear.

The risk for testicular, skin cancer and lymphomas in patients with ichthyosis are discussed in several studies, but irradiation was not used to treat the tumor or radiation complications were not scored [13–17]. Therefore, whether ichthyosis does or does not increase the cellular radiosensitivity will not be known until more cases are reported.

Conclusion

There is evidence in the literature that post-irradiation subcutaneous calcification is linked to other late radiation complications and can be regarded as a possible end-stage tissue damage for long-term survivors after radiation therapy. In our case the calcification occurred in a pre-existing abnormal ichthyotic skin, and developed after radiation therapy for Hodgkin's disease. Ichthyosis is a systemic cutaneous disease, and may increase the risk of late radiation complications.

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