

# Radiation-induced low-grade fibromyxoid sarcoma of the chest wall nine years subsequent to radiotherapy for breast carcinoma: A case report

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**Abstract.** The present study reports a case of low-grade fibromyxoid sarcoma that occurred in a 62-year-old woman 9 years subsequent to whole breast irradiation for a carcinoma of the left breast, and 18 years following chemotherapy and radiotherapy (RT) for non-Hodgkin's lymphoma (NHL; diagnosed at the age of 43). The patient was 53 years of age when a cT2N0M0 stage IIA breast tumor was identified and excised. A 2.5 cm diameter nodule with dimpling in the upper-outer region of the left breast was detected. Pathological examination revealed that the tumor was an invasive ductal carcinoma, of a solid tubular type. The patient was treated with post-surgical whole breast RT. The left breast received 46 Gy in 23 fractions (2 Gy per fraction) for 4 weeks and 3 days, followed by a cone down boost of 14 Gy in 7 fractions (2 Gy per fraction); therefore a total dose of 60 Gy in 30 fractions was administered. In total, 9 years subsequent to RT, the patient observed a small lump in the left chest wall. The patient underwent excision of the tumor and pectoralis major fascia. Microscopically, the tumor consisted of atypical spindle cells with myxoid stroma. Pathologists concluded that the tumor was a low-grade fibromyxoid sarcoma. Since the tumor developed from tissue in a previously irradiated region, it was considered to be RT-induced, and was classified using the radiation-induced sarcoma (RIS) criteria as dictated by Cahan. Although the majority of RIS cases are angiosarcomas, a rare, low-grade fibromyxoid sarcoma was observed in the present study. The present study hypothesizes that there may have been an overlap region between the RT for supraclavicular nodes of NHL and the whole breast RT for primary breast cancer, due to the results of a retrospective dose reconstruction undertaken

by the present study. The patient remained clinically stable for 4 years thereafter, until 2008 when the patient experienced a local relapse and underwent surgery. On 19 October 2011, the patient succumbed to RIS. The current study suggests that the RT history of a patient requires consideration due to the possible development of RIS, including the development of a low-grade fibromyxoid sarcoma, which may lead to a poor prognosis.

## Introduction

Radiotherapy (RT) subsequent to breast-conserving surgery for the treatment of breast cancer decreases recurrence and improves survival rate (1). Whole breast irradiation (WBI) is recommended for all patients who undergo breast-conserving surgery. Side effects that are commonly experienced during the acute period include radiation dermatitis, esophagitis, pharyngitis and nausea. In the subacute phase (2-12 months post-RT), there is a risk of radiation pneumonitis. Late morbidities occurring >1 year post-RT include arm edema, rib fractures, brachial plexopathy, secondary malignancies and long-term cardiac toxicity. Meric *et al* (2) reported the frequencies of such complications and stated that of 294 patients that received WBI for breast cancer, 29 (9.9%) presented with grade 2 or higher complications at 1 year post-treatment, consisting of arm edema (n=13), breast skin fibrosis (n=12), a decreased range of motion (n=4) and pneumonitis (n=2). Treatment-induced secondary malignancies following RT are rare, and include contralateral breast cancer and non-breast primary malignancies, such as sarcoma, lung cancer, esophageal cancer and leukemia (1-4). The risk of secondary non-breast malignancy is ~1% (3).

Previously, a case of osteosarcoma following RT was reported by Beck in 1922 (5) and the development of a soft tissue sarcoma of the breast following RT was reported by Warren *et al* in 1936 (6). In 1948, Cahan *et al* described the following criteria for the diagnosis of radiation-induced sarcoma (RIS) (7): A history of RT; an asymptomatic latency period of several years; an occurrence of sarcoma within a previously irradiated tissue region; and a histological confirmation of the sarcomatous nature of the lesion.

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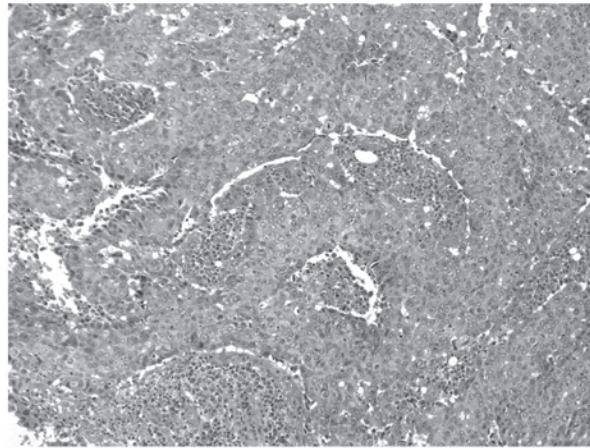


Figure 1. An invasive ductal carcinoma of a solid tubular type was identified in the left breast 9 years subsequent to radiation therapy for non-Hodgkin's lymphoma (staining, hematoxylin and eosin; magnification, x100).

Angiosarcoma is the most common of all RIS, and it accounts for ~50% of all RIS. In general, sarcomas are classified according to histological grade, which may indicate the histological malignancy and distant recurrence rate of the tumor and mortality prognosis of the patient (8). Patients with RIS have a poorer prognosis compared with patients with primary sarcoma (9). In addition to poor survival outcomes, local recurrence rates are also increased in patients with RIS compared with those with primary sarcomas (10). This may be due to the failure of complete surgical resection or deficiency of RT as a treatment (11).

The current study presents a rare case of RIS of the chest wall 9 years subsequent to RT of the whole breast. In the present case, the histological type of the tumor was classified as a low-grade fibromyxoid sarcoma.

### Case report

The present patient was a 62-year-old Japanese woman that was originally diagnosed with non-Hodgkin's lymphoma (NHL) of the right parotid at in September 1985 (at 43 years of age) at the University of Tokyo Hospital (Tokyo, Japan). The patient possessed no other notable personal or familial medical history. The NHL was a diffuse B-cell lymphoma stage II small-cell type tumor. Following the diagnosis of NHL in 1985, the patient underwent a resection of the affected parotid and received chemotherapy. The chemotherapy regimen administered was two cycles of cisplatin and peplomycin therapy, which consisted of 100 mg cisplatin (day 1) and 5 mg peplomycin sulfate (day 1-4), and four cycles of cyclophosphamide, vincristine and prednisone/prednisolone therapy, which consisted of 800 mg cyclophosphamide (day 1) and 1 mg vincristine (day 1). Furthermore, the patient received RT, which consisted of 39.6 Gy in 22 fractions administered for 4 weeks, to the whole neck and supraclavicular region using cobalt-60. The whole neck RT was performed in lateral 12x14 cm opposed fields and the supraclavicular RT was treated in the antero-posterior 8x20 cm opposed fields.

In May 1995, when the patient was 53 years of age, a small lump in the left breast was identified at the University of Tokyo

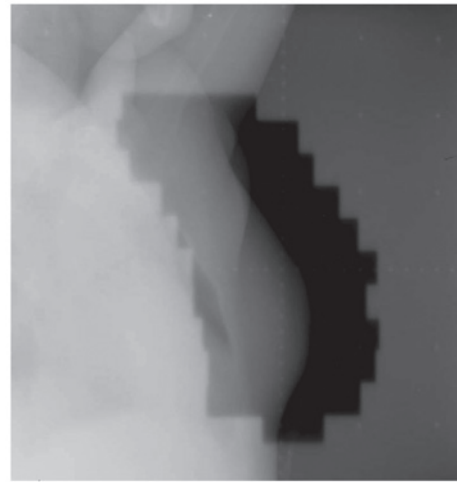


Figure 2. Irradiation portal of post-operative whole breast irradiation for breast cancer 9 years subsequent to radiation therapy for non-Hodgkin's lymphoma.

Hospital, and a surgeon was consulted. A 2.5 cm diameter nodule with dimpling in the upper-outer region of the left breast was identified. A clinical examination resulted in the diagnosis of primary breast carcinoma (cT2N0M0; stage IIA). On 4 October 1995, the patient underwent a tumor excision. Pathological examination revealed an invasive ductal carcinoma of a solid tubular type (Fig. 1). No immunohistological examinations (for example, human epidermal growth factor receptor 2, estrogen receptor and progesterone receptor tests) were performed. Post-operatively, the patient received RT, which was delivered as 6 MV photons to the whole left breast using a tangential irradiation technique. The whole breast region was 210x115 mm in size (Fig. 2). The whole breast received 46 Gy radiation in 23 fractions (2 Gy per fraction) for 4 weeks and 6 days, followed by a cone down boost of 14 Gy in 7 fractions (2 Gy per fraction), therefore a total dose of 60 Gy in 30 fractions was administered. RT was completed on 25 November 1995. The patient tolerated the therapy well; however, the patient suffered from grade 2 dermatitis (12). The patient did not receive adjuvant chemotherapy or hormonal therapy.

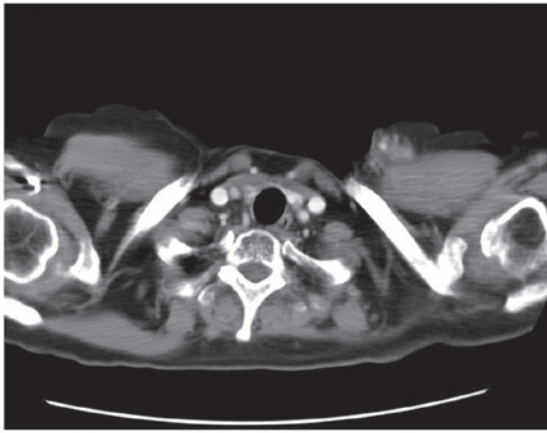


Figure 3. Chest computed tomography scan performed 18 years subsequent to radiation therapy for non-Hodgkin's lymphoma. A 2.5 cm diameter nodule anterior to the insertion of the left sternocleidomastoid muscle was identified.

Overall, the patient remained active and clinically stable until August 2004, 9 years subsequent to the breast-conserving therapy, when the patient observed a small lump in the left chest wall. On 1 November 2004, a chest computed tomography scan revealed the presence of a tumor mass. A 2.5 cm diameter nodule anterior to the insertion of the left sternocleidomastoid muscle was identified (Fig. 3). A biopsy confirmed that the tumor consisted of atypical spindle cells. On 13 January 2005, the patient underwent excision of the tumor and pectoralis major fascia and a biopsy of the left axillary lymph nodes was performed. Macroscopically, the resected tumor measured 7x7x2 cm in size and was tan and poorly-margined. Microscopically, the lesion consisted of atypical spindle cells with myxoid stroma that were mainly in the subcutaneous fatty tissue, which invaded the dermis (Fig. 4). Immunohisto-logically, the tumor cells were positive for vimentin, a type III intermediate filament protein that is often used as a sarcoma marker (4). In total, 50% of the tumor cells expressed molecular immunology borstel-1, but the tumor did not express other markers, including S-100 protein, desmin, mouse monoclonal muscle actin antibody HHF-35, sulfotransferase 1A-4, cluster of differentiation (CD)-31, CD34 and lymphatic endothelium monoclonal antibody D2-40. Pathologists concluded that the tumor was a low-grade fibromyxoid sarcoma. Pathology identified malignant cells within the surgical margin. In total, 5 lymph nodes that contained no malignant cells were removed. Since the tumor developed from tissue that had been previously irradiated, it was considered to be RT-induced. Although additional surgery and chemotherapy were advised, the patient declined.

The patient remained clinically stable for the following 4 years. In 2008, the sarcoma recurred locally and the patient underwent multiple surgeries for mass reduction. In September 2011, the patient developed uncontrolled bleeding from the recurrent mass. The patient succumbed to the sarcoma on 19 October 2011, 18 years subsequent to whole breast RT, and 9 years subsequent to the initial symptoms of the sarcoma.

The present study retrospectively reconstructed the RT field of the RT the patient received for the treatment of NHL and invasive ductal carcinoma of a solid tubular type, observed 9 years later, using the Pinnacle 3 three-dimensional radiation

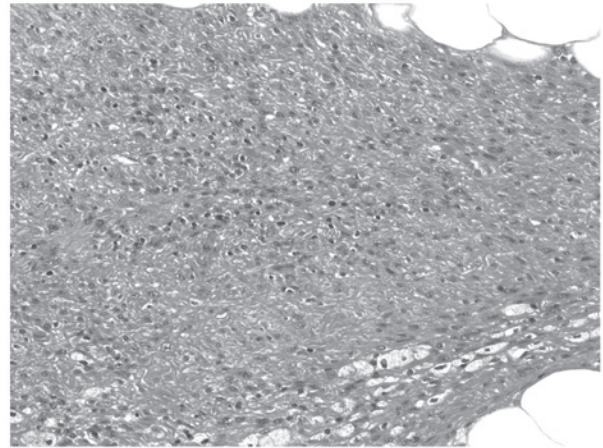


Figure 4. Pathological findings of a resected tumor that had developed 18 years subsequent to radiation therapy for non-Hodgkin's lymphoma and 9 years subsequent to radiation therapy for an invasive ductal carcinoma of a solid tubular type, which was stained using the hematoxylin-eosin method. Atypical spindle cells with myxoid stroma mainly in the subcutaneous fatty tissue, which had invaded the dermis, were observed. The tumor was diagnosed as low-grade fibromyxoid sarcoma (staining, hematoxylin and eosin; magnification, x100).

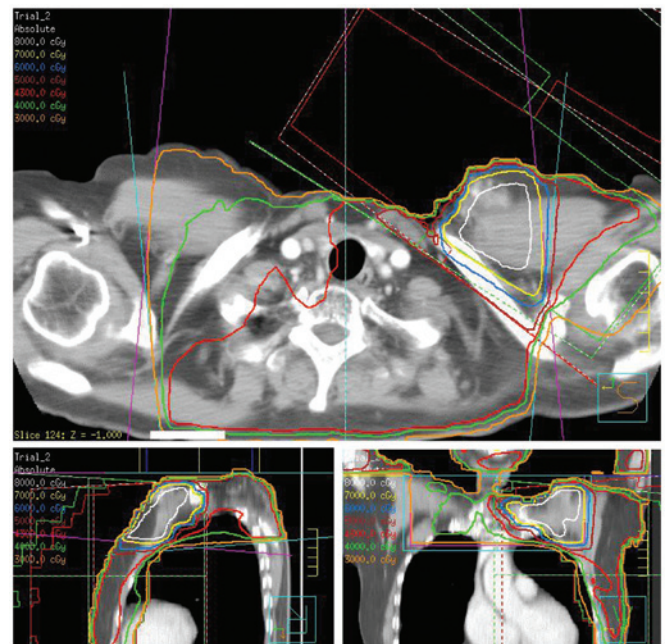


Figure 5. The radiation field of the radiotherapy the patient received for non-Hodgkin's lymphoma and invasive ductal carcinoma of a solid tubular type was reconstructed retrospectively, using the Pinnacle 3 three-dimensional radiation therapy system. Upper image, horizontal view; left image, sagittal view; and right image, coronal view.

therapy system (Hitachi Medical Corporation, Tokyo, Japan; Fig. 5).

## Discussion

RT for the treatment of breast cancer increases the risk of developing all types of soft tissue sarcoma, particularly rare angiosarcoma (13,14). Although women that undergo RT for breast cancer demonstrate an increased risk of in-field

sarcomas, the absolute magnitude of risk for a post-irradiation sarcoma is small (15). In 274,572 cases of primary breast cancer identified from the Surveillance, Epidemiology and End Results database, the 15-year cumulative incidence rates for any sarcoma in women that received and did not receive RT were 3.2 and 2.3 per 1,000 women, respectively (15).

In patients with primary breast sarcoma, angiosarcoma, fibrosarcoma and pleomorphic cell sarcoma occur at a frequency of ~24% for each type of sarcoma, followed by fibromyxoid sarcoma at 12% (16). However, angiosarcoma accounts for ~50% of all RIS. The patient in the present study possessed a low-grade fibromyxoid sarcoma tumor, which is an uncommon type of RIS. Low-grade fibromyxoid sarcoma, also termed Evans tumor, was first reported by Evans in 1987 (17). Evans presented 2 cases where the pathological features appeared to be benign or possessed low-grade atypical cytology at the first presentation, but local and metastatic recurrences occurred. In 1993, Evans reported 12 additional cases, which were similar to the previous 2 cases (18).

In an analysis of the Swedish Cancer Registry, Karlsson *et al* identified that the amount of radiation energy used for the treatment of breast cancer was associated with the risk of developing a non-angiosarcoma secondary soft-tissue sarcoma, whereas upper extremity edema was the only risk factor associated with the development of angiosarcoma (19). Karlsson *et al* revealed that the risk for the development of sarcoma, other than angiosarcoma, increased linearly with an integral dose of 150-200 J and reached a plateau at higher energies. The odds ratio was 2.4 (95% confidence interval, 1.4-4.2) for energy of 50 J, which is equivalent to the RT received by the breast following breast-conserving surgery. In an additional study, which analyzed >6,500 women with breast cancer, the risk of developing sarcoma, including malignant fibrous histiocytoma, fibrosarcoma and angiosarcoma, increased with a higher radiation dose, regardless of edema (20). RIS incidence is considered to be a function of the RT dose (21,22). The majority of RIS studies following breast irradiation have been concerned with doses of 60-80 Gy, with a minimal dose of 10 Gy in standard fractionations (23).

In the current study, the whole neck and bilateral supraclavicular region of the patient had been irradiated for the treatment of NHL. The present study retrospectively reconstructed the RT field of that treatment, using the Pinnacle 3 three-dimensional radiation therapy system. The reconstructed dose distribution indicated that there may have been an overlapping region of supraclavicular irradiation in 1986 and whole breast irradiation in 1995, and that the sarcoma of the patient possibly developed from this overlapping irradiated region. In this region the total biological effective dose ( $\alpha/\beta=10$ ) was estimated to be almost 95 Gy, which may have augmented the risk of the patient developing sarcoma. In addition, the patient possessed a history of chemotherapy; cyclophosphamide has been hypothesized to be a risk factor for the development of a secondary cancer (24).

Overall, the present study reported the case of a low-grade fibromyxoid sarcoma in a 62 year old woman, which developed 9 years subsequent to whole breast irradiation for carcinoma of the left breast, and 18 years following chemotherapy and RT for NHL. The patient succumbed to the tumor 25 years subsequent to RT for NHL, 18 years subsequent to whole breast RT and 9 years subsequent to the initial symptoms of the sarcoma.

The present study indicates the importance of considering the RT history of a patient, due to the potential development of RIS, including the development of a low-grade fibromyxoma, which possesses a poor prognosis.

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