

Radiation-Induced Sarcoma After Breast Cancer Treatment: Two Cases with Different Prognosis

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Radiation therapy is considered as a standard treatment after breast conservation surgery in breast cancer. The purpose of radiation therapy is to eradicate the potential residual lesions and to reduce local recurrence. Radiation-induced sarcoma (RIS) is a rare and late complication after radiation therapy. When a mass was found in the irradiation field after breast surgery, although local recurrence is the most commonly encountered, the possibility of RIS should be kept in mind. It is known that osteosarcoma, malignant fibrous histiocytoma, and fibrosarcoma are the most common histological subtypes occurring after breast cancer treatment. The tumor size of RIS is an important prognostic factor in RIS. Here we have two additional cases of RIS with different size after breast cancer treatment which histological entity was undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma and showed different prognosis.

Index words: Breast Cancer; Prognosis; Radiation-induced Sarcoma; Undifferentiated Pleomorphic Sarcoma; Malignant Fibrous Histiocytoma

A long-term follow up is necessary after the treatment of breast cancer patients because of the increased survival rate and secondary adverse effects of the used therapies. Adjuvant radiation therapy to the breast plays a crucial role to prevent local failure

and reduce the breast cancer death rate after breast surgery. The development of a secondary neoplasm, known as a late complication after radiation therapy, is more important, especially in sarcomas.

Radiation-induced sarcoma (RIS) is a rare and late complication after radiation therapy, with a reported incidence of 0.03% to 0.2% in 5 years and up to 0.8% overall in the literature (1). A reported incidence of RIS surveyed by a single institute of Korea was 0.9% (2). The most common primary

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diagnoses related to RIS were breast cancers, ranging from 27.3% to 33.4% (2, 3). According to the Surveillance, Epidemiology and End Result (SEER) database, leiomyosarcoma is known to be the most common sarcoma occurring after breast cancer, while others reported that osteosarcoma, malignant fibrous histiocytoma, and fibrosarcoma are the most common histological subtypes (3).

Although RIS is a rare complication after radiation therapy, its clinical significance should be considered because it is associated with a lower survival rate than sporadic soft-tissue sarcoma. Tumor size seems to be an important prognostic factor (4). RIS is slightly more difficult to identify by physical examination because of changes after radiation therapy. Therefore, enhanced awareness and early detection are necessary to improve outcomes. Here, we have two cases of RIS manifested as undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma with different size and different prognosis.

Case Report

Case 1

A 65-year-old woman complained of a palpable mass at the margin between her right lower inner breast and chest wall. She underwent breast-conservation surgery of her right upper inner breast and sentinel lymph node biopsy 8.5 years prior. The lesion was demonstrated as 2-cm regionally distributed pleomorphic microcalcifications that were confirmed as low-nuclear-grade ductal carcinoma in situ without evidence of lymph node metastasis. The surgical margins were clear. Immunohistochemistry was positive for estrogen receptor (ER) and progesterone receptor (PR) and negative for C-erbB2. Approximately 1 month later, adjuvant radiation therapy for 6 weeks was administered. The dose delivered to the whole breast was 50.4 Gy in 28 fractions, and the boost

dose to the primary tumor bed was 10 Gy in 5 fractions. After completion of radiation therapy, she took tamoxifen for 5 years. Routine checkup for both breasts and axillae was performed using routine mammography and ultrasonography for 8.5 years.

To evaluate the palpable mass, ultrasonography was performed, and a 6.4-cm circumscribed solid mass was found in the deep portion of the lower chest wall (Fig. 1a). Computed tomography (CT) of the chest showed about a 6-cm circumscribed solid mass with intense enhancement, and the cortical margin of the adjacent rib looked ragged (Fig. 1b). Positron emission tomography (PET) showed a hypermetabolic mass with involvement of the right 5th and 6th ribs, without distant metastasis (Fig. 1c). Complete surgical excision of the mass and adjacent ribs was performed, and the confirmed pathology was undifferentiated pleomorphic sarcoma without involvement of adjacent ribs (Fig. 1d-f). The size of mass was 6.1 × 3.5 cm with during the 1.5-year follow up, a suspected metastatic lung mass was found in her right upper lobe. She was administered pazotinib (a tyrosine kinase inhibitor).

Case 2

A 57-year-old woman underwent ultrasonography for routine checkup. She underwent nipple-sparing mastectomy in her right breast for two invasive ductal carcinomas and sentinel lymph node biopsy 2.5 years prior. The size of two masses was 2.2 cm and 1.2 cm, respectively. Immunohistochemistry was positive for ER and PR and negative for C-erbB2. After 3 weeks, six cycles of adjuvant chemotherapy started using fluorouracil, doxorubicin, and cyclophosphamide, followed by daily anastrozole. Approximately 5 months later, adjuvant radiation therapy was performed for 3 weeks. The dose delivered to the whole breast and the axilla was 39 Gy in 13 fractions, and the boost dose to the primary tumor

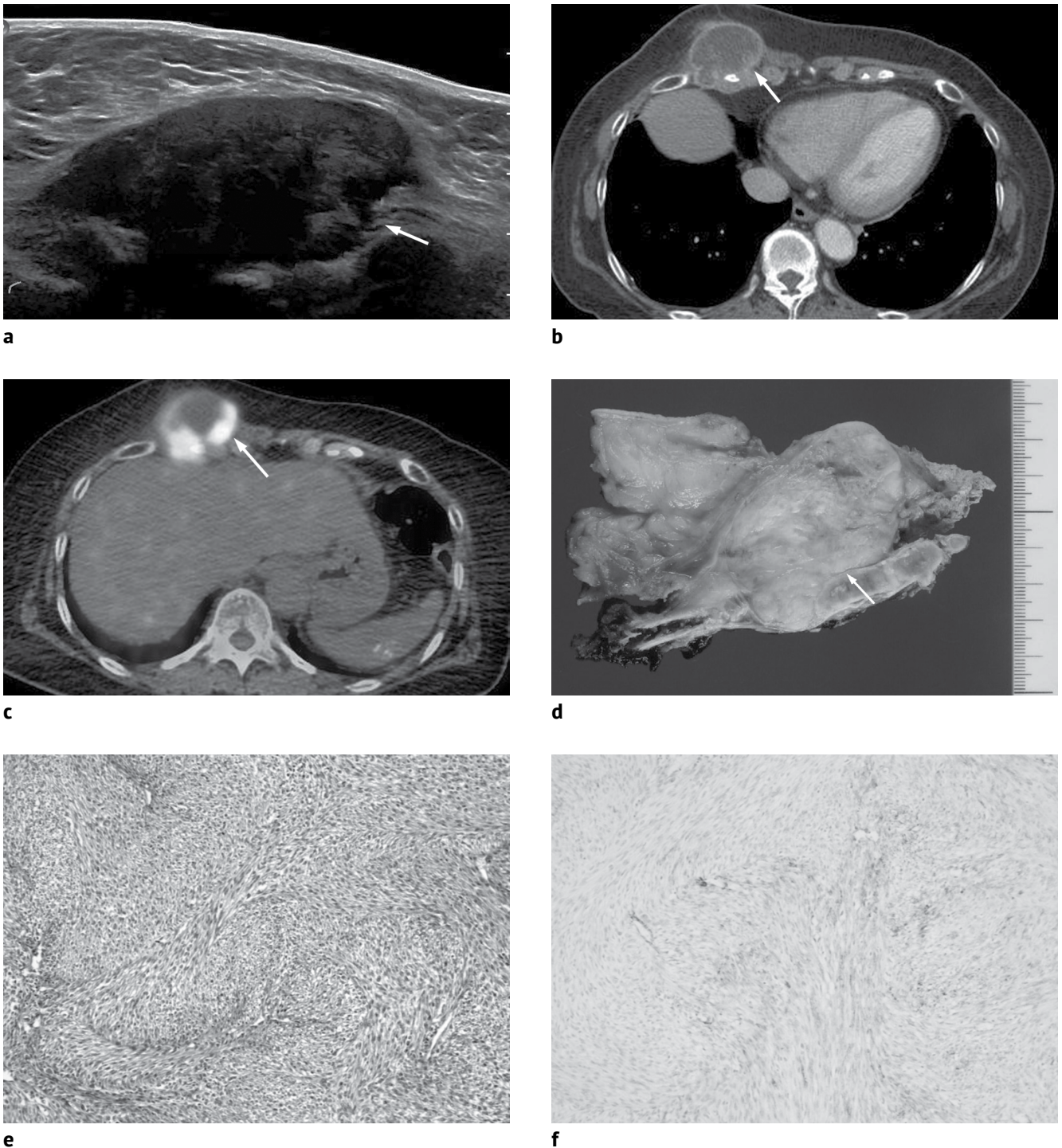


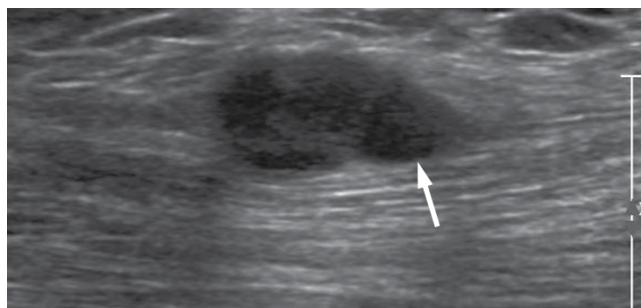
Fig. 1. Radiation-induced undifferentiated pleomorphic sarcoma in a 65-year-old woman that was found in 8.5 years after the completion of radiation therapy.

(a) Ultrasonographic image shows a 6.4-cm circumscribed solid mass in the deep portion of the lower chest wall (arrow). (b) CT of the chest shows 6-cm circumscribed solid mass with intense enhancement, and the cortical margin of the adjacent rib looked ragged (arrow). (c) PET scan shows a hypermetabolic mass with involvement of the right 5th and 6th ribs (arrow). (d) Specimen after complete surgical excision of the mass and adjacent ribs (arrow). The final pathologic finding was undifferentiated pleomorphic sarcoma without involvement of adjacent ribs. (e) Microscopic finding shows a fascicular architecture with pale eosinophilic cytoplasm and tapering nuclei (H & E, x100). (f) Immunohistochemically, tumor cells stain focal positively for SMA and negatively for C-kit, desmin, CD34.

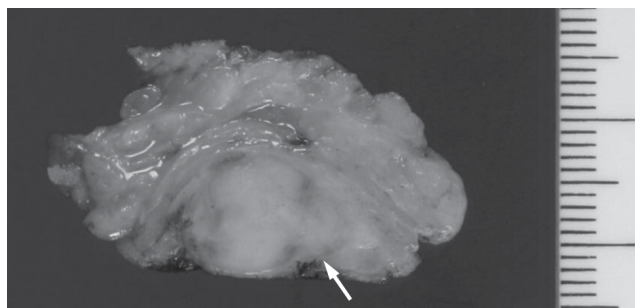
bed was 9 Gy in 3 fractions. Two and a half years after the completion of radiation therapy, a 1.5-cm circumscribed solid mass was found in the left axilla during routine follow-up ultrasonography that was considered as local failure (Fig. 2a). PET-CT showed mild uptake in her left axilla that was not seen 6 months prior. Ultrasonography-guided axillary biopsy was performed, and the pathology was sarcoma. Wide excision confirmed malignant fibrous histiocytoma (Fig. 2b-d). During the 6-year follow up after complete surgical excision of the left axillary sarcoma, no evidence of local recurrence or metastasis was found.

Discussion

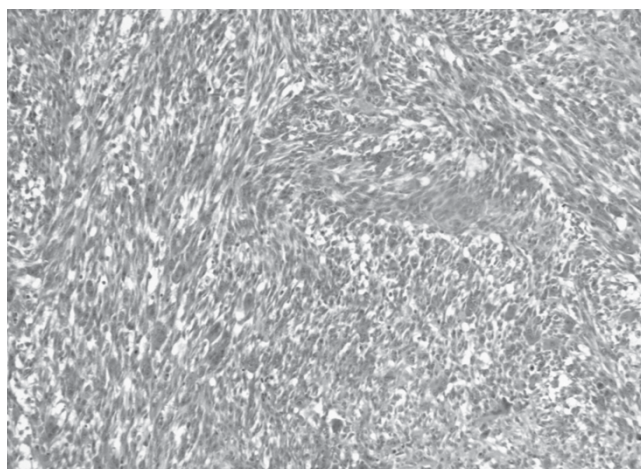
Multiple trials have demonstrated that adjacent radiation therapy plays an important role in the treatment of breast cancer by decreasing local failure and increasing the rate of breast conservation and survival. A rare but significant complication of radiation therapy is the development of sarcoma within or at the edge of the radiation field, usually after a long latency period. Cohan et al. defined the diagnostic criteria of RIS in 1948 (5): a history of radiation therapy, an asymptomatic latency period (usually > 4 years), the occurrence of sarcoma



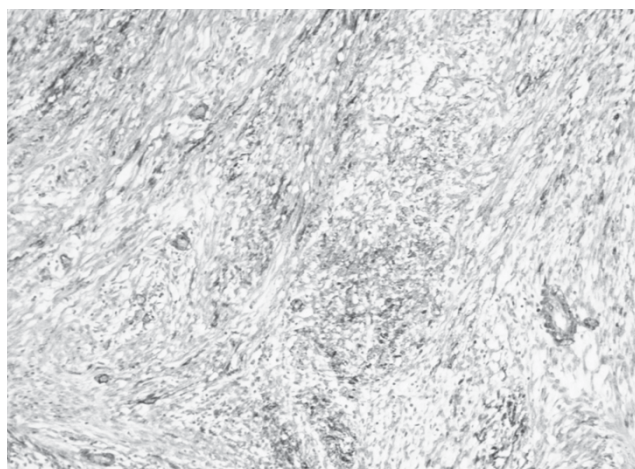
a



b



c



d

Fig. 2. Radiation-induced malignant fibrous histiocytoma in a 57-year-old woman that was found in her right axilla after nipple-sparing mastectomy and irradiation therapy in her right breast for two invasive ductal carcinomas and sentinel lymph node biopsy 2.5 years prior.

(a) Ultrasonographic image shows a 1.5-cm circumscribed solid mass in the left axilla (arrow). (b) Surgical specimen after wide excision confirmed malignant fibrous histiocytoma (arrow). (c) Microscopic finding (H & E, x100) shows that this pleomorphic sarcoma is patternless with frequent bizarre multinucleate tumor giant cells. (d) Immunohistochemically, tumor cells stain focal positively for SMA.

within a previously irradiated field, and histological confirmation of the sarcomatous nature of the post-irradiated lesion. The Cohan criteria have been modified by several groups. Among them, Gladdy et al. suggested that a much shorter latency period of 6 months was sufficient to confirm the diagnosis of RIS (6). Rubino et al. concluded that RIS is less likely to arise in very low-dose regions and more likely to arise in intermediate- to high-dose regions above 5 Gy (7). The risk of sarcoma was 30.6 times higher for doses of more than 44 Gy than for doses less than 15 Gy, and high doses of radiation strongly increase the risk of bone and soft-tissue sarcoma (7).

A reported incidence of RIS surveyed by a single institute of Korea was 0.9% (2), while the overall reported incidence in the literature reached up to 0.8% (1). Among the cases, the most common primary diagnoses related to RIS were breast cancers, which ranged from 27.3% to 33.4% (2, 3). Leiomyosarcoma is known to be the most common sarcoma occurring after breast cancer in the SEER database, while others reported that osteosarcoma, malignant fibrous histiocytoma, and fibrosarcoma are the most common histological subtypes (3).

Several studies have reviewed the clinical and imaging findings of RIS. No differences have been found in the risk of RIS after breast-conservation surgery versus mastectomy, similar to the results of our study. In general, CT is more sensitive to evaluate the bony cortex and new bone formation. Most sarcomas developed after radiation therapy for breast cancer are related to soft-tissue neoplasms, as observed in our cases. Our first case had suspicious bony destruction adjacent to a soft-tissue mass that was confirmed as malignant fibrous histiocytoma with a clear bony margin. Although mammography is the only imaging modality commonly recommended for breast cancer surveillance, the edge of the radiation field in the patients undergoing conservation surgery and operation bed of the mastectomy site could not be included in routine mammography. An approximately 6-cm

soft-tissue mass was developed at the margin of the irradiation field in our first case, and the mass was not included in mammography. This mass was detected through ultrasonography and CT (Fig. 1a, b). Hot uptake of the mass and the adjacent ribs was seen on PET-CT (Fig. 1c), the clear bony margin and undifferentiated pleomorphic sarcoma with fascicular architecture were found (Fig. 1d-f). The second case with axillary sarcoma underwent mastectomy 2.5 years prior, and a 1.5-cm oval solid mass was found only on ultrasonography after breast surgery (Fig. 2a, b). PET-CT and ultrasonography performed 6 months before biopsy showed no abnormality, indicating that the mass grew rapidly and the histology was high-grade sarcoma with marked cellularity and highly mitotic figures (19–20 per 10 high-power field) (Fig. 2c, d). Fortunately, this mass was completely removed with a clear margin, and no abnormal finding was found at her left axilla for 6 years. The term malignant fibrous histiocytoma was renamed as undifferentiated pleomorphic sarcoma not otherwise specified (NOS) in 2002 by the World Health Organization (WHO) whose disease entities are the same. The 5-year survival rate of RIS patients was in the range of 27–48% (4).

Tumor size appeared to be an important prognostic factor. For RIS patients with tumors less than 2 cm, the median survival time was 80 months; for those with tumors more than 5 cm, the survival time was only 20 months (8). Our first case showed a 6-cm mass on the initial ultrasonography image. Although she is still alive, a metastatic lung mass appeared 1 year after excision of the RIS of her left chest wall. Brady et al. reported three important factors that have an unfavorable effect on the mortality rate; presentation with metastatic disease, incomplete or no surgical resection, and tumor size more than 5 cm (9). Local recurrence rates after surgical therapy alone ranged from 50 to 68. Our second case was a rapidly growing 1.5-cm mass that was completely removed without evidence

of local recurrence for 6 years. Complete surgical excision is known to be the most effective treatment for RIS patients, and *en bloc* chest wall excision is mandatory with negative surgical margins. Sarcoma is not expected to metastasize to regional lymph nodes. Therefore, axillary lymph node dissection plays no role in RIS patients (8). The role of adjuvant chemotherapy remains ambiguous and that of radiation therapy for RIS is still unclear (4).

Knowledge and experience regarding post-radiation sarcomas in Korea is limited to a few case reports (10). Given the younger age at diagnosis and the increased use of RT as a primary treatment for breast cancer, longer survival after treatment could lead to more cases of post-radiation sarcoma.

In summary, we report two cases of post-radiation sarcoma after breast cancer treatment with a latent period of 8.5 and 2.5 years each at the margin of the irradiation field. Although RIS is a rare complication related to a poor prognosis, enhanced awareness and early detection are very important to improve clinical outcome.

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유방암 치료 후 발생한 방사선 유발 육종: 두 개의 증례와 예후 보고

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방사선치료는 유방암의 수술적 치료 후 이루어지는 표준치료로 여겨지고 있다. 방사선치료는 잠재적으로 잔존할 수 있는 악성 종괴를 제거하고 재발의 가능성을 낮추기 위해 사용된다. 방사선치료 후 생기는 육종은 드문 지연성 합병증으로, 방사선치료를 받고 오랜 시간 후 방사선치료 부위에 생기며 예후는 나쁜 것으로 알려져 있다. 유방암 수술 후 방사선치료를 받은 부위에 새로 종괴가 생겼다면 가장 먼저 국소 재발의 가능성을 생각해야 하지만 방사선치료와 관련된 육종의 가능성도 염두해 두어야 한다. 방사선치료와 관련하여 발생한 육종의 가장 흔한 병리는 골육종, 악성 섬유성 조직구종, 섬유육종 등이며 발현 당시 크기가 가장 중요한 예후요소로 알려져 있다. 저자들은 유방암 수술 후 방사선치료를 받았던 부위에 발생했던 미분화 다형성 육종/악성 섬유성 조직구종으로 발현한 두 개의 방사선 유발 육종의 증례와 그 예후를 보고하고 문헌을 고찰하고자 한다.

Index words: Breast Cancer; Prognosis; Radiation-induced Sarcoma; Undifferentiated Pleomorphic Sarcoma; Malignant Fibrous Histiocytoma

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