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Radiation-Induced Sarcoma of the Chest Wall Following Breast Cancer Treatment: A Case Report

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Radiation-induced sarcoma (RIS) is a rare secondary malignancy arising in previously irradiated tissue, often after a prolonged latency. Presented here is a 62-year-old woman who developed a left chest-wall mass with overlying ecchymosis 15 years after chemoradiotherapy for invasive ductal breast carcinoma. Ultrasound demonstrated an inhomogeneous, predominantly hyperechoic subcutaneous lesion corresponding to the area of ecchymosis. Core-needle biopsy revealed a spindle cell neoplasm with vascular differentiation. The patient underwent wide local excision; final histopathology showed a malignant spindle cell neoplasm with positive anterior and posterior margins, necessitating consideration of further management. RIS is associated with poor outcomes, and treatment remains challenging because of its rarity. This case highlights the importance of long-term surveillance, appropriate radiologic and histopathologic evaluation, and aggressive surgical management for suspected RIS after breast cancer radiotherapy.

Key words: radiation induced sarcoma, chemoradiotherapy, breast neoplasms, survivorship

Radiation induced sarcoma (RIS) is a rare, iatrogenic malignancy, with a 10-year incidence of 0.2% that is associated with poor outcomes.[1] Sarcomas following therapeutic radiation after mastectomy or lumpectomy for breast cancer was first described by Warren and Sommer in 1936.[2] Since its introduction, case reports have been published discussing the disease entity noting an increase in the number of reported cases after the introduction of breast conserving surgery.[3]

Patients who receive radiotherapy for primary breast cancer were noted to be at higher risk to have RIS. A review of Surveillance, Epidemiology, and End Results (SEER) by Snow et al in 2020 found an incidence of 0.02% in a population of breast cancer patients diagnosed from 1973 to 2013.[4] A study done by Lalla et al in Canada in 2023 reviewed a single center experience on radiation induced sarcoma of the breast that spanned 20 years (2000 to 2020).[5] They were able to identify 19 out of 8,700 patients who received radiotherapy for breast cancer and were later diagnosed with RIS. Median age at diagnosis was 72 years with a latency period for development of 112 months.

Due to its rarity, there are currently no systematic reviews regarding radiation-induced sarcoma (RIS) of the breast in Asia, and case reports detailing its incidence in the Philippines remain limited. The authors therefore present a case of post-radiation sarcoma occurring 15 years after treatment for breast cancer. This case is being reported because of the rarity of the disease and to discuss its management. To the authors' knowledge, this is the first documented case in their institution.

The Case

A 62-year-old Filipino female consulted at the outpatient department for a palpable mass in the left breast. Initial core-needle biopsy of the mass revealed invasive ductal carcinoma. The patient subsequently underwent a left total mastectomy with axillary lymph-node dissection. Histopathologic examination of the mastectomy specimen showed grade II invasive ductal carcinoma with clear resection margins and lymphovascular invasion. Six of 16 axillary lymph nodes were positive for metastatic tumor. Based on the histopathologic findings, the patient was diagnosed with stage IIIA (pT2N2M0). Postoperatively, she underwent six cycles of chemotherapy (Fluorouracil, Epirubicin, and Cyclophosphamide regimen) and 30

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sessions of post-mastectomy radiation therapy with regional nodal irradiation.

In the interim, the patient remained asymptomatic. She was a known hypertensive and diabetic who was compliant with her maintenance medications. During this period, she was also diagnosed with pulmonary tuberculosis and completed a six-month course of antituberculosis therapy. She attended annual follow-up appointments with her oncologist and underwent regular evaluations for possible tumor recurrence, all of which remained negative.

Fifteen years later, however, she developed a lump at the site of the primary tumor, associated with an enlarging, tender hematoma (Figure 1). Breast ultrasound (Figure 2) revealed an inhomogeneous predominantly hyperechoic subcutaneous area measuring 4 cm x 1.3 cm x 1.4 cm (W x AP x L), with few cystic/fluid-filled foci. The largest focus measuring 0.8 cm x 0.3 cm x 0.8 cm and corresponded to the area of discoloration or ecchymosis. A core needle biopsy with subsequent immunohistochemical analysis showed CD31 positivity and features consistent with spindle cell neoplasm of vascular differentiation.



Figure 1. Ecchymosis (arrows) left chest wall noted 15 years after radiation treatment for breast cancer.

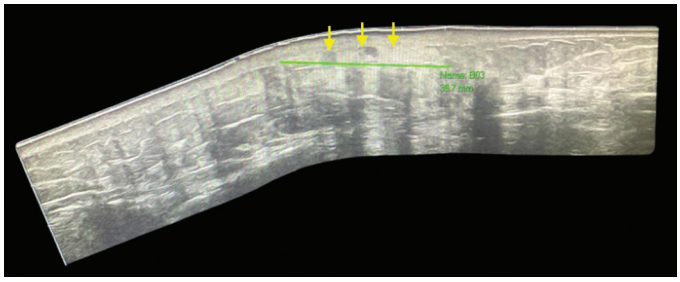


Figure 2. Breast ultrasonography demonstrating an inhomogeneous, predominantly hyperechoic subcutaneous area with a few cystic, fluid-filled foci (arrows) corresponding to the region of ecchymosis.

Contrast enhanced CT of the chest and abdomen (Figure 3) revealed an ill-defined nodular density overlying the left chest wall, with associated skin thickening. No pulmonary or hepatic nodularity was noted. Given the patient's history and these findings, a radiation-induced sarcoma was strongly suspected. She was counseled and subsequently admitted for wide excision of the tumor.

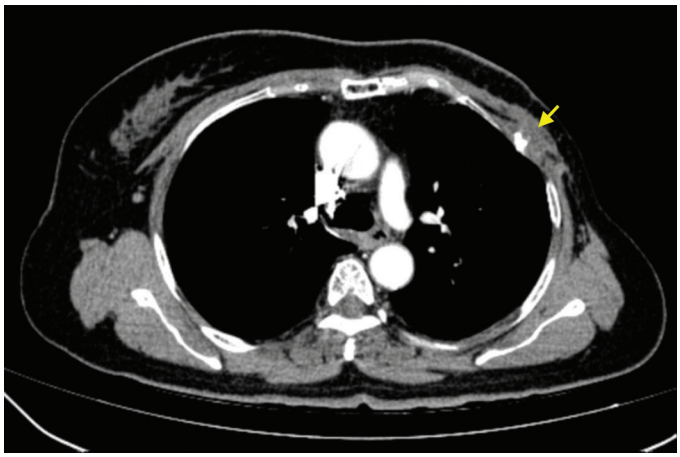


Figure 3. Contrast-enhanced chest CT demonstrating an ill-defined nodular density (arrow) in the left chest wall.

Preoperatively, the breast mass and planned 2-cm resection margins were marked on the skin (Figure 4). Intraoperatively, a 7 cm x 7 cm mass adherent to the chest wall was excised and sent to pathology. Frozen-section analysis revealed the anterior and basal margins were positive for tumor involvement, whereas the superior, inferior, lateral, and medial margins were negative.



Figure 4. Preoperative marking showing the 2 cm margin from the chest wall tumor.



Figure 5. Chest wall with titanium clips (arrows) placed as guides for radiotherapy planning.

Since the basal margin remained positive, rib resection was considered to achieve clear margins. The patient was referred to the thoracic and vascular surgery service for intraoperative assessment. The third and fourth ribs were found to be directly involved in the affected segment, and resection of the involved ribs, including the second through fifth ribs, was recommended. The patient's relatives were consulted regarding the available options: rib resection or placement of metallic clips followed by postoperative radiotherapy. After discussing the potential risks and outcomes, the decision was made to proceed with metallic clip placement (Figure 5). The plastic surgery service subsequently performed a thoracoabdominal advancement flap for wound closure (Figure 6).

Final histopathologic examination of the specimen showed an irregular, yellow, doughy tissue fragment measuring 10.0 cm x 9.0 cm x 2.5 cm and weighing 145.0 g (Figure 7). The overlying skin ellipse exhibited reddish-purple, hemorrhagic, rough patches. Serial sections revealed an ill-defined, nodular, reddish-purple, doughy lesion measuring 3.5 cm × 2.5 cm × 1.5 cm in the central portion of the specimen. Grossly, the



Figure 6. Thoracoabdominal flap closure.

lesion involved the anterior (skin) and posterior (basal) resection margins. The superior, inferior, medial, and lateral margins measured 4.0 cm, 5.5 cm, 5.0 cm, and 3.0 cm, respectively, from the lesion.

Microscopic examination (Figure 8) revealed sheets of atypical spindle cells with mildly pleomorphic, hyperchromatic nuclei, vesicular chromatin, inconspicuous nucleoli, and moderate amounts of

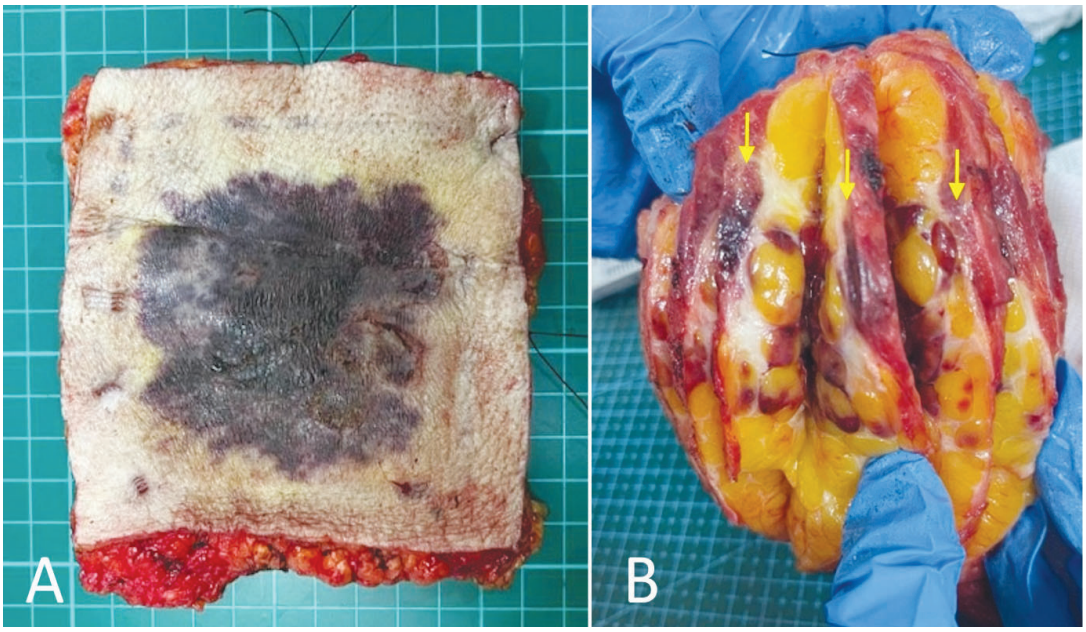


Figure 7. A. Gross section showing an ill-defined nodular, reddish purple, doughy lesion, located in the central region measuring 3.5 cm x 2.5 cm x1.5 cm.
B. Cut sections of gross specimen showing the centrally located mass (arrows) with involvement of the posterior (basal) margin of resection.

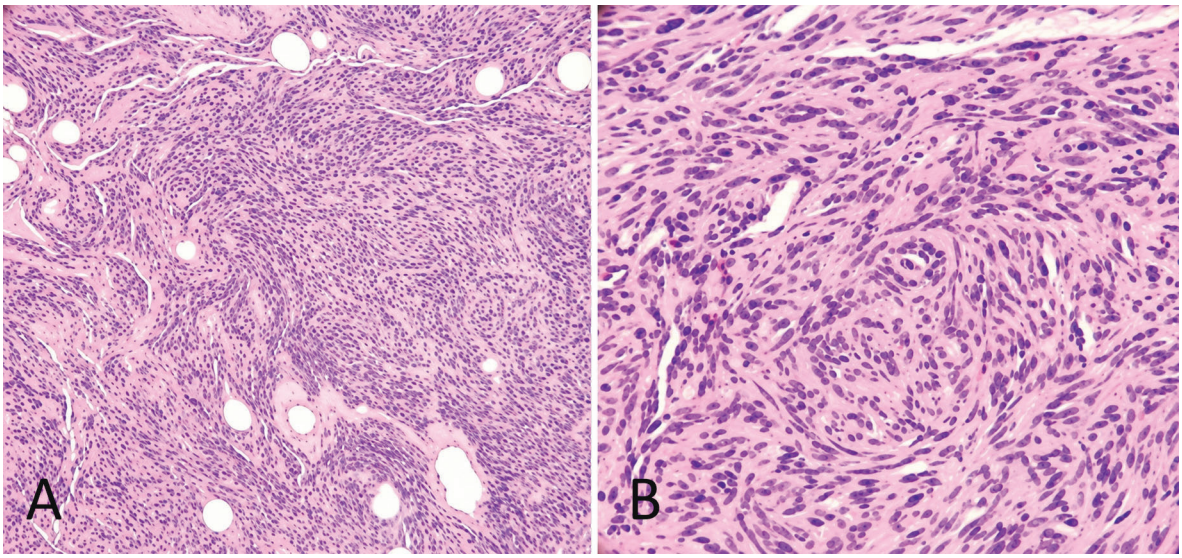


Figure 8. A. Low power and **B**. High power photomicrographs showing sheets of atypical spindle-shaped cells characterized by mildly pleomorphic, hyperchromatic nuclei, vesicular chromatin, inconspicuous nucleoli, and moderate cytoplasm with mild mitotic activity (6 mitotic figures per 10 high power fields)

cytoplasm. Mitotic activity was mild, with six mitotic figures per 10 high-power fields. Areas of hemorrhage and benign breast tissue were also identified. The anterior and posterior (basal) resection margins were positive for tumor involvement. The specimen was diagnosed as a malignant spindle-cell neoplasm. Additional immunohistochemical analysis revealed strong nuclear positivity for ERG and diffuse, strong membranous positivity for CD31 and CD34, while staining negative for pancytokeratin. This endothelial immunoprofile, combined with histomorphological findings and a history of prior radiotherapy, is consistent with a diagnosis of an angiosarcoma.

Postoperatively, the status of breast margins was discussed with the patient. A positron emission tomography (PET) scan revealed non-FDG-avid cortical irregularities and sclerotic changes in the anterior aspects of the left third and fourth ribs suggestive of metastatic lesions with post treatment changes. The patient was referred to medical and radiation oncology, and both services agreed that rib resection would offer the best clinical outcome. The risks and potential complications of the procedure were discussed with the patient and her family, who consented to proceed.

The patient was readmitted and underwent chest wall resection, including resection of the 3rd, 4th, 5th ribs,

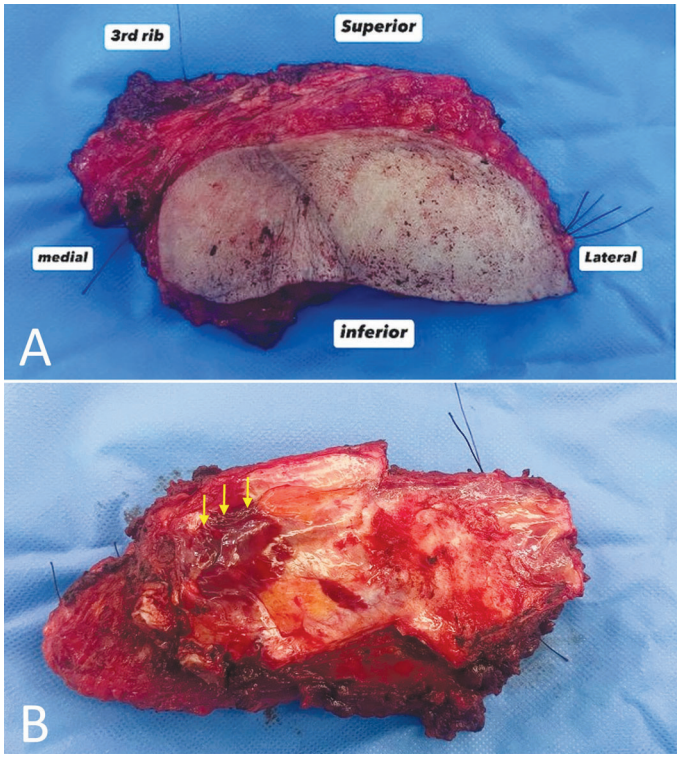


Figure 9. A. Resected chest wall with 3rd to 5th rib measuring 17.0 cm x 9.0 cm x 3.5cm. **B**. Pleural surface of the resected chest wall with 3rd to 5th rib showed a well circumscribed, dark red, hemorrhagic, smooth lesion (arrows), that was positive for tumor cells on frozen section analysis.

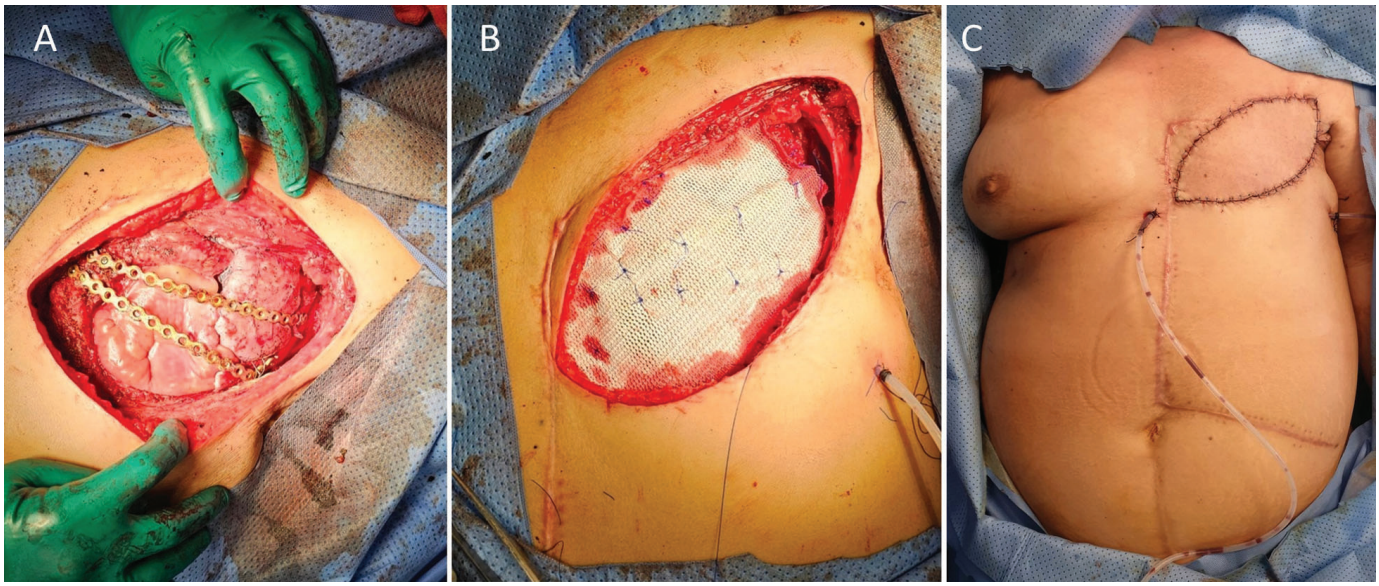


Figure 10. A. Chest wall reconstruction using titanium plates and screws. **B**. Application of mesh on the chest wall. **C**. Skin closure achieved using thoracodorsal flap.

with intraoperative frozen-section analysis. The basal margin of the 3rd rib was positive for tumor involvement (Figure 9) so the thoracic and cardiovascular surgery team proceeded with a wedge resection of the left upper lobe of the lung. Rib reconstruction was subsequently performed using titanium plates and screws. The plastic surgery team then achieved skin closure with a thoracodorsal flap (Figure 10).

Discussion

Radiation is an important component of treatment of patients with primary breast cancer, from early-stage disease to locally advanced and metastatic cases. Despite advances in radiation therapy to allow targeted treatment and reduce doses, studies showed that breast cancer patients have a fivefold higher risk for RIS than controls who received no radiation.[6]

Radiation induced sarcoma is a well-known treatment complication and constitutes 2.5-5.5% of all sarcomas. The post-radiotherapy 10-year cumulative risk for developing RIS is estimated to be 0.03-0.8%.[7] The etiology of RIS in the breast remains to be controversial, however, some studies have reported that DNA damage repair might induce some gene variants associated with second malignant neoplasm.[8] Several studies have suggested a dose-response effect between the amount of radiation and the risk for RIS with studies suggesting that a minimum total dose of 10 Gy in conventional doses per fraction appears necessary to result in RIS.[9,10] For this case, the patient underwent radiotherapy over a period of a month, unfortunately, the authors were unable to retrieve radiation dose given.

To classify a tumor as a RIS, Cahan and colleagues proposed the following criteria: (a) there must be evidence of an initial malignant tumor of a different histology than the putative RIS, (b) development of the sarcoma must occur in the previously irradiated field, (c) a prolonged latency period, typically greater than 4 years, between the two malignancies, and (d) histopathologic confirmation that the second malignancy is a sarcoma.[3]

In this case, the patient was able to satisfy all the criteria mentioned as she was initially treated for and subsequently developed a mass within the irradiated field 15 years after radiotherapy. Final histopathologic examination revealed a malignant spindle-cell neoplasm with vascular differentiation, supported by CD31 positivity.

Consistent with the patient's presenting complaint during follow-up, which was a palpable lump at the site of the primary tumor associated with an enlarging, tender hematoma, RIS of the breast typically present as a painless mass or diffuse breast enlargement, often accompanied by bluish, reddish, or purple discoloration of the overlying skin.[11] Mammography and breast ultrasonography may not initially raise suspicion for malignancy. [11] Therefore, a high index of suspicion and careful clinical evaluation are essential. Biopsy should be performed because histopathologic examination is required to establish the diagnosis.

Due to the rarity of RIS, no prospective trials have established a standard of care for its management. Existing studies have shown that neither chemotherapy nor radiotherapy alone was sufficient for RIS treatment and do not improve overall survival.[3] However, systematic reviews have emphasized that complete surgical excision, particularly wide local excision with negative margins, is critical.[11,13]

Positive resection margins are associated with a significantly higher risk of local recurrence. In 2015, Thijssens et al reported that patients who underwent R0 resection, defined as microscopically negative margins, had better survival than those who underwent either R1 resection, defined as microscopically positive margins, or R2 resection, defined as grossly positive margins. No significant difference in survival was observed between patients who underwent R1 and R2 resections.[14]

In this case, the absence of preoperative planning and counseling regarding possible chest-wall involvement resulted in an R1 resection during the initial operation. This highlights the importance of maintaining a high index of suspicion for chest-wall involvement in patients with breast RIS. The possibility of chest-wall excision should be discussed with all patients preoperatively.

Studies have shown that patients with RIS generally have poor prognosis with a 5-year survival rate reported to be in the range of 27% - 48%.[15] Tumor size was noted to be the most important prognostic factor with 80 months median survival time for tumors < 2 cm vs 20 months for tumors > 5 cm.[16] Given these statistics, it is imperative that surgical treatment be planned and offered to patients once diagnosis has been established.

Conclusion

Radiation induced sarcoma is a rare and aggressive disease with poor overall survival. Due to its rarity, uncertainty regarding its diagnosis and management remains. Patients should be counseled on the importance of surveillance, long term oncologic follow-up, and prompt evaluation of any new lesions within the irradiated field. A high index of suspicion is essential for early diagnosis. Complete surgical resection with negative margins remains to be the treatment option associated with the most benefit. Preoperatively, patients should be counseled and prepared for the possibility of chest wall resection to achieve R0 resection.

Consent for Publication

Informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Ethical Approval

This case report had been deemed exempt from ethics review by the East Avenue Medical Center Institutional Review Board, as it involved a single patient with anonymized data who consented for its publication.

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