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Radiation-induced undifferentiated pleomorphic sarcoma of the breast: a rare but serious complication following breast-conserving therapy. A case report and literature review

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SUMMARY: **Radiation-induced undifferentiated pleomorphic sarcoma of the breast: a rare but serious complication following breast-conserving therapy. A case report and literature review.**

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Background. *Undifferentiated pleomorphic sarcoma (UPS) of the breast is an extremely rare, but aggressive subtype of sarcoma that can develop in radiotherapy (RT)-treated breast cancer patients. Due to the low incidence, there are many uncertainties regarding the adequate management of these tumors. We present a rare case of radiation-induced UPS in a 63-year-old woman who had undergone breast conserving therapy for invasive ductal carcinoma of the left breast, six years prior to presentation.*

Case presentation. *A 63-year-old woman presented with a rapidly growing left breast mass. She had been diagnosed with invasive ductal carcinoma of the left breast for which she underwent a left upper outer quadrantectomy and ipsilateral axillary dissection followed by RT, six years previously. During her routine oncologic follow-up, the mammography revealed a dense, nodular opacity with microcalcifications. The breast ultrasound (US) confirmed the presence of the nodule. US-guided fine needle aspiration biopsy was performed and the diagnosis of UPS was made, the reason for which the patient underwent wide local excision of the left breast.*

Conclusion. *The diagnosis of RT-induced UPS is challenging and often missed due to the low incidence, long latency period, unspecific imaging findings, and difficulties in clinical and histological detection of these lesions. These tumors should be considered in differential diagnoses of rapidly-growing breast masses in previously RT-treated breast cancer patients, as they can mimic the local recurrence of the primary tumor. Since the prevalence of breast-conserving surgery followed by RT has been increasing, the careful monitoring of at risk patients is of utmost importance, as UPSs are highly aggressive tumors associated with very poor outcomes.*

KEY WORDS: Breast cancer - Radiation therapy - Sarcoma - Radiation-induced sarcoma - Undifferentiated pleomorphic sarcoma - Breast conserving therapy - Case report.

Introduction

In the last two decades, breast-conserving therapy (BCT), consisting of breast-conserving surgery (BCS) followed by adjuvant radiotherapy (RT), has become the standard treatment modality for early-stage breast cancer (1). Adjuvant RT has been shown to be highly effective in reducing the risk of local disease recurrence, increasing the rate of breast preservation, and improving the quality of the patient's life; however, it is not devoid of complications (2).

Radiation-induced sarcoma (RIS) is a rare, but recognized complication of RT and is associated with very poor outcomes. RISs of the breast account for 0.5% to 5.5% of all sarcomas. The cumulative risk of soft tissue and bone sarcomas in breast cancer patients treated with RT has been reported to be 0.2% at 10 years (2, 3). The diagnostic criteria for RIS was first described by Cahan et al. (4) in 1948 and later modified by Murray et al. (5) and include (a) development of the sarcoma within the previous-

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ly irradiated field or its adjacent tissue, (b) the latency period of at least 3-4 years, and (c) a histologic confirmation of sarcoma.

Undifferentiated pleomorphic sarcoma (UPS) of the breast is an extremely rare subtype of sarcoma that can develop in previously RT-treated breast cancer patients. The low incidence of this tumor, in addition to the lack of published data in the literature, has led to many controversies regarding the adequate management of affected patients. Since BCT has become highly popular, the careful monitoring and close follow-up of BCT-treated patients are of utmost importance, as these tumors once developed, are extremely aggressive and associated with very poor outcomes.

We present a rare case of radiation-induced UPS in a 63-year-old woman who had undergone BCS followed by adjuvant RT for invasive ductal carcinoma, six years prior to presentation.

Case report

A 63-year-old Caucasian woman was referred to the General Surgery Unit, Breast Division of the University Hospital of Messina, Messina, Italy, with a rapidly growing left breast mass. Her family history was unremarkable. Her past medical history included hypertension for which she was taking antihypertensive drugs. Moreover, she had been diagnosed with the cancer of the left breast for which she underwent a left upper outer quadrantectomy and ipsilateral axillary dissection six years previously. The primary tumor was a 3.0 x 2.0 cm invasive ductal carcinoma with intermediate nuclear grade (G2), with no evidence of lymph node metastasis (pT1cN0Mx). The resection margins were all negative. Immunohistochemistry showed estrogen receptor (ER) positivity of 30%. Progesterone receptor (PR) was negative (0%) and androgen receptor (AR) positivity was 10%. HER-2 was negative. The right breast and axillary lymph nodes were normal.

One month after the operation, she received four cycles of adjuvant chemotherapy consisting of epirubicin and cyclophosphamide, and consequently, on the third postoperative month, she received adjuvant RT for a duration of six weeks. The dose delivered to the whole breast was 50 Gy in 25 fractions using tangential fields of 4 MV photons, and the boost dose to the primary tumor bed was 10 Gy in 5 fractions using 9 MeV electron beam. Adjuvant RT was well-tolerated and no specific complications were observed. After completion of RT, she started hormone therapy with letrozole.

She has been undergoing outpatient oncologic follow-up since then. On the last mammographic control performed one month prior to the patient's presentation, a dense, nodular opacity with microcalcifications was incidentally detected in the left upper outer peri-areolar region (Figure 1).

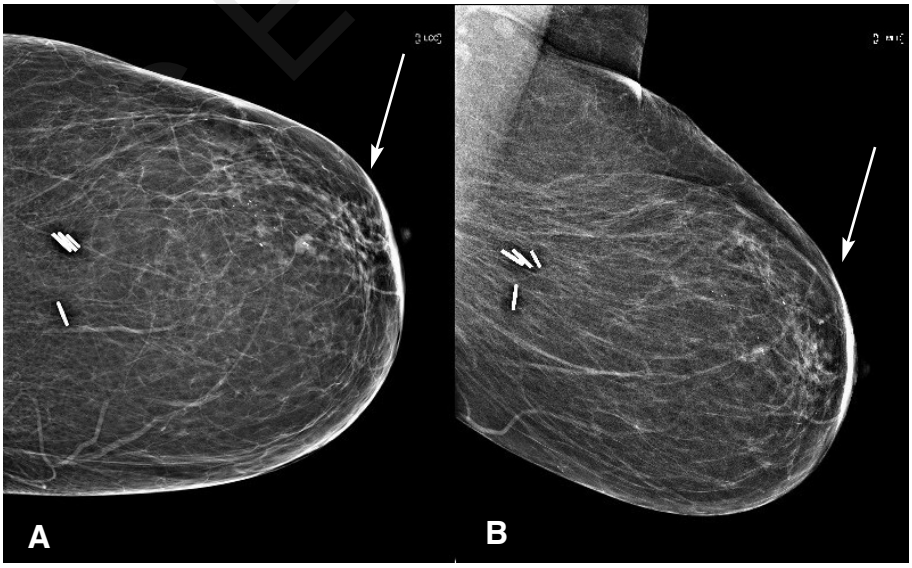

Figure 1 - (A) Craniocaudal and (B) mediolateral oblique views of the mammogram demonstrating a dense, nodular opacity with microcalcifications (arrows) in the left upper outer peri-areolar region.

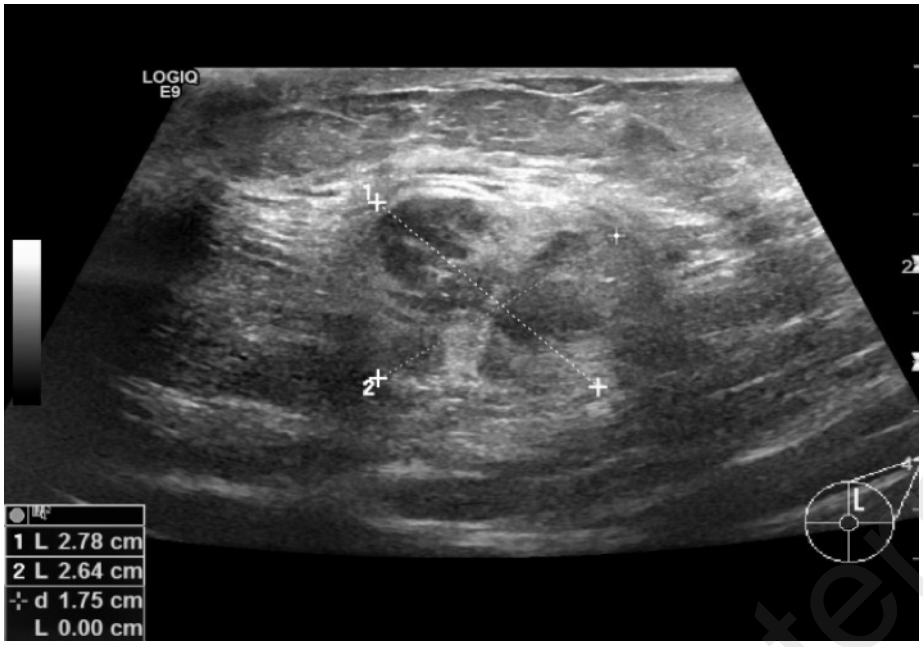

Figure 2 - Ultrasound of the left breast demonstrating a 17 mm oval, lobulated, inhomogenous, hypoechogenic mass with solid echostructure.

The nodule had not been seen on mammography and ultrasound (US) exams performed one year before. The right breast was normal. US examination was conducted using a 5-12 MHz linear probe and revealed a 17 mm oval, lobulated, inhomogeneous, hypoechogenic mass with solid echostructure (Figure 2). On the color Doppler ultrasonogram, the mass showed some vascularity. On physical examination, a firm but painless oval mass, with distinct margins, around 2-3 cm in diameter, was palpated in the upper outer quadrant of the left breast. The ipsilateral and contralateral axilla and the right breast physical examination were unremarkable.

US-guided fine needle aspiration biopsy (FNAB) of the mass was performed. The histologic results showed cellular connective tissue with spindle-shaped, fibroblast-like cells and enlarged, hyperchromic, atypical nuclei. Extensive fibroblast proliferation associated with collagen necrosis was reported as post-radiation changes. The diagnosis of UPS was made and the patient underwent a wide local excision (WLE) of the left breast.

On gross examination, the surgical specimen revealed a 3 cm greyish-whitish, solid, firm central tumor arising in the deep soft tissue, around 4 cm beneath the overlying skin. The microscopic examination of the prepared sections from the surgical specimen showed a highly cellular neoplastic proliferation of mesenchymal origin composed of voluminous oval to spindle-shaped cells, arranged in interlacing bundles, fascicles, and sheets. Tumor cells showed marked pleomorphic hyperchromic nuclei with hyperchromic, eosinophilic cytoplasm tapering at the end intersecting with each other in a diffuse pattern. Multinucleated giant cells were seen interspersed within the tumor. Numerous atypical mitotic figures and neoplastic emboli were also observed. Wide areas of necrosis and mitotic count of 15-20/HPF were noted. Bizarre cells and lymphocytes were seen admixed with the spindle cells that focally infiltrated adipose tissue. The tumor coincided with the margins of the previous surgical scar tissue. The surgical resection margins were all negative (Figure 3).

On immunohistochemical studies, the tumor cells showed strong and diffuse vimentin positivity. The other immunohistchemical markers such as cytokeratin (CK), CK 5, CK 7, epithelial membrane antigen (EMA), GATA 3, smooth muscle actin (SMA), S-100, MDM-2, desmin, P63, CD 30, CD 31 and CD 34 were negative. Ki-67 expression levels were > 70% (Figure 4). Based on the clinicopathological, histological and immunohistochemical characteristics, the diagnosis of radiation-induced UPS of the breast was confirmed.

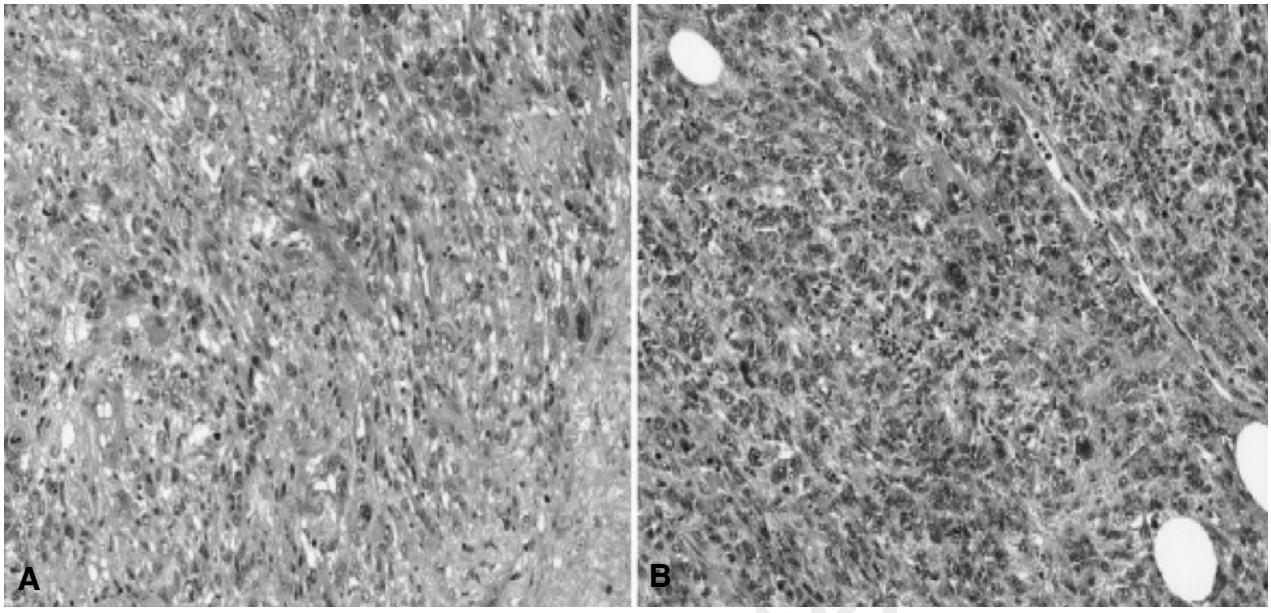

Figure 3 - Histopathological examination of the surgical specimens demonstrating (A) voluminous oval spindle-shaped tumor cells with marked pleomorphic hyperchromic nuclei, with hyperchromic eosinophilic cytoplasm, arranged in interlacing bundles, fascicles, and sheets. (B) Large areas of necrosis with bizarre cells and lymphocytes are seen admixed with the spindle cells that focally infiltrate the adipose tissue.

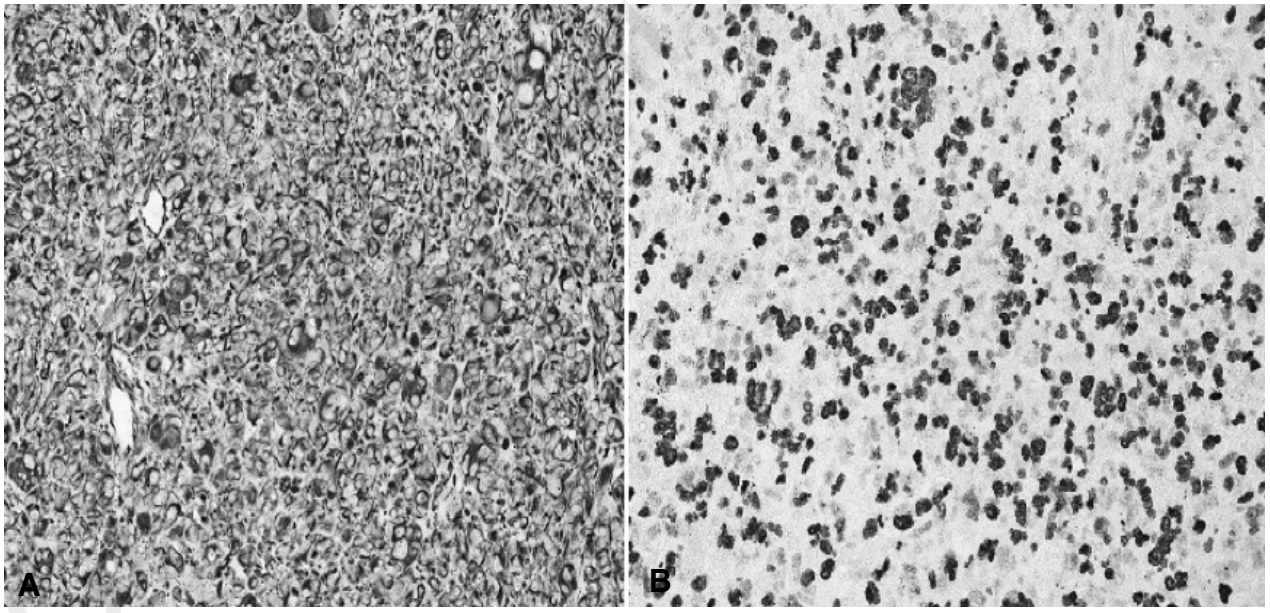

Figure 4 - (A) Immunohistochemical studies demonstrating the tumor cells that exhibit strong and diffuse vimentin positivity. (B) Other immunohistchemical markers such as cytokeratin (CK), CK 5, CK 7, epithelial membrane antigen (EMA), GATA 3, smooth muscle actin (SMA), S-100, MDM-2, desmin, P63, CD 30, CD 31 and CD 34 are negative.

Discussion

RIS, a rare iatrogenic malignancy, is recognized as a late complication of RT and is associated with very poor outcomes. In the last two decades, the growing popularity of BCS followed by adjuvant RT in the treatment of early-stage breast carcinoma has led to an increased tendency for the development of these sarcomas (6). Multiple clinical trials have documented that adjuvant RT significantly increases

the rate of sarcomas in breast-cancer treated patients (7). The reported cumulative incidence of sarcoma at 15 years is 0.32% for patients receiving RT, which is higher compared to the patients who do not receive it (0.23%) (8). Patients who develop RIS are generally young when diagnosed with primary breast cancer (range 26-54; median 43 years) (9). Angiosarcoma, UPS, and fibrosarcoma are known to be the most common subtypes of RIS of the breast following BCT (2, 5).

Radiation-induced neoplastic transformation is thought to be a multistage carcinogenesis process. Over the course of the years, irreversible DNA damage can lead to the accumulation of dominant gene mutations and gene deletions in the genome that can progressively lead to the development of sarcoma (10). Although the exact molecular mechanisms of tumor promotion are unknown, expression of Proto-oncogene c-jun and inactivation of tumor suppressor genes P53 and Rb have been thought to be the most probable theories (11). The exact relationship between the total irradiation dose and RIS is unknown; however, it is clear that the higher the radiation dose, the higher the risk of development of breast sarcomas (12). Minimum total radiation doses of 10 Gy per fraction appear to be enough to cause RIS; however, most cases of RIS occur in association with total radiation doses of about 40-50 Gy (13).

UPS is an extremely rare subtype among RISs of the breast. Although the precise histogenesis of the tumor still remains unclear, it is believed that it probably originates from the tissue histiocytes that are capable of acting as facultative fibroblasts. Another presumption is that it is a primitive mesenchymal tumor capable of dual differentiation towards fibroblast or histiocyte (14).

Breast UPS needs to be distinguished from undifferentiated carcinomas and other sarcomas. Pathological diagnosis is challenging and often delayed due to lack of symptoms, atypical imaging features, unusual histological texture, and a low incidence after a long latency period (15). There are no pathognomonic imaging features of RIS (2). Mammographic studies may reveal an irregular high-density mass, although in some cases they can even be negative (16, 17). On the US exam, the tumor usually presents as a well-demarcated, oval, inhomogeneous, solid and cystic mass with areas of necrosis, associated with increased blood flow in the solid component on color Doppler ultrasonogram (18). Magnetic resonance imaging (MRI) can be helpful in pre-operative surgical planning as it can reveal the local extension of the tumor and predict the degree of chest wall involvement (3, 15).

A definite diagnosis could be based on a careful histopathological and immunohistochemical examination on tissue samples taken by tru-cut or FNAB (14). The presence of fibroblast-like and histiocyte-like cells, mixed with pleomorphic giant and inflammatory cells in a previously irradiated area, after an appropriate latency period, could be useful hints for diagnosis of radiation-induced UPS (19). On immunohistochemical studies, the cells stain positive for vimentin and negative for cytokeratin, intermediate proteins typically used as specific markers for cellular differentiation toward mesenchymal and epithelial type, respectively (20, 21). The tumors generally present after a long latency period, generally ranging from 3 to 34 years (22).

The UPS of the breast is a very aggressive tumor with a high rate of local recurrence and distant metastases, particularly in the lungs, but also to bony skeleton, pleura, and liver; regional lymph nodes involvement ranges from 12% to 32% (20, 23). Occasional skin and subcutaneous soft tissue metastases have also been reported at terminal stages (24, 25).

The treatment of choice for the UPS or any other sarcoma of the breast is surgery. The standard therapy is mastectomy preferably with excision of pectoral muscles, in order to minimize the rate of local recurrence (14, 25). Another surgical approach is breast-preserving WLE with adequate negative margins, particularly for tumors smaller than 5 cm (26). The usefulness of axillary lymph node dissection in breast UPS is still questioned. While some authors believe that due to the low incidence of regional lymph node involvement axillary lymph node dissection is unjustified (14, 27), others strongly recommend the procedure due to the aggressive nature of the tumor (20, 26).

The role of adjuvant therapy in the treatment of breast UPS is controversial (21). The RT and chemotherapy are generally not recommended in

cases of negative surgical margins. RT could be considered for patients with histopathologically observed tumor cell involvement of surgical margins (20, 27). Chemotherapy has been shown to be ineffective in the treatment of these tumors, and hormone therapy by far has no place in clinical practice (14, 23, 27).

The prognosis of radiation-induced UPS of the breast is very poor. Deep and large tumors at the time of presentation have been found to be associated with a higher rate of local recurrence, distant metastasis, and mortality (28, 29). High rates of local recurrence after WLE and simple mastectomy have been reported, 67% and 54%, respectively (14). The reported survival rate in the literature ranges from 40% to 60% after 2 years, and from 20% to 35% at 5 years (13).

Conclusion

Radiation-induced UPSs of the breast are extremely rare, but highly aggressive iatrogenic malignancies that are associated with very poor outcomes. The diagnosis of these tumors is hindered and often even missed due to the their low incidence, long latency periods, unspecific imaging characteristics, and difficulties in their clinical and histological detection in the previously irradiated, fibrotic, and distorted breast tissue. Surgeons should consider these tumors in differential diagnoses of rapidly-growing breast masses, especially in previously RT-treated breast cancer patients, as they can easily mimic the local recurrence of the primary tumor. As the prevalence of BCT has been increasing, the careful monitoring and close follow-up of BCT-treated patients is of utmost importance. We believe that documentation of the sporadic cases of radiation-induced UPS of the breast and their management by different surgeons is essential as it can aid in increasing the surgeons' knowledge and awareness regarding the most suitable diagnostic and therapeutic approaches to these tumors.

Declarations

All Authors declare that they have no conflict of interests or disclosures.

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

Ethical approval: N/A.

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