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SARCOMA PLEOMÓRFICO DE MAMA RADIOINDUZIDO PÓS-TRATAMENTO CONSERVADOR DE CÂNCER DE MAMA INICIAL – RELATO DE CASO

Radiation-Induced Undifferentiated Pleomorphic Sarcoma after Breast Conservative Therapy: A Case Report

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Radiation-Induced Undifferentiated Pleomorphic Sarcoma after Breast Conservative Therapy: A Case Report

Trabalho de Conclusão de Curso apresentado ao Instituto Nacional de Câncer José Alencar Gomes da Silva como requisito parcial para a conclusão da Residência Médica em Mastologia

Orientador: Prof. Dr. Marcelo Morais Barbosa

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ABSTRACT

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Introduction: Breast sarcoma is a rare form of malignancy that arises from connective tissue, comprising less than 5% of all sarcomas. Undifferentiated pleomorphic sarcoma (UPS) of the breast is a rare and aggressive subtype of radiation-induced sarcoma that can arise in treated breast cancer patients. The diagnosis is challenging and often missed due to the low incidence, long latency period, unspecific imaging finding, and difficulties in clinical and histological detection.

Case report: A 56-year-old woman was diagnosed with early-stage triple-negative breast cancer in 2013 and underwent breast-conserving therapy (BCT). After 5 years follow-up, she developed mastalgia and breast induration, and behind mammography and ultrasound without suspicious lesions, a Magnetic Resonance Imaging (MRI) was performed and showed a highly suggestive of malignancy mass measuring 8.0cm and invading chest wall. The core biopsy revealed a spindle cells malignant tumor, negative for pan cytokeratine and most of immuno-histochemical (IH) markers, suggesting sarcoma, but requiring study of surgical specimen to exclude Metaplastic Carcinoma. She underwent Halsted Radical Mastectomy, full-thickness left anterior chest wall resection contemplating segments of the 4th and 5th ribs and reconstruction with synthetic mesh. The surgical specimen evidenced a UPS, with clear margins. The patient had good postoperative recovery, and remains the follow up with the Ma team.

Keywords: Sarcoma; Breast Neoplasms; Neoplasms, Radiation-Induced; Neoplasms, Second Primary.

LIST OF ILLUSTRATIONS

LIST OF ABBREVIATIONS

RT	Radiation therapy
SLNB	Sentinel lymph node biopsy
Gy	Gray
UPS	Undifferentiated pleomorphic sarcoma
BCT	Breast-conserving therapy
MRI	Magnetic Resonance Imaging
IH	Immuno-histochemical
RIS	Radiation-induced Sarcomas
US	Ultrasound

SUMMARY

INTRODUCTION

Radiation therapy (RT) is an essential component of breast conservation therapy; its use provides control of microscopic residual disease, permitting lower rates of recurrent disease and improved survival[1]. Despite the proven benefit, the appearance of neoplastic events is a recognized complication attributed to RT [1].

The potential for the development of radiation-induced sarcomas (RIS) is increasing because of the growing popularity of breast conservation surgery followed by irradiation in the treatment of mammary carcinomas [2]. Breast sarcoma is a group of heterogeneous non-epithelial tumours that arise from mesenchymal tissues of the breast. Subtypes include angiosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma and undifferentiated pleomorphic sarcoma (UPS), which was previously known as malignant fibrous histiocytoma [3].

Sarcomas are a rare, but recognized, complication of RT for breast carcinoma, and are associated with poor prognosis [4]. A case of breast UPS secondary to a RT for mammary cancer is presented with discussion of the challenges in the diagnostic and management.

CASE REPORT

A 56 years-old woman, obese, diabetic, negative family history of cancer, was diagnosed in 2013 at “Instituto Nacional do Câncer” (INCA) with a high grade Invasive Ductal Carcinoma of no special type (IDC-NST) in the left breast, hormone receptors and HER-2 (human epidermal growth factor receptor-type 2) negative, Ki67 60%, clinical stage IA. The patient underwent breast conservative surgery and sentinel lymph node biopsy (SLNB), in the surgical piece the tumor had 1,0cm, clear margins and lymph nodes free of metastatic cells. After surgery she had adjuvant chemotherapy (Adriamycin/ Cyclophosphamide), 21 sessions of radiotherapy and hormone therapy.

After 5 years follow up, the patient complained of pain and induration of the left breast, and physical examination, mammography and ultrasound were performed, with changes attributed to previous cancer therapy. In July of 2020, beyond the induration (Figure 1), she presented chest pain limiting arm movement and no suspicious axillary lymph nodes, then was requested a new mammography with BI-RADS® (Breast Imaging-Reporting & Data System) assessment category 2: benign findings (Figure 2).

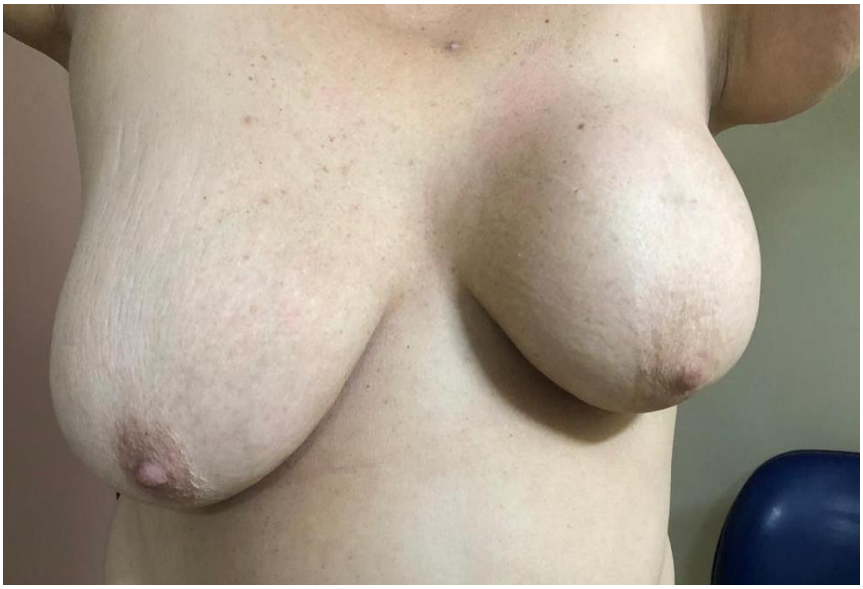

Figure 1 — Alteration of the morphology of the left breast, showing to be more globose, which can be confused with the post-surgical aspect.

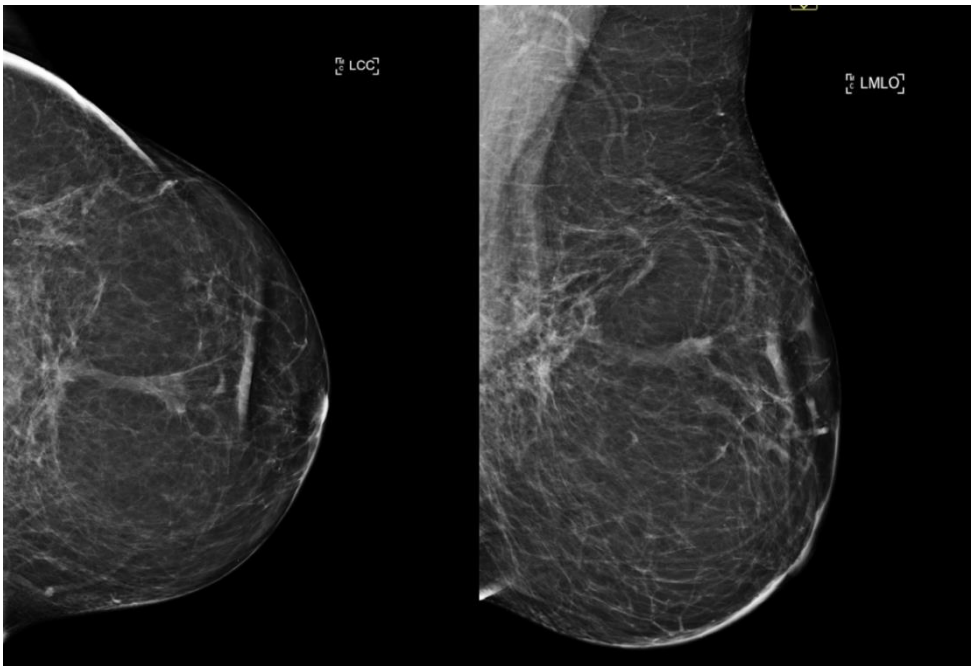

Figure 2 — Mammography showing architectural distortion by surgery on the left breast. BIRADS 2 (benign findings).

As there was clinical-radiologic disagreement a 1,5 Tesla breast Magnetic Resonance Imaging (MRI) was performed that showed an irregular, spiculated, contrast-enhanced mass, invading chest wall, including the 4th e 5th left ribs, measuring 8,0 x 7,0 x 4,5

cm, in the posterior third of the central area of the left breast, BI-RADS® 5 (highly suggestive of malignancy) (Figure 3).

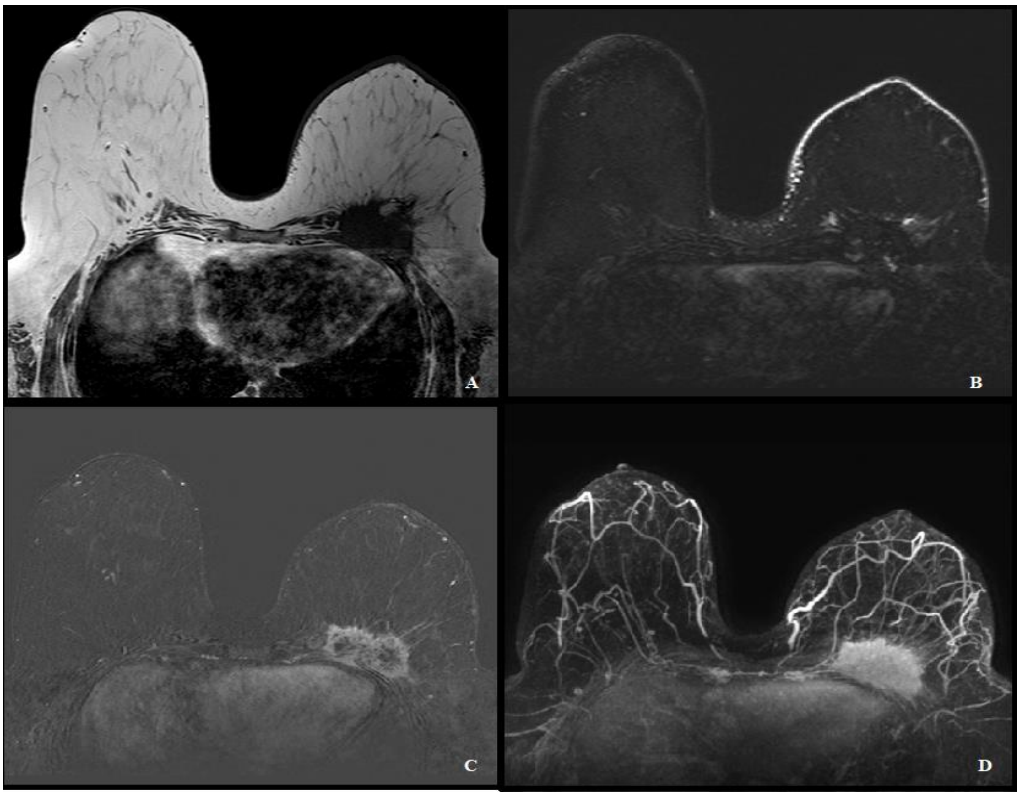

Figure 3 — MRI was performed that showed an irregular, spiculated, contrast-enhanced mass, invading chest wall, including the 4th e 5th left ribs, measuring 8,0 x 7,0 x 4,5 cm, in the posterior third of the central area of the left breast, BI-RADS® 5 (highly suggestive of maligancy). A) Hypointense mass at T1-weighted. B) Edema and thickening skin, which may represent post-surgical and post-actinic changes on the left breast. Hypointense mass in T2-weighted. C) Mass in the left breast showing heterogeneous contrast enhancement. Some areas do not impregnate contrast and may represent a necrotic component. D) Maximal intensity projection (MIP) image from contrast-enhanced MRI shows an irregular and piculated mass.

Afterwards a MRI-Directed (“Second-Look”) Ultrasound (US) was performed to guide a histopathological study, in the US it corresponded a hypoechoic, irregular, spiculated mass, in the posterior third of the breast, near to the anterior axillary line (Figure 4).

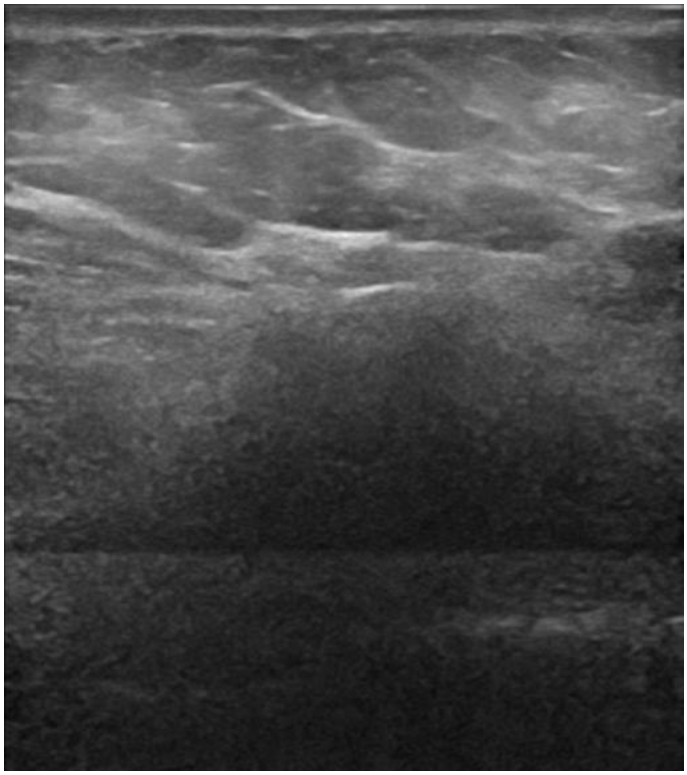

Figure 4 — US “Second-Look” corresponded to a hypoechoic, irregular, indistinct mass, no significant flow on color Doppler, of a posterior location that was only possible to be observed in the vicinity of the left anterior axillary line. This case highlights the importance of always looking at the entire breast, which ranges from the infraclavicular region to the inframammary fold and the middle axillary line to the sternal region.

Through a core needle biopsy, 5 good samples were obtained, revealing a spindle cells malignant tumor, hormone receptors and HER-2 negative, ki67 80%, Pan Cytokeratin [AE1/AE3] negative, CK5/6 negative, p63 weakly positive, suggesting sarcoma, but requiring study of surgical specimen to exclude Metaplastic Carcinoma. In the Clinical Staging, head, chest, abdomen and pelvis Computed Tomography scan did not show metastasis.

The patient underwent Halsted Radical Mastectomy, full-thickness left anterior chest wall resection contemplating segments of the 4th and 5th ribs and reconstruction with synthetic mesh (Figure 5). The surgical specimen evidenced an undifferentiated pleomorphic sarcoma (UPS), measuring 8,0cm and infiltrating scheletic muscles and ribs, clear margins and 13 lymph nodes free of metastatic cells. In the postoperative,

the patient had seroma, which was solved after 3 punctures, and remains the follow up with the Mastology team.

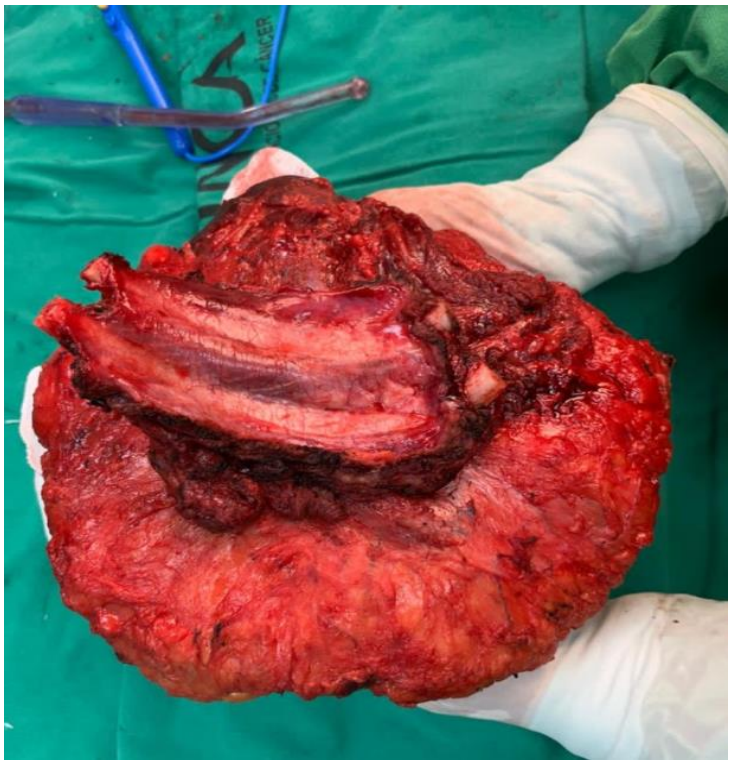

Figure 5 — Surgical specimen of Halsted Radical Mastectomy, total resection of the left anterior chest wall including segments of the 4th and 5th ribs.

DISCUSSION

Breast sarcomas can occur as a primary form without a known precursor and as a secondary form associated with a history of radiation therapy. Some authors describe UPS as the most common histopathological type [5], another's describe angiosarcomas as most common [3,6], regardless, sarcomas following irradiation of breast cancer are rare and cumulative incidence is about 0.2% at 10 years [7]. Occur predominantly in women, primarily in those between 45 and 50 years of age[8]. The average time for the development of the disease is about 10 years after radiation exposure, but the latency period can be as long as 20 years or even as short as 6 months [9,10].

Risk factors are difficult to elucidate and previous radiotherapy has always been considered the principle one [5]. Women who were treated with radiotherapy as part of their initial treatment for breast carcinoma had a 16-fold increase in the risk of

angiosarcoma and a 2-fold increase in the risk of other sarcomas, the increase was especially heightened in the chest wall/breast for any soft tissue sarcoma [9]. Other possible predisposing factors include BRCA mutations, hereditary diseases (such as LiFraumeni syndrome), the radiation site for the initial tumor and the use of alkylator-based chemotherapy [4,6], which, in this case, was used Cyclophosphamide.

Pathogenesis of RIS, including UPS, is poorly understood. Genetic alterations and gebcsnomic injury are proposed mechanisms for radiation-induced tumorigenesis in normal tissues [7,11]. RIS incidence is considered to be a function of radiotherapy dose, most reports of RIS after breast irradiation have been concerned with doses of 60 – 80 Gray (Gy) with a minimal dose of 10 Gy in standard fractionation [4,5]. Establishing a causal relationship between the diagnosis of sarcoma and radiation therapy can be challenging. Cahan's criteria were given by Cahan et al [12] in 1948, which were used to define a RIS. They are currently being used as the standard for demonstration of radio-induced malignancies. The criterias includes 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 an irradiated field, there must be a prolonged latency period (typically 4 years) between the two malignancies, and d) the second malignancy must histopathologically be a sarcoma.

Diagnosis radiation-induced UPS can be challenging, as breast sarcomas are often asymptomatic and radiation-induced changes to the architecture of the breast tissue poses an additional challenge to the physical examination [3]. Breast sarcomas most commonly manifest as a large, painless, mobile mass (mean diameter of 3 cm, reaching up to 30 cm), with a rapid enlarging. Bilateral and axillary involvement are rarely described. [8,13,14].

The initial evaluation of breast sarcoma follows that of any breast mass suspicious for cancer, this includes mammography, ultrasonography and occasional MRI for discordant or equivocal findings [2]. Findings of UPS at mammography and US are nonspecific because may be obscured by the expected posttreatment changes of breast conservation therapy.

The sonographic appearance of UPS of the breast has a similar appearance in the other sites sarcomas. The US depicts usually mass nonhomogeneous and hypoechogenic, with areas of necrosis. Our case has no expression on mammography, presenting changes due to therapy that may have made perception difficult for subtle findings and may also have made mammographic positioning

difficult, without ensuring that most of the tissue was included. In this patient, we observed a hypoechoic, irregular, indistinct mass, and no significant flow on color doppler, of a posterior location that was only possible to be observed in the vicinity of the left anterior axillary line (Figure 3). This case highlights the importance of always looking at the entire breast, which ranges from the infraclavicular region to the inframammary fold and the middle axillary line to the sternal region. MRI provides superior characterization and extent of UPS disease over mammography and US. Also, MRI may help show disease extent, define residual disease after excisional biopsy, and guiding surgical and treatment planning.

Diagnosis of sarcoma in the post-BCT patient is, therefore, similar to other mesenchymal tumors, with core needle biopsy. UPS is typically negative for most Immuno-histochemical (IH) markers.

Metaplastic carcinoma is a differential diagnosis, once, morphologically; it is also a poorly differentiated heterogeneous tumor that contains ductal carcinoma cells mixed with other histological elements, such as squamous cells, spindle cells or other mesenchymal differentiation. IH of metaplastic carcinoma should show at least some keratin or myoepithelial marker expression, although, as in this case, the final diagnosis comes only with the surgical specimen.

The prognosis for post radiation sarcomas is generally poor with 27%-36% 5-year survival and has a high local rate of recurrence and metastasis [3]. Surgery is a standard treatment approach in patients without distant metastasis, and complete resection is considered as the most important factor for long-term prognosis. Lymphatic metastasis is rare in breast sarcoma. Based on the lack of evidence for improved prognosis, lymph node dissection is not performed routinely [15].

Currently, the standard treatment of breast UPS consists in surgical resection with clear margin. Although total mastectomy is often required, partial mastectomy with negative margins does not necessarily compromise the outcome, and SLNB is not warranted. Adjuvant radiation is often utilized in large tumors or following incomplete (R1/ R2) surgical resections. Response to adjuvant chemotherapy is typically low but may be used in patients with large, unresectable tumors. Therefore, treatment for the individual patient must be determined with a multidisciplinary approach, as there are no standard treatment algorithms but a decision considering known prognostic factors and the surgery’s outcome [3].

CONCLUSION

Radiation-induced UPS of the breast is a rare form of radiation-induced breast sarcomas. Diagnosis can be difficult due to its resemblance to benign breast tissue changes in a post irradiation field. All doctors should be aware of this condition, as early diagnosis can change your prognosis. Current treatment for radiation-induced UPS is mainly surgical. Future challenges involve optimizing management to prevent local and distant recurrences to achieve a better prognosis

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