

Case Report

Triple-Negative Synchronous Medullary Carcinoma in a Young Woman Submitted to Mastectomy and Immediate Reconstruction with Prosthesis

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Abstract

Purpose: To describe a case of synchronous bilateral medullary carcinoma with a triple-negative immunohistochemical phenotype in a young woman treated with modified radical mastectomy with skin-sparing, followed by immediate reconstruction by the muscle pouch technique with the inclusion of a prosthesis. **Methods:** This is a case report treated by a Madden modified bilateral radical mastectomy, with skin sparing of the upper quadrants of the breasts by a technique pioneered in Brazil by Figueira in 1984, followed by immediate bilateral reconstruction with a prosthesis. Immunohistochemistry markers were: clone ER-ID5 (DAKO®) for estrogen hormone receptors, clone PgR 636 (DAKO®) for progesterone receptors, c-erb B2, polyclonal (DAKO®) for Her-2 neu protein, clone MIB-1 for Ki-67 and p53 (DAKO®), clone D5/16B4 for CK5/6 (DAKO®), and clone H11 for EGFR (DAKO®). **Results:** This is a rare case of synchronous bilateral medullary carcinoma with a triple-negative immunohistochemical phenotype associated to positivity of Ki-67 and p53 markers and negativity of CK5/6 and EGFR.

Conclusion: To decide surgical management of synchronous bilateral medullary carcinoma in a young women, histological characteristics and immunophenotype must be considered.

Keywords: Mastectomy. Carcinoma, Medullary. Reconstructive Surgical Procedures. Prosthesis Implantation

Introduction

Pure, synchronous medullary carcinoma is rare. Its incidence ranges from 0.1 to 1% because it associates the incidence of pure medullary carcinoma, estimated to be 0.5% of all cases of breast cancer, with that of bilaterality with synchronism, which varies between 0.8 and 3%.¹⁻³ This variation in incidence is due to the different concepts that encompass synchronous carcinoma and to the method of screening for the primary malignant lesion in the contralateral breast. The diagnosis of synchronous bilaterality by means of physical examination, ultrasound and mammography is less accurate for diagnosing women at high risk or with dense breasts, resulting in a lower incidence.⁴ However, when MRI with contrast is used in such cases, the

screening is more accurate and the incidence increases to 1.5%.²

Some of the characteristics of medullary carcinoma are important for its diagnosis. It is more common in young women under the age of 50⁵ and is associated with the predominant familial mutation of the BRCA1⁶⁻⁸ gene and with the immunohistochemical negativity of the hormone receptors for estrogen and progesterone.^{3,5}

As for the prognosis, synchronous medullary carcinoma presents distinct features. The synchronism in these cases causes the lesion to be regarded as being a potential risk for metastasis rather than as a monoclonal

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multifocal lesion.⁵ Nonetheless, the pure medullary type paradoxically affords a better prognosis with a long survival, despite the greater incidence in young patients and the high grade histological characteristics and high rate of proliferation.³

A case of synchronous bilateral medullary carcinoma with a triple negative immunohistochemical phenotype is described in a young woman treated with modified radical mastectomy with skin-sparing, followed by immediate reconstruction by the muscle pouch technique with the inclusion of a prosthesis.

Method

A 35-year-old woman was referred to the Discipline of Mastology (Breast Diseases) of Oswaldo Cruz University Hospital in 2006 as she was complaining of a palpable lump in both breasts.

The patient had a family history of breast cancer, which had been diagnosed in a paternal aunt at the age of 60, and of ovary cancer in a paternal cousin. When asked about symptoms, she reported moderate premenstrual mastalgia associated with a feeling of heaviness and discomfort on touching the breasts. On physical examination, she was found to have average-sized breasts and clinically negative axillae. Well-delimited lumps with a firm and elastic consistency were located at the junction of the lower quadrants, one in the right breast measuring 3.0 cm in diameter and the other in the left breast with a diameter of 1.5 cm, clinically staged as T₂N₀M₀ and T₁N₀M₀, respectively.

On mammography, the breasts displayed a heterogeneous density (3+/4), with a bilateral nodular image, without calcifications or any distortion of the architecture. Ultrasound of the breast confirmed this diagnosis on identifying a hypoechoic, solid, nodular image measuring 2.2 x 1.5 mm in the right breast and 1.3 x 0.9 cm in the left breast, the tumors lying at the junction of the lower quadrants.

After 30 days, the interval between the initial consultation and the patient's return, a tumor diameter of 4.4 cm was seen in the right breast (representing a growth of 130%) and one of 3.5 cm in the left breast (corresponding to a tumor growth of approximately 50%), associated with edema of the skin overlying the tumor mass. A bilateral excisional biopsy with safety margins was performed. The skin was also biopsied in the left breast. The anatomopathological result was a pure bilateral medullary carcinoma with the skin free of neoplasia in the left breast.

The marking of the skin incision used for a reduction mammoplasty was performed on both breasts, followed by a Madden modified radical mastectomy,⁹ with ski-sparing of the upper quadrants of the breasts, a technique pioneered in Brazil by Figueira, in 1984. For the immediate bilateral reconstruction of the breast, divulsion of the pectoris major muscle was performed medially as far as the lateral border of the sternum and, inferiorly (below the insertion of the pectoral muscle), as far as the cranial edge of the *musculus rectus abdominis* and *musculus obliquus* extemus. Laterally, part of the serratus muscle was then divulsioned to create a space in which to insert the prosthesis. The muscle pouch was then prepared by drawing together the pectoris major and the serratus muscles, with a prosthesis, by continuous suture and the remaining skin molded over the pouch. The final appearance of the surgical wound was a T inverted (Figure 1).

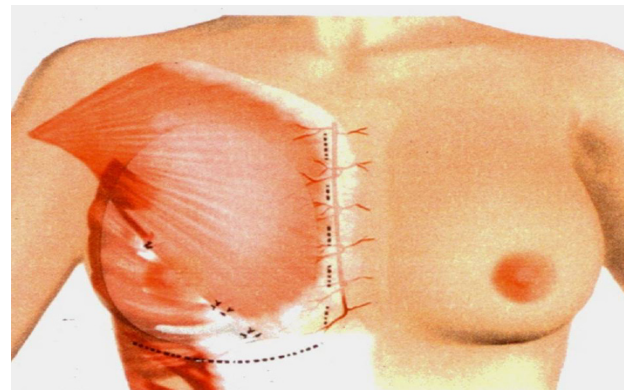


Figure 1 - Inclusion of the prosthesis with suture of the greater pectoral and serratus muscles: The dotted line shows the limits of the dissection with sparing of the intercostal perforating arteries. Prosthesis inserted in the retro-muscular position.

The anatomopathological examination of the surgical specimens of the breasts and content of the axillae revealed a bilateral medullary carcinoma, histological grade 3 / poorly differentiated (tubular formation: score 3; nuclear grade: score 3; mitotic index: score 3 ; sum of the scores = 9), skin, and margins without neoplasia (Figure 2A,2B). Immunohistochemistry revealed negativity of hormone receptors for estrogen (clone ER-ID5; DAKO®) and progesterone (clone PgR 636; DAKO®) Her-2/neu protein (c-erb B2, polyclonal) (Figure 3), associated with positivity of Ki-67 markers (clone MIB-1; DAKO®) (70%) (Figure 3) and p53, and negativity of CK5/6 (clone D5/16B4, DAKO®) and EGFR (clone H11, DAKO®).

The patient was submitted to adjuvant chemotherapy using fluorouracil (500 mg/m²/

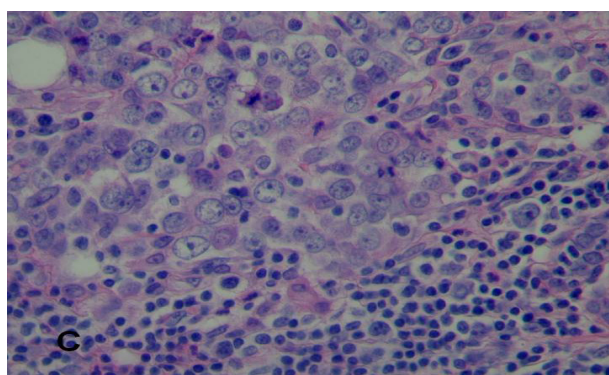
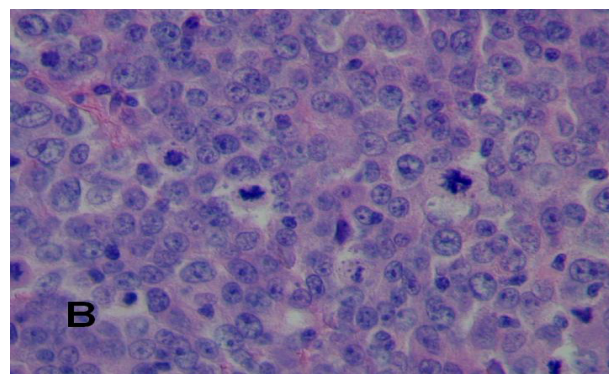
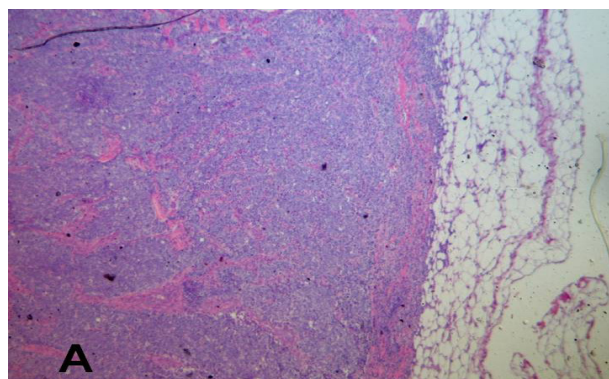
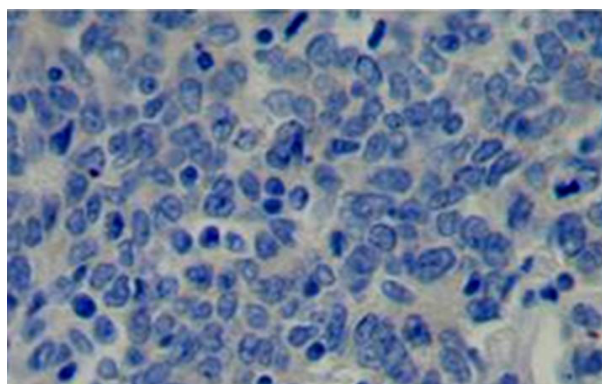


Figure 2 (A-C) – Histopathological features of the lesion: (A) Rounded expansive margins (HE, 25X); (B) Nuclear grade 3 neoplastic cells with a high rate of mitosis (HE, 400X) ; (C) Pattern of syncytial growth with infiltration of lymphocytes in the stroma (HE, 400X)

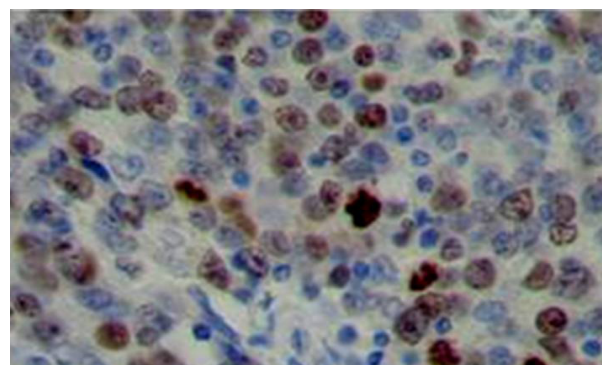
adriablastine (50 mg/m²) / cyclophosphamide (500 mg/m²) (FAC), every 21 days (six cycles). The preparation of the areola and nipple complex was done after the chemotherapy with rotation of the local flap and free graft.

Discussion

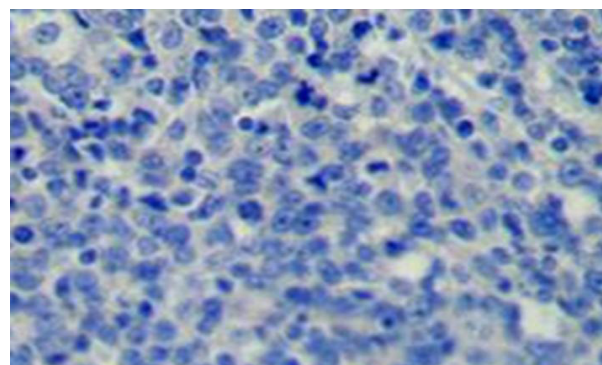
This is a rare case of pure bilateral synchronous carcinoma, particularly on account of the triple



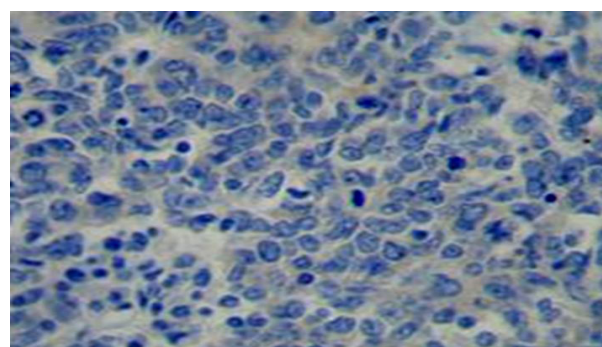
Absence of immunosuppression of cytoplasmic membrane for HER-2(score 0) (400x)



High proliferative index expressed by nuclear positivity for KI-67 in 70% of the neoplastic cell



Negativity forestrogen receptor



Negativity for progesterone receptor

Figure 3 – Histochemical immunophenotypes

negativity and probable association with the phenotype of basal-like carcinoma, which was not confirmed by immunochemistry. There are three important independent, but complementary aspects to be addressed in this case: the medullary histological type, the synchronism and the immunophenotype.

A study involving 1,490 cases of breast cancer identified a frequency of 2.6% pure medullary carcinomas and sounded the alert to the need to obey to diagnosis criteria, including: expansive tumor margins, syncytial growth pattern in over 75% of the tumor, total absence of glandular or tubular structures, diffuse lymphoplasmocytic stromal infiltrate (Figure 2C), poorly differentiated nuclear grade 2 or 3 cells, and numerous mitotic cells (Figure 2B).³ All these criteria were present in the histopathological examination of this case.

The medullary histological type, although rare, is considered to have a good prognosis. A cohort study comparing disease-free survival for ten years following Mastectomy, in 46 medullary carcinoma patients with that of 1,444 patients with infiltrating ductal carcinoma, taken as the control group, identified a significantly higher rate of survival for the former (94.9% and 77.5%, respectively).³

Vo et al.,¹⁰ following up 1,645 breast cancer patients at stages I and II, 1,485 of them with infiltrating ductal carcinoma and 37 with medullary carcinoma, all of whom underwent conservative surgical treatment, report that the disease-free period and rate of local regional recurrence are the same for both types, which does not justify mastectomy for medullary carcinomas. This being so, the histological type of the carcinoma of the patient in question would not, in itself, justify the radical management adopted, so other parameters were taken into consideration.

The bilaterality of carcinoma is classified as synchronous or metachronous (or asynchronous), in accordance with the elapsed time prior to the appearance of the lesion in the contralateral breast. This period varies from author to author, from one month to two years, which makes difficult to estimate frequency and make comparisons between studies.^{2,11} Disregarding the classification of synchronicity, the rate of bilaterality of breast cancer ranges from 1.2 to 20%,^{5,12-13} but synchronous bilaterality shows a much lower rate, ranging from 0.8 to 3%^{2,14} and when medullary, is even more rare. Gao et al.,¹² estimating the rate of contralaterality of breast cancer 5, 10, 15 and 20 years after diagnosis of the primary tumor, report rates of 3.2%, 7.5%, 10.8% and 17%, respectively, for medullary carcinomas.

The present case can thus be classified as a very rare one, with a less than 3.2% likelihood of occurrence on

account of the synchrony. Nonetheless, more important than the rareness of these tumors is a rate of distant metastasis significantly greater than that of unilateral breast cancer (30.8% versus 15.1%, respectively).² Montoro et al.¹⁵ report symptom-free survival of 4 to 10 years after a primary tumor, falling to less than four years in women with bilateral tumors.

On consideration of the risk factors regarding an age of 35 years, tumor of the medullary type, synchrony, tumor size and risk of distant metastasis, it was decided to perform a bilateral mastectomy with skin-sparing and lymphadenectomy of the axillae.

With regard to skin-sparing, it is considered safe for breast cancer up to clinical stage II and anatomopathological stage up to T₂¹⁶⁻¹⁷ Slavin et al.¹⁸ on examining 114 skin biopsies of 32 patients consecutively submitted to mastectomy with skin-sparing, did not identify any structure of malignant ductal epithelium on the margins of the spared skin, thereby demonstrating that, when the procedure is oncologically correct, the possibility of recurrence or residual disease is eliminated. The risk of local recurrence following mastectomy with skin-sparing depends far more on other factors, such as the biology and size of the tumor, the histopathological grade, the positivity of lymph nodes and the status of receptor hormones than on skin resection margins.¹⁹

Considering the likelihood, referred to by Gong et al.,⁵ of bilateral negativity of estrogen (36%) or progesterone (64%) receptors and the possibility of negativity for Her-2/neu (43%), the estimated probability of a patient under 50 years of age having triple-negative synchronous cancer for these markers is a mere 4.99%.

By associating the triple negativity⁷ with the results of the markers (high proliferative rate by antibody Ki-67 and positivity for p53), it proved possible to characterize a high likelihood of the patient being BRCA1-mutated^{6, 20-21} and therefore with a poor response to a number of chemotherapeutic agents and to adjuvant hormone therapy, thus requiring that she be submitted to more strict controls.²² According to Rogozinska-Szczepka et al.,¹³ mastectomy is indicated in such cases.

In accordance with the premises of modern-day mastology, in which adherence to the oncological principles, in association with aesthetic repair, known as oncoplasty is advocated, a variation of the mastectomy technique was adopted, permitting a good result, which contributed to patient's satisfaction and quality of life (Figures 4-6).

The skin incision for mastectomy and emptying of the axillae was a variation of the technique employed

in mammoplasty, with a margin of oncologic safety, given the location of the tumors in lower quadrants. The



Figure 4 – Appearance of patient's breasts at preoperative evaluation



Figure 5 – Appearance of the patient's breasts 60 days after surgery



Figure 6 – Areola and nipple complex at 10 days.

reconstruction of breast was performed by constructing a muscle pouch with the pectoris major and serratus muscles for the insertion of the silicone prosthesis and the achievement of a good aesthetic outcome, using an operation that demands less time, is less aggressive than TRAM procedure and permits a good adaptation of the molding of skin to the type of breast reconstruction.²³

As regards to the immunophenotype, the medullary carcinoma in question may be classified as typical, excluding the basal-like type because of the negativity of the CK5/6 and EGFR markers, which signifies a better prognosis. Basal-like carcinoma most often metastasizes for bones and viscera and produces

a variable response to adjuvant treatment. However, the prognostic value of the classification of medullary tumor with regard to basal immunophenotype remains unclear.⁵

Much has been written on medullary carcinoma and there is a consensus on the need to strictly adhere to histological diagnosis criteria because this type of cancer has often been underdiagnosed or overdiagnosed.²¹ Once the diagnosis has been confirmed, the prognosis is good. However, one should take into consideration bilaterality, the young age of the patient and the biological characteristics of tumor regarding triple negativity and the degree of differentiation, which may be related to a poor prognosis.

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