Metaplastic breast cancer.
A case series

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Special type breast cancers display a wide range of different histological types in which clear recommendations on clinical and therapeutic management still lack and most of the information available derive from case report and case studies. In particular metaplastic breast cancer (MBC) is a rare and aggressive type of breast cancer accounting for around 1% of breast malignancies. We reported our experience in the management of five patients with MBC diagnosed and treated in our institution during the last few years (2016-2020).

KEY WORDS: Metaplastic breast cancer, Special type breast cancers

Introduction

Breast cancer is the most frequent cancer in women with a low incidence rate in the young women and a maximum incidence rate in 25-49 class age (44% of all cancers), 34% in 50-74 class age and 21% in over 75 years old [1]. Histopathological classification is a crucial step in cancer diagnosis and, in this regard, breast cancer is a heterogeneous condition with low frequency variants not yet well defined. The most common histological type that accounts for about 60% of cases, is represented by the invasive ductal carcinoma (IDC), often also reported as invasive carcinoma of no special type (NST); the second most common histotype is invasive lobular carcinoma (ILC) (10-15% of the cases), while breast cancer special types represent about 25% of all breast cancers[2]. Special type breast cancers include a wide range of different histological types in which clear recommendations on clinical and therapeutic management still lack and most of the information available derive from case report and case studies [2]. We reported our experience in the management of five patients with metaplastic breast cancer (MBC), a rare and aggressive type of breast cancer, diagnosed and treated in our institution during the last few years (2016-2020).

Case Reports

CASE 1: MIXED METAPLASTIC BREAST CARCINOMA (CARCINOSARCOMA)

Patient: 78 year-old women with cardiovascular comorbidity. Diagnosis: June 2019, mammography (MX) and breast ultrasound (BU) showed a 6 cm nodule in the inferior quadrant of the left breast showing solid necrotic structure without axillary nodes involvement. Biopsy report: morphological finding compatible with mixed

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metaplastic carcinoma (carcinosarcoma). Surgical treatment: July 2019, radical left mastectomy plus sentinel lymph node biopsy (SLNB). Histopathology report: mixed metaplastic carcinoma with aspects of squamous differentiation (positivity for pan-cytocheratin and p 63) and with mesenchymal differentiation high-grade sarcoma like, with necrosis areas, positivity for vimentin, CD10 focal positivity, negativity for S-100 and desmin (Fig. 1). Prognostic factors: triple negative (negative for estrogen receptor "ER", progesterone receptor "PgR" and human epidermal growth factor receptor 2 "HER-2/neu"), Ki 67 55-60%. Stage: pT3pN0 with negative sentinel lymph node (sn-)Mx, R0 G3. Treatment: adjuvant chemotherapy (CHT) with 4 cycles of weekly paclitaxel (a cardiomiopathy hindered the use of anthracyclines), followed by breast radiation therapy (BRT). Clinical follow-up at 14 months showed no evidence of disease (NED).

Case 2: Keratinizing squamous cell metaplastic breast carcinoma

Patient: 54 year-old women with no significant comorbidities. Diagnosis: February 2014, MX and BU revealed the presence of a heteroplastic lesion (4x3 cm) in the upper outer quadrant (UOQ) of the left breast. Biopsy report: IDC. Prognostic factors: triple negative, Ki 67 30%. Treatment: neoadjuvant CHT with 4 cycles of Epirubicin-Cyclophosphamide (EC) followed by 4 cycles of docetaxel. Surgical treatment: July 2015, left radical mastectomy with skin sparing and protesis implantation. Histopathology report: IDC, ypT2ypN0 (0/25)Mx, G2. Prognostic factors: triple negative, Ki 67 30%. A strict follow-up is prescribed. After 12 months (October 2016) there was a locoregional recurrence. Treatment: breast recurrence surgical resection. Histopathology report: IDC not otherwise specified (NOS) extended to structures referring to the pre-pectoral fascia. Presence of large component of metaplastic carcinoma/squamous cell carcinoma focally keratinizing (CK5/6 +, p63 +, CK34 BetaE12 +), with vascular invasion, poorly differentiated G3, score 8 according to Elston-Ellis. Prognostic factors: triple negative, Ki 67 35-40%. Treatment: adjuvant CHT with CMF (Cyclophosphamide, Methotrexate, Fluorouracil) and BRT. Follow-up: February 2017, further locoregional recurrence and appearance of pulmonary metastases. Treatment: surgical radicalization of locoregional recurrence (March 2017). Histopathology report: recurrence of NST invasive carcinoma/ductal NOS, with large component of metaplastic carcinoma/ focally keratinizing squamous cell carcinoma, G3. Prognostic factors: triple negative, Ki 67 35-40%. Treatment: first line CHT for metastatic disease with paclitaxel plus bevacizumab for 6 cycles followed by maintenance treatment with bevacizumab until february 2019 and stereotactic RT for pulmonary lesions.
February 2019: due to detection of progressive lung disease the patient received 4 cycles of second line CHT with eribulin. June 2019: exitus for further disease progression (PD).

Case 3: Metaplastic breast carcinoma with chondroid mesenchimal differentiation

Patient: 45 year-old women with no significant comorbidities. Diagnosis: November 2017, MX and BU showed a solid nodule of 14 mm in UOQ of the left breast. Biopsy report: NST invasive carcinoma/ductal NOS, moderately/poorly differentiated (G2-G3), with mild perilesional inflammatory infiltrate, B5: malignant. Surgical treatment: December 2017, quadrantectomy + SLNB. Histopathology report: NST invasive carcinoma/ductal NOS, with chondroid mesenchymal differentiation (10-15%); poorly differentiated G3. Detection of Infiltrating Lymphocytes (TILs): 35-40%; minimal component of intraductal carcinoma of intermediate nuclear grade with solid pattern equal to 5% (DCIS/DIN2). Stage pT1cpN0(sn-)Mx R0, G3. Prognostic factors: triple negative, Ki 67 65-70%. Treatment: adjuvant CHT with EC (4 cycles) followed by weekly paclitaxel (12 cycles) and BRT. Follow-up at 32 months: no evidence of disease (NED).

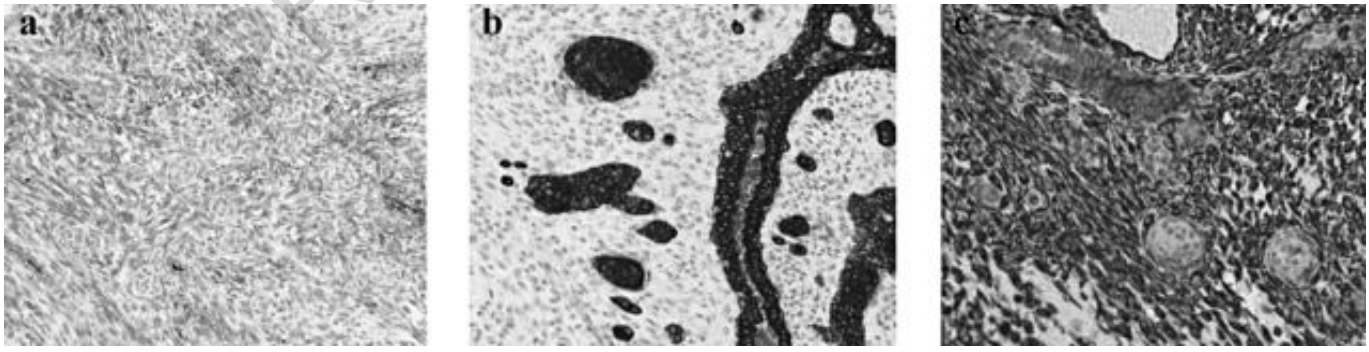

Fig. 1: Mixed metaplastic carcinoma (carcinosarcoma). Immunohistochemistry patterns show positivity for a) CD10; b) pan-cytocheratin; c) vimentin.

Case 4: Metaplastic breast carcinoma with chondroid mesenchimal differentiation

Patient: 42 year-old women with no significant comorbidities. Diagnosis: September 2004, MX and BU showed an 1,5 cm nodule in the UOQ of the right breast. Biopsy report: IDC, G3. Surgical treatment: UO quadrantectomy + SLNB. Histopathology report: IDC, pT1pN0(sn-) R0, G3. Prognostic factors: ER 0%, PgR 0%, HER-2/neu score 3+, Ki 67 80%.
Treatment: 6 cycles of FEC (fluorouracil, epirubicin and cyclophosphamide) adjuvant CHT (trastuzumab therapy was not considered because not yet authorized at that time in Italy) and BRT. In 2013 (9 years later) MX + BU showed a neoformation of 1,3 cm in the UOQ of the left breast. Biopsy report: IDC, G3. Surgical treatment: quadrantectomy plus SLNB. Histopathology report: IDC, G3 stage pT1bpN0(sn-)Mx R0. Prognostic factors: triple negative.
Treatment: 3 cycles of adjuvant CHT with liposomal anthracyclines (patient treated with anthracyclines also in the adjuvant setting), followed by 12 cycles of weekly paclitaxel, then BRT. Follow-up: July 2016 (3 years later) a MX showed microcalcifications in the right breast. Biopsy report: neoplasm with carcinomatous component and foci of cartilagineous mesenchymal tissue. Surgical treatment: August 2016, right mastectomy+SLNB.
Histopathology report: chondroid metaplastic carcinoma, stage pT1bpN0(sn-)Mx. Prognostic factor: triple negative, Ki 67 40%. In March 2017 the patient received also a left prophylactic mastectomy after discovering to be BRCA 1-2 positive. In July 2017 a computed tomography (CT) scan revealed the appearance of pulmonary metastases. Report of CT-guided fine-needle aspiration biopsy (FNAB) of a pulmonary nodule: mixed neoplasm, characterized by chondroid differentiated component with atypical nuclei and several epithelial elements, mostly isolated, iperchromated showing cytokeratin 7 positivity, TTF-1 and mammaglobin negative. Morphological sample suggestive of metaplastic carcinoma (chondroid differentiation carcinoma). Prognostic factors: triple negative.

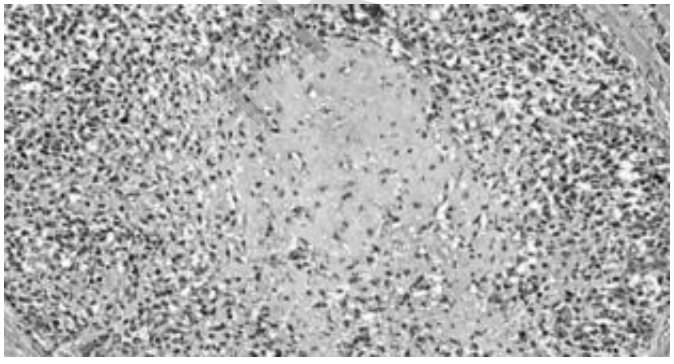

Fig. 2: Metaplastic carcinoma with chondroid differentiation. Morphological pattern.

Treatment: CHT with paclitaxel + bevacizumab for 6 cycles. Two months later the end of CHT a new total body CT scan showed multiple metastases (bone, brain, liver, peritoneal carcinomatosis).
Treatment: olaparib administered for three months (mo) followed by, due to further PD, weekly carboplatin for another 2 mo. Three mo later the patient died.

Case 5: Invasive ductal carcinoma NST with chondroid differentiated metaplastic component

Patient: 82 year-old women with hypertension as comorbidity. Diagnosis: April 2020, Mx+ BU revealed two opacities (22 and 12 mm) with calcifications, net and regular margins in the Upper Inner Quadrant (UIQ) of the right breast. Biopsy report: invasive NST carcinoma, poorly differentiated (G3) with fibro-hyalin and mixoid stroma, B5: malignant. Prognostic factors: ER 15%, PgR 5%, Ki 67 30%, Herceptest score 2+, HER-2/neu FISH amplified. Surgical treatment: May 2020, right radical mastectomy. Histopathology report: IDC NST, numerous metaplastic aspects with chondroid differentiation (Vimentin+, S100+) and chondro-mixoid matrix, poorly differentiated G3, in situ component that represents the 25% of the neoplastic tissue.
Presence of focal necrosis areas, scarce inflammatory peritumoral infiltrate and lymphovascular invasion (Figure 2). Prognostic factors: ER10% PgR 2% Ki 67 30%; Herceptest score 2+ with HER-2/neu FISH amplification, stage pT2pN0Mx. Treatment (medical advice): paclitaxel+ trastuzumab adjuvant CHT followed by hormonal therapy with letrozole. The patient refused CHT and began hormonal therapy. At 4 mo of follow up there is no evidence of diseases.

Discussion

MBC represents a heterogeneous group of breast carcinomas accounting for around 1% of all breast malignancies [2] . They are generally poorly differentiated, triple negative and with high Ki 67 [2]. The term "metaplastic" stands for a differentiation of epithelial cells in a squamous or mesenchymal type.
Morphologically, it is a heterogeneous tumor that contains ductal carcinoma cells mixed with other histological elements, such as squamous cells, spindle cells or other mesenchymal differentiation, such as chondroid cells, bone cells and myoepithelial cells. The World Health Organization (WHO) classification of breast tumors classifies MBC as low-grade adenosquamous carcinoma, fibromatosis-like, squamous cell carcinoma, spindle cell carcinoma, and metaplastic carcinoma with mesenchymal differentiation (chondroid, osseous and other types of mesenchimal differentiation) [3]. All of these metaplastic variants are aggressive and chemoresistant and have a

high propensity to metastasize, except fibromatosis-like carcinoma and low-grade adenosquamous carcinoma [4]. The majority of MBCs have a triple negative phenotype and such as triple-negatives breast cancers, are characterized by an high level of genetic instability. They harbored frequently TP53 mutations and a higher number of mutations in the PI3K/AKT/mTor pathway respect to triple negative invasive ductal carcinomas [5]. However, as reported by Rakha et al., no single immunophenotype or specific marker have been identified in all MBCs, reflecting the morphological and molecular heterogeneity of this tumor [6]. Among the series reviewed by González-Martínez et al. about 35% of patients presented lymph nodes involvement and 13% visceral metastases at diagnosis [7]. Due to its rarity and heterogeneity, there isn't a recognized standard therapy treatment for MBC and patients usually receive a treatment similar to that of more common types of breast cancer. A large retrospective analysis of a national oncology database reported that MBC patients were more likely to receive mastectomy (59% vs 44.9%), chemotherapy (74.1% vs. 43.1%), and axillary lymph node dissection, than non-MBC patients [8]. The same study showed that among MBC patients multimodal therapy (chemotherapy + radiotherapy) was associated with improved survival, while axillary lymph node dissection was associated with decreased survival [8].

Our case series was composed by five patients with MBC (one with mesenchymal differentiation high-grade sarcoma like, one metaplastic carcinoma/squamous cell carcinoma focally keratinizing and three with chondroid mesenchimal differentiation). According to the literature, the majority of them were triple negative (one out of five cases showed a slight positivity of hormone receptors and HER2/neu FISH amplification). All cases were high grade (G3) with Ki 67 > 20% and none of our cases presented axillary lymph nodes involvement. Only one case showed the presence of TILs in the histological sample, and according to literature that reports as a greater number of stromal TILs in MBC is associated with longer disease-free survival, the patient experienced no evidence of disease at 32 mo [9].

In conclusion, also in our experience MBC resulted to be an aggressive tumor with a poor prognosis. As previously reported, treatment of MBC is similar to that of more common types of breast cancer and includes local therapy (surgery, radiotherapy) and systemic therapy (chemotherapy, hormone therapy and anti-HER2 therapy). However, considering the poor response to conventional CHT, novel therapies are needed. Immunotherapy, in this regard, in view of the recent results reported in the treatment of triple negative breast cancer, could play a role also in MBC patients that are often, though not always, triple negative [10-12]. In any case, considering the difficulty of performing specific clinical trials, we need to share our data with the aim of improving the management of this rare entity.

Riassunto

Il carcinoma della mammella (BC) rappresenta la forma più frequente di cancro nelle donne. Dal punto di vista istologico circa il 25% dei casi è rappresentato dai cosiddetti tumori di tipo speciale che comprende un gruppo eterogeneo di tumori, inclusi alcuni rari istotipi per i quali le informazioni cliniche disponibili derivano principalmente dalla pubblicazione di case report o case series. In particolare, il carcinoma metaplastico della mammella (MBC) rappresenta una rara (circa 1% delle neoplasie maligne mammarie) ed aggressiva forma di BC caratterizzata dalla contemporanea presenza di elementi epiteliali e mesenchimali. Essi sono generalmente triple negative (ER, PgR, HER2-neu negativi), scarsamente differenziati (G3), con un Ki 67 elevato ed a cattiva prognosi. A causa della sua rarità ed eterogeneità non esiste un trattamento standard per i pazienti con MBC che pertanto ricevono terapie simili a quelle impiegate nelle forme più comuni di BC. Noi abbiamo riportato cinque casi di pazienti con MBC diagnosticati e trattati nella nostra istituzione negli ultimi anni (2016-2020) convinti che la condivisione di tali dati possa aiutare a migliorare la gestione dei pazienti con questa rara forma di tumore mammario.

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