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Metaplastic breast carcinoma with osseous remnant post standard treatment of invasive ductal carcinoma: case report and review of the literature

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Summary. Metaplastic breast carcinoma (MBC) is a rare subgroup of breast cancers that behave more aggressive in comparison with other breast cancer subtypes. Among them, the osseous variant is the rarest variant. Histologically, it consists of a metaplastic component beside main adenocarcinoma component. Consequently, this extra metaplastic part of MBC can justify more aggressive and chemoresistant behavior of metaplastic breast carcinoma. We present a case of a middle-aged female with metaplastic breast cancer that following standard chemotherapy of invasive ductal carcinoma, modified radical mastectomy with axillary lymph node dissection was performed. Surprisingly, related pathology report referred only to the mesenchymal component. The optimal treatment of MBC is not well-known yet, and the current approach is paralleled with other IDC subtypes. Therefore, studies about the MBC biologic markers can demonstrate new treatment approaches. This issue can be a milestone in the management of MBC, which targeting mesenchymal component in systemic therapy can improve clinical consequences.

Key words: metaplastic breast carcinoma, osseous differentiation, treatment, remnant

Background

Metaplastic breast carcinoma (MBC) is an infrequent and histologically diverse group of malignancies that make up less than 1 percent of all kinds of breast cancers (1). Invasive ductal carcinoma was detected as the most common type of all breast cancers, followed by invasive lobular and medullary carcinoma (2). But, the incidence of MBC (based on WHO 2012 report) has increased steadily since 2000 (3). The prevalence of breast cancer with osseous/cartilaginous metaplasia is very rare that estimated to occur in only 0.003-0.12 percent of breast cancer cases (4). It is called heterogeneous because of various kinds of histologies that may co-exist beside main histology of adenocarcinoma (e.g. squamous, spindle, chondroid and less commonly osseous variants) (5). MBC cases in comparison with patients diagnosed with invasive ductal carcinoma (IDC) have higher-grade and larger tumors with less hormone receptor (HR) positivity and also less inclusion of regional lymph nodes (6, 7). Generally, the prognosis and optimal treatment blueprint of MBC is not well-known. Treatment of MBC is largely analogous to other IDC subtypes, but growing evidence depict that MBC is a distinct entity of breast cancers (8). We report our experience with clinical status of a 41-year-old female diagnosed with metaplastic breast cancer that developed sarcomatous-only remnant after receiving treatment paralleled with IDC.

Case presentation

A 41-year-old woman with past medical history of metaplastic breast cancer referred to our department for

management of localized recurrence. Her initial clinical presentation was as follows; a painless lump located in the upper outer quadrant (UOQ) of left breast detected two months earlier. She had no history of trauma or nipple discharge and there was no known family history of breast cancer. On clinical examination, no dimpling, changes of skin color or nipple retraction detected. Through palpation a firm and mobile lump, measuring 3.0 cm × 3.0 cm, revealed. Mammogram demonstrated one well-circumscribed, dense and round mass in UOQ of the left breast, measuring 3.2 cm × 3.1 cm, but no micro-calcification detected. The mass corresponded to category 5 according to the BI-RADS Mammography Lexicon classification (8). Breast ultrasonography depicted an oval-shaped, complex echoic lesion measuring 3.0 cm × 2.8 cm with undetermined margins in UOQ of the left breast. But, no axillary lymphadenopathy detected. Accordingly, the lesion graded as BI-RADS 5 (8). Thereafter, the patient candidate for excisional biopsy. Pathology reported as follows:

"Sections of breast mass showed sheets of highly malignant medium to large cells with vesicular anisonuclei and eosinophilic cytoplasm with rare duct formation intermingled with the osteoid formation. This histologic picture is in favor of metaplastic carcinoma with the mesenchymal osseous formation." (Figure 1).

As is clear, the patient was a candidate for adjuvant treatment; but she had known as a candidate for close follow up by her primary physician. Three months later, based on physician physical examination another breast lump detected in her left breast, adjacent to previous mass. Accordingly, she was referred to our department to manage local recurrence of breast cancer.

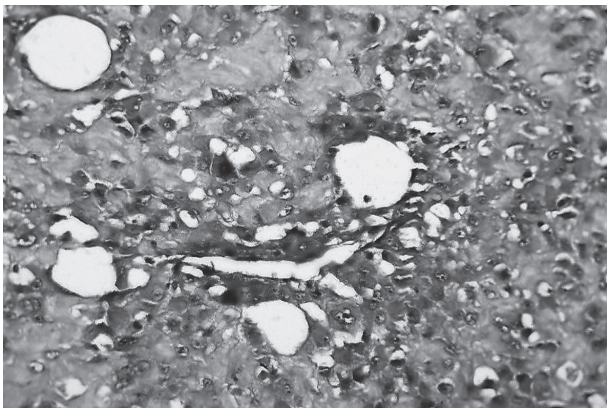

Figure 1.

On our clinical examination, no nipple retraction, skin dimpling or color change recognized. Palpation revealed a firm and immobile lump, measuring 5.0 cm × 4.0 cm in UOQ of the left breast. Furthermore, enlarged lymph nodes detected, measuring 2.0 cm × 2.0 cm, in her left axilla. The physical examination of her right breast and axilla was detected as normal. Mammogram depicted one poorly-defined, dense and irregular mass in UOQ of the left breast, measuring 7.0 cm × 5.2 cm, but no micro-calcification detected. The mass graded as category 5 according to the BI-RADS classification (8). Breast ultrasonography depicted one pear-shaped, complex echoic lesion measuring 7.5 cm × 6.0 cm with undetermined margins in UOQ of the left breast. An axillary lymphadenopathy detected with diffuse cortical thickening and loss of hilum. Accordingly, the lesion graded as BI-RADS 5 (8). Metastatic workup revealed no metastatic lesion. Consequently, the clinical stage assigned as IIIA (T3 N1 M0), according to AJCC 2010 reported TNM staging (9). Pathology review confirmed the initial diagnosis of metaplastic breast carcinoma. Immunohistochemistry (IHC) demonstrated that the cancer cells had a negative expression of P63, CK 5/6, ER, PR, c-erbB2 and the result of KI-67 reported as 20%.

Based on patient's demand for trying to save her breast, she was designated for neoadjuvant chemotherapy. Following chemotherapy with standard regimen of "Doxorubicin (60 mg/m^2, biweekly for 4 cycles) + Cyclophosphamide (600 mg/m^2, biweekly for 4 cycles) with Pegfilgrastim support, then Paclitaxel (80mg/m^2, weekly for 12 weeks)", the patient evaluated for breast conservation surgery, but because of small breast size, she was nominated for modified radical mastectomy (MRM). The specimen contained a firm white mass, measuring 8.0 cm × 6.5 cm × 5.0 cm, which showed bony consistency in some parts and the microscopic report was as follows:

"Numerous sections were taken from the tumor reveal a diffuse proliferation of polygonal cells with atypical nuclei with scattered bizarre cells, producing abundant osteoid and prominent woven bone" (Figure 2). Likewise, the tumor extended up to dermis but no lymphovascular invasion reported. Moreover, surgical

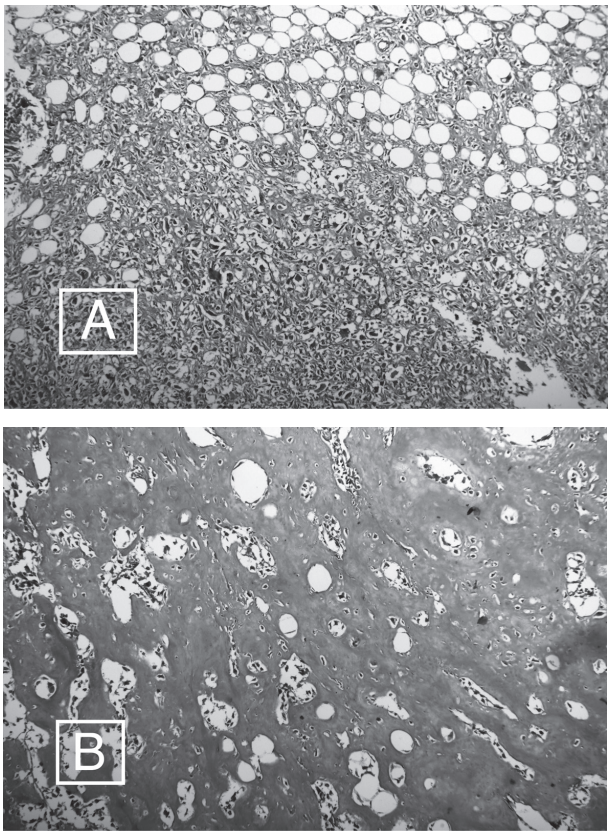

Figure 2.

margins were free and all ten left axillary lymph nodes dissected reported as reactive. The final diagnosis was consistent with osteosarcoma (no epithelial component was seen in the specimen) but granted that the patient had past medical history of MBC, the final diagnosis became "mesenchymal only MBC". The related IHC was as follows: negative result for P63, CK5/6, Bcl2, CD34, and B-catenin.

Thereafter, given that high probability of local recurrence, adjuvant chest wall, and regional nodal radiotherapy was done (5000 cGy in 25 fractions during 5 weeks). After 10 months, she is now in close follow-up setting, and fortunately, no evidence of recurrence was found.

Discussion

Metaplastic breast carcinoma was first characterized in 1973 by Huvos et al, as mammary ductal carcinoma combined with epithelial and sarcomatoid components (10). Nowadays, MBC constitutes 0.25-1.0 percent of all breast cancers (1, 11). MBC allude to a variety of histopathologies that contains both epithelial and mesenchymal components. Because it was not nominated as a distinct subtype until 2000, the current information about its characteristics is limited. The world health organization have categorized MBC into two distinct subtypes; 1) pure epithelial type, 2) mixed epithelial and mesenchymal type. The pure epithelial type subcategorized into adenosquamous carcinoma (ASC), squamous cell carcinoma (SCC) and adenosquamous with spindle cell differentiation (SPC); mixed epithelial and mesenchymal type subdivided into carcinoma with osseous and chondroid metaplasia (COC) and carcinosarcoma (CS) (12). MBC with osseous/cartilaginous components is one of the rarest subtypes of breast cancer that accounts for just 0.003-0.12 percent of all breast cancer subtypes (4). Among MBC cases with osseous/cartilaginous component, 51 percent of cases demonstrate cartilaginous metaplasia alone, 42 percent show both cartilaginous and osseous components, and the remainder 7 percent related to cases with osseous metaplasia alone (13).

The clinical presentation of MBC contains several properties that make it distinct from other IDC. The median age at diagnosis ranges from 48 to 59 years (14). Its growth rate is more than other IDC and generally represents larger than 2 cm at diagnosis. Despite larger tumor size, MBC involves regional lymph nodes less frequently than other IDC subtypes (15). In comparison with other IDC subtypes, lymph node involvement in patients with MBC does not essentially correlate with poor prognosis (16). Additionally, the expression of estrogen receptor (ER), progesterone receptor (PR) and c-erbB2 are lower in MBC in comparison with other IDC subtypes (17). The presence of metaplastic element beside epithelial element makes the prognosis of IDC poor, especially when it is prevailing component (18). Meanwhile, similar to soft tissue sarcoma, MBC demonstrates a high tendency for local recurrence and hematogenous spread to liver, lung, and bone (19).

Our patient represented many properties of MBC including large tumor size, lack of nodal involvement (at initial presentation), early loco-regional recurrence and triple-negative phenotype.

Breast cancer patients with MBC have a worse prognosis, in comparison with other IDC subtypes. Its 5-year survival ranges from 49 to 68 percent (20). Song et al. (21) compared prognosis of MBC subtypes and triple negative IDC (TN-IDC). The related result was as follows: the prognosis of TN-IDC was better than any subtype of MBC, with 5-year overall survival (OS) rate of 73.3% for TN-IDC in comparison with 50.0% in SCC, 56.3% for ASC, 40.0% in SPC and 75.0% in CS. Almost all MBC recurrences occur during initial five years, as long as recurrence curves of IDC steadily fall over time, suggesting that MBC recurrence may occur earlier than other subtypes of IDC (22). Some histopathologic factors that determine the poor prognosis of MBC including high cellularity, high mitotic activity, high nuclear grade and a high percentage of intervening spindle cells similar to sarcoma (23). Meanwhile, the presence of skin invasion, regional lymph node involvement with SCC as well as age less than 39 at presentation can be predictors of poorer outcome in patients with MBC (24).

The optimal treatment of MBC is not well-known yet, and the current approach is paralleled with other IDC subtypes. There are some uncharted issues regarding MBC that make its treatment results less efficacious than other subtypes of IDC. For instance, the pattern of MBC biologic markers are so different. I.e. they express HR and c-erbB2 less, whereas express EGFR-1 more than other IDC subtypes (25).Therefore, studies about the MBC biologic markers can demonstrate new treatment approaches. The second issue regards to various subtypes of MBC that seems to request distinct treatment approaches.

Growing evidence has appeared that demonstrate the distinct behavior of MBC. For instance, MBC tends to grow faster, involve regional lymph nodes less, spread hematogenous, and recur locally more in comparison with other IDC subtypes. This issues may be due to a metaplastic component of MBC. A report from the Mayo Clinic demonstrated the results of nine MBC cases that received standard IDC related chemotherapy regimens. The result was disappointing; just one partial response recorded (26). According to this, some modifications have been made in a few studies for the treatment of MBC with satisfactory results. For example, in a series reported by Hennessy et al, no recurrence recorded in three patients with MBC who had treated with Doxorubicin and Ifosfamide regimen (27). The second evidence relates to Gutman et al. (19) report that proposed sarcoma-directed therapy approach for MBC cases. Moreover, according to Brown-Glaberman et al. (28) report dramatic clinical response was seen with the sarcoma-based regimen in a patient with metastatic MBC status.

The result of our report can affirm the novel treatment approach. As mentioned our patient following receiving chemotherapy with the IDC-based regimen, revealed metaplastic only compartment in MRM related pathology report. It means that the epithelial component responded dramatically to conventional treatments of IDC, but the metaplastic component didn't. This issue suggests that changing attitudes regarding choices of systemic therapies can improve the results of MBC treatment.

Conclusion

Metaplastic carcinoma is a rare and heterogeneous subgroup of all breast cancers. These issues make its treatment approach uncharted. Current MBC treatment is paralleled with other subtypes of IDC, but there was some vague evidence in the literature regarding its behavior and type of recurrence that gave estimable clues to experts for running valuable studies to improve the treatment results. Consequently, targeting metaplastic component of MBC can improve the systemic therapy more efficacious in further clinical trials.

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