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Metaplastic breast carcinoma with mesenchymal differentiation: A rare diagnosis with difficult management

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Abstract

Introduction: Metaplastic breast cancer with mesenchymal differentiation, previously known as carcinosarcoma, is a rare subtype of metaplastic carcinoma of the breast composed of epithelial and mesenchymal components. This subtype of breast cancer associates with a poor prognosis and sparse response to standard treatments.

Case report: 39-year-old-women diagnosed with stage IV metaplastic breast carcinoma with mesenchymal differentiation and lung metastases at diagnosis. The patient was treated with three lines of chemotherapy with disease progression. She passed away 9 months after diagnosis.

Conclusion: This case report intends to illustrate the difficulty on treatment management of this uncommon and aggressive disease. Given the rarity of this diagnosis, prospective studies are not expected, and patients should be encouraged to enroll biomarker driven clinical trials.

Keywords

breast neoplasms; carcinosarcoma; mesenchyma; metaplastic carcinoma

Introduction

Metaplastic Carcinoma of the Breast with Mesenchymal Differentiation (MCBMD), previously known as carcinosarcoma, is a rare subtype (less than 0.2% of all breast cancers) of metaplastic carcinoma of the breast composed of epithelial and mesenchymal components without a transitional zone [1-3].

The origin of MCBMD is still unknown, but it is thought to originate from a single totipotent cell with biphasic differentiation (epithelial and mesenchymal): Sarcomatous component was immunoreactive for epithelial marker (cytokeratin) and component epithelial marked to actin and S-100. Myoepithelial and

myofibroblastic cells may also have a role [5].

This subtype of breast cancer is very aggressive, with poor prognosis probably due to the absence of response to conventional treatment. This histologic subtype is usually triple negative profile and associated with Tumor protein p53 (TP53), Phosphatase and tensin homolog (PTEN) and DNA topoisomerase II Alpha (TOP2A) mutations [3]. Not surprisingly, it is poorly differentiated, with high nuclear grade, highly cellular and mitotically active [5-9]. There are no clinical or imaging pathognomonic features, so histology and immunohistochemistry play an essential role in diagnosis [3,10,11]. It should be noted that complete excision is the best approach for correct diagnosis, since fine needle aspiration biopsy and core biopsy have high false negative rates. The reports only describe correct diagnosis pre-operative in only 4.2% of cases [3,5,10,13].

The treatment, although based on the guidelines for ordinary breast cancer, has suboptimal responses [3-14]. Surgery is the most important treatment mainly in localized disease, radiotherapy plays an essential role in the prevention of local recurrence and chemotherapy has a small role with no impact on overall survival (OS) or Disease Free of Survival (DFS) [3,8,10,12-15].

The typical route of metastasis is hematogenous dissemination, with most occurring in lung [3,8,10,12,16]. Treatment for metastatic disease is based on chemotherapy, with most patients having progression or stable disease (response rates on stage IV is around 17%), with a 5-year OS ranges from 49-68% [5, 7, 8,11].

Clinical Case

A thirty-nine-year-old woman (with no relevant past medical history) presented a 5 cm nodule in the left breast and underwent a surgical excision in October 2016. Histology examination determined the presence of metaplastic carcinoma. She was then referred to our institution. The histological examination revision confirmed the diagnosis: biphasic neoplasia, type carcinosarcoma with a high grade epithelial component (positive for cytokeratin 8/10 and AE 1/3) and a high grade fusocellular component (CD10 positive and calponin), triple negative profile and proliferative index (Ki67) of 90%. (Figure 1) She performed staging Positron-Emission Tomography (PET) that showed tumor persistence in the left breast, axillary and thoracic lymph nodes, lung metastases and invasion of the chest wall (Figure 2). She was proposed to first line palliative chemotherapy with doxorubicin (cumulative dose 342 mg/m2) and cyclophosphamide, and after 3 cycles, the PET documented progressive disease, with new lesions having developed under anthracycline based chemotherapy (Figure 3). Given the absence of a clinical trial and her ECOG status 0 she was proposed for second line treatment with cisplatin and ifosfamide. She completed 3 cycles of treatment with good clinical tolerance but again with imaging evaluation showing progressive disease (Figure 4).

In a multidisciplinary team discussion and considering the good general condition and her will to pursue active treatment, she was proposed for third line chemotherapy with weekly paclitaxel. Even before the beginning of this treatment, patient developed dysarthria and had a convulsion. Brain Magnetic Resonance Imaging (MRI) showed cortical-subcortical lesion with intense contrast capture with maximum

diameter of 20 mm and four foci in the right cortical frontal and left cerebellar hemisphere (Figure 5). For which she started steroids and received holocranial radiotherapy (30 Gray in 10 fractions), with sparse clinical improvement.

One week after the end of brain radiation and still under steroids therapy, the patient was admitted with progressive dyspnea and orthopnea. Chest x-ray showed massive left-sided pleural effusion, for which she needed multiple thoracentesis for symptomatic relief. Due to progressive worsening of her general status, it was decided palliative care and end-of-life supportive measures. The patient passed away 9 months after surgery.

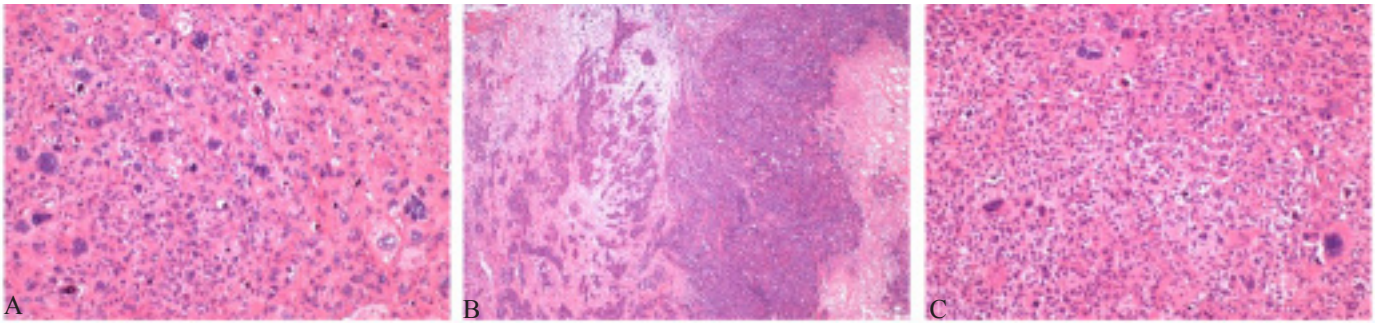


Figure 1: Carcinosarcoma. A - Giant cels (HE); B - Epithelial componente (HE); C - Fusocelular component (HE)

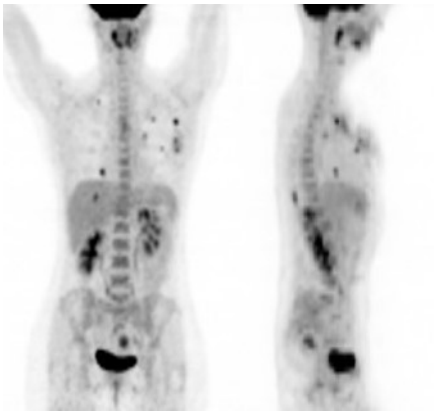


Figure 2: PET-CT at diagnosis

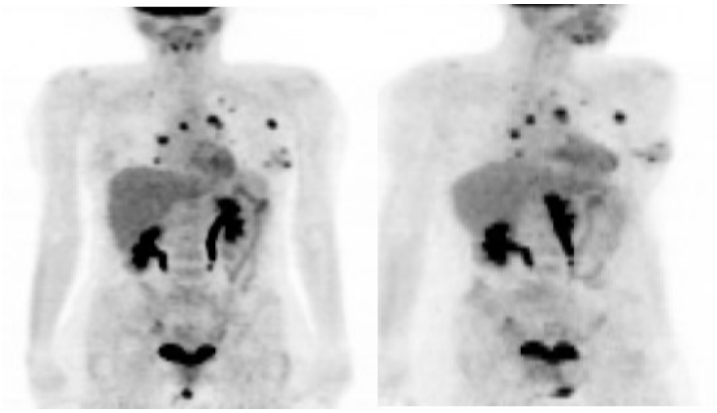
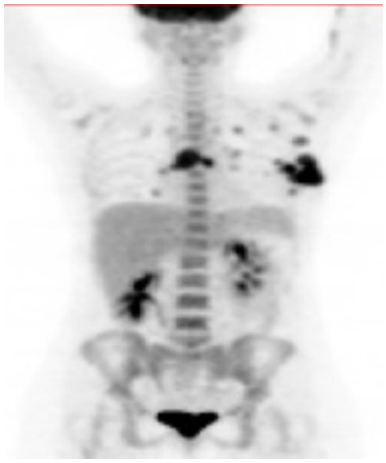


Figure 3: PET-CT after first line palliative chemotherapy



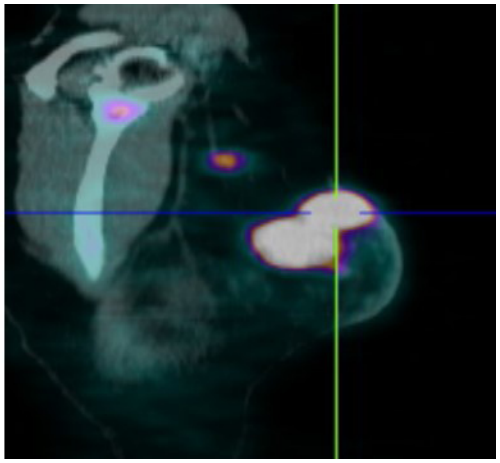


Figure 4: PET-CT after second line palliative chemotherapy

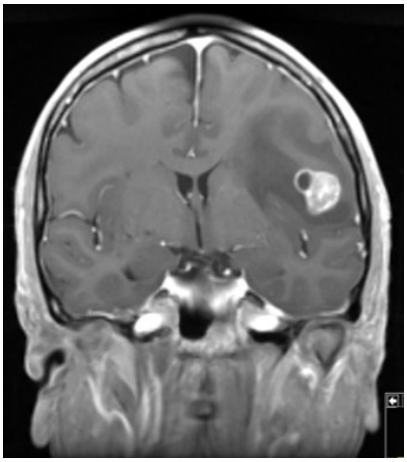


Figure 5: PMRI with frontal left lesion

Discussion

Metaplastic breast carcinomas are a group of neoplasms consisting of epithelial and mesenchymal cells, representing <5% of all breast cancers [1]. According to the WHO classification, there are several subtypes of metaplastic carcinomas, one of which is the MCBMD, previously called carcinosarcoma [2,3]. MCBMD is a type of biphasic carcinoma composed of mesenchymal and carcinomatous component [1-3,10]. It is a rare (0.08-1.2%) and very aggressive BC subtype, with few cases reported in the literature [3-15]. It seems to be more common in the 5th decade of life, but there are cases described between 16-90 years [3].

Usually, MCBMD appears as a palpable rapidly growing and painful breast mass; nipple discharge or retraction and skin ulceration are uncommon and in rare cases it could be similar to inflammatory carcinoma [3,7-9,15].

On imagiology, mammogram and breast MRI have low specificity and MCBMD can be confounded with benign lesions [3,9,14]. They are not usually associated with microcalcifications or architectural distortion, in mammography it is usually seen as a well-defined lesion with lobulated contours and high density and in MRI, the lesion is hypointense in T1 by the glandular tissue and hyperintense in T2 [11].

For histological diagnosis, it is important the analysis of multiple tissue sections, so that, fine needle aspiration biopsy and core biopsy may not be enough to correct diagnosis, with high false negative rates [3,5,10,13]. Surgical excision with detailed immunohistochemical study is the standard approach [4,9].

Histologically, most of MCBMD are poorly differentiated, with triple negative profile, high proliferative index, cytokeratins 1/3, 5/6 and 7, EMA, vimentin, actin and S100 positive [7,11]. These tumors have higher rates of TP53, overexpression, epidermal growth factor receptor (EGFR), PIK3CA, loss of PTEN [3,8-10].

Given the rarity of the diagnosis there is no consensus for MCBMD treatment [3,8-14]. Tumor size is an important prognostic factor [10], being surgery the cornerstone treatment, with total mastectomy considered the preferred approach, especially for T3 tumors. Tumors smaller than 5 cm may be treated with lumpectomy, essentially if an extensive surgical (> 3 cm) margins can be achieved [8]. There is no significant difference in OS and DFS between the 2 surgical approaches [3]. The effectiveness of chemotherapy is very limited, and these tumors are usually resistant to systemic treatment [8]. Mutations in PTEN and TOP2A genes appear to play a role in the weak response to chemotherapy: down-regulation of PTEN, linked to chemoresistance and TOP2A is the molecular target of anthracycline. So, taxane-based regimens seem to be more effective [3,14].

Usually the more common drugs for breast cancer are used, but with suboptimal results (more favorable when the treatment is used in early-stage disease) [3,8,10]. Studies have shown that anthracycline-free regimens, such as CMF (cyclophosphamide, methotrexate and 5-fluorouracil), have worse outcomes [5,15]. Thus, in the absence of new data, anthracyclines and taxanes based chemotherapy remain the standard treatment [4,9]. However, it does not associate with improved OS, regardless of whether it is in

neoadjuvant or adjuvant setting [8,13,14].

Radiotherapy improves DFS and OS across notably in the prevention of local recurrence [10,14,16].

Despite the lower rate of axillary node involvement (around 20-26%), this tumour metastasize mainly through the hematogenous route, particularly to the lungs (8,12,13) MCBMD has a higher rate of stages IV at diagnosis (10%) as compared to invasive ductal carcinoma. The likelihood of recurrent metastatic disease is also greater (50%) [8]. Liver, bone and brain are rare metastatic sites, but they confer a poorer prognosis [3,7,13]. Chemotherapy is ineffective in the metastatic setting regardless of the regimen used (anthracyclines, taxanes, capecitabine, vinorelbine) and several combinations have been studied but with no encouraging results [8,10,11].

MCBMD has a high risk of local recurrence, since neoplastic cells often extend into the perivascular tissue and beyond the tumor capsule [5,14]. All recurrences occurred during the first 5 years (early recurrences). Even though most of these tumors are triple negative, they behave differently and more aggressively than other triple negatives histological subtypes [11,14].

Age (younger), tumors larger than 5 cm or with skin or chest wall invasion, lymph nodes and distance metastases appear to be adverse prognostic factors (16). Overall survival at 5 years is 49-68% [5,8,10] and median survival of metastatic disease is 8-14 months [3].

Conclusion

MCBMD has a poor prognosis with a weak response to systemic treatments in every disease stage, having our patient rapidly progressed to different lines of combination chemotherapy.

Considering the unique biology and rarity of this entity, clinical trials with target agents should be encouraged, particularly in those with targetable EGFR and PIK3CA mutations. Umbrella trials may identify some other targetable genetic alterations that allows target treatment with better responses. In summary this case report intends to illustrate the difficulty on treatment management of this rare and aggressive disease.

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