

Synchronous Mammary Metastasis Mimicking a Primary Breast Cancer: A Case Report and Review of Literature

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Abstract

Background: Breast metastasis from ovarian cancer is a rare event with a poor prognosis, causing death between 3 to 18 months with a median overall survival of 6 months. Ovarian cancer accounts for 239.000 new cases and 152.00 deaths worldwide annually. The 5-year overall survival rate is 38% which is dramatically lower compared to the OS of patients affected by breast cancer. This aspect draws the attention to the necessity to make an early diagnosis of ovarian cancer in presence of a breast metastasis which might be confused mistakenly with a primary breast cancer. The diagnosis is often difficult because the lesion might present some histological features shared with metastases from ovarian cancer like psammoma bodies (round collections of calcium). In order to distinguish an ovarian metastasis from a primary breast cancer, many immunohistochemical markers have been developed.

Case report: A 64-year-old caucasian woman was referral to the Breast Unit of the Cardarelli Hospital with a suspected nodule in the left breast. The combination of Immunohistochemical and Histologic analysis of samples defined the nodule as an ovarian cancer metastasis. Our patient undertook a treatment based on Bevacizumab, carboplatin and paclitaxel for 12 cycles. Then she started a maintenance therapy with Bevacizumab and she is still in treatment with this regimen. The CA-125 level was high at the diagnosis (8911.9 U/ml) and it showed to be a good prognostic index of either remission or relapse. The patient is still alive after 25 months.

Conclusion: Breast metastases are uncommon because of their histological characteristics such as the abundant fibroadipose tissue and low grade of vascularization. In literature, almost 110 cases were reported. The treatment of choice is a complete resection of metastases that allows to make also a firm diagnosis or mastectomy. However, it does not have a significant impact on the OS.

Keywords: Neoplasm; Metastases; Effusion; Inflammation

Introduction

The ovarian cancer is an uncommon type of malignant neoplasm, which continues to have a low overall survival (OS) due to the difficulties to make an early diagnosis. Unfortunately, metastases are detected lately, and this delay worsen the prognosis drastically. Most frequent breast metastases are those deriving from the contralateral breast cancer followed by hematologic neoplasms, melanoma and, finally, those originating in other organs mainly the stomach, lung, liver, colon, thymus, ovary, thyroid, soft tissue. The most common histological subtype of ovarian neoplasm related to breast metastases is papillary serous high-grade adenocarcinoma.

Case Report

The present study describes the case of a 64 years-old caucasian woman affected by ovarian cancer with a breast metastasis. In November 2015 the patient presented to our attention with a palpable mass in the left breast. The patient had no family history of breast cancer. Mammography revealed a lump with a maximal diameter of 2.2 cm and irregular borders. Then FNAC was performed and the results were initially suggestive for primary breast cancer. Clinical staging by CT scan showed a 9 × 8 cm diameter mass in pelvis together with peritoneal carcinomatosis and peritoneal effusion. A breast quadrantectomy and a peritoneal resection were performed in December 2015. The histologic examination of breast samples found a poorly-differentiated adenocarcinoma (picture). Immunohistochemistry was positive for the expression of PAX8, CA125, PgR (30%), ki-67 (90%), while it was negative for WT1, GCDFP15, ER, Mammaglobin and Her2. The absence of typical breast markers like Mammaglobin together with the expression of PAX8, which is a characteristic ovarian cancer marker, brought us to the diagnosis of a synchronous breast metastasis from

ovarian cancer. After defining the diagnosis, tumour marker levels were assessed (CEA 4.1 ng/ml, CA125:8911.9 U/ml; CA15.3:161.4 U/ml; CA19.9 < 1 U/ml).

The immunohistochemical analysis of samples from peritoneal resection showed the expression of PAX8, WT1 and CA 125 while Mammaglobin was negative. The definitive diagnosis was of a high-grade serous papillary cystic carcinoma. Therefore, it was decided to start a regimen of Bevacizumab+Carboplatin AUC 5+Paclitaxel, q21, for 6 courses. At the end of the 6 cycles, the patient underwent a total body CT scan combined with PET to assess her response to the treatment. The result of these exams showed a complete response (RC) and a focus of increased FDG uptake located in the left adrenal gland (SUV 3.2). Markers' assessment at the end of the 6 cycles showed a drastic reduction of all of them (CEA: 1.5 U/ml; CA125:43.4 U/ml; CA 15.3:20.6 U/ml; CA19.9<2). The patient underwent major surgery again because the previous procedure was not therapeutic, but only for diagnostic purpose (Figure 1). A complete hysterectomy together with bilateral salpingo-oophorectomy, omentectomy and appendicectomy was performed in June 2016. Pathologic specimen analysis showed

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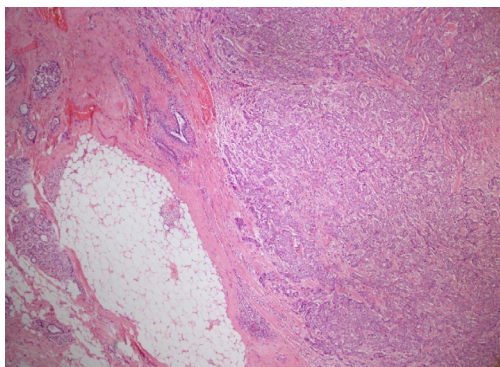


Figure 1: 40x magnification, haematoxylin/eosin staining. Breast parenchyma (left) and breast metastasis from high grade ovarian serous carcinoma (right) is here shown.

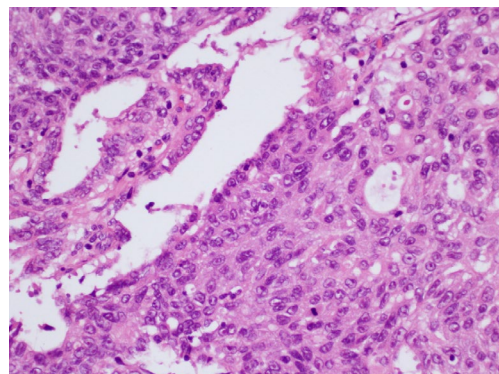


Figure 4: 200x magnification, haematoxylin/eosin staining. Ovarian cancer is here shown. It grows in solid sheet and it shows high grade cytology like its breast metastasis.

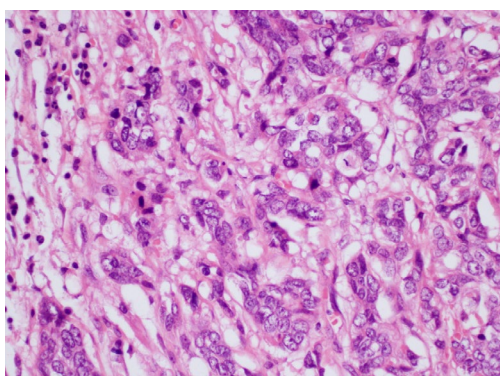


Figure 2: 400x magnification, haematoxylin/eosin staining. Higher magnification shows high grade tumor cells with no glandular differentiation and a high mitotic index.

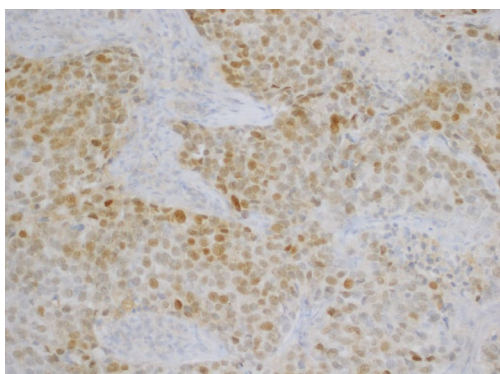


Figure 3: 200x magnification, immunohistochemistry anti-PAX8. This antibody is expressed in nuclei of tumor cells. Breast cancer is not known to carry this expression, while ovarian cancer typically does.

extension of tumor throughout appendix, omentum and ovaries. In December 2016 her CA125 level rose to 1635 U/ml and PET/TC showed peritoneal carcinomatosis with peritoneal and pleural effusion. Because it had been only 6 months since the interruption of therapy, the patient was still considered responsive to Carboplatin. Therefore, we decided to re-administer the last treatment for other 6 cycles. In April 2017, at the latest clinical staging, a FdG-PET showed regression of the previous findings and persistence of adrenal gland increased

Authors/Year	Study year	No of patients	Age	Histology	Time between ovarian cancer diagnosis and breast metastasis
Clemens B Tempfer et al. (2016)	2011-2013	2	52 51	Nr Nr	3 yrs 1 yr
Andrew HS Lee (2017)	1996-2005	4	58 71 70 72	serous papillary carcinoma serous papillary carcinoma serous papillary carcinoma serous papillary carcinoma	9 months 93 months 94 months
Florian E Buisman et al. (2016)	1985-2014	6	--	--	1-43 months
Tressera F et al. (2014)	--	2	50 59	serous papillary carcinoma serous papillary carcinoma	--
De Lair TF et al. (2013)	1990-2010	14	10 3 1	--	--
Fulciniti F et al. (2007)	--	3	49 53 71	serous papillary carcinoma serous papillary carcinoma serous papillary carcinoma	2 yrs 9 yrs 2 yrs
Susini T et al. (2010)	--	1	44	serous papillary carcinoma	--

Table 1: Characteristics of ovarian cancer patients with metastases to breast in a clinical series.

uptake (SUV 2.5) with new uptake sites located in sternum (SUV 2.1), small bowel (SUV 2.1), left iliac wing (SUV 5.2). CT scan performed in the same date showed the evidence of a modest pleural effusion. Tumor markers' values were the following: CEA 1.6 ng/ml; CA125:8.50 U/ml, CA 19.9<2 U/ml. At the end of the 6 cycles the patient started a maintenance therapy with Bevacizumab which she continued for 10 cycles. After completing the treatment, the PET/CT was negative. So far, the patient is doing well, and she is still in maintenance treatment with Bevacizumab (Figure 2).

Discussion

Metastasis of ovarian or peritoneal serous carcinoma to the breast is

a rare event. Nevertheless, its recognition and distinction from primary mammary carcinoma are of great clinical importance because the treatment and prognosis differ significantly [1]. In general, symptoms are similar in those of primary breast cancer, including palpable relatively well-circumscribed and freely movable masses within the breast, pain, tenderness and inflammation. Non-primary breast malignancies are generally well defined and rounded, and calcification is common in serous papillary carcinoma of the ovary or peritoneum [2]. According to Rebecca L et al., a breast metastasis is traditionally described as a superficial mass poorly fixed to the superficial and deep tissue planes, differently from what is observable in a primary tumor. In 85% of cases the metastasis presents as a solitary nodule and in 62% it is in the upper quadrant [3]. Abbas et al., stated that intramammary masses and architectural distortion were the two main radiological patterns exhibited by the metastases in their study. Considering the imaging of breast metastases (Figure 3), they described ultrasonographic and mammographic features in a series of 280 women with intramammary metastases, 41 of which were diagnosed with metastases of ovarian cancer. The lesion typically exhibited microlobulated margins and posterior enhancement at the ultrasound [4]. De Lair et al., analyzed 85 cases of non-mammary metastases to the breast and axilla, 14 of which were from ovarian cancers. Morphologically most cases presented as a solitary nodule and lacked pathognomonic pathologic features. However, there were recurrent histological findings identified, such as the often relatively well-circumscribed growth pattern of the metastatic lesion surrounded by a fibrous pseudo-capsule, and the absence of an *in situ* carcinoma [5].

Pathologists play a key role in considering the diagnosis of metastasis if the histological features are unusual for a primary breast carcinoma. In approximately 30% of patients, metastasis to the breast is the first sign of malignancy [6].

Fulciniti et al., studied the role of fine needle cytology samples in metastases to the breast. The cytopathological diagnosis of metastatic neoplasm to the breast is not always straightforward, mainly due to the paucity of definite mammographic criteria and to the often confusing clinical-cytological picture of metastases especially in the absence of a clinical history of cancer (Figure 4). The usage of improved cytopathological criteria as the presence of psammoma bodies and the papillary architecture of the cell clusters combined with immunocytochemistry may be of great diagnostic help in the identification of breast metastases [7]. A mammary origin can be supported by the expression of estrogen receptor, progesterone receptor, her2neu, and GCDFP-15. GATA 3 has been shown to be a sensitive marker for breast cancer. However, these markers are not entirely specific as estrogen receptor can be expressed in ovarian cancer and GATA3 is a sensitive marker for urothelial cancer. These markers should always be used together in a panel of antibodies since no single marker is completely specific. These markers are readily available on core biopsies but can also be applied to cytological specimens [8].

In a retrospective study based on 95 patients with ovarian carcinoma at early stage and high risk, the CA 125 level at the end of adjuvant therapy with Paclitaxel and carboplatin resulted to be an independent prognostic factor for the progression free survival (PFS). The 5-year PFS was 83.3% in patients with Ca 125 blood level <12 U/ml while it was 37.5% in those with a higher value [HR]=10.567, $p < 0.001$ [9]. Other studies suggest that the expression of some microRNA (mi-RNA) has a remarkable prognostic utility [10]. Specifically, the miR181a seems to be involved in the mechanism of cancer cell spread and resistance. This type of microRNA is detectable mainly in women

who had a relapse during the 6 months after chemotherapy. miR181a causes the increase of cancer cell life time, resistance to treatment and facilitates the metastatization. Moreover, it promotes the epithelial mesenchymal transition (EMT) stimulating the production of TGF beta. The EMT causes the loss of epithelial phenotype and cytoskeletal rearrangement making the cancer cells mobile and more invasive. A cohort study conducted by MITO group identified 35 miRNA as predictive of progression and relapse. They were used to create a diagnostic model defined as MiROvaR [11]. This tool gave the possibility to divide patients in two groups based on the risk of relapse. The high risk group included 89 patients with a median PFS of 18 months, while the low risk group was made of 90 patients with a median PFS of 38 months (HR=185, 97%ci=1.29-2.64). Karam et al., investigated 29 ovarian cancer patients with malignant breast lesions, 10 of whom exhibited metastases and the remaining 19 presented primary breast cancer (Table 1). The study found marked differences between the two groups regarding disease free survival time and the mean time interval between the diagnosis of ovarian cancer and the diagnosis of breast metastasis. The OS was significantly shorter for women with metastases [12]. Cormio et al., determine the incidence and prognostic factors of distant metastases consistent with stage IV disease in ovarian cancer patients and conclude the most important prognostic factor associated with survival is the interval time between diagnosis of ovarian cancer and documentation of distant metastases.

Conclusion

Ovarian cancer with breast metastases is associated with a poor prognosis being a late stage manifestation of this type of cancer. The most common histological subtype related to this site of metastasis is high-grade papillary serous carcinoma. From a clinical point of view, there aren't pathognomonic patterns which allow us to make a differential diagnosis with a primary tumor. Instead, our case showed the presentation of the metastatic tumor mass to the breast synchronous with the primary ovarian cancer, and in this case IHC is useful for the purpose to distinguish the primary neoplasm from the metastatic one. The main objective for future studies is to identify methods and techniques to make an early diagnosis; considering the different prognosis and rate of survival between primary tumor and breast metastasis, this would be a crucial tool to treat properly women affected by this insidious disease and potentially save their life.

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