OVARY AND UTERUS, RARE SITES OF METASTASES FROM BREAST CANCER: A CASE SERIES

Rizyl Suratos Dominguez∗,1 and Jimmy Awisan Billod∗

1Baguio General Hospital and Medical Center

ABSTRACT Summary: Bones, lungs, and liver are frequent sites of metastases of breast cancer. However, female genital tract (ovaries, uterus, etc.) metastases of breast cancer often present as challenge for diagnosis. The distinction between primary and metastasis may be difficult. Immunostaining have a pivotal role in determining the distinction of breast cancer metastases to ovaries and uterus and primary ovarian and uterine cancer. We herein report rare cases of ovarian and uterine metastases in women who have prior carcinoma of breast and the role of immunohistochemistry in diagnosing these cases. Case 1 highlights a 42 year old with breast cancer, stage IV who presented with breast mass and nipple retraction and an enlarging abdominal mass, probably an ovarian new growth, probably malignant by transvaginal sonography. Exploratory laparotomy, peritoneal fluid cytology, total abdominal hysterectomy with bilateral salpingo-oophorectomy, random peritoneal biopsy, bilateral lymph node dissection were done revealing metastatic ovarian cancer probably invasive lobular carcinoma of breast origin. Case 2 reports a 42 years old diagnosed with hormone receptor positive breast cancer stage IV, received 4 cycles of systemic chemotherapy and 20 cycles of radiation therapy of mediastinal mass. On Tamoxifen as maintenance drug hence ovarian ablation was recommended. Total abdominal hysterectomy with bilateral salpingo-oophorectomy, intraabdominal omentectomy were done with histopathologic result of metastatic carcinoma with mixed lobular and ductal features probably breast in origin on bilateral ovaries. Case 3 is a 38 y/o with 8 month-history of breast mass with associated pain, diagnosed with invasive ductal carcinoma, right stage IIIB (T4N0M0) after modified radical mastectomy of the right breast. On follow-up, abdomino-pelvic CT scan done showed multiple intraabdominal and retroperitoneal and pelvic lymphadenopathies probably metastasis. Exploratory laparotomy, drainage of ascitic fluid, infracolic omentectomy, bilateral salpingo-oophorectomy, peritoneal biopsy were done with histopathologic findings of metastatic poorly differentiated carcinoma, probably ductal carcinoma, bilateral ovaries.

KEYWORDS Breast cancer, Metastatic ovarian cancer, Metastatic uterine cancer, Immunostaining

Introduction

Breast cancer is the most common cancer worldwide, and the second leading cause of cancer mortality among women[1]. Most breast cancer deaths are related to distant metastases; the division of breast cancer into histologic subtypes and molecular subtypes is known to have significant prognostic and predictive value[2].

Less than 10% of patients with breast cancer have evidence of distant metastases at diagnosis, but 30% of them will have recurrent metastatic disease. After breast cancer screening for distant metastases should become the focus of increased concern because of a predictable improvement in breast cancer survivorship[3].

The most common metastases of breast cancer are the lungs, bones, liver, and brain, whereas metastases in the female genital
tract are uncommon. With genital tract metastases, the ovary is the most common metastatic site accounting for 75.8%, followed by the vagina (13.4%), cervix (3.4%), vulva (2%), fallopian tubes (0.7%) and uterine corpus (4.7%)[3,4].

Metastatic tumours of the ovary comprise a significant group of ovarian neoplasms, not only because of their incidence rate but also because of diagnostic difficulties occurring when tumours histopathologically similar to primary ovarian neoplasm give metastases to the ovary. Ovarian metastases account for 2 in 10% of all ovarian neoplasia, and 7 in 54 (2%) are from mammary origin2. Uterine metastases demonstrated that myometrium's involvement accounts for 63.5%, followed by myometrium and endometrium (32.7%) and endometrium only (3.8%)[4].

Patients may often present with no symptoms; hence it should be considered that routinely follow up gynecologic examinations should be performed. The distinction between ovarian and uterine metastases and primary ovarian and uterine cancer may be difficult. We herein report the rare cases of ovarian and uterine metastases in women who have prior carcinoma of the breast and the role of immunohistochemistry in diagnosing the case.

Case Presentation

Case 1

This is a case of a 42-year-old female, gravida 3 para 2 (2012), who came in due to abdominal pain a few months prior to admission. The patient was seen at the outpatient department 10 months prior to consult with a chief complaint of gradually enlarging abdomen with no associated vaginal bleeding, vaginal discharge and abdominal pain. Physical examination and abdominopelvic CT scan were done, revealing ovarian new
growth, bilateral, probably malignant (appendix, figure 5,6) hence scheduled for exploratory laparotomy, peritoneal fluid cytology, total abdominal hysterectomy with bilateral salpingo-oophorectomy, random peritoneal biopsy, lymphadenectomy. The specimen was then sent for histopathology analysis. On follow up, histopathology result revealed peritoneal fluid cytology negative for malignant cells and a metastatic poorly differentiated carcinoma, consider invasive lobular carcinoma of breast origin, uterus and ovaries. (Appendix, Figure 1, 4, 5) Because of this, the patient was referred to surgery for further evaluation and management. Upon further reviewing the case, the patient had a 7-month history of breast mass with noted nipple retraction left. There was no associated nipple discharge nor breast pain. On physical exam, the mass was noted to be solid, fixed over the left breast. It was non-tender, but there was noted nipple retraction. Mammogram of bilateral breast and core needle biopsy were requested, but the patient was lost to follow up hence not done until Few hours before admission; the patient had severe abdominal pain with a noted feeling of bloatedness, vomiting and loss of appetite; hence consult at a local hospital wherein she was managed as a case of post-surgical adhesions hence referred to our institution for further evaluation and management. The patient was then admitted to the surgical ward, where the biopsy was requested, but then decided to go home against medical advice and was lost to follow up.

Case 2
A 43-year-old, gravida 4 para 4 (4004), a known case of Breast Cancer stage IV. She underwent a modified radical mastectomy, left (12/2015), with a pathological study showing a lobular carcinoma breast cancer. She received 4 cycles of Doxorubicin and Cyclophosphamide (2016) with excellent clinical outcome. A local progression of mass at the mediastinal area was noted, thus subjected to radiotherapy. Immunohistochemistry revealed positivity to ER/PR stains; hence Tamoxifen was started as a maintenance medication. Her medical oncologist recommended ovarian ablation hence the surgery. She underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy. Intraoperative findings revealed a grossly normal cervix, bilateral ovaries and appendix. There were palpable liver nodules and omental thickening. Uterus was 6x5x2 cm, and on the cut section revealed endometrial polyp, multiple leiomyoma, and thin endometrium.

The final histopathologic diagnosis is metastatic carcinoma with mixed lobular and ductal features, probably breast in origin on bilateral ovaries. Adjuvant therapy was continued by her primary oncologist. (Appendix, Figure 2)

Case 3
A 38-year-old, gravida 7 para 6 (6015), a known case of Invasive ductal carcinoma, right breast, stage IIB (T4N0M0), s/p right modified radical mastectomy (01/10/2017). Immunohistochemistry of the breast mass showed a triple-negative result of ER, PR/HER2-neu. The patient underwent 8 cycles of chemotherapy with anthracycline with concomitant radiotherapy. Regular follow up was done; however, 3 months after chemotherapy, a pelvic mass with consideration of malignancy was noted on abdominopelvic CT scan. Tumour markers showed a high result of CA 125 at 1,963 (0-35), 145.10 (0-32) for CA 15-3 and a CEA of 0.5 (0.25). An exploratory laparotomy was recommended to determine the nature of the pelvic masses (primary or metastatic), which will determine subsequent treatment. She underwent exploratory laparotomy, drainage of ascitic fluid, bilateral salpingo-oophorectomy infracolic omentectomy, and peritoneal biopsy. Intraoperatively, Moderate ascites was noted. The uterus was small and grossly normal. Bilateral ovaries and fallopian tubes were grossly normal. There were noted multiple implants over the peritoneum wall. The omentum and appendix were grossly normal. Palpation of lymph nodes revealed matted and enlarged pelvic and para-aortic lymph nodes. The final histopathologic diagnosis is a metastatic, poorly differentiated carcinoma, probably ductal carcinoma, bilateral ovaries. (Appendix, Figure 3). The patient was advised adjuvant chemotherapy but refused treatment.

Discussion
Breast cancer is the most common malignancy in women and one of the leading causes of death among women[1]. Invasive ductal carcinoma and invasive lobular carcinoma of the breast account for 75% and 15% of all breast cancer cases, respectively. Despite its lower incidence in all breast cancers, invasive lobular carcinoma is the most frequent histologic type that metastasizes the female genital tract in more than 80% of all cases[4]. The
most common sites of the breast’s metastases are bones, liver, lungs and brain, whereas metastases to the female genital tract are rare[1],[4]. When it occurs, it mostly involves the ovaries, possibly due to the nature of the stromal metabolic environment in terms of pH and oxygen tension and peritoneal spread accounting for 75.8%, while metastases to the uterus account for less than 10% of all cases. With the uterus, the myometrial involvement predominates over endometrial and that the histologic type predominantly is invasive lobular carcinoma of the breast[1]. According to Stemmer Mann, the majority of the uterine metastases are the result of local lymphatic spread from earlier ovarian metastases. While tumours arising from primary organs spread to the ovaries by various routes. Direct spread is one of the pathways for cancer invasion to adjacent organs. Spread from more distant sites is mainly via other routes like blood vessels, lymphatics and surface implantation[2,4,5].

Population screening with mammography has increased the numbers of breast cancer diagnosed in younger patients at an early stage and has contributed to improved survival from the disease[6]. The average age of patients during the diagnosis of ovarian metastasis is situated in the first half of about fifty. The interval separating the diagnosis of primitive cancer that of ovarian metastasis is longer for breast cancer than of other primitive sites[2]. In our case, the patients presented symptom about 1-2 years after diagnosis of breast cancer.

All the cases mentioned were diagnosed with breast cancer before ovarian metastases. The discovery of a suspected pelvic mass to a patient presenting with breast cancer history raises the following problem: primitive ovarian neoplasia or metastasis...
of breast cancer[2]. Thus, Uterine and ovarian metastases of extragenital cancer can present as a diagnostic challenge for physicians.

In ovarian metastases, it may show a smaller size1. Bilaterality of the ovarian lesion, presence of peritoneal carcinomatosis, and preoperative cancer antigen 125 (CA 125) can help in the diagnosis but of minimal significance[2,6]. Primary ovarian tumours were more often unilateral, while bilateral tumours were encountered in metastatic disease. The level of carcinoembryonic antigen (CEA) is higher in metastases but is also elevated in primitive cancer[2]. While metastatic involvement of the endometrium should be considered when vaginal bleeding or an enlarged uterus is present. Histopathologically, it is difficult to distinguish since both have a glandular architecture, and both are likely to demonstrate positivity for hormone receptors[3].

Even with appropriate workup, it may be difficult to distinguish between uterine or ovarian cancer and the cancer metastases of the breast. Both may demonstrate positivity for hormone receptors, although positivity is not specific for metastatic breast cancer since many primary ovarian and other gynaecological malignancies are commonly positive[6]. Serum markers can also be detected in primary and secondary ovarian and uterine malignancies. Patient with metastatic ovarian cancer may have high CA 15-3 levels and high CA 125 (but lower with primary ovarian cancer). Immunohistochemical stains should be employed since it has a role in differentiating primary and secondary ovarian carcinoma, which have a sensitivity of 86% for breast. Breast cancer metastases express cytokeratin 7 (CK7), particularly lobular and GATA3, on immunohistochemistry most compared to extragenital metastasis[3]. In our cases, the high
Figure 12 LPO view (H&E, 100x)

Figure 13 HPO view (H&E, 400x)

Figure 14 Abdomio-pelvic CT scan showing uterine mass

Figure 15 Abdomio-pelvic CT scan showing mesenteric thickening
clinical and pathologic evidence obtained from the history and surgical specimens precluded the need to perform the test. It has been reported that differential cytokeratin (CK7 and CK20) staining can distinguish primary and secondary ovarian and uterine adenocarcinoma and ascertain the likely site of origin of a disseminated peritoneal tumour. Metastatic breast carcinoma is usually positive for CK7 and negative for CK20. Estrogen receptor (ER) and progesterone receptor (PR) are often positive\[8\]. In ovarian carcinomas, cytoplasmic staining is generally seen with antibodies against CK7. Most tumours may express CA 125 at the cell membrane, usually at the luminal site but occasionally in the cytoplasm. Only in mucinous ovarian carcinoma was cytoplasmic staining for CK20, and membranous staining for CEA sometimes are seen. While breast carcinoma usually shows cytoplasmic staining for CK7 and nuclear ER staining. In a few cases, vimentin and CK20 were seen\[9\].

Tamoxifen has been a well-established drug for the management of breast cancer, and the risk of uterine cancer after its use has been increasing after its long term use. The majority of uterine metastases are positive for hormone receptors, and that Tamoxifen use leads to endometrial hyperplasia\[3\]. These endometrial changes lead to a favourable microenvironment for the seeding of breast cancer metastases\[1\]. Hence, Metastatic involvement of the endometrium should be considered when vaginal bleeding or an enlarged uterus is present after Tamoxifen use\[1\].

We have described three cases of breast cancer with metastases to the uterus and ovaries. These cases are unique due to their unusual pattern of metastases involving the ovaries and uterus. Gynaecological oncologists are often challenged regarding the choice of appropriate treatment planning for women with a history of breast cancer who are asymptomatic and those who present with adnexal mass suspicious of malignancy since there are no clear guidelines regarding the role of surgical cytoreduction in metastatic breast cancer to ovaries\[6\]. It is important to know the nature of these masses to guide the oncologists in the subsequent therapy.

Conclusion
In conclusion, genital tract metastases (uterine and ovarian) from breast cancer are extremely rare and can pose a significant diagnostic and therapeutic challenge. In the setting of a diagnosed breast cancer prior to ovarian cancer, Immunohistochemical stains should be employed since it has a major role in differentiating primary and secondary genital tract carcinoma from breast cancer, especially that hormone receptors even serum markers may be positive for both. It is imperative to know the pathology of these lesions to provide guidance in the appropriate management of patients.

Funding
No Funding was obtained.

Conflict of Interest
The authors and co-authors declare no conflict of interest

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