Case Report
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Isolated Endometrial Metastasis of Invasive Ductal Carcinoma Simulating a Primary Uterine Malignancy: A Rare Case Report

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Abstract

Most common sites of metastasis from breast cancer are the lungs, bones, liver, and brain. Although metastasis to the uterus from breast cancer is uncommon, there have been some case reports on uterine metastasis. Among them, myometrium is involved more frequently comparing to endometrium. The majority of breast cancer metastases to endometrium are lobular type, and there have been only 7 reported cases of ductal type since 1984. In this study, a new case of invasive ductal carcinoma with metastases to endometrium and isolated presentation of abnormal uterine bleeding is described. If an endometrial abnormality is detected, the differential diagnosis of whether the uterine tumor is metastatic or primary is very important to determine the course of treatment. Atypical bleeding in patients with known breast carcinoma should prompt screening for endometrial metastasis by a gynecologist. Metastasis to the uterus carries a grim prognosis. We herein report a case in which we detected a uterine tumor during follow-up after treatment with tamoxifen, and demonstrate that GCDFP-15 is useful in diagnosing metastatic uterine tumors arising from breast cancer.

Keywords: Breast carcinoma, Invasive Ductal Carcinoma, Menorrhagia, Tamoxifen, Uterine metastases

Introduction

The female genital tract is rarely involved by metastatic tumors. The most common site of metastasis is ovary followed by the vagina, cervix, uterine corpus, and fallopian tubes. Uterine metastases from extragenital cancer are extremely rare.[1] Among extra genital cancers metastasizing to the uterus, breast is affected in only 3.8% of cases.[2] Approximately 80% of the genital metastases from breast carcinoma are of invasive lobular carcinoma (ILC), whereas invasive ductal carcinoma (IDC) is the rarest. In the literature, there have been only 6 cases reported of IDC metastases to endometrium from

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1985 to 2017.[2, 3] When breast cancer metastasizes to the uterine corpus, it is mainly in the myometrium; however, in a minority of cases, the metastasis is confined to the endometrium.[1,2] As well, if the uterus is infiltrated, abnormal uterine bleeding is the most common manifestation. Nonetheless, most of the cases of uterine metastases are found on autopsy.[4]

Tamoxifen has played a critical role in the treatment of patients with hormone receptor-positive breast cancer. However, it is known that tamoxifen increases the risk of endometrial cancer. This is due to the agonistic effect of tamoxifen on the endometrium. Therefore, gynecological follow-up is mandatory during tamoxifen treatment.[5] If any abnormality is detected, differential diagnosis whether the tumor is metastatic or primary is very important for determining the type of treatment which should be administered. GCDFP-15 is a specific immuno-histochemical marker for breast carcinoma, which is very important in defining whether the primary site was the breast or not.[6] In current study, in reporting a unique case of uterine metastasis from IDC breast in a postmenopausal woman who presented with abnormal uterine bleeding (AUB) after treatment with tamoxifen, and later the usefulness of GCDFP-15 as a diagnostic marker for metastatic uterine tumors arising from breast cancer was confirmed.

Case Report

A 45-year-old female presented to gynaecologic outpatient department with complaint of abnormal uterine bleeding as menorrhagia for 5 months. A diagnostic work-up was initiated to detect possible causes of vaginal bleeding. She underwent transvaginal ultrasound, which revealed endometrial heterogeneous echogenicity; however, no evidence of focal thickening, myometrium, and adnexa were unremarkable (Figure 1). Therefore, she underwent a dilatation and curettage (D&C) biopsy for tissue diagnosis of the endometrium. Pathological assessment of the endometrial tissue revealed isolated or sheets of neoplastic epithelial cells infiltrated within endometrial stroma and glandular formation at places, which is not typical

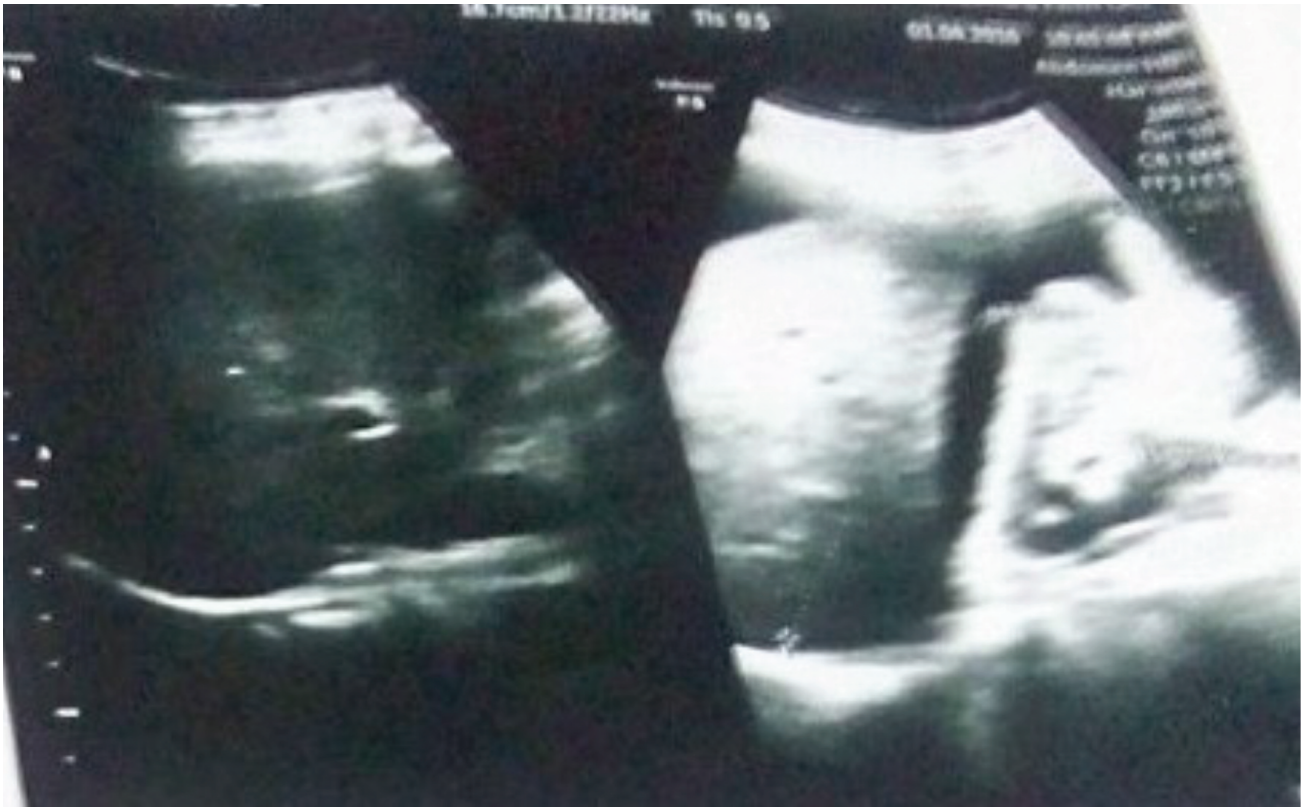

Figure 1. Ultrasonography revealing endometrial heterogeneous echogenicity; however, no evidence of focal thickening and normal adnexa.

of primary uterine tumors. Occasional normal endometrial glands were identified (Figure 2 A & B). The immunohistochemical staining was strongly positive for estrogen receptors (ER), progesterone receptors (PR), HER2 neu and gross cystic disease fluid protein-15 (GCDFP-15) (Figure 3 A-D). Previous history revealed that she was diagnosed with breast carcinoma two years ago. Left modified radical mastectomy and axillary lymph node dissection were performed. Histopathology showed infiltrating ductal carcinoma grade II (Bloom and Richardson), measuring 7 cm in its largest diameter, stage T3N0M0. All axillary lymph nodes were negative. Immunohistochemistry revealed tumor cells to be positive for ER, PR, and HER2 neu. Therefore, the patient received three cycles of adjuvant chemotherapy. Furthermore, radiotherapy of 5000 cGy was performed to the chest wall and the patient started tamoxifen. Nine months after treatment with tamoxifen, the patient complained of abnormal uterine bleeding. Endometrial curettage was performed to confirm the diagnosis of metastatic uterine carcinoma compatible with breast origin. Similarly, reviewing the previous breast tumor showed identical morphology confirming the diagnosis. These findings were consistent with breast cancer that had metastasized to the uterus. Systemic examinations, including upper endoscopy, were performed and there was no evidence suggesting other primary or metastatic diseases. Thereafter, the patient received systemic chemotherapy. Patient is on regular follow-up and is doing well.

Discussion

Breast cancer is the most common female cancer and the second most common cause of cancer-related deaths in women.[7] The most frequently reported metastatic sites of breast cancer are the lungs, followed by bones, liver, and brain. Moreover, metastases in the female genital tract are uncommon.[1, 2] Extra-genital metastases to the female genital organs are rarely documented and they usually arise from gastrointestinal tract (37%) and breast (34%) cancer.[1] Histologic types of breast cancer are IDC and ILC). IDC contributes 70-75% of breast cancers as compared to IL that only accounts for 5-20%. Despite of the lower incidence, ILC is the most frequent histological type that metastasizes to the female genital tract in more than 80% of all cases.[8] Loss of expression of the adhesive molecule E-Cadherin in infiltrating lobular; however, not ductal carcinomas has been proposed to partially explain the differences in metastatic patterns.[9] However, it should be kept in mind that IDC can also metastasize to the gynecologic organs alone, as it was seen in this case.

Ovaries are most frequently affected by metastases accounting for 75.8%, followed by vagina (13.4%), uterine corpus (4.7%), cervix (3.4%), vulva (2%), and salpinx (0.7%).[1] The ovaries are often first in the path of spread of

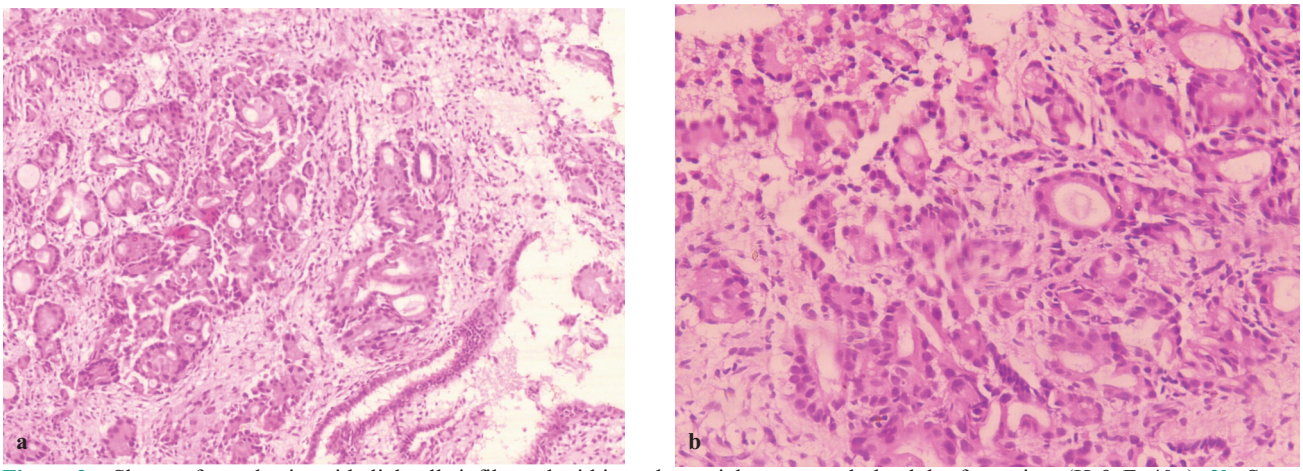

Figure 2a. Sheets of neoplastic epithelial cells infiltrated within endometrial stroma and glandular formation. (H & E, 40×); **2b.** Same figure with higher magnification (H&E, 100×).

malignant cells. They provide an optimal environment for implantation of malignant cells, because they are highly vascular with a well-developed lymph network. Additionally, the stroma of ovaries has a favorable pH and oxygen tension.[10] On the other hand, the other female genital tract organs, including the uterus, seem resistant to metastasis. Uterine metastases from extra genital cancers are quite rarer than metastases to the ovary, and when these occur, they are secondary to lymphatic spread from previous ovarian metastases. Stemmer Mann proposed that metastases restricted to the uterus without involvement of the ovaries are indeed very rare and can be explained by hematogenous spread.[11] Anatomic distribution of metastases in the uterine corpus was investigated, and it was demonstrated that involvement of the myometrium only accounts for 63.5%, followed by 32.7% myometrium and endometrium and endometrium is only 3.8%. When the endometrium is involved, the tumor usually tends to infiltrate the stroma, sparing the endometrial glands.[1] Initial symptoms of the uterine involvement depend on the site of involvement. Abnormal uterine bleeding is often the first symptom when the endometrium is involved. However, if the infiltration affects myometrium only, patients may often be asymptomatic.[4] Imaging techniques can be helpful as they can reveal a myometrial nodule or a hypertrophied endometrium, which may mimic a primary tumor.[12]

Pathologically, metastatic carcinoma to the endometrium may be suspected if one of the following signs is present:

1. A tumor with an unusual gross or histological pattern for primary endometrial carcinoma.
2. Diffuse replacement of endometrial stroma

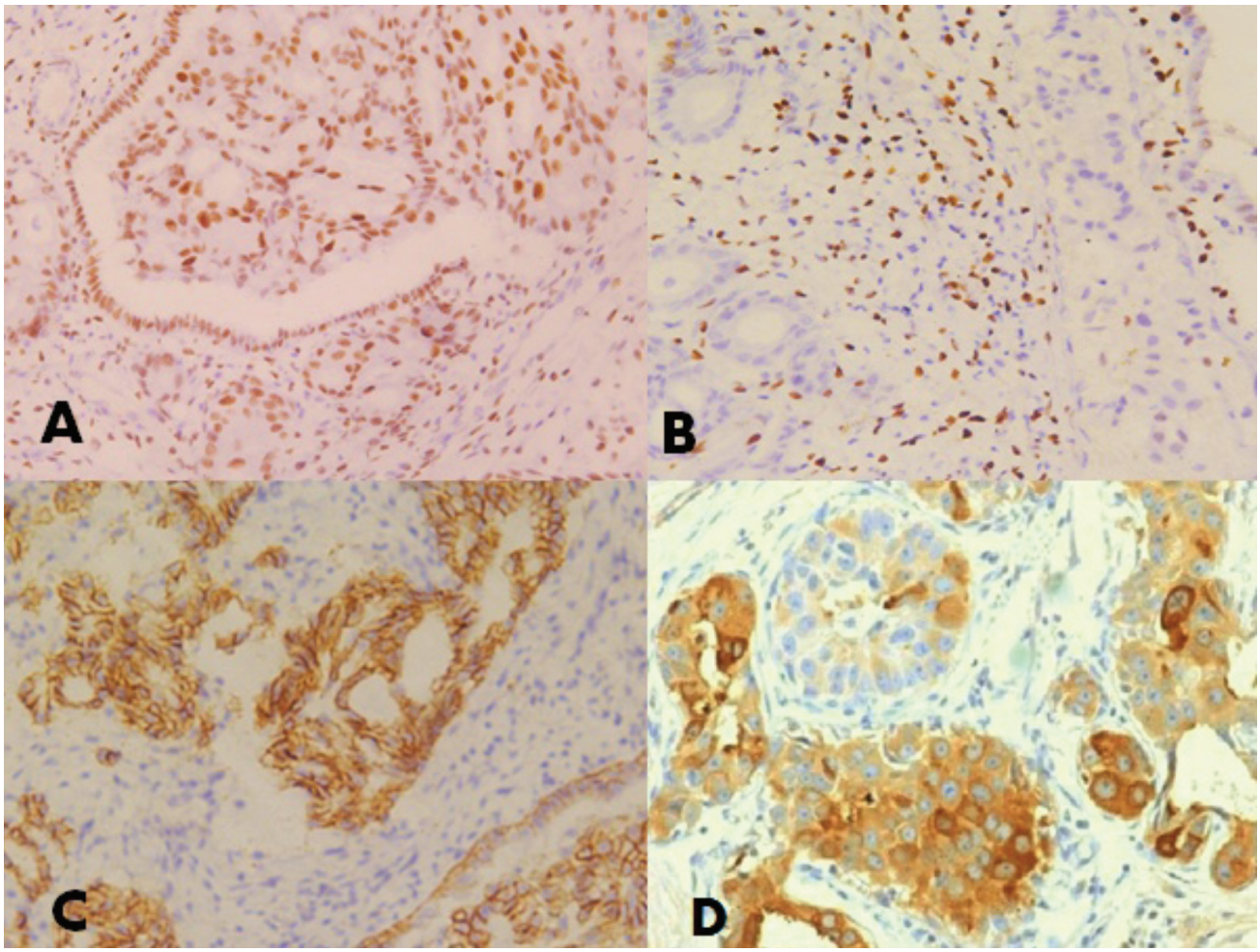

Figure 3. On IHC tumor cells are ER(A), PR (B), HER2 NEU (C) and GCDFP-1 (D) positive (40×).

with preservation of endometrial glands.

3. Lack of accompanying premalignant changes in the residual benign endometrium.

4. Lack of tumor necrosis.

For the past 2 decades, tamoxifen has played an essential role in the management of both early and metastatic breast cancer. Based on the data generated during the Early Breast Cancer Trialists' Collaborative Group's (EBCTCG) meta-analysis, five years of treatment with tamoxifen can reduce the risk of both recurrence and mortality of breast cancer by approximately 30%.[5] This is caused by the antagonistic effect of tamoxifen on breast cancer cells. However, tamoxifen exerts a partial agonistic effect on the endometrium of the uterus. Therefore, treatment with tamoxifen increases the incidence of endometrial hyperplasias, polyps, and neoplasms. The relative risk of developing endometrial cancer following treatment with tamoxifen is approximately 2-4 times higher comparing to patients who have not received the drug. These uterine tumors are frequently detected because patients experience unusual uterine bleeding.[13]

It is very difficult to diagnose whether a uterine tumor is a primary or arising because of tamoxifen therapy, or whether it is a metastasis. Correct diagnosis affects critical decision with regard to the treatment of the uterine malignancy.When uterine metastasis from breast carcinoma is diagnosed, surgical intervention does not seem to be indicated, because the disease usually widespreads and involves other extragenital sites as well. Palliation and conservative management were advised for metastatic breast disease, in view of the fact that metastases to the uterus and to other organs of the genital tract can be considered as a pre-terminal event.[14] On the other hand, when primary endometrial carcinoma is diagnosed, surgical intervention is indicated as part of the primary treatment, even in patients with a history of breast carcinoma. A positive immuno-histochemical stain for hormone receptors suggests metastatic breast carcinoma; however, GCDFP-15 is more specific for breast carcinoma. GATA3, a recent breast immunohistochemical stain, was found to be more sensitive than GCDFP-15 in metastatic breast carcinomas.[6,15]

According to the review of literature, there have been only six reported cases of endometrial metastases which are of IDC origin. This case report and literature review emphasizes the importance of complete work-up and exact diagnosis in patients with AUB, particularly in the presence of prior breast cancer history. Routine gynecological follow-up examination should be carried out in breast cancer patients under tamoxifen therapy. It should be noted that breast cancer patients undergoing hormonal regimens may have primary endometrial cancer as well as uterine metastases. Therefore, it is necessary to differentiate a metastatis of breast tumor from a primary genital neoplasm, since the treatments and prognoses are completely different. On the other hand, because of the limited number of case reports, there is not enough data about the prognosis. However, the majority of studies considered uterine metastasis as a poor prognostic preterminal event, even though more studies are a need of an hour to improve our knowledge about the best treatment and precise prognosis.[15]

Conclusion

To conclude, it is prudent to entertain the possibility of uterine metastasis, whether isolated or in association with other sites in the female genital tract, from a breast cancer primary in patients presenting with vaginal bleeding after their breast cancer management. Tamoxifen use in itself predisposes to an array of conditions that can cause vaginal bleeding; however, its use does not rule out a possible concomitant uterine metastasis from the mammary primary location. Routine gynecological follow-up examination should be carried out in breast cancer patients under tamoxifen. Additionally, it is important to distinguish the uterine lesions whether primary or metastatic because of the different treatment options. Abnormal uterine bleeding in patients with a history of breast carcinoma should always alert the physician to consider the diagnosis of metastatic spread to the genital tract. Metastasis

to the uterus carries a grim prognosis.

Informed Consent

The patient signed the written informed consent for the case report to be published.

Conflict of Interest

None declared.

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