Clinical Case Reports

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CASE REPORT

The potential role of HER2 upregulation in metastatic breast cancer to the uterus: a case report

Melissa Y. Y. Moey[1], Omer A. Hassan[1], Christos N. Papageorgiou[2,3], Stephanie L. Schnepp[4] & John T. Hoff[4,5]

[1]Saba University School of Medicine, The Bottom, Saba, Dutch Caribbean, The Netherlands
[2]SSM Cancer Care, St. Mary's Health Center, St. Louis, Missouri, USA
[3]Division of Hematology and Oncology, Department of Internal Medicine, Saint Louis University School of Medicine, St. Louis, Missouri, USA
[4]SSM Health St. Mary's Health Center, St. Louis, Missouri, USA
[5]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Saint Louis University School of Medicine, St. Louis, Missouri, USA

Correspondence
Christos N. Papageorgiou, SSM Cancer Care, St. Mary's Health Center, 6400 Clayton Road, Suite 302, St. Louis, MO 63117, USA.
Tel: +1-314-645-3370; Fax: 314-645-0576;
E-mail: christos_papageorgiou@ssmhc.com

Funding Information
No sources of funding were declared for this study.

Received: 18 October 2015; Revised: 29 January 2016; Accepted: 22 May 2016

***Clinical Case Reports* 2016; 4(10): 928–934**

doi: 10.1002/ccr3.602

Key Clinical Message

Abnormal uterine bleeding in a patient on maintenance hormonal therapy for breast cancer should raise concern for endometrial abnormalities including rare uterine metastasis from the breast. Hormonal receptor profile changes in metastatic lesions favoring human epidermal growth factor receptor 2 (HER2) overexpression may be involved in the pathogenesis of metastasis to the uterus.

Keywords

Human epidermal growth factor receptor 2, metastatic breast cancer, tamoxifen, uterus.

Introduction

Abnormal uterine bleeding (AUB) observed in a patient on tamoxifen therapy raises concern for primary endometrial abnormalities including atypical endometrial hyperplasia, endometrial polyps, and endometrial cancer [1], while metastatic breast cancer (MBC) is often overlooked as part of the differential diagnoses workup due to its rare incidence [2]. While there have been previously reported cases of uterine metastasis from the breast, its pathogenesis has not yet been elucidated. We present a similar case of this uncommon presentation; however, with unique features that have allowed us to exclusively shed light on the possible link between tamoxifen exposure in the uterus and hormonal-growth receptor pathway cross talk that contribute to increased tumor aggressiveness and invasiveness favoring uterine metastasis.

Case Presentation

A 49-year-old African-American perimenopausal female with a history of metastatic estrogen receptor-positive, progesterone receptor, and human epidermal growth factor receptor negative (ER+/PR−/HER2−) invasive ductal breast carcinoma (IDC) (Fig. 1) on maintenance tamoxifen therapy presented to a regular oncology clinic follow-up visit with complaints of AUB. She was previously diagnosed with IDC that had metastasized to her liver (biopsy proven shown in Fig. 2) 8 months ago and had since completed 4 months of anthracycline-based combination (epirubicin and cyclophosphamide) chemotherapy. Maintenance endocrine therapy with tamoxifen was started 3 months after completing chemotherapy when she noticed AUB. At the time of visit, she denied abdominal pain, distension, bowel movement, or urinary changes.

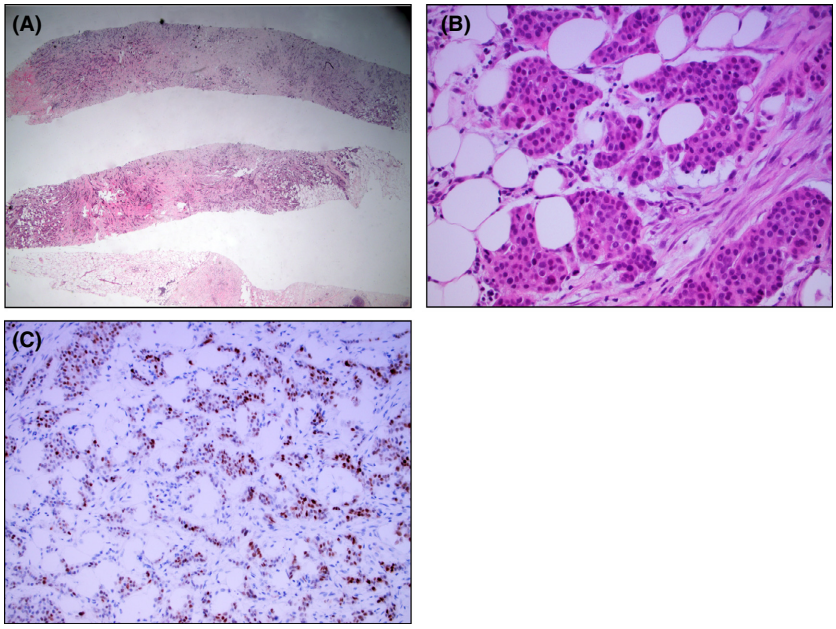

Figure 1. Breast Core Biopsy. (A) Low power: moderately differentiated invasive ductal carcinoma. The invasive tumor exhibits stromal desmoplasia and is composed of infiltrating small irregular solid nests of cells with absent glandular formation. (B) High power: the tumor cells are large with amphophilic cytoplasm and moderate nuclear hyperchromasia and pleomorphism. Some nuclei show prominent nucleoli. Mitoses are identified. (C) Immunohistochemical stains show an intensity of 3+ for ER and a 1+ score for HER2 (not shown).

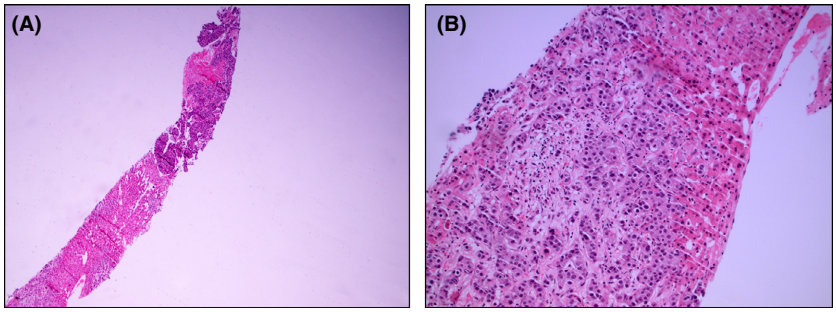

Figure 2. Liver core biopsy. (A) Low power: fragments of liver parenchyma diffusely infiltrated by metastatic carcinoma. (B) High power: tumor is in nests and aggregates and is composed of malignant cells with nuclear grade 2, mitoses. Abundant lymphovascular invasion is present. The cytomorphology and history is similar to the previous breast mass biopsy confirming the diagnosis of metastatic breast carcinoma.

Routine blood work showed Hgb 11.2 g/dL and Hct 35.5%. Serum cancer markers CA 15.3 (23.5 U/mL) and CA 27.29 (31.3 U/mL) were within normal limits. Carcinoembryonic antigen (CEA) was mildly elevated at 5.5 ng/mL. She was subsequently referred to a gynecologist who noted only blood at the cervical os and a bulky and firm uterus on bimanual pelvic examination. A pelvic ultrasound demonstrated an enlarged uterus without any visualization of uterine fibroids and a thickened endometrial lining of 9.0 mm. Endocervical curetting showed detached portions of squamous epithelium including portions of the transformation zone admixed with a rare focus of atypical cells characterized by marked nuclear enlargement, nuclear chromatin abnormalities, increased nuclear to cytoplasmic ratio, and numerous mitoses. Endometrial biopsy tissue showed invasive carcinoma characterized by sheets of cells with round, ovoid nuclei with relatively smooth nuclear outlines but with normal chromatin and abundant finely granular cytoplasm. The tumor was positive for CK7 (cytokeratin 7), GCDFP-15 (gross cystic disease fluid protein-15), HER2, Ki-67 with mild CEA staining, and negative for ER, PR, CK20, p40, and p16, indicative of MBC (Fig. 3).

To guide appropriate treatment, repeat computed tomography (CT) scan was performed to assess for

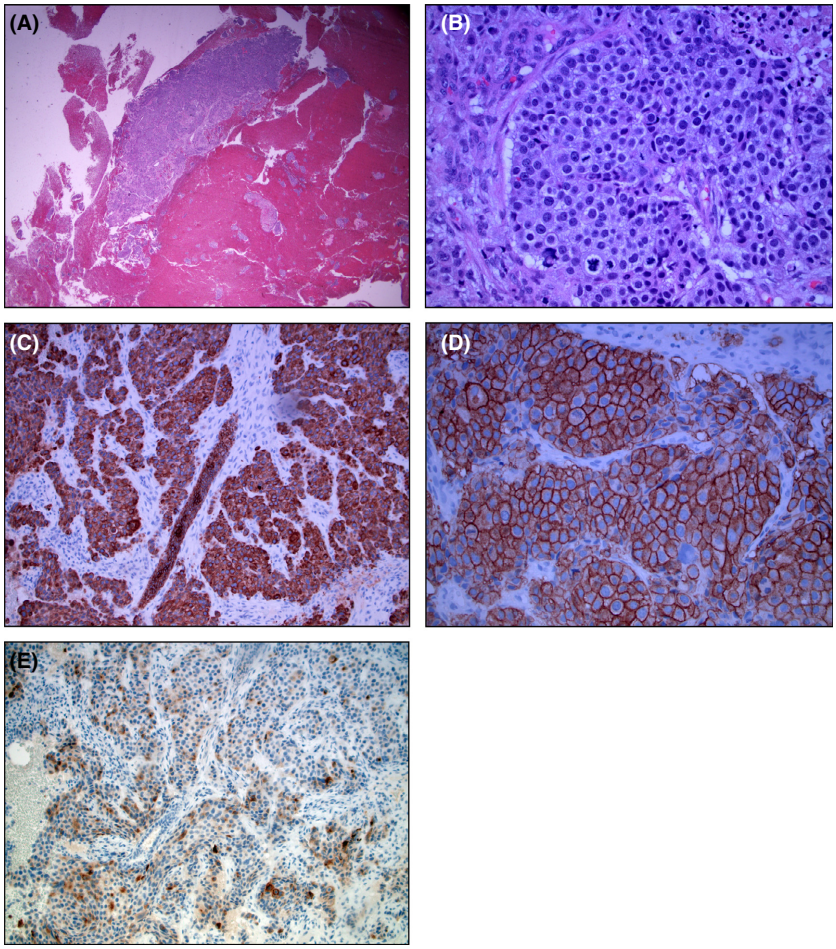

Figure 3. Endometrial biopsy. (A) Low power: tumor aggregates and nests of cells in a background of blood. (B) High power: the tumor is in nests and aggregates composed of malignant cells with high-grade nuclear features of prominent nucleoli and frequent mitoses. Immunohistochemical stains show positivity for (C) CK7 and (D) HER2 and are negative for (E) ER.

metastatic involvement which showed persistent minimal nodularity within the left breast and no evidence of axillary or internal mammary lymph node adenopathy, or lung nodule in the chest. Compared to the initial CT scan, there was a significant interval increase in diffuse hepatic metastases with the largest seen measuring 5.5 cm. There was a new low-density mass within the fundal myometrium measuring 3.0 × 5.2 cm and new likely thickening in the endometrial stripe without adnexal mass or retroperitoneal adenopathy. Although there are no standard treatment guidelines for MBC to the uterus, total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) was advised as palliative treatment to relieve her AUB over minimally invasive surgery given the patient's initial diagnosis of metastatic disease as well as a surgical history of two prior laparotomies with evidence of extensive adhesive disease. Gross pathology demonstrated multiple foci of tumor present in the mucosa, submucosa, muscularis propria, and serosa of the uterus (Fig. 4). There was evidence of adenomyosis and leiomyoma in areas of uninvolved myometrium (not shown).

Three weeks after TAH-BSO, the patient was readmitted to the hospital for intractable right upper quadrant pain associated with nausea and vomiting with CT scan demonstrating worsening hepatic metastatic disease. As we were concerned for potential new metastatic lesions, a whole body scan was performed which fortunately did not show presence of osseous metastasis. Her symptoms eventually improved and she was subsequently discharged home. At her follow-up visit 1 week after hospital discharge, she presented with new complaints of right-sided upper extremity motor weakness suspicious for likely brain metastasis. The family made the decision to seek hospice and palliative chemotherapy with trastuzumab given the new hormone receptor (HR) profile of ER−/PR−/HER2+.

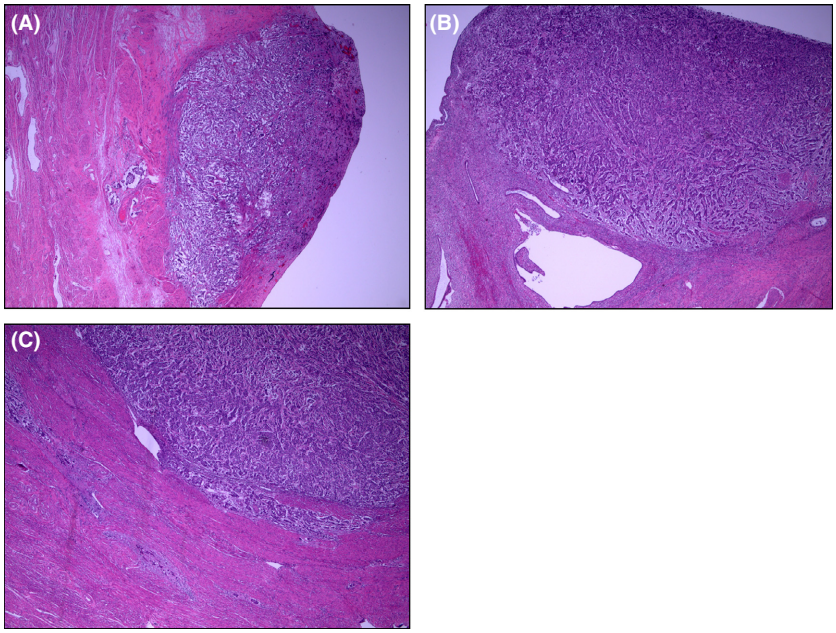

Figure 4. Metastatic breast cancer in the uterus. H&E staining of the patient's hysterectomized uterus showing metastatic breast cancer nodules in (A) the serosa (B) endometrial mucosa and submucosa and (C) muscularis propria (myometrium) with evidence of lymphovascular invasion. The tumor is morphologically similar to that of the previous breast, liver, and endometrial biopsy. It is composed of solid aggregates and nests of cells with necrosis, moderate to high-grade nuclear features and frequent mitoses. The uninvolved endometrial mucosa shows proliferative pattern without atypia.

Discussion

Metastatic breast cancer to the uterus seen as AUB is an often overlooked phenomenon due to its rare incidence. Unlike the ovary, vagina and cervix, the uterus consists of only 2–5% of cases of extragenital metastatic sites, typically from the breast or gastrointestinal malignancies [2]. It has been well understood that uterine metastasis with ovarian involvement is a result of retroperitoneal lymphatic spread from pre-existing ovarian metastasis; however, sole metastasis to the uterus occurs via hematogenous spread [3]. When metastasis to the uterus occurs, it commonly involves the myometrium in 64.5% of cases, both the myometrium and endometrium in 32.7% of cases and only the endometrium in 3.8% of cases [2] which translates to presenting symptoms as abdominal pain, abdominal distension, or commonly AUB. While there were two cases [4, 5] (reviewed in Table 1) that noted an elevation in cancer markers associated with MBC to the uterus, these are often unreliable as indicators of metastasis as was observed in our patient. Despite its rarity, there have been a surprising number of cases reporting this peculiarity of MBC to the uterus (summarized in Table 1). Although the cases are varied, studies have demonstrated invasive lobular carcinoma (ILC) as the most common type to metastasize to the uterus, understood to be a result of its loss of the E-cadherin molecule in comparison to IDC [6]. Reports have also suggested concomitant uterine pathology of polyps or leiomyoma and longer years of use with different endocrine therapy (selective estrogen receptor modulators [SERMs] and aromatase inhibitors [AIs]) as additional predisposing factors.

A literature review of case reports in the past decade compiled in Table 1 show a similarity of HR (estrogen) positivity in patients with MBC to the uterus as was observed in our patient. Interestingly, however, in our case, was the reversal of the HR profile in the new metastatic lesion compared to the primary breast cancer from ER+/HER2− to ER−/HER2+, respectively. This supports the understanding of breast cancer existing as a polyclonal neoplasm, whereby endocrine therapy selectively diminishes the malignant ER+ clonal cells allowing for ER-cells to travel via the lymphovascular supply to seed other sites of the body [7, 8]. Unfortunately, a comparison cannot be made with the prior published case reports as the majority lacked the pathological reporting of the HR profile of the new uterine metastasis. In addition, it is worth mentioning that studies have observed a minimum duration of several months to years for the development of uterine metastasis while undergoing endocrine therapy; however, in our patient, uterine metastasis was detected at 3 months despite clinically proven evidence of significantly reduced disease during routine clinical follow-up.

Table 1. Reported case studies of metastatic breast cancer to the uterus.

Patient age and presenting symptom	History of uterine pathology	Breast cancer type, stage, and receptor profile	Metastatic breast tumor receptor profile	Adjuvant endocrine therapy used and duration
62 y/o with abdominal distension [16]	Leiomyoma	Stage IIA ILC (pT2, N1, M0) ER+/PR+/HER+	NR	Anastrozole – 5 years
57 y/o with abdominal pain and distension [17]	None	Stage IIIC IDC (pT1b, N3a, M0) ER+/PR+/HER2−	NR	Anastrozole – 16 months
43 y/o with abnormal uterine bleeding [18]	Leiomyoma	Stage IIA IDC (pT2, N0, M0) ER+/PR+/HER2−	NR	Tamoxifen – 2 years
47 y/o, asymptomatic [4]	Leiomyoma	Stage IIA IDC (pT2, N0 M0) ER−/PR+/HER2−	ER−/HER2−	Tamoxifen – 38 months
48 y/o with abdominal distension and urinary incontinence [19]	NR	Stage IV ILC ER+/PR−/HER2−	NR	Letrozole – 15 months
44 y/o with abnormal uterine bleeding [20]	NR	Stage IIIA ILC (cT3a, N1, M0) ER+/PR−/HER2−	NR	Tamoxifen – 2 years Anastrozole – 2 months
55 y/o with abdominal pain [21]	Leiomyoma	Stage IV IDC ER+/PR−/HER2−	NR	Tamoxifen – 14 months
60 y/o with abnormal uterine bleeding [22]	NR	Stage NR, IDC ER+/PR+/HER2−	ER+/PR+/HER2−	Tamoxifen – 8 months
58 y/o with abnormal uterine bleeding [23]	Leiomyoma	Stage II ILC HR profile NR	NR	Tamoxifen – 1 year
66 y/o, asymptomatic [5]	NR	Stage I IDC ER+/PR+/HER2+	ER+/PR−/HER2−	NR
58 y/o, asymptomatic [24]	Leiomyoma	Stage III IDC ER+/PR+/HER2−	NR	Tamoxifen – 4 years
57 y/o with abnormal uterine bleeding [25]	Leiomyoma	Stage IIB ILC (pT2, N1, M0) ER+/PR+/HER2−	NR	Tamoxifen – 2 years
58 y/o, asymptomatic [26]	NR	Stage IIA IDC (pT1c, N1, M0) ER+/PR−/HER2−	NR	Tamoxifen – duration NR
76 y/o, asymptomatic [27]	NR	Stage NR, ILC HR profile NR	NR	Tamoxifen – 36 months

C, clinical; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; M, metastasis; N, node; NR, not reported; p, pathological; PR, progesterone receptor; T, tumor; y/o, year old.

Early recurrence of breast cancer, such as in our patient, raises the concern for endocrine therapy refractoriness of which several pathways have been implicated in its pathogenesis reviewed in details elsewhere [9]. One such observation is the demonstration of mutations in the ligand-binding domain of the ER, encoded by the ESR1 gene, in response to estrogen deprivation; however, this occurs in a small population of breast cancers [10]. An area of increasing interest is the cross talk between the nuclear genomic activation of ER and the growth factor activation of HER2 pathways. The finding of ER negativity and HER2 overexpression in the uterine metastatic lesion of our case may be a compensatory response as an "escape mechanism" by which HER2 serves as an alternative, now dominant survival pathway for tumor progression as a result of decreased ER activation with endocrine therapy. In fact, studies have shown that tamoxifen-resistant cells demonstrate increased levels of activation of HER2 and EGFR (epidermal growth factor receptor) by phosphorylation with subsequent downstream ERK1/2 (extracellular signal-regulated protein kinases 1 and 2) activation responsible for disruption of cellular polarity, promotion of tumor invasion, angiogenesis, and cellular proliferation [11].

Tamoxifen, a nonsteroid anti-estrogen, has become the standard of care as endocrine therapy for ER-positive breast neoplasms in premenopausal women since its recognition in 1995 for proven reduction in breast cancer recurrence and improvement of the 10-year survival rate [12]. While the primary application of tamoxifen exploits its antagonistic effect on ER in the breast, its dual agonistic effect in the uterus has been shown to increase the risk for development of new leiomyoma, increase the size of existent uterine leiomyomas, and induce cystic and edematous changes as a result of elevated PR expression [13–15]. Although IDC and ILC are known to metastasize to the common sites of the liver, lung, bone, peritoneal, and retroperitoneal spaces, it is likely because of proliferative changes in the endometrium with increased vascularization observed with tamoxifen exposure secondary to

overexpression of PR that creates a "primed" hospitable environment for tumor seeding. We therefore postulate that, in conjunction with tamoxifen-induced priming of the uterus, tumors that are refractory to endocrine therapy activate an escape pathway via HER2 upregulation that ultimately promotes aggressiveness of tumor growth, invasiveness, and hematogenous spread to the uterus at a much faster pace that would have otherwise been observed in a HER2− setting.

In comparison to the reported incidences of MBC to the uterus, our case is unique as our patient presented with the unanticipated findings of HR profile reversal to a dominant HER2+ pathway and AUB within a short period of time while on endocrine therapy. These findings highlight a plausible mechanism of tamoxifen uterine "priming" that has set the stage and invited tumors that are endocrine therapy-resistant and highly aggressive via HER2 activation to metastasize to the rare site of the uterus.

Conclusion

Abnormal uterine bleeding in a breast cancer patient with a HR-positive profile treated with endocrine therapy should always raise concern for endometrial abnormalities that warrant immediate gynecological workup. While atypical hyperplasia and endometrial cancer are well-known common adverse effects of tamoxifen therapy, it is important to consider MBC as a differential diagnosis to properly guide therapy. A possible explanation of the pathogenesis of favorable metastasis to the tamoxifen-exposed uterus may involve HER2 upregulation in the tumor that has lost ER expression or demonstrates refractoriness to endocrine therapy.

Acknowledgments

We thank Dr. Guihua (Mark) Cao at SSM Health St. Mary's Hospital Pathology Department for providing us with the selected histological figures and Mr. David Weaver at SSM Health Library Services at St. Mary's Hospital for assisting us in the retrieval of articles for literature review.

Conflict of Interest

None declared.

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