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Lobular breast carcinoma metastatic to the endometrium in a patient under tamoxifen therapy: A case report

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Abstract

Metastatic carcinomas to the uterus are rare and usually originate from nearby gynecologic sites, most commonly from the ovaries. Among non-gynecologic origins, breast tumors are the most frequent primaries, predominantly the lobular carcinoma type. A 69-year-old postmenopausal woman diagnosed with lobular breast carcinoma 5 years ago, status post modified radical mastectomy, and currently on tamoxifen therapy presented with post-menopausal bleeding. Subsequent endometrial biopsy confirmed the diagnosis of metastatic lobular breast carcinoma to the endometrium. Breast carcinomas rarely metastasize to the uterus, especially lobular carcinoma type. Abnormal uterine bleeding in a patient with known history of breast carcinoma and under tamoxifen therapy should prompt a complete diagnostic workup to rule out metastatic disease.

Keywords

Breast cancer, lobular carcinoma, tamoxifen, uterine metastasis, tamoxifen

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Introduction

Abnormal uterine bleeding is the most classical initial manifestation of primary and/or secondary endometrial neoplasia. Breast cancer is the most common extra-gynecologic secondary source of endometrial neoplasia by being the main primary site that metastasizes to the uterus,[1] especially lobular type.[2]

Tamoxifen therapy has been shown to be an excellent treatment option for patients with estrogen receptor (ER) positive breast cancer. Despite its promising results, its well stablished mixed agonist/antagonist estrogenic effects can provoke endometrial hyperplasia, subsequently increasing the risk of endometrial cancer.[3,4]

Herein, we report a case of invasive lobular breast carcinoma metastatic to the endometrium with initial presentation of abnormal uterine bleeding while the patient was under tamoxifen therapy.

Case report

A 69-year-old female with a clinical history significant for grade 2 invasive lobular carcinoma (ILC) of the breast status post modified radical mastectomy in 2013, and currently on tamoxifen therapy presented in June 2018 to her obstetrician/gynecologist (OBGYN) with complaints of post-menopausal bleeding. Pelvic ultrasound (U/S) showed a poorly defined and thickened endometrium without distinct lesions. Endometrial biopsy was performed showing fragments of endometrial stroma infiltrated by a single-cell and sheet-like proliferation of deeply basophilic, medium-sized cells with focal signet ring-like features (Figure 1(a) and (b)) suggestive of metastatic disease.

Immunohistochemical (IHC) stains showed these cells to be positive for CK AE1/AE3, CAM5.2, GATA-3, mammaglobin and ER (Figure 2(a)–(e)), confirming the diagnosis of metastatic mammary carcinoma, consistent with her known history of ILC.

Discussion

Metastases from extra-gynecologic primary sites to the uterus are infrequent, with breast and the colon being the most common sites. On the contrary, ovarian tumors are by

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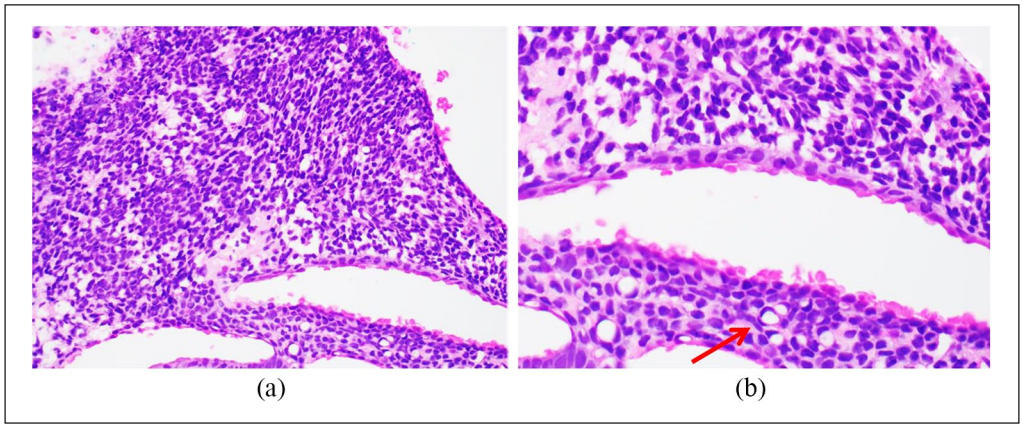

Figure 1. Endometrial biopsy (H&E): (a) sheets of deeply basophilic cells (low power) and (b) cells with signet ring-like features (arrow) (high power).

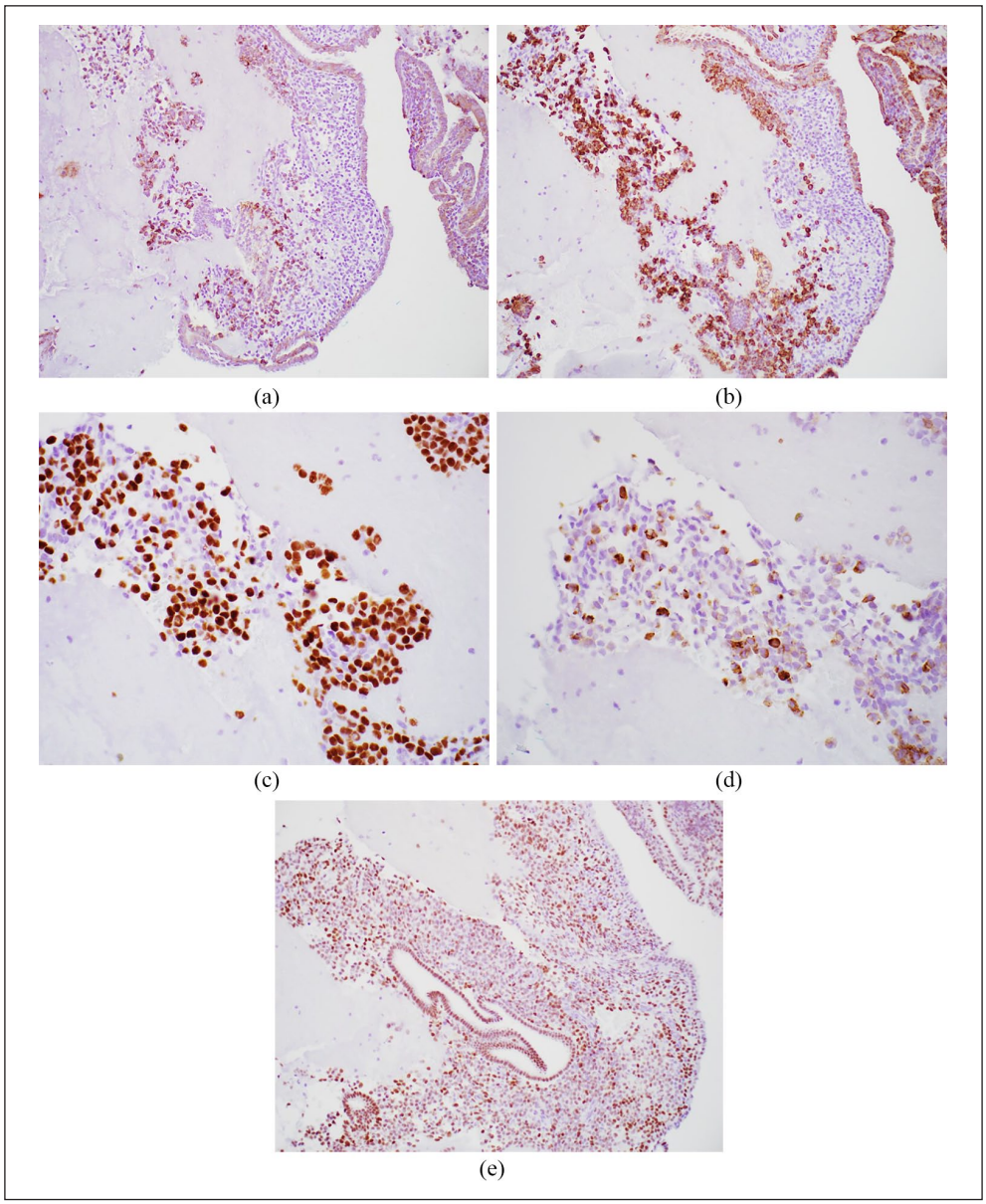

Figure 2. Endometrial biopsy (IHC): cells staining positive for (a) CK AE1/AE3, (b) CAM5.2, (c) GATA-3, (d) mammaglobin, and (e) ER.

far the most common gynecologic primary site to metastasize to the uterus.[1,2] Mazur et al.[2] studied the anatomic localization of metastases in the uterine corpus and concluded that involvement of the endometrium itself accounted for 3.8% of the cases, both the myometrium and endometrium 32.7%, and myometrium only 63.5%. Of the cases limited to the endometrium, ILC is the most predominant histologic type,[1] and given the site, these tumors are more likely to present with abnormal uterine bleeding than those arising in the myometrium only.[3] A case report and literature review made by Razia et al.[4] summarize the incidence of metastatic breast carcinoma specifically to leiomyomas. A total of 8 out of a total of 14 cases (57.1%) consisted of ductal carcinoma, while lobular carcinoma comprised 6/14 (42.9%), which included their current case, and less than a half of all the cases presented with uterine bleeding.

According to G Le Bouëdec et al.,[5] seven out of eight cases of uterine metastasis of breast origin were ILC type with a commonly positive hormone receptor status. The authors also noted that the breast metastasis occurs many years after the initial diagnosis. C Alvarez et al.[6] reported a case of hormone receptive metastatic ILC to the uterus presenting in a post-menopausal patient 4 years after initial treatment. Exceptional cases, including the case reported by H Trihia et al.,[7] might occur 19 years after initial diagnosis. A Aytekin et al.,[8] S Dessole et al.,[9] and A Famoriyo et al.[10] have also reported hormone receptive metastatic ILC in patients treated with tamoxifen therapy.

Invasive ductal carcinoma (IDC) and ILC are the two most frequent histologic subtypes of breast cancer. IDC accounts for approximately 76% of all breast cancers while ILC accounts for 8%.[5] Despite its lower incidence, ILC is the most likely histologic subtype to metastasize to the female genital tract.[1] It has been proposed that this phenomenon is due to the small size of the ILC tumor cells, and their loss of expression of their cell–cell adhesion molecule E-cadherin, which confers them a discohesive property resulting in cell adhesion alterations, which is not seen in IDC.[11,12] The presence of abundant signet ring-like cells, as in our case, was not considered specific for ILCs as it may be seen in the setting of IDC as well. In addition, it has been proven that metastatic breast carcinomas with signet ring cell differentiation do not represent a distinct entity by itself, and no specific prognosis is believed to be associated with signet ring cell differentiation.[13] The overlapping morphologic features of the background endometrial stromal cells with the single-cell and sheet-like proliferation of the metastatic tumor cells was a major diagnostic challenge in our case, especially that both cell types are likely to demonstrate positivity for hormone receptors. However, the positivity for both epithelial markers CAM 5.2 and CK AE1/AE3 as well as the breast origin sensitive markers GATA3 and mammaglobin in the tumor cells helped in reaching the correct diagnosis.

Tamoxifen is the most widely used oral anti-breast cancer drug. It is a nonsteroidal drug that acts as a selective estrogen receptor modulator (SERM) in the breast, thus representing an excellent option for the treatment of hormone receptor positive breast cancer. Paradoxically, it acts as an estrogen agonist in other tissues, mainly the endometrium, promoting epithelial thickening.[14] Tamoxifen is metabolized by a series of enzymes in the liver, including CYP2D6, which further breaks it into other compounds. Gene polymorphisms affecting the activity of this enzyme might explain why some patients have a better response to tamoxifen compared with others.[15]

O Metzger et al.[16] presented the "BIG 1-98 trial" in September 2015, comparing the effectiveness of tamoxifen (ER antagonist) versus Letrozole (aromatase inhibitor) in ILC patients. Letrozole showed a better reduction in the disease burden and increased disease-free survival events compared with tamoxifen. These results created confusion about the best first line therapy for ILC. In 2014, Dr Jankowitz R launched a new national study, in collaboration with the translational breast cancer research consortium, which objective is to compare the efficacy of three endocrine therapies: fulvestrant, tamoxifen, and anastrozole in treating ILC. Outcomes are still to be reported.

Conclusion

Endometrial metastasis from a breast primary poses a significant diagnostic challenge given its low incidence rate. A complete diagnostic workup to rule out metastatic disease should be warranted when confronted with complaints of abnormal uterine bleeding, especially in patients with a known history of carcinoma, regardless of its location.

Declaration of conflicting interests

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

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