CASE REPORT

Diagnostic Pitfalls of Metastatic Lobular Breast Carcinoma to the Endometrium in a Patient on Long-Standing Tamoxifen Therapy

Chew Pong Keong[1,2], Lai Shau Kong[2], Razana Mohd Ali[2], Huzlinda Hussin[2]

[1] Department of Pathology, Hospital Raja Permaisuri Bainun, Jalan Raja Ashman Shah, 30450 Ipoh, Perak, Malaysia.
[2] Department of Pathology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia

ABSTRACT

Metastatic carcinoma from extragenital sites to the uterus, particularly the endometrium, is rare and usually a sign of advanced disease. It is necessary to differentiate between metastatic and primary tumours since the treatment and prognosis are entirely different. We discuss a case of a 61-year-old woman who presented with postmenopausal bleeding due to metastatic breast cancer to the endometrium. She had been diagnosed with breast cancer and on tamoxifen for six years. This case highlights the possibility of isolated breast cancer metastasis to the endometrium without ovarian involvement and the overlapping histological features due to tamoxifen therapy. Abnormal uterine bleeding in a case of breast cancer should raise the suspicion of metastatic breast disease. The immunohistochemical study is critical to support the microscopic findings in conjunction with clinical history and radiological findings.
Malaysian Journal of Medicine and Health Sciences (2022) 18(SUPP21): 137-139. doi:10.47836/mjmhs18.s21.23

Keywords: Breast carcinoma, Tamoxifen, Endometrial

Corresponding Author:
Huzlinda Hussin, MPath
Email: huzlinda@upm.edu.my
Tel: +60397692781

INTRODUCTION

Metastases to the female genital tract from extragenital cancers are rare. The gastrointestinal tract and breasts are the most common primary tumour sites. Ovaries are most frequently affected by metastases, followed by the vagina, uterine corpus, cervix, vulva, and fallopian tubes (1). The myometrium appears to be the most often affected part of the uterine corpus. Metastatic breast carcinoma to the ovary is usually by the lymphatic spread. A metastatic tumour confined to the uterus without involving the ovaries is extremely unusual and can be explained by hematogenous dissemination.

Tamoxifen is the most prescribed anti-breast cancer medication. It is a nonsteroidal medication that acts in the breast as a selective oestrogen receptor modulator, making it a good treatment choice for hormone-receptor-positive breast cancer (2). In other tissues, particularly the endometrium, it works as an oestrogen agonist, causing an epithelial thickening. Tamoxifen-related endometrial changes that had been reported include endometrial polyp and hyperplasia in most cases, as well as serous carcinoma, leiomyosarcoma, low-grade endometrial stromal sarcoma, adenofibroma and adenosarcoma in a small percentage.

It is crucial to distinguish between metastatic and primary endometrial carcinomas because their treatments differ. When breast cancer spreads to the uterus, surgical treatment does not appear to be necessary because the cancer is frequently extensive and affects other extragenital organs. On the contrary, surgical intervention is indicated when primary endometrial carcinoma is diagnosed.

CASE REPORT

A 61-year-old, para 4, postmenopausal Malay woman was diagnosed with infiltrating lobular carcinoma of the left breast in 2011 from a trucut biopsy in a private hospital. The breast lump size at diagnosis was 50 x 50 x 60 mm. She was referred to the government hospital for further management due to financial issues. She opted for conservative treatment and agreed to tamoxifen therapy, 20 mg daily, with six months follow up. In early 2022, she complained of per vaginal bleeding associated with abdominal pain for two months. Per speculum examination revealed an endometrial polyp extending and occupying the cervical canal. The vagina and vulva were unremarkable. The polyp was partially avulsed and sent for histological examination. Histological findings showed diffuse epithelioid cells and some signet ring cells exhibiting mild nuclear atypia (Fig. 1, A-D). The endometrial glands were normal.

Immunohistochemistry studies revealed that those cells were diffusely positive for cytokeratin (Fig. 1, E), estrogen receptor (ER), progesterone receptor (PR) and mammaglobin (Fig. 1, F), and negative for E-cadherin. The diagnosis was concluded as metastatic breast carcinoma, invasive lobular carcinoma histological type. Abdominal ultrasound revealed an ill-defined focal hypoechoic region in segment V of the liver. However, the nature of the lesion could not be confirmed, and other metastatic tumours could not be assessed as she refused further radiological investigations such as CT scan of the chest, abdomen, and pelvic regions. She was also offered neoadjuvant chemotherapy and a left mastectomy, but again she declined due to personal matters. To date, clinical examination during follow-up did not detect any palpable axillary lymph nodes, and the breast lump's size was unchanged. There were no skin changes or nipple discharge. She did not complain of left breast pain, shortness of breath or any constitutional symptoms. She claimed to be compliance with the medications. Her management plan was lifelong tamoxifen therapy, 20 mg daily with six months follow up.

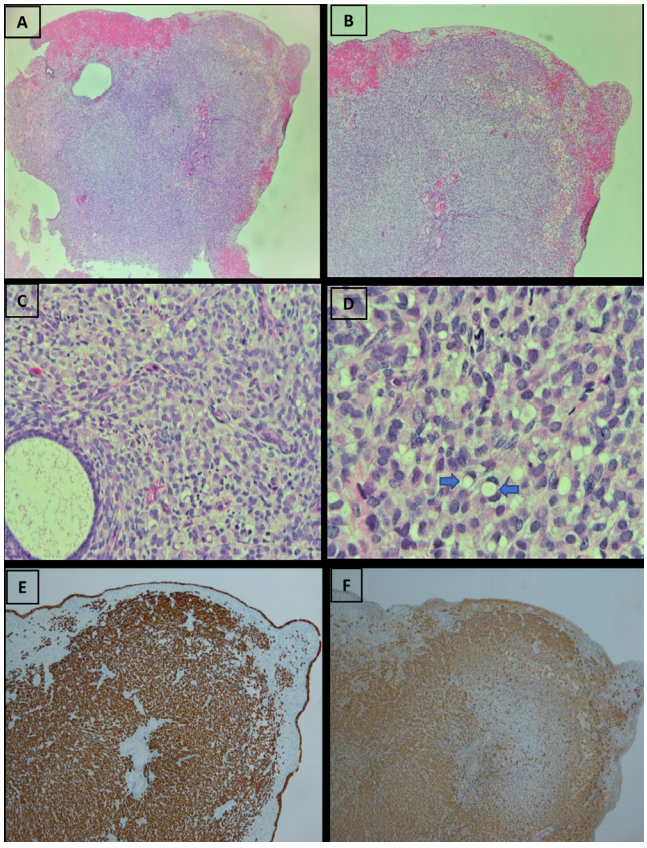

Figure 1: (A, B) A polypoidal tissue covered by normal columnar epithelium with cellular stroma (A:H&E 20x, B: H&E 40x). (C) The cellular stroma is composed of malignant epithelioid cells. A normal dilated endometrial gland is present at the left lower corner (H&E 100x). (D) Higher magnification shows the malignant epithelioid cells composed of sheets of round cells displaying mildly pleomorphic nuclei and clear to eosinophilic cytoplasm. Occasional signet-ring cells (blue arrow) are also present (H&E 200x). The malignant cells are diffusely immunoreactive to CKAE1/AE3 (E, 40x) & Mammaglobin (F, 40x).

DISCUSSION

In Malaysia, breast carcinoma is the commonest cancer among women and the primary cause of cancer death. The ovaries are commonly the first site of tumour metastases in the genital tract as they have a well-developed lymph network and are highly vascular. Isolated metastasis to the uterus without ovarian involvement is rare as in this case. The small size of the uterus, its restricted blood flow and distal circulation, and the presence of dense fibrous tissue are all hypotheses explaining the rarity.

Metastatic breast cancer at the isolated site in the uterus poses a diagnostic challenge, especially when the histological features are not typical, as in this case. The diagnosis is impossible without proper history and immunohistochemistry study. The background hormonal changes secondary to tamoxifen therapy made the interpretation became challenging. Tamoxifen is widely used in adjuvant therapy for positive hormonal markers in breast carcinoma patients. It is relatively safe with minimal risks of endometrial proliferative lesions, polyps, and adenocarcinoma. There are various hormonal background changes related to tamoxifen therapy, such as signet-ring or epithelioid changes of stromal cells and accumulation of mucin within macrophages which might be confused for a carcinomatous process. In the earlier phase, the dilemma was to decide whether it was a reactive, benign, or malignant process. Based on the histomorphological features of deciduoid or epithelioid cells and signet ring-like cells, the possibilities include stromal decidualisation secondary to tamoxifen therapy, neoplastic stromal lesions such as endometrial stromal sarcoma or metastatic carcinoma. However, the expression of both epithelial markers CK AE1/AE3 and breast origin sensitive marker Mammaglobin in cancer cells have aided in making the correct diagnosis.

There are morphologic spectrums in non-neoplastic decidualised endometrial stroma from non-vacuolated to signet-ring cells. The mechanisms are due to degenerative decidual change producing cytoplasmic vacuoles and accumulation of mucin within tissue macrophages exhibiting the signet ring cells.

Several features suggest that a uterine tumour could be a metastasis instead of a primary disease. These include the absence of dysplasia or in situ carcinoma, a tumour limited to the myometrium or endocervical stroma with normal surface epithelium, a multinodular or permeative growth patterns within the endometrial or endocervical stroma with tumour entrapping normal glands, and lymphatics or blood vessels involvement. (3). Most of the features are present in this case.

Metastatic adenocarcinoma could be missed due to the deciduoid or epithelioid appearance of the cells or when there is poor or no reactivity towards epithelial or specific cells by the immunohistochemical stain. As

for endometrial stromal sarcomas, they may display a variety of cellular differentiation and morphologic patterns, including epithelioid appearance, and their expression of cytokeratin could also be included as a possible differential diagnosis.

In a study involving 44 patients, the median time between the initial diagnosis of breast cancer and the diagnosis of uterine metastasis was 43 months (4). However, in this case, the interval was quite long, that is 11 years. However, the size of her breast lump was unchanged despite six years of tamoxifen treatment. Even though tamoxifen chemoprevention improved survival, tamoxifen resistance and cancer spread occurred in certain patients. Endocrine resistance has been linked to deregulation of the ER signaling pathway, changes in cell cycle and survival signaling, and the initiation of escape pathways that equip tumours with additional proliferative and survival cues. As one of the potential mechanisms for endocrine resistance, ER66 and related signaling pathways such the growth factor receptor, cell survival (PI3K/AKT), stress, and/or cytokine signaling pathway have been proposed. ERα66 mutations, loss of expression, or post-translational changes may promote tamoxifen resistance in breast cancer cells. ER66 has been the most widely used biomarker for tamoxifen treatment till now (5). A large cohort analysis of breast cancer patients who had surgery and tamoxifen treatment found that ER36, a variant of ER66, is linked to a poor prognosis (5). According to the study, tamoxifen increases breast cancer metastasis by activating ERα36 which mediates chemoprevention resistance. Aldehyde dehydrogenase 1A1 (ALDH1A1), a marker of breast cancer stem cells, is mediated by tamoxifen via ERα36, and ERα36 expression was found to be highly associated with ALDH1A1 (5).

CONCLUSION

In patients with a history of breast cancer, abnormal per vaginal bleeding should always alert the presence of metastatic dissemination to the genital system, especially with subtle and overlapping histological features. A complete and relevant clinical history, with radiological and biopsy findings, should be correlated to arrive at the diagnosis. An accurate histopathological diagnosis could be obtained with the aid of immunohistochemistry studies.

ACKNOWLEDGEMENT

The authors would like to thank the Director of Health Malaysia for the permission to publish this article.

REFERENCES

1. Karpathiou G, Chauleur C, Hathroubi S, Peoc'h M. Secondary Tumors of the Gynecologic Tract: A Clinicopathologic Analysis. International Journal of Gynecological Pathology. 2019 Jul;38(4):363–70. doi: 10.1097/PGP.0000000000000516.
2. Gomez M, Whitting K, Naous R. Lobular breast carcinoma metastatic to the endometrium in a patient under tamoxifen therapy: A case report. SAGE Open Med Case Rep. 2020 Feb 16;8:2050313X20907208. doi: 10.1177/2050313X20907208.
3. Eleni K, Katerina P, Catherine D, Evi K-V, Dimitris H, Constantinos G.G, Agatha K-P. Abnormal uterine bleeding as a presentation of metastatic breast disease in a patient with advanced breast cancer (2009). Arch Gynecol Obstet (2009) 279:199–201. doi: 10.1007/s00404-008-0665-9.
4. Bouvier A-S, Panchbhaya N, Brochard C, Marchand E, Mezzadri M, Leveau-Vallier A-S, et al. Uterine metastasis from invasive ductal breast carcinoma: A case report with literature review. Journal of Gynecology Obstetrics and Human Reproduction. 2021 Jan 1;50(1):101993. doi : 10.1016/j.jogoh.2020.101993
5. Wang Q, Jiang J, Ying G, Xie X-Q, Zhang X, Xu W, et al. Tamoxifen enhances stemness and promotes metastasis of ERα36+ breast cancer by upregulating ALDH1A1 in cancer cells. Cell Res. 2018 Mar;28(3):336–58. doi: 10.1038/cr.2018.15.