Metastatic Breast Cancer to the Cervix Presenting with Abnormal Vaginal Bleeding During Chemotherapy: A Case Report and Literature Review

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Rezumat

Cancer mamar cu metastaze ale colului uterin, cu sângerare vaginală anormală în timpul chimioterapiei: studiu de caz și analiza literaturii

Cele mai întâlnite metastaze ale cancerului mamar invaziv sunt metastazele pulmonare, pancreatice, osoase și cerebrale. Localizările mai puțin frecvente includ tractul gastrointestinal, pancreasul, splina, tiroida, glanda suprarenală, rinichii, cordul și tractul genital feminin. Uterul este o localizare rară pentru metastaze, cu atât mai mult pentru metastaze izolate. Alte localizări ale metastazelor uterine, cu surse extragenitale, includ colonul, stomacul, pancreasul, plămânii, colecistul, melanomul cutanat, vezica urinară și tiroida. Raritatea cancerului mamar cu metastaze ale colului uterin poate fi explicată prin faptul că acesta din urmă are o mică rezervă de sânge și un sistem de drenaj limfatic aferent individuale. Diagnosticarea metastazelor colului uterin înainte de descoperirea bolii mamare primare este rară. Metastazele carcinomului lobular invaziv în sistemul genital feminin sunt mai frecvente decât carcinomul ductal invaziv. Această lucrare prezintă un caz cu cancer mamar și metastaze ale colului uterin.

Cuvinte cheie: adenocarcinom mamar, cancer de col uterin, Citokeratină 7

Abstract

The most common sites of invasive breast cancer metastasis are

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the lungs, liver, bones and brain. Less frequent sites include the gastrointestinal tract, pancreas, spleen, thyroid, adrenals, kidneys, heart and female genital tract. The uterus is reported as a rare site for metastasis, and even more so for an isolated metastasis. Other sites of extra-genital sources for uterine metastases include the colon, stomach, pancreas, gallbladder, lung, cutaneous melanoma, urinary bladder and thyroid. The rarity of breast cancer metastasis to the uterine cervix could be explained by the fact that the cervix has a small blood supply and an afferent lymph drainage system alone. It is rare to diagnose a cervical metastasis prior to eliciting the primary breast disease. Invasive lobular carcinoma metastasises to the female reproductive system more frequently than invasive ductal carcinoma. This paper presents a case of breast cancer metastasis to the cervix.

Key words: breast adenocarcinoma, cervical cancer, Cytokeratin 7

Introduction

The most frequent sites for breast cancer metastasis are the lungs, bones, liver, and brain (1). However breast adenocarcinoma is the most common extra-genital malignancy that metastasises to the uterus (2).

Extension of the endometrial uterine adenocarcinoma to the cervix is not unusual, but metastases to the cervix from extra-genital sites are rare (3). The reported primary sites are ovarian adenocarcinoma, pancreatic carcinoma (4), primary peritoneal clear cell carcinoma (5), breast, stomach lung and kidney (6). It is important to know the exact nature of the cancer, otherwise it could be mistaken for a

primary cervical adenocarcinoma. Despite the occurrence of breast cancer metastasis to the uterus being rare, it usually presents as part of widespread metastatic disease (7).

Case Report

The paper presents a young lady, who has been diagnosed with left breast cancer with metastatic disease in the ipsilateral axilla at the age of 32 years. She has no family history of breast or ovarian cancer. The histology confirmed Grade II invasive ductal carcinoma (*Fig. 1*), Oestrogen Receptor (ER) negative (*Fig. 2*), Progesterone Receptor (PR) negative, Her-2 positive and Ki67-70%. She was treated

Figure 1. Breast tissue core biopsy infiltrated by Grade 2 invasive ductal carcinoma

Figure 2. Oestrogen receptor (ER) negative breast invasive ductal carcinoma

initially with upfront chemotherapy of Adriamycin and Docetaxol, in addition to Trastuzumab. This was followed by a left mastectomy and axillary clearance, in addition to radiotherapy. After finishing the Trastuzumab, she developed skin recurrence in the mastectomy site and chest wall. She received Lapatinib and Capecitabine. The patient had regular gynaecological review all the time, no abnormally detected. Nine months before the cervical metastasis was detected, the patient presented with irregular vaginal bleeding and has Mirena coil in situ. Clinical gynaecological examination including colposcopy which was unremarkable. Cervical smear also was done at the same time, the results showed borderline changes and a repeat screening test in 3 years has been suggested. Trans-vaginal ultrasound, revealed no abnormality other than right ovarian small cyst at that time. In addition, HPV screening was done and found to be negative. The hysteroscopy showed retroverted bulky, mobile uterus and in pipelle biopsy revealed no evidence of infection or malignancy.

Sometime later, she presented with increased irregular vaginal bleeding. CT scan of the

Figure 3. CT abdomen & pelvis – Coronal view: Prominent cervix with mixed density

Figure 4. CT abdomen & pelvis – Sagittal view: Prominent cervix with mixed density

abdomen and pelvis revealed a prominent cervix with mixed density, predominantly hypodense with some partial heterogeneous enhancement (*Figs. 3,4, 5*).

The hysteroscopy showed a suspicious polyp in the cervix and an endometrial polyp. Biopsy tissue from both areas was composed of extensive high grade malignant tumour cells, forming sheets in areas of a gland-like structure; the features were consistent with adenocarcinoma (*Figs. 6, 7*).

Figure 5. CT pelvis- Axial view: Prominent cervix with mixed density

Figure 6. Endometrial biopsy showing metastatic ductal carcinoma

Figure 7. Metastatic deposit in endocervical polyp

On IHC (Immuno-histochemistry), the tumour cells were positive for CK7, GCDFP15 (*Fig. 8*) and p53. There was patchy positivity for p16, Vimentin and BCL2, but negativity for CK5, p63, ER (*Fig. 9*), PR, Napsin A and TTF1. The Ki67 proliferation fraction was 80%. The original breast cancer was reported as ER and PR negative, and Her-2 positive. This makes the metastatic breast IDC the most probable diagnosis.

Discussion

Breast cancer is considered the most frequently detected worldwide female cancer and the dominant cause of cancer death among women (8).

The usual sites for breast cancer metastasis other than the axillary lymph nodes, are non-axillary lymph nodes, lungs, pleura, bones, liver, and brain (9,10,11). Less frequent sites are identified as the stomach (12) rectum (13, 14), pancreas (15), spleen, thyroid, adrenals, kidneys, heart, vagina (16, 17), uterus and ovaries.

Invasive lobular carcinoma (ILC) is reported as the second most common type of invasive breast cancer after invasive ductal carcinoma (IDC), accounting for 10% of all breast cancer cases (18).

ILC with a lower grade and positive oestrogen receptors at the time of diagnosis is considered to have a good prognosis (18,19).

Figure 8. IHC - GCDFP-15 is positive in the metastatic cancer area. This is consistent with a breast primary

Figure 9. IHC - ER expression is negative in the metastatic cancer. There is positive staining in adjacent normal endometrial glands and stroma

However ILC metastasises more frequently to the female reproductive system than invasive ductal carcinoma (20). More than 80% of breast cancers that metastasise to the female genital organs are found to be ILC (21).

Metastatic disease to the female genital organs from an extragenital primary tumour is unusual. A paper published in 1984 by Mazur et al, analysed 325 cases and found that breast and gastrointestinal tract carcinomas are the most frequent extragenital primary tumours (22).

The uterus was reported as a rare site of metastasis, and it is even rarer to be the site of an isolated metastasis (23). Breast adenocarcinoma is the most common extragenital malignancy that metastasises to the uterus (2). The Mazur et al paper from 1984 reported, that in a series of cases of metastatic disease to female genital organs, it was found that 47.3% of uterine disease came from breast cancer (22).

Other sites of extra-genital sources for uterine metastasis are the colon, stomach, pancreas, gallbladder, lung, cutaneous melanoma, urinary bladder and thyroid (24).

Metastasis to the cervix is rare; it accounts for only 3.7% of female genital organs metastatic disease (25). The cervix is a less favourable site for metastatic disease from an extra-genital malignancy because of its small size, composition of mainly dense fibromuscular components, restricted blood supply and an afferent lymphatic drainage alone (26).

Age plays an important factor in breast cancer behaviour. Patients of a younger age group are associated with liver and gynaecological metastases (11). A further factor is hormonal sensitivity. It is the hormone sensitive invasive lobular carcinoma subtype which more frequently metastasises to the uterus (7,27,28).

The tumour may present with regional symptoms and signs identical to primary cervical carcinoma. If the uterus is infiltrated, abnormal vaginal bleeding is usually the most frequent presenting symptom. Other symptoms also may present, such as lower abdominal pain and vaginal discharge (2).

Diagnosis of cervical metastasis before the diagnosis of the primary disease is rare; in most

cases, the primary breast cancer is diagnosed before the discovery of the metastasis (3).

IHC (Immuno-histochemistry) panel is crucial to differentiate primary from metastatic cervical malignancy. Cytokeratin 7(CK7), is a type II keratin of simple non-keratinizing epithelia. CK7+/CK20+ pattern is seen in endo-cervical cancer (29), and CK7+/CK20- pattern is seen in breast cancer (30), endo-cervical and endometrial carcinoma (31).

Gross cystic disease fluid protein 15 (GCDFFP 15) is a glycoprotein originally isolated in human breast gross cystic fluid. It is used as a specific IHC diagnostic marker for tumours originating in the breast (32,33).

Another useful marker is p53, a tumour suppressor gene. It differentiates malignant conditions, which are often p53+, from reactive and metaplastic conditions, which are usually p53- (34).

The marker p16 is a tumour suppressor protein, which prevents progression into the S-phase of cell cycle. Its overexpression is more frequently seen in high grade endometrial and ovarian carcinoma (28,35,36). In our case it showed patchy positive.

Vimentin is an intermediate filament for mesenchymal tissue, known to be expressed in some epithelial carcinomas. It distinguishes endo-cervical from endometrial adenocarcinoma (37). Its expression is also seen in breast carcinomas (38); it showed uneven positivity in our case.

BCL2 is a regulator protein that regulates cell death (apoptosis); it derives its name from B-cell lymphoma 2. Its gene was detected in chromosomes 14 and 18 in follicular lymphomas. BCL-2 is overexpressed in ~75% of breast cancer cases; in our case it showed fragmentary expression (39).

The myoepithelial marker p63 rarely stains adenocarcinoma (40); it was negative in our case. Napsin A is a novel aspartic proteinase of the pepsin family, found primarily in lung and kidney (Turner); it was also negative in our case.

Patients with metastatic breast disease who are potentially suitable for curative therapeutic strategy represent only 1–3 % (41). Metastases-

tomy in breast cancer is a good option if the metastatic disease is limited to a single operable lesion or to multiple lesions at a single organ site (17).

Other treatment modalities include systemic or regional chemotherapy (taxanes, vinorelbine, capecitabine), hormonal manipulation (third-generation aromatase inhibitors and fulvestrant) and radiofrequency ablation (41). Despite the poor prognosis of this group of patients in general (42), some patients who achieve a complete response remain disease free for prolonged periods, some even beyond 20 years (43).

Conclusion

This paper highlights the importance of considering a metastatic cancer in the differential diagnosis of abnormal vaginal bleeding, suspicious pelvic examination, or radiological findings in women of perimenopausal ages, with a previous history of breast cancer.

In general, the biologic phenotype of ILC is quite favourable. However patients with ILC do not have a better clinical prognosis than patients with IDC phenotype.

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Conflicts of Interest

None declared.

Authors' Contributions

All authors listed on the title page have contributed significantly to the work, have read the manuscript, attest to the validity and legitimacy of the data and its interpretation.

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