Breast cancer metastasis to the reproductive system: Report of 2 cases and literature review: A case report

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Abstract. Metastatic involvement of the reproductive system in patients with breast cancer is rare and has been reported only a few times in the literature. Notably, among patients without clinical symptoms, reproductive system metastases are easily overlooked and difficult to distinguish from primary tumors of the reproductive system, especially when the patient is receiving endocrine therapy. The prognosis of breast cancer is better than that of other aggressive cancers. However, if distant metastasis occurs, survival decreases greatly. In the present study, 2 cases of reproductive system metastasis from breast cancer were reported and the relevant literature was reviewed to provide support for the accurate diagnosis and appropriate treatment of affected patients.

Introduction

Breast cancer is the most common malignancy in women (1), negatively affecting women's health, and distant metastasis is the main factor affecting prognosis (2). The most common sites of distant breast cancer metastasis are the lung, liver, bone and brain. Luminal breast cancer is most likely to metastasize first to bone. Furthermore, among the breast cancer types, $HR^-/HER2^+$ tumors have the highest rates of liver metastasis, and $HR^+/HER2^-$ tumors have the highest rates of lung metastasis. The brain has been previously reported to be a preferred site of metastasis in patients with triple-negative cancers (3). However, metastasis to the female reproductive system is less common, but when breast cancer does metastasize to the reproductive system, it is most commonly observed in the ovaries. The small size of the uterus, limited blood flow to the distal region, and abundant fibrous tissue within the uterus collectively create an environment that is not conducive to the spread of malignant tumors (4). Consequently, uterine metastatic cancer represents <10% of female reproductive system metastases (5). The metastatic patterns of lobular and ductal invasive breast cancer differ, although it is not explicitly known why this is the case. Invasive lobular carcinoma (ILC) metastasis usually involves the peritoneum, gastrointestinal tract and ovaries, whereas invasive ductal carcinoma (IDC) more commonly involves the lungs and pleura (6). The results of prior studies based on tumor registry data have demonstrated that ILC metastasizes to gynecologic organs in ~4.5% of cases, whereas IDC metastasizes to these organs in 0.8% of cases (7). Currently, the number of reported cases of breast cancer metastasis to the reproductive tract, both domestically and internationally, is limited. Therefore, additional data are needed to enhance our understanding of this phenomenon. In the present study, two cases of breast cancer combined with reproductive system metastasis and a synthesis of the clinical characteristics of this disease are presented on the basis of the previous literature. The characteristics of the patients are shown in Table I.

Case presentation

Patient 1. A 54-year-old female patient underwent local excision of the primary tumor in the left breast and axillary sentinel lymph node biopsy at Peking Union Medical College Hospital (Beijing, China) in February 2023. The postoperative pathological diagnosis was IDC of no special type that was poorly differentiated (Fig. 1A), with no evidence of metastasis in the sentinel lymph nodes. Immunohistochemical analysis (Paraffin-embedded, light microscope) revealed the presence of HER2 protein (3+), a negative result for estrogen receptor (ER) and progesterone receptor (PR), and a Ki-67 index of

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60%. Accordingly, the patient was diagnosed with invasive carcinoma in the left breast, stage IA, human epidermal growth factor receptor 2 (Her-2) overexpression type. Following surgical intervention, the patient underwent six cycles of chemotherapy comprising 120 mg docetaxel, 600 mg carboplatin and trastuzumab-targeted therapy. Additionally, the patient underwent a course of adjuvant radiotherapy to the left breast with 42.4 Gy in 16 treatment fractions followed by a boost to her lumpectomy cavity with 10.6 Gy in 4 fractions. During the radiotherapy course, the patient developed minor vaginal bleeding without accompanying clinical symptoms such as abdominal pain. Initially, the patient did not seek medical attention for this symptom. However, the volume of bleeding subsequently increased. On gynecological ultrasound, the endometrial assessment revealed a thickness of 11 mm, with heterogeneous echogenicity but no evidence of focal thickening, and the myometrium and adnexa were unremarkable. Magnetic resonance imaging indicated the possibility of a hysteromyoma, with CA125 at 14.2 U/ml and CA19-9 at 21.1 U/ml. Therefore, she underwent a dilatation and curettage (D&C) biopsy for histological diagnosis of the endometrium. Postoperative pathology revealed that the lumps of neoplastic cells suggested poorly differentiated carcinoma and, in combination with the immunohistochemistry results and medical history, metastatic invasive breast carcinoma of no special type (Fig. 1B). Immunohistochemistry revealed ER (-), PR (-) and Ki-67 (index 70%). The immunohistochemical analysis revealed positive staining for E-cadherin; partial positivity for CEA and CK5; and negative staining for GCDFP-15, P63, P16 and vimentin. The positron emission tomography/computed tomography (PET/CT) exam was refined on 13 November 2023 and confirmed a heterogeneous increase in metabolic activity in the uterine body and cervix, the nature of which has yet to be determined. The patient subsequently underwent hysterectomy and bilateral salpingo-oophorectomy laparoscopically at our institution. Postoperative pathology suggested chronic cervicitis and endometritis, which were subsequently treated with oral capecitabine for chemotherapy.

Patient 2. A 36-year-old woman was admitted to Peking Union Medical College Hospital (Beijing, China). In December 2020, she underwent right modified radical mastectomy. The pathological examination of the tumor revealed a mixed nonspecial type and ILC, intermediate differentiation, with lymph node metastasis (15/15 in the axilla, 5/5 at the third station) (Fig. 2A). Immunohistochemical analysis revealed the presence of ER protein in moderate quantities (90%), PR protein in moderate quantities (80%), Her-2 protein in the 1+ category, Ki-67 protein in the 70% category, and androgen receptor (AR) protein in high quantities (80%). The patient was diagnosed with mixed invasive breast cancer, stage III C, luminal B type. After the surgical procedure, the patient was administered a course of epirubicin and cyclophosphamide for a total of four cycles, followed by four cycles of paclitaxel. Intensity-modulated radiotherapy was initiated for the right chest wall and the region of the supraclavicular and axillary lymph nodes, with 50 Gy in 25 treatment fractions. The patient was subsequently treated with exemestane and leuprolide. On 6 February 2024, when the patient revisited the institution for breast cancer, a gynecological ultrasound revealed the presence

Table I. Patient characteristics.

	Age PT (year)	Age met (year)	Time PT-Mets (months)	Histology	Stage	Her-2	ER	PR	Pt Treatment	Endocrine therapy	Met Symptoms	Other site	Met Treatment
Case 1	53	54	9	IDC	IA	3+	-	-	Surgery, Chemotherapy, Radiotherapy, Targeted therapy	-	Vaginal bleeding	-	-
Case 2	32	36	38	IDC (Mixed)	IIIC	+	+	+	Surgery, Chemotherapy, Radiotherapy, Targeted therapy	Exemestane Leuprolide	-	-	-

IDC, invasive ductal carcinoma; ER, estrogen receptor; PR, progesterone receptor.

Table II. Incidence and mortality rates of breast cancer across different ethnic groups.

Ethnicity	Incidence rate (per 100,000)	Mortality rate (per 100,000)	Hazard ratio (95% confidence interval)	Risk Factor characteristics
Caucasian (European-American)	132.5	19.8	1.0 (Reference)	High hormone replacement therapy usage rate (25%), Late childbirth (average first birth age of 28 years)
African American	126.7	28.3	1.12 (1.05-1.19)	High proportion of triple-negative breast cancer (21% vs. 10% in Caucasians), High rate of medical treatment delay (34% delayed for more than 3 months)
Asian American	89.4	11.2	0.68 (0.63-0.73)	Protective effect of traditional diet (high intake of beans), But the incidence rate increases by an average of 3.5% annually due to Westernized lifestyle
Hispanic	92.1	14.3	0.83 (0.78-0.89)	High proportion of obesity-related breast cancer (38% with BMI>30), Lower screening rate than Caucasians (65% vs. 73%)
Ashkenazi Jewish	215.0	24.5	2.1 (1.9-2.3)	High BRCA1/2 mutation carrier rate of 2.5% (0.2% in the general population), 28% of early-onset cancer under the age of 50

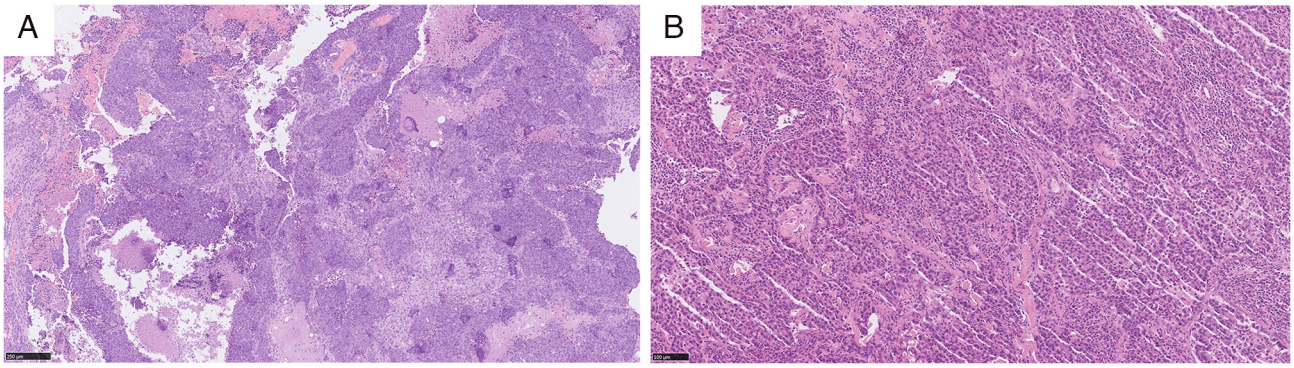

Figure 1. Immunohistochemical analysis. (A) Morphology of invasive breast carcinoma of no special type. (B) Pathological manifestations of metastatic invasive ductal carcinoma of the uterine cervix.

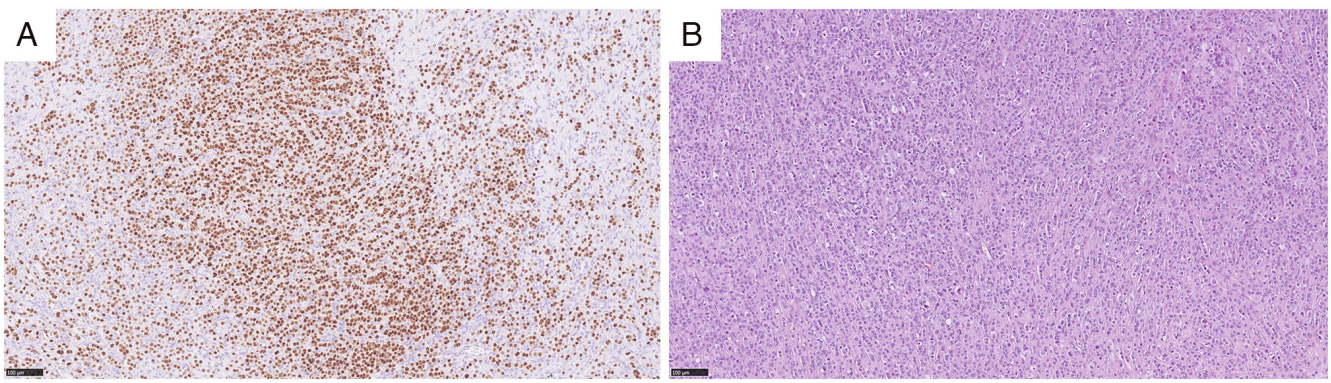

Figure 2. Immunohistochemical analysis. (A) Immunohistochemical stain: GATA-3 (nuclear^{+}). (B) Ovarian metastasis of breast cancer.

of a hypoechoic mass in the right adnexal area (4.0x3.8 cm), as well as a hyperechoic lesion in the left ovary (2.1x2.1 cm). The CA-125 level was 99.2 U/ml, while the CA-153 level was 123.3 U/ml. At this time, the patient did not exhibit any abnormal vaginal bleeding or abdominal pain, nor were there other notable clinical symptoms. A professor of gynecology in our hospital suggested surgical treatment. On 26 February 2024, the patient underwent hysterectomy and bilateral salpingo-oophorectomy, high ligation of the ovarian vessels, and pelvic adhesion lysis laparoscopically at our hospital. The pathological examination revealed that the heterotypic cells infiltrated the fallopian tube and ovarian tissue (right side), which was consistent with metastatic breast cancer. The endometrium was observed to be in the proliferative stage in the uterus, heterotypic cells were observed in the uterine wall, and metastatic cancer was not excluded (Fig. 2B). The results of the immunohistochemical analysis were as follows: ER (moderate positive, 95%), PR (moderate positive, 20%), Her-2 (2+), Ki-67 (index 30%), E-cadherin (membranous+), GATA3 (+), TRPS1 (+), PAX (-), AE1/AE3 (+), AR (strongly positive, 95%), P120 (cytoplasmic+), and β-catenin (membranous and cytoplasmic+). Fluorescence *in situ* hybridization revealed HER2(-) cells (data not shown). After the surgical procedure, the patient was administered abemaciclib and fulvestrant for endocrine therapy.

Discussion

In 2022, the incidence rates of breast cancer (23.8%) far exceeded those of other cancers in women, followed by lung cancer (9.4%). Breast cancer is the most common cancer in women and has a high mortality rate. The incidence and mortality of breast cancer are significantly influenced by demographic characteristics and geographical factors. White European and American women exhibit the highest incidence rates, ~130 per 100,000 individuals; however, women of African descent experience a higher mortality rate, which may be related to disparities in healthcare resources. By contrast, the incidence of breast cancer is relatively low among Asian women, although it has increased rapidly in recent years (Table II). The highest incidence rates were observed in France, Australia/New Zealand, North America and Northern Europe, where they are ~4-fold higher than those reported in South-Central Asia and Middle Africa (8). Among the pathological breast cancer subtypes, IDC accounts for >70% of cases, and ILC accounts for 5-15% of cases; however, the latter is the most common pathological type of metastatic breast cancer (9). In their study, Wang *et al* (10) analyzed 18,322 patients with metastatic breast cancer and reported that bone metastasis accounted for 39.8% of metastasis cases, followed by lung (10.94%), liver (7.34%) and brain metastasis (1.51%). Metastases of extragenital malignancies to the reproductive system are rare, most commonly in the digestive system (37.6%), followed by breast cancer, which often involves the ovaries (75.8%) and vagina (13.4%), followed by the endometrium (4.7%), cervix (3.3%) and salpinx (0.7%) (5,11). Since the cervix is composed mainly of fibrous muscle tissue with a limited blood supply and only incoming lymphatic drainage, metastasis to the cervix is extremely rare (12).

The timing of the occurrence of reproductive system metastasis in patients with breast cancer is inconsistent, and the precise mechanism of reproductive system metastasis remains unclear. At present, the literature on breast cancer metastasis to the reproductive system both domestically and internationally is composed primarily of case reports. The most frequently observed presentation of metastasis is vaginal bleeding (13). Additionally, the diagnosis of asymptomatic metastases among these patients is incidental, and asymptomatic metastasis is more likely to be overlooked than metastasis with abnormal vaginal bleeding symptoms. Despite the presence of uterine lesions, as evidenced on gynecological ultrasound or CT, there was no previous history of gynecological disease or current symptoms among these patients. Consequently, no further diagnosis was made. Metastatic uterine malignant tumors are frequently misdiagnosed as uterine fibroids or primary uterine malignant tumors on imaging, particularly following tamoxifen treatment. Endocrine medication is associated with a 5-30% incidence of increased endometrial thickness, a 26-60% incidence of endometrial polyps, and an endometrial cancer (EC) incidence of 0.8-8%, all of which are 2-7 times greater than those of the general population (14). Furthermore, international researchers have discovered that in individuals receiving endocrine therapy following breast cancer surgery, age is a risk factor for the development of EC. Premenopausal patients account for ~52% of endometrial disease cases, and EC is more common in patients older than 35 years (15). Patients are advised to receive routine examinations. Because the symptoms of endometrial alterations can be mistaken for those of other gynecological disorders, there is a chance of misdiagnosis even though the actual incidence of EC caused by endocrine therapy is low, at 0.1-0.2% (16). In such cases, a differential diagnosis of endocrine drug-induced primary EC is essential (17). Mazur *et al* (5) reported that ~42% of metastatic cervical tumors are incorrectly identified as primary cervical tumors. Nevertheless, importantly, some metastases are detected prior to or concurrently with the primary tumor (18,19). A pathological biopsy is typically the most rigorous criterion for differentiating a primary mass from a secondary mass that has metastasized beyond the reproductive tract. In cases of highly suspicious but difficult to differentiate findings on the basis of the imaging presentation, accurate immunohistochemistry is needed. It is therefore of particular importance to consider the contributions of pathology and immunology.

GATA3 is one of six members of the GATA family of transcription factors. It plays a specific role in regulating mammary gland morphogenesis and the differentiation of luminal epithelial cells in the breast (20,21). The expression rates of GATA-3 in IDC and ILC are 91 and 100%, respectively, whereas in EC, the expression rate is only 2%. Furthermore, GATA-3 is not expressed in cervical adenocarcinoma or ovarian mucinous carcinoma (22,23). In the present study, Patient 2 had GATA3 expression in the reproductive system tissues and a history of breast cancer. Therefore, in such cases, breast cancer metastasis to the reproductive system has to be strongly considered.

Treatment and prognosis. In patients with breast cancer metastasis to the reproductive tract, the disease prognosis is typically poor, and there is currently no uniform diagnosis

or treatment plan. In some studies, it has been indicated that palliative hysterectomy and bilateral salpingo-oophorectomy were suggested as effective forms of castration therapy; however, the evidence supporting this is inconclusive with respect to survival outcomes. In other studies, systemic chemotherapy was suggested to be more efficacious when it is administered alone. Despite the generally poor prognosis among this group of patients, some patients achieve complete remission and remain disease-free for extended periods, with survival exceeding 20 years in some patients (24).

The present article presents two cases. In Patient 1, metastasis occurred in the uterine body and cervix, with abnormal vaginal bleeding as the initial symptoms. The patient was diagnosed at an early stage, with metastasis already present. In this patient, metastasis occurred when the primary tumor was in an early stage, almost at the same time as the primary tumor, and there was no metastasis to the lymph nodes or other sites, which is quite rare and has not been reported previously. The patient is currently undergoing regular follow-up, with no evidence of tumor recurrence or metastasis to other sites. In Patient 2, metastasis to the common ovary and uterus occurred, with no clinical symptoms. However, high echogenicity in the adnexa was observed on ultrasound. The disease was staged as an advanced stage malignancy, with an ILC component, and the pathological examination of the metastatic lesion indicated that it was primarily a metastasis of the ILC component. The GATA3 result was positive, whereas the PAX8 result was negative. Immunohistochemistry provided clear evidence that the tumor had originated in the breast, thus providing a means of distinguishing it from primary ovarian cancer. The patient underwent surgical intervention in conjunction with endocrine therapy, and the current status remained stable with regular follow-up.

In summary, although breast cancer metastasis to the reproductive system is rare, for patients with breast cancer, regular gynecological ultrasound should be performed during follow-up, even in the absence of clinical symptoms. Caution should be exercised in the event of the occurrence of metastatic tumors in the reproductive tract, particularly in patients with late-stage infiltrating lobular carcinoma and a history of similar drug treatments, such as tamoxifen. GATA-3 and other immunohistochemical markers are helpful in differentiating primary reproductive system tumors. At present, there is no consensus regarding the optimal treatment approach for these patients; the most important issue in clinical studies is the low number of patients because this type of metastasis is uncommon. It is considered that once more related cases are reported both domestically and internationally, a meta-analysis will be the next step, and on the basis of the findings of the meta-analysis, the best course of treatment can be chosen.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LHL, CXY and HXR contributed to the study conception and design. CXY prepared material and performed data analysis. LHL wrote the first draft of the manuscript. All authors commented on previous versions of the manuscript. HXR and CXY confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The case report was approved (approval no. K24C3535) by the Ethics Committee of Peking Union Medical College Hospital Chinese Academy of Medical Sciences & Peking Union Medical College (Beijing, China). Written informed consent was obtained by the patients prior to registration.

Patient consent for publication

Patient consent for publication of relevant data was provided by the patients.

Competing interests

The authors declare that they have no competing interests.

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