Metastatic Signet-Ring-Cell Carcinoma of Bladder From Breast Invasive Lobular Carcinoma Found By CT: A Case Report And Literature Review

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Research Article

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Abstract

Background: Secondary bladder tumors are relatively rare in all bladder tumors, while bladder metastases from breast cancer were rarely reported. And interestingly, signet-ring differentiation may appear in metastases from a breast invasive lobular carcinoma regardless of whether or not the primary breast tumor had signet-ring cells, which may cause diagnostic uncertainty.

Case presentation: We report a case of a 55-year-old female patient with diffuse bladder thickening as the chief complaint. There was no special clinical manifestation, while cystoscopy showed multiple scattered red protuberances and the biopsy suggested signet-ring-cell carcinoma. Result of gastroscopy suggested poorly differentiated adenocarcinoma with signed-ring cells. Considering the patient's previous history of invasive lobular carcinoma of the breast, chronic myeloid leukemia and metastatic endometrial carcinoma from the breast, we performed the immunohistochemistry and the results indicated that signet-ring-cell carcinomas of the stomach and bladder originated from the breast invasive lobular carcinoma. we performed Positron Emission Tomography/Computed Tomography (PET/CT) and the results showed that there were multiple bone metastases already.

Conclusion: This is the first English case report of invasive lobular carcinoma of breast metastasizing to uterus, stomach, bladder and bones with multiple signet-ring-cell variations. We also focus on the Computed Tomography (CT), immunohistochemistry (IHC) and cystoscopy findings and share the clinical diagnosis ideas summarized by this case.

Background

Primary bladder tumor is the most common tumor of the urinary system, while secondary tumors of the bladder are rare, accounting for less than 2% of all bladder neoplasms(1). The most common primary sites include the colon, prostate and rectum, and the tumors from these sites mainly invade the bladder directly. Tumors from stomach, lung or breast invade the bladder with distant metastasis(2). Secondary signet-ring-cell carcinoma (SRCC) is even rarer. We report a case of a 55-year-old female patient with metastatic SRCCs in stomach and bladder from the breast invasive lobular carcinoma. The patient's chief complaint was abnormal findings in CT instead of significant urinary symptoms.

Case Presentation

The patient, a 55-year-old female, was diagnosed with invasive lobular carcinoma (ILC) of the breast in November 2013. After two times of preoperative neoadjuvant chemotherapy, modified radical mastectomy was performed. Biopsy showed invasive lobular carcinoma of the breast (T2N2M0) with right axillary lymph node metastasis. After postoperative chemotherapy and radiotherapy many times, the patient recovered gradually and followed up regularly.

In May 2017, the patient found Cancer antigen 125 (CA-125) increased in a regular follow-up. Pathological biopsy and immunohistochemistry analysis were performed. The expressions of estrogen
receptor (ER), progesterone receptor (PR) and GATA-3 were positive, which showed that it was the metastatic endometrial carcinoma from the breast (Fig. 1). Then the total hysterectomy and bilateral salpingectomy were performed after two times of preoperative chemotherapy, followed by four times of postoperative supplementary chemotherapy.

In May 2018, bone marrow aspiration was performed due to the unexplained rise of platelet and the diagnosis of chronic myeloid leukemia was made. Then the patient was treated with imatinib (800mg qd). In June 2020, treatment was changed to flumatinib (600mg qd) and in March 2021, it was changed to flumatinib (400mg qd). The result of P210/ABL has turned negative now.

During the routine follow-up of pelvic CT in August 2020, it was found that the bladder wall thickened and the thickest part was about 9.2mm. The CT value was about 36U on plain scan and about 56HU on the enhanced scan. The bilateral ureter was slightly dilated and no obvious enlarged lymph nodes were found in the pelvic cavity (Fig. 2A, B). The cystoscopy showed that the appearance of the mucous membrane of each wall was normal with only locally thickening and no new organisms were found. Bilateral ureteral openings were normal (Fig. 2C, D). The patient felt bladder distension after injecting about 300ml of normal saline. Cause the patient had no obvious hematuria, frequent urination, voiding pain or other discomforts, we didn't perform any biopsy and only suggested patient to follow up.

In March 2021, the pelvic CT showed that the bladder wall was significantly thickened (Fig. 3A). The CT value was about 39U on plain scan and about 47HU, 63HU, and 79HU on enhanced scan in arterial phase, venous phase, and delayed phase, respectively. The bilateral ureter was still slightly dilated, but unlike last time, there was hydronephrosis in the right kidney (Fig. 3B). The patient had no chief complaint of urinary symptoms, so we didn't perform any cystoscopy or biopsy this time.

In May 2021, the pelvic CT showed that the bladder wall was significantly thicker than before. The CT value was about 39U on plain scan and about 45HU, 64HU, and 74HU on enhanced scan in arterial phase, venous phase, and delayed phase, respectively. The bilateral ureter dilated more severely than before and there was hydronephrosis in bilateral kidneys (Fig. 4A, B). Based on a progressive aggravation in CT manifestation, we suggested a cystoscopy should be performed immediately even though there was no significant clinical symptom. The cystoscopy showed that some small red protuberances could be seen around left ureteral opening. The bladder wall was tough like leather. The right ureteral opening could not be seen (Fig. 4C, D). After injecting about 100ml of normal saline, the patient felt bladder distension. No pathological biopsy was performed, and the patient was told to follow up regularly.

On May 24, 2021, due to the special condition, a cystoscopy was performed again after communicating with the patient. The findings of cystoscopy were similar to previous condition and a biopsy was performed this time. The pathological biopsy revealed signet-ring-cell carcinoma. Then immunohistochemistry was operated and the results suggested Caudal-type homeobox 2 (CDX-2), Cytokeratin 20 (CK20) and Villin were negative and GATA-3 was positive (Fig. 5). Based on histological findings and previous diagnosis of breast invasive lobular carcinoma, a diagnosis of metastatic bladder SRCC from breast was made. Then gastroscopy and enterostomy were suggested to be performed.
Gastroscopy showed there were hypertrophic protuberances of the mucous membrane in the fundus and body of the stomach and the biopsy suggested poorly differentiated adenocarcinoma with signed-ring cells. The neoplastic cells were positive for ER, PR and GATA-3 and negative for CDX-2, CK20 and Villin (Fig. 6). The result showed that the gastric carcinoma also originated from the breast. Then we performed PET/CT, and the results showed that there were multiple bone metastases already.

Considering the presence of multiple metastases, the patient was treated with apatinib mesylate (250mg qd) and Tegafur Gimeracil Oteracil Potassium Capsule(40mg bid). The patient come back to us on 27 September, 2021 after three months chemotherapy. She still had no typical urinary symptoms with only a little gastrointestinal discomfort because of the chemotherapy. the CT showed that the bladder wall was still significantly thick. The CT value was about 38U on plain scan and about 45HU, 62HU, and 76HU on enhanced scan in arterial phase, venous phase, and delayed phase, respectively. The bilateral ureter dilation and hydronephrosis were slightly less than before (Fig. 7 A, B). The cystoscopy showed there were still some small red protuberances on the bladder wall. The right ureteral opening could not be seen (Fig. 7C, D). In the present case, chemotherapy appeared to be effective and the patient was advised to follow up regularly.

**Discussion**

Metastatic lesions in the bladder represent less than 2% of all bladder neoplasms. Bladder metastatic tumors were mainly obtained from autopsy series(1, 3, 4). Most of them reach to the bladder by direct invasion from the prostate, female genital tract, and lower gastrointestinal tract. The other primary tumors originate from the stomach, breast, or lung(2). About 45 percent of breast cancers have metastases, which can occur in almost any organ. Breast cancer often metastasizes to the bones, lungs, liver and brain, known as organotropism(5). Bladder metastases from breast cancer are extremely rare, with only about 65 cases reported(5, 6). The average time of urinary bladder metastases from the primary diagnosis of breast cancer is about 90 months(5). The main pathological subtypes of breast cancer are ductal and lobular carcinoma. Invasive lobular carcinoma, accounting for 8% to 14% of cases, is the second most common subtype(6). Urinary bladder metastases from breast cancer are more common in ILC than invasive ductal carcinoma (IDC)(5-10).

Primary SRCC of the bladder is extremely uncommon, with an estimated prevalence of 0.24% of all primary bladder cancer(11, 12). Metastatic SRCC of the bladder is even rarer(12-24). We searched PubMed, MEDLINE, Embase, and Google Scholar using the key words such as “gastric or stomach”; “signet-ring-cell carcinoma”; “breast or mammary”; “bladder” and “metastasis.” To our knowledge, there is no case report of invasive lobular carcinoma of breast metastasizing to uterus, stomach, bladder and bones with multiple SRC variations.

It is necessary to determine whether the tumor is primary or secondary for treatment. IHC study is helpful for differential diagnosis(25, 26). Recently, GATA-3 has been known as a specific marker for breast cancer, with almost 100% invasive lobular carcinoma of the breast expressing GATA-3, while the positive
rate of GATA-3 expression may be less than 5% in primary tumors of the gastrointestinal tract and bladder(27). CDX-2 is a marker expressed only in normal gastrointestinal epithelial cells and tumors with more than two thirds of cases of gastric adenocarcinomas expressing CDX2. But in breast cancer, CDX2 is usually negative. Thus, it can also be used to identify tumors from the gastrointestinal tract or the breast(27). ER is expressed exclusively in breast carcinoma, but approximately 20% of breast SRCCs can be negative for ER(27, 28), whereas some studies have found that up to 30% of gastrointestinal adenocarcinomas were positive for ER. PR is also a common biomarker in breast carcinoma. In breast and ovarian adenocarcinoma, CK20 is commonly negative. In the gastrointestinal tumors, CK20 is positive(29-31). ER combined with CK20 and PR may be helpful in differentiating tumors of gastrointestinal and breast origin(32, 33). Villin are produced mainly by epithelial cells that form brush borders. Villin producing cells have been reported to be found in the epithelial cells of the intestinal mucosa and gallbladder. Thus, Villin could also be a useful marker for gastrointestinal cancer(34). In our case, the bladder SRCC expressed GATA-3 and was negative for CDX-2, CK20 and Villin. The gastric SRCC expressed GATA-3, ER, PR and was negative for CDX-2, CK20 and Villin. The endometrial carcinoma expressed ER, PR and GATA-3. Therefore, we considered that all three metastatic tumors were from breast cancer.

But the result of immunohistochemistry is not accurate sometimes. It should be judged based on clinical manifestations, pathological biopsy and images. For primary SRCC, surgical treatment is generally suggested at present, and it is possible for patients to have a long-term disease-free survival(35). For secondary SRCC, chemotherapy is mainly used, but the overall prognosis is poor. Our patient chose the chemotherapy plan of apatinib mesylate (250mg qd) and Tegafur Gimeracil Oteracil Potassium Capsule(40mg bid). The chemotherapy appeared to be effective for now because the hydronephrosis was slightly less than before.

There are three special points in this case. First of all, the patient was not diagnosed accurately for about 9 months. When finally diagnosed, there was bone metastasis revealed by PET/CT, which was undoubtedly regrettable. Generally, the manifestations of bladder metastatic tumors can be divided into two types: protuberant type and diffuse type. Almost all the patients with gross hematuria showed a protuberant mass in imaging. While in patients with lower urinary tract symptoms (LUTS) as the first symptom, the imaging findings are often diffuse wall thickening(12-23, 36). In our case, the pelvic CT had the manifestation of diffuse thickening of the bladder wall for 9 months before the diagnosis of SRCC. However, no further treatment was made at that time because the patient had no obvious clinical symptoms. Also, the rarity of urinary bladder metastases made us relax our vigilance. We analyzed the reasons for the missed diagnosis of the patient: 1) In general, the most common manifestations of bladder malignant tumors were hematuria, obvious space-occupying lesions or obvious lower urinary tract symptoms(5). However, the urinary symptoms of this patient were not obvious all the time. This made us ignore the possibility of a tumor when there were only atypical bladder wall thickening in CT and negative findings in cystoscopy, resulting in missed diagnosis. 2) Metastatic bladder cancer is extremely rare and it is often not included in the differential diagnosis when it is encountered with negative findings under cystoscopy and inconspicuous clinical symptoms. In fact, the metastatic pattern of ILC tends to
occur as a diffuse thickening of mucosa rather than a discrete nodule(5). The subsequent progressive thickening of the bladder wall and the patient's previous medical history of breast ILC should have prompted us to consider whether there is a risk of metastatic bladder cancer.

Secondly, there is a history of multiple cancers in this case. At present, the patient has a history of invasive lobular carcinoma of the breast, metastatic endometrial carcinoma from the breast and chronic myeloid leukemia. Combined with bones metastasis and metastatic SRCC of bladder and stomach, she has suffered from 6 cancers in different sites. It reminds us that there may be some mutations in the patient's genes, and we are planning to perform the detection of related genes if the patient agrees in the future.

Thirdly, there was no signet-ring cell in breast ILC but signet-ring cells were found in gastric and bladder metastases. Signet-ring cell breast cancer was characterized in 1976(37, 38). This type of tumor accounts for approximately 1% of all breast cancer(29, 37, 39). It is characterized by a particularly high proportion of signet-ring-shaped cells and is considered as a subtype of lobular carcinoma(37, 38, 40-45). And interestingly, after searching Pubmed, Embase and Web of science, we found that signet-ring cells may indeed occur in metastases only and not in the primary tumor(37, 46). In other words, signet-ring differentiation may appear in metastases from a breast cancer regardless of whether or not the primary breast tumor had signet-ring cells(37, 47), which may cause diagnostic uncertainty(39, 41). Due to this particularity of breast ILC, in our opinion, as long as there is breast ILC combined with signed-ring cell carcinoma of other organs, we should consider whether there is a metastasis from breast.

**Conclusions**

Metastatic bladder SRCC from breast ILC is extremely rare in the clinic. Atypical clinical symptoms and negative cystoscopy results often lead to a very high rate of missed diagnosis, which may delay the treatment and affect the prognosis. The missed diagnosis of this case is a wake-up call for us. Clinically, when we meet patients presenting us with only atypical findings in CT such as bladder wall thickening, we should be careful about whether there is a possibility of metastatic bladder carcinoma no matter urinary symptoms and cystoscopy changes are typical or not, especially for those who have multiple cancer histories. Also, when we find signet-ring cell carcinomas in patients with histories of breast ILC, we should immediately consider whether there is a signet-ring-cell type variation during the metastasis from breast ILC. Biopsy should be made as early as possible and immunohistochemistry is helpful in determining the primary lesion.

**Abbreviations**

SRCC: Secondary signet-ring cell carcinoma; CT: Computed tomography; IHC: immunohistochemistry; CA125: Cancer antigen 125; H&E: hematoxylin-eosin staining; ER: estrogen receptor; PR: progesterone receptor; CDX-2: Caudal-type homeobox 2; CK20: Cytokeratin 20; PET/CT: Positron emission
tomography/Computed tomography; ILC: Invasive lobular carcinoma; IDC: invasive ductal carcinoma; LUTS: lower urinary tract symptoms.

Declarations

Availability of data and materials

All datasets generated or analyzed during this study are included in the article.

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Consent for publication

Written informed consent was obtained from the patient’s family for the publication of this case report and any accompanying images. A copy of the written consent form is available for review by the Editor-in-Chief of this journal.

Authors’ contributions

XX contributed to conception and design of the study. GC provided study materials and patients. HB and HL collected and assembled data. XX wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Competing interests

The authors have no competing interests to declare.

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Figures
Figure 1

The representative staining results of endometrial carcinoma (A. H&E, ×200; B. estrogen receptor, ×200; C. progesterone receptor, ×200; D. GATA-3, ×200)
Figure 2

A. The bladder wall thickened; B. The bilateral ureter was slightly dilated; C. Left ureteral opening. Bladder wall was locally thickening without new organisms. D. Right ureteral opening.
Figure 3

A. The bladder wall was significantly thickened; B. Hydronephrosis in the right kidney.
Figure 4

A. The bladder wall was significantly thicker than before; B. Hydronephrosis in bilateral kidneys. C. Small red protuberances could be seen around left ureteral opening. D. Right ureteral opening could not be seen.
Figure 5

The representative staining results of bladder carcinoma (A. H&E, ×200; B. CDX-2, ×200; C. CK20, ×200; D. GATA-3, ×200; E. Villin, ×200)
Figure 6

The representative staining results of gastric carcinoma (A. H&E, ×200; B. CDX-2, ×200; C. CK20, ×200; D. GATA-3, ×200; E. Villin, ×200; F. estrogen receptor, ×200; G. progesterone receptor, ×200)
Figure 7

A. The bladder wall was still thick; B. Hydronephrosis was slightly less than before. C. Left ureteral opening. D. Small red protuberances on bladder wall. Right ureteral opening could not be seen.