Metastasis to the bladder from primary breast cancer: A case report and literature review

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Abstract. Breast cancer is the most prevalent malignant tumor affecting women and represents the leading cause of female cancer-related mortality worldwide. Although distant organ metastasis accounts for the majority of breast cancer-related deaths, reports on bladder metastasis are limited in the existing literature. The present study describes the case of a patient with bladder metastasis originating from breast cancer. In addition, the present study also provides a review of 54 cases of similar disease that have been documented in the currently available literature. The literature review aims to elucidate the clinicopathological characteristics and therapeutic approaches for such conditions. The median time from breast cancer diagnosis to bladder metastasis was found to be 5.6 years (range, 0-28 years). The origin of the bladder metastases was predominantly invasive ductal carcinoma (IDC) accounting for 52.3% of cases, followed by invasive lobular carcinoma, accounting for 40.9% of cases. The pathology in the primary tumor was the same as the pathology of the bladder metastases in all cases. There was an 88.9% concordance rate for estrogen receptor status, while the progesterone receptor status was 83.3% and the human epidermal growth factor receptor 2 expression status was 100%. The primary initial symptoms included urinary system manifestations, such as increased frequency, urgency, dysuria, urinary incontinence, nocturia and gross hematuria. For the cystoscopic examination, the predominant findings were bladder wall thickening or masses, along with ureteral orifice masses. Overall, the present study demonstrated that the occurrence of bladder metastasis often follows the metastasis of other organs, with IDC being the most prevalent subtype. The pathological characteristics between the primary tumor and bladder metastasis exhibit a high degree of concordance.

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Introduction

Breast cancer is the most prevalent malignant tumor affecting women (1). The incidence of breast cancer is currently increasing worldwide and is projected to surpass 3 million new cases annually by 2040 (2). Related studies have demonstrated that the incidence of breast cancer in China is rising, but the survival rate is not high, with a 5-year survival rate of 40-60% (3,4). Despite an increased understanding of the disease and advancements in treatment strategies, breast cancer remains the leading cause of cancer-related mortality among women worldwide (5). The majority of breast cancer-related deaths are primarily attributed to metastasis. Approximately 12% of patients with breast cancer will develop metastatic disease (6). The most important parameters that influence development of metastases include tumor size, histological grade, lymphovascular spread, nodal involvement, presence of hormonal receptors and human epidermal growth factor receptor-2 (HER2) status (7). Although there are various sites for metastasis, such as the lungs, liver, bones, brain and lymph nodes, bladder metastasis is exceedingly rare (8). Metastatic bladder cancer includes involvement of lymph nodes beyond the pelvis or other visceral organs. The prognosis at this stage is poor, with <10% of patients surviving over 5 years after the diagnosis (9).

For patients with metastatic breast cancer, 30-60% of lesions are in the bones, 4-10% in the brain, 15-32% in the liver and 21-32% in the lungs (10); bladder metastases are rare and reported in the literature occasionally. Due to the rarity of bladder metastasis from breast cancer, large-scale retrospective or prospective cohort studies are not possible. Currently, global coverage mainly consists of clinical research in the form of case reports or autopsy reports. Previous literature based on autopsies has reported a disease incidence rate as low as 2% (11). Conversely, there is a high incidence of direct invasion of the bladder by malignant tumors originating from peripheral organs (12). Furthermore, there is a lack of relevant studies investigating the treatment and its correlation

with the pathological classification of primary breast lesions. The present study describes the case of a patient with bladder metastasis from breast cancer, providing a comprehensive account of the clinical and pathological characteristics, progression and course of treatment. Additionally, a concise review of cases reported in the existing literature is provided.

Case report

A 58-year-old woman with a diagnosis of breast cancer and a performance status score of 0, underwent a left radical mastectomy at Cancer Hospital of Henan University (Zhengzhou, China) in August 2013. The post-operative pathology revealed invasive ductal carcinoma (IDC) in the left breast, along with metastasis to 10 of the 16 ipsilateral axillary lymph nodes dissected. Immunohistochemical analysis (data extracted from the medical records) revealed the positive expression of estrogen receptor (ER), progesterone receptor (PR), HER2 and Ki-67 antigen (1%). The post-operative pathological stage was determined as IIIc (pT2N3M0) according to the 8th edition of the American Joint Committee on Cancer staging system (13). Adjuvant chemotherapy with 80 mg doxorubicin intravenous (iv) + 1.0 g cyclophosphamide (iv) on day 1 every 3 weeks for 4 cycles, followed by 130 mg docetaxel on day 1 every 3 weeks for 4 cycles, was administered after surgery. This was followed by 40 Gy/20 fractions of local radiotherapy. Subsequently, maintenance therapy with tamoxifen (10 mg, oral, twice a day) was administered for 4 years. In February 2018, multiple bone metastases were detected in the thoracic vertebrae, ribs and clivus via a bone scan due to chest pain. Local radiotherapy was performed on the thoracic spine, followed by oral anastrozole treatment at a dose of 1 mg once daily for 2 years.

In April 2020, a routine follow-up examination with computed tomography (CT) examination revealed progressive bone metastases in the neck, chest and lumbar vertebrae. Subsequently, endocrine treatment with fulvestrant (500 mg, every 4 weeks) was initially performed until September 2021. In September 2021, a urological ultrasound examination indicated hydronephrosis in the right kidney and no apparent abnormalities in the bladder. A CT examination (Fig. 1A and B) revealed dilation and hydronephrosis of the right renal pelvis, calyces and upper ureter, and the bladder wall exhibited roughness. Furthermore, it revealed no contrast agent concentration in the ureter during excretion phase. A lower degree of arteriovenous enhancement was observed in the right kidney in the parenchymal phase compared with that on the contralateral side. Intravenous pyelography (Fig. 1C and D) demonstrated poor function of the right kidney, and a liquid level of contrast medium was found in part of the renal pelvis with pressure release after 50 min. There was no gross hematuria and no urinary symptoms, such as frequent urination, urgency or dysuria, were observed. The urine occult blood test yielded negative results. Cystoscopy (September 2021; Fig. 1E and F) revealed that the ureteral orifice was normal, while the right ureteral cavity was narrow at 1 cm in diameter; in addition, two raised masses were observed behind the ureteral orifice on the left side of the bladder, with one mass measuring ~1.0x0.8 cm and another measuring ~1.2x0.8 cm. The post-operative pathological analysis (Fig. 2A) revealed the infiltrative growth of adenocarcinoma cells within the lamina propria of the bladder mucosa, consistent with metastatic breast invasive carcinoma. The protocol for histopathological staining was as follows: Tissue samples from the operation were fixed with 3.7% neutral formaldehyde solution for 24 h at room temperature, followed by routine dehydration and embedding in paraffin. The paraffin blocks were cut into sections with a thickness of 4 μm, stained with eosin staining solution for 5 min at room temperature and observed by conventional light microscopy.

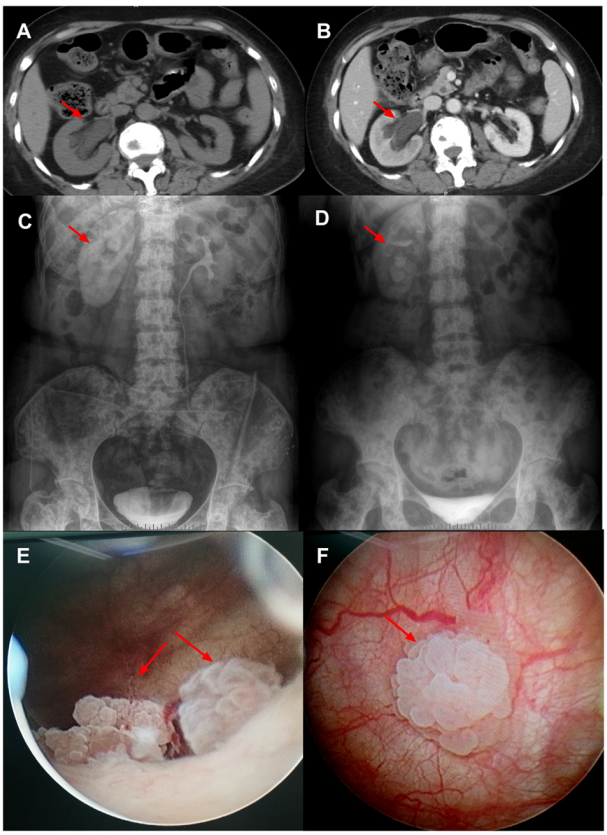

Figure 1. Patient images upon initial diagnosis of bladder metastasis. (A and B) Abdominal computed tomography revealed a dilated and hydronephrotic right renal pelvis, calyces and an upper ureter with thickened walls (arrow). (A) Non-contrast CT scan. (B) Contrast-enhanced CT scan. (C and D) Right renal dysfunction was detected via intravenous pyelography. (C) Pelvis and calyces of the right kidney were not visible during the excretory phase (arrow). (D) Post-excretion period showed a contrast fluid level in part of the renal pelvis in the right kidney (arrow). Cystoscopy revealed two lesions in the bladder wall, as shown by arrows in (E), the larger of which was 1.2x0.8 cm^2 as shown by arrow in (F).

Paraffin sections were immunohistochemically stained using the EnVision two-step method. Immunohistochemistry (IHC) was performed on formalin-fixed (10% formalin for 48 h at room temperature) and paraffin-embedded tissue sections (4 μm thick). IHC was performed automatically using the BenchMark Ultra platform (Ventana Medical Systems, Inc.) according to the manufacturer's instructions. the protocol for immunohistochemistry (IHC) staining was as follows: 4-μm-thick tumor sections from a paraffin block were deparaffinized and rehydrated in a descending alcohol series (80, 90, 95 and 100%) and water. For quenching of endogenous peroxidase activity, the slides were incubated with 3% hydrogen peroxide(H_2O_2) solution in methanol for 30 min at room temperature. slides were rinsed three times with 0.01 M PBS, then treated with antigen retrieval reagent (CC1, Roche,

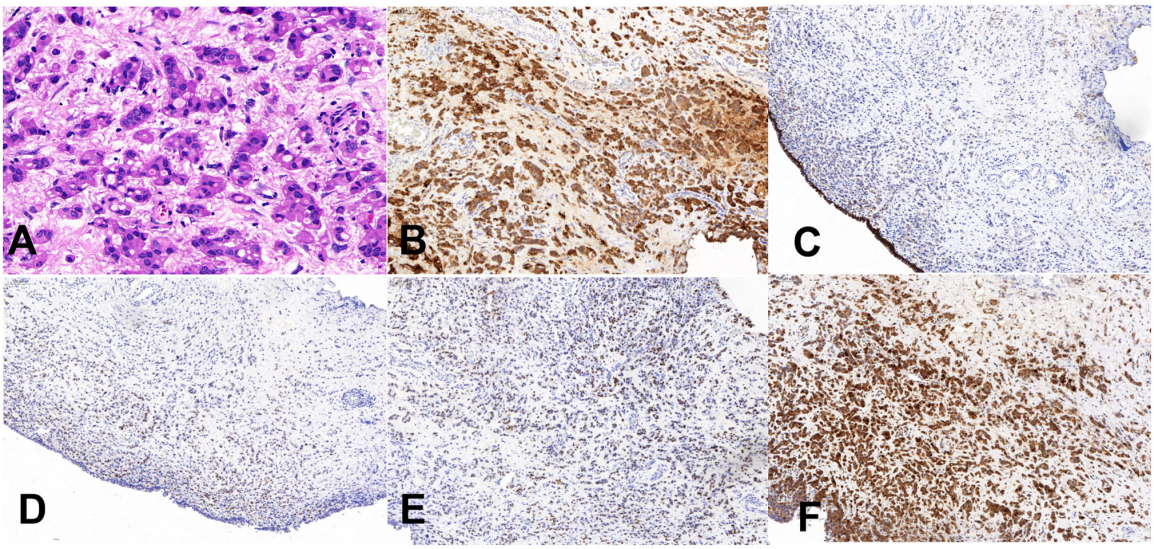

Figure 2. Pathological and immunohistochemical analysis. (A) Routine pathological staining (hematoxylin and eosin; magnification, x40) was performed upon electrosurgical resection of the bladder lesions. Immunohistochemical analysis was performed for (B) CK7, (C) E-cadherin, (D) estrogen receptor, (E) GATA binding protein 3 and (F) mammaglobin. (C-E) Magnification, x10. (B and F) Magnification, x20.

LTD.) in 100˚C for 60 min. Slides were washed three times with 0.01 M PBS (pH 7.4; 10min/wash) at room temperature and were then blocked with 10% goat non-immune serum (SP KIT-B1; Fuzhou Maixin Biotech Co., Ltd.) for 30 min at room temperature. Sections were rinsed three times with 0.01 M PBS (pH 7.4; 10 min/wash), and were then incubated with these monoclonal primary antibodies from Ventana Medical Systems, Inc. at 37˚C for 32 min: CD138 (1:200; KIT-9921), cytokeratin (CK)7 (1:200; KIT-7604), CD38 (1:200;KIT-3351), p63 (1:200; KIT-9922), P504S (1:200; KIT-6627), CK20 (1:200; KIT-5630), HER-2 (1:200; KIT-0048), GATA-3 (1:200; KIT-3535), p53 (1:200; KIT-5001), Ki-67 (1:200; KIT-5002), E-cadherin (1:200; KIT-5020), ER (1:200; KIT-5010), PR (1:200; KIT-5011) and mammaglobin (1:200; KIT-3433). Primary antibodies were diluted with PBS. Slides were washed three times with 0.01 M PBS (5 min/wash), then incubated with ultra View Universal HRP(ready to use; Roche, Ltd.) for 8 min at 37˚C. Ultra View Universal DAB (ready to use; K01773; Roche, Ltd.) with 3% H_2O_2 was used as the chromogen for 8 min at 37˚C, and sections were counterstained with Mayer's hematoxylin for 8 min at room temperature. Subsequently, slides were sealed with Permount Mounting Medium and observed under a light microscope (Olympus BX143) with 20x and 40x magnifications. The immunohistochemical analysis demonstrated positive staining for CD138 and CK7 (Fig. 2B), negative staining for CD38, p63, P504S, paired box-8, CK20 and HER2 (1+), and positive staining for GATA binding protein 3 (Fig. 2E), p53 (minority), Ki-67 (20% of hotspots), E-cadherin (partial) (Fig. 2C), ER (moderate intensity, ~30%) (Fig. 2D), PR (moderate intensity, ~5%) and mammaglobin (Fig. 2F). The patient received a 3-month treatment with palbociclib (125 mg, every day for 21 days and discontinued for 7 days) + fulvestrant (500 mg, every 4 weeks), which had to be discontinued due to severe myelosuppression caused by palbociclib. Due to the absence of a standardized treatment regimen for third-line and subsequent therapies, particularly in hormone receptor-positive patients following resistance to endocrine therapy, the patient was subsequently administered an 8 mg lenvatinib by mouth once daily(qd) + 500 mg fulvestrant by intramuscular injection every 3 weeks (q3w) combination until January 2023. However, meningeal metastasis occurred and despite receiving one cycle of chemotherapy with albumin-paclitaxel (300 mg on day 1) + carboplatin (0.6 g on day 1) + bevacizumab (600 mg on day 1) and repeated every 3 weeks the patient exhibited a poor response and succumbed to tumor progression in March 2023.

In summary, the histological subtypes of the primary breast cancer and bladder metastases in the patient exhibited marked concordance, the interval between the breast cancer diagnosis and the onset of bladder metastases was 8 years and the progression-free survival (PFS) and overall survival (OS) times following the diagnosis of bladder metastasis were 16 and 18 months, respectively.

Discussion

A comprehensive literature search was conducted in the Chinese database, China National Knowledge Infrastructure (https://www.cnki.net/), utilizing 'breast cancer and bladder metastasis' as the search terms in Chinese from the beginning of database construction until June 30, 2022. Out of the four studies retrieved, two were excluded based on their titles and abstracts. Additionally, relevant studies in the English language were retrieved from PubMed (https://pubmed.ncbi.nlm.nih.gov) and Web of Science (webofscience.com) using the search terms 'breast cancer AND bladder AND metastasis' from the beginning of database construction until June 30, 2022. The initial search led to the identification of 242 studies, with 54 being preliminarily deemed as relevant following a thorough examination. Subsequently, two criteria were applied and 33 studies were selected out of the 54 studies. The inclusion criteria were as follows: i) Case reports or serial case studies related to breast cancer with bladder

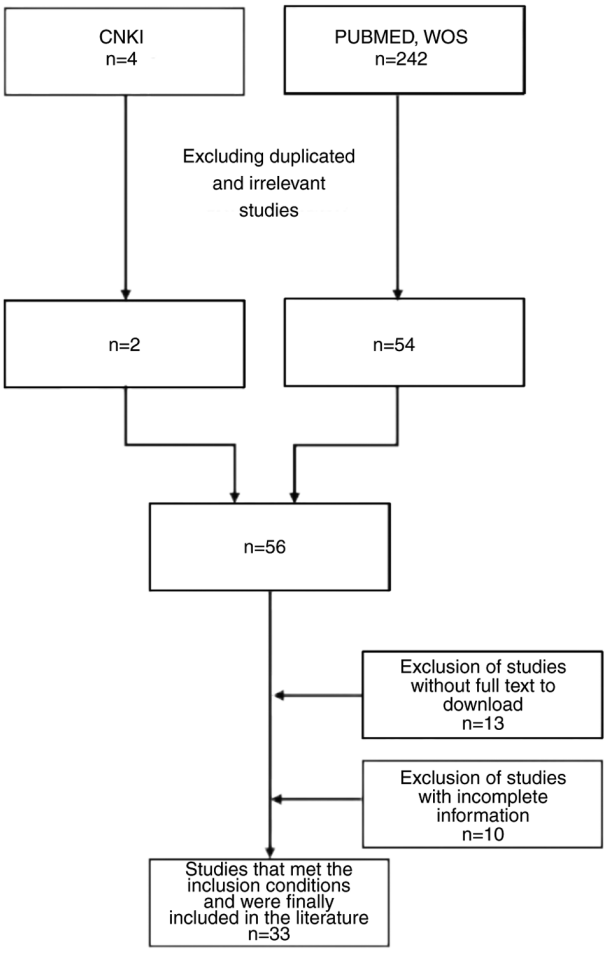

Figure 3. Steps for conducting the literature search.

metastasis; and ii) provision of complete general information including sex, age and duration from the diagnosis of breast cancer to the appearance of bladder metastasis. The literature screening process is presented in Fig. 3.

A total of 54 patients were included in the 33 articles, coupled with this present case, resulting in a cohort of 55 female patients diagnosed with bladder metastases originating from breast cancer for the present literature review (Table I). The median age of onset was 65 years (range, 40-91 years) (14,15), while the median interval time from breast cancer diagnosis to the appearance of bladder metastases was 5.6 years (range, 0-28 years) (16,17). Out of the 55 patients, 44 patients presented with definitive pathological types of primary breast cancer, consisting of 23 cases (12,16,18-25) classified as IDC (52.3%), 18 cases(14-16,25-33) classified as invasive lobular carcinoma (ILC) (40.9%) and 3 cases categorized as mixed-type (6.8%) (18,34,35). An analysis of the pathological information obtained from primary lesions and bladder metastases revealed 100% pathological consistency in the 36 cases with clear reports. Furthermore, there was a consistent presence of ER results in 33 out of 37 cases (89.2%), while PR results exhibited consistency in 25 out of 30 cases (83.3%). Notably, concordance in HER2 expression was 100% in the 20 patients with clearly reported HER2 results. ER, PR and HER2 were all reported in 11 cases (1 2,14,15,19,26-29,36,37), and the expression of all three was completely consistent in 9 cases (81.8%) (15,26,28,29,32,36). These data are summarized in Table II.

The main initial symptoms exhibited by the 55 patients were related to the urinary system, including frequent urination, urgency, dysuria, urinary incontinence, nocturia and gross hematuria. A small subset of patients presented with lower back pain, and edema in the lower limbs, feet and ankles (27,28). Notably, some patients exhibited no overt urinary system symptoms, and signs were detected only through a CT examination (16). Cystoscopy revealed the thickening of the bladder wall, a mass within the bladder wall or a mass at the ureteral orifice. In addition to the involvement of the bladder, combined metastasis to other sites was observed in 46 patients. Specifically, bone metastasis was reported in 20 cases (43.5%), while liver or lymph node metastases were found in 7 cases (15.2%) each (25,26,30,31,36,38,39). Metastases to the lungs, brain and meninges were observed in 5 cases (10.9%) each (25,30,38-40), whereas other sites including the peritoneum (17), ovaries (41), pleural effusion (27), pleura (16), bone marrow (30), ampullary region (16) and skin (16) were involved in only one case each (totaling 7 cases) (Table II).

Following a diagnosis of bladder metastases, appropriate treatment measures should be implemented based on the size of the lesions, the clinical characteristics and the pathological typing. The majority of the reported cases spanned from 1970 to 2022 (35,38), with a distribution of 16 cases prior to 2000 (21,30,31,38-40,42,43), 14 cases between 2001 and 2010 (18,20,22-24,32-34,41,44), 7 cases between 2011 and 2017 (14,15,17,19,25,26,45), and 18 cases after 2018 (12,16,28,29,35-37). Prior to the advent of molecular classification for breast cancer, radiotherapy and chemotherapy were the primary treatments. However, subsequent to the year 2000, endocrine therapy, as well as targeted therapies such as trastuzumab (anti-HER2 therapy) were incorporated into the treatment regimens. In those cases for which treatment outcomes were reported following the diagnosis of bladder metastases, the median time until final mortality or follow-up cut-off was 9 months (Tables I and II).

Breast cancer has emerged as the most prevalent malignancy worldwide, with ~2.3 million new cases reported in 2020. These figures accounted for ~25% of all female malignancies and surpassed the incidence of lung cancer for the first time (46). As a result, breast cancer currently stands as the foremost cause of mortality among female malignancies. Despite advancements in screening technology, scientific education and diagnosis, this issue continues to pose a significant challenge to the health of women.

Of all patients with breast cancer, ~45% develop metastases to various organs, including the lungs, brain, liver, bones, lymph nodes, skin and other sites (47). Nevertheless, the occurrence of bladder metastasis is extremely uncommon. Bladder carcinoma usually manifests primarily as urothelial carcinoma, which has the second highest prevalence among urinary system malignancies (48,49). Bladder metastasis constitutes a small fraction of malignant tumors within bladder carcinoma, reaching reported incidences as low as 2.3% (50). Differentiating between primary and metastatic bladder cancer poses a significant diagnostic challenge. The majority of cases involving this organ are linked to the direct

Table I. Clinical presentations of breast carcinoma metastatic to the bladder in literature cases (n=55).

First author (year)	Age, years	Primary breast lesion (pathology/ ER/PR/HER-2 status)	Metastases of the bladder (pathology/ ER/PR/HER-2 status)	First sign of bladder metastasis	Cystoscopic findings	Time from diagnosis of breast cancer to bladder metastasis, years	Incorporation of other site metastases	Treatment for breast cancer after bladder metastasis	Treatment outcome	Survival or follow-up time after bladder metastasis, months	(Refs.)
Pontes and Oldford (1970)	68	NR	NR	Abdominal pain, hematuria, leg cramps	Right ureteral orifice mass	1.0	Lung and lymph nodes	Chemotherapy	NR	2	(38)
	57	NR	NR	Backache	Cauliflower-like mass on the right side wall	4.0	NR	Radiation therapy	NR	1	
Haid *et al* (1980)	45	NR	NR	Intermittent painless gross hematuria	Two irregular masses	5.5	Bone, liver, meninges	No	NR	1	(30)
	83	ILC/NR/NR/NR	ILC/NR/NR/NR	Urinary incontinence, increased nocturia	Multiple nodules in the bladder wall with limited volume	2.7	None	Radiation therapy	NR	13	
	76	NR	NR	Microscopic hematuria and lethargy	NR	2.7	Bone, meninges, lung, liver, bone marrow	Chemotherapy	NR	1	
	71	NR	NR	Left adnexal mass	Walnut size lump	3.2	Lymph nodes in the left axilla and clavicle	Chemoradiotherapy	NR	>7	
Silverstein *et al* (1987)	66	NR/+/NR/NR	NR/+/NR/NR	Frequent urination, urgency, dysuria,	Raised lesion of the right lateral wall,	14.0	None	Chemotherapy	NR	24	(40)

Table I. Continued.

First author (year)	Age, years	Primary breast lesion (pathology/ ER/PR/HER-2 status)	Metastases of the bladder (pathology/ ER/PR/HER-2 status)	First sign of bladder metastasis	Cystoscopic findings	Time from diagnosis of breast cancer to bladder metastasis, years	Incorporation of other site metastases	Treatment for breast cancer after bladder metastasis	Treatment outcome	Survival or follow-up time after bladder metastasis, months	(Refs.)
				intermittent abdominal pain	smooth surface						
	54	IDC/-/-/NR	NR	Gross hematuria and dysuria	Extensive nodules in the trigone of the right lateral wall of the bladder	0.6	Brain, bone	Chemoradiotherapy	NR	12	
Rigatti *et al* (1991)	NR	IDC	NR	Bladder irritation, urinary incontinence	Unilateral wall uplift	5.3	Lungs, lymph nodes	NR	NR	NR	(39)
	NR	IDC	NR	NR	NR	13.7	NR	NR	NR	NR	
Williams *et al* (1992)	79	NR	NR	Frequent urination, increased nocturia	Large mass in bladder vault	6.0	NR	No		<1	(42)
Berger *et al* (1992)	78	IDC/-/-/NR	NR	Microscopic hematuria	Mass in the right lateral wall, posterior wall and bladder neck	6.5	NR	NR	NR	NR	(31)
	70	NR	NR	Uroschesis, aginal mass, gross hematuria	NR	6.0	Supraclavicular lymph nodes, brain, bone	Chemoradiothe rapy	NR	<12	

Table I. Continued.

First author (year)	Age, years	Primary breast lesion (pathology/ ER/PR/HER-2 status)	Metastases of the bladder (pathology/ ER/PR/HER-2 status)	First sign of bladder metastasis	Cystoscopic findings	Time from diagnosis of breast cancer to bladder metastasis, years	Incorporation of other site metastases	Treatment for breast cancer after bladder metastasis	Treatment outcome	Survival or follow-up time after bladder metastasis, months	(Refs.)
	65	ILC/+/-/NR	NR	Gross hematuria	NR	5.7	Retroperitoneal lymph nodes, liver	Chemotherapy	NR	<12	
Schneidaue *et al* (1995)	54	NR	NR	Dysuria, intermittent painless hematuria	Diffuse bullous edema of the bladder base and posterior lateral wall	2.0	NR	NR	NR	NR	(43)
Elia *et al* (1999)	87	IDC/+/+/NR	IDC/-/+/NR	Urgent urination	Small polyp in the left ureteral orifice	5.0	None	Endocrine therapy	Effective		(21)
Poulakis *et al* (2001)	65	IDC/+/+/NR	IDC/+/+/NR	Frequent urination, urgent urination and increased nocturia	Multiple tumors in the bladder wall	4.0	None	Chemotherapy + endocrine therapy	Effective	>60	(22)
Feldman *et al* (2002)	61	ILC+IDC/-/-/NR	ILC/+/NR/NR	Gross hematuria	Nothing abnormal, but CT shows an irregular bladder wall	10.0	NR	Radiation therapy	NR	>9	(34)
Soon *et al* (2004)	87	ILC/+/+/-	Same as the primary lesion	Abdominal pain and gross hematuria	Thickening of the bladder wall	17.0	None	Endocrine therapy	Effective	26.4	(32)

Table I. Continued.

First author (year)	Age, years	Primary breast lesion (pathology/ ER/PR/HER-2 status)	Metastases of the bladder (pathology/ ER/PR/HER-2 status)	First sign of bladder metastasis	Cystoscopic findings	Time from diagnosis of breast cancer to bladder metastasis, years	Incorporation of other site metastases	Treatment for breast cancer after bladder metastasis	Treatment outcome	Survival or follow-up time after bladder metastasis, months	(Refs.)
Gatti *et al* (2005)	49	IDC + ILC/-/+/NR	NR	NR	Ulcerated mass	5.0	NR	Chemotherapy	NR	11	(18)
Kleinmann *et al* (2005)	65	IDC/NR/NR/NR	NR	Painless gross hematuria	Papillary tumor of the right ureteral orifice	2.4	NR	NR	NR	NR	(23)
Lawrentschuk *et al* (2005)	74	ILC/+/-/NR	ILC/+/-/NR	Increased nocturia	-	NR	Bone	NR	NR	NR	(33)
	44	IDC/+/+/NR	IDC/+/-/NR	Lower back pain	Groin pain and hydronephrosis	NR	NR	Chemotherapy	NR	NR	
Ryan *et al* (2006)	71	NR	ILC/+/-/-	Urinary incontinence	A hard infiltrating mass in the bladder wall	22.0	Ovary	Chemotherapy + endocrine therapy	NR	>3	(41)
Zagha and Hamawy (2007)	67	IDC/+/+/NR	IDC/-/-/NR	Intermittent gross hematuria	Ulcerated mass in the vault of the bladder	7.9	None	Surgery + endocrine therapy	NR	NR	(20)
Lin and Chen (2007)	68	IDC/-/-/+	IDC/+/+/+	Lower back pain, hydronephrosis, occult blood, oliguria	Multiple nodules in the bladder wall	3.0	None	Chemotherapy + trastuzumab	Effective	2	(24)
Xiao *et al* (2012)	46	ILC/+/+/NR	NR/+/NR/NR	Dysuria, hydronephrosis	Nodules in bladder neck region	NR	Lung, liver	NR	NR	0.5	(25)

Table I. Continued.

First author (year)	Age, years	Primary breast lesion (pathology/ ER/PR/HER-2 status)	Metastases of the bladder (pathology/ ER/PR/HER-2 status)	First sign of bladder metastasis	Cystoscopic findings	Time from diagnosis of breast cancer to bladder metastasis, years	Incorporation of other site metastases	Treatment for breast cancer after bladder metastasis	Treatment outcome	Survival or follow-up time after bladder metastasis, months	(Refs.)
	53	ILC/+/+NR	NR/+/NR/NR	Hematuria	Nodules around the bladder neck and urethra	NR	None	NR	NR	Lost to follow-up	
	76	IDC/+/+/NR	NR	Dysuria	Nodule	NR	Lung, liver	NR	NR	<1	
Luczyńska *et al* (2010)	53	ILC/NR/NR/NR	ILC/NR/NR/NR	CA153 increased	Left ureteral mass	6.0	Local recurrence	Chemotherapy	Effective	NR	(44)
Shah *et al* (2011)	45	ILC/+/-/NR	ILC/+/-/NR	Oliguria, urinary tract infection, foot and ankle edema	Thickness of the bladder wall increased and irregular	At the same time as the primary breast cancer	Peritoneum	Chemotherapy	Effective	6	(17)
Reichman *et al* (2012)	68	NR	ILC/+/+/NR	Urinary incontinence, urinary tract infection	Lesions in the trigone and bladder wall	23.0	None	Endocrine therapy	Effective	10	(45)
Ghaida *et al* (2013)	64	IDC/+/+/-	IDC/+/-/NR	Urinary incontinence, urinary tract infection	Thickening of the bladder wall	5.0	None	Chemotherapy	Ineffective	12	(19)
Zhai *et al* (2013)	40	ILC/+/+/+	Same as the primary lesion	Left lower abdominal pain	Urethral stricture, cystitis	3.0	Bone	Chemotherapy	Effective	NR	(14)
Nieder *et al* (2014)	91	ILC/+/-/-	Same as the primary lesion	Anemia, renal dysfunction, hydronephrosis	Bladder mass rupture and bleeding	4.5	None	Endocrine therapy + radiation therapy	Effective	12	(15)

Table I. Continued.

First author (year)	Age, years	Primary breast lesion (pathology/ ER/PR/HER-2 status)	Metastases of the bladder (pathology/ ER/PR/HER-2 status)	First sign of bladder metastasis	Cystoscopic findings	Time from diagnosis of breast cancer to bladder metastasis, years	Incorporation of other site metastases	Treatment for breast cancer after bladder metastasis	Treatment outcome	Survival or follow-up time after bladder metastasis, months	(Refs.)
Cormio *et al* (2014)	45	ILC/+/+/-	Same as the primary lesion	No	The urethral opening is surrounded by a mass	8.0	Bone and lymph nodes	Chemotherapy	Effective	NR	(26)
Al Ibraheemi (2016)	50	ILC/+/+/-	ILC/-/-/-	Edema of the left lower extremity	The posterior wall of the bladder is thickened	9.0	Bone and pleural effusion	NR	NR	NR	(27)
Yoneyama *et al* (2018)	83	IDC/+/+/+	Same as the primary lesion	Left lower abdominal pain, anuria, general edema	Large mass in the bladder	15.0	Bone	Chemotherapy	NR	NR	(28)
De Rose *et al* (2019)	57	IDC/+/+/-	Same as the primary lesion	Lower backache, dysuria	Thickening of the bladder wall	5.0	Lymph node	Targeted therapy + endocrine therapy	Effective	NR	(36)
Wang *et al* (2019)	57	IDC/-/NR/+	Same as the primary lesion	Kidney failure	Ureteral obstruction	8.1	Bone	Chemoradiotherapy	NR	23	(16)
	83	IDC/+/NR/-	Same as the primary lesion	Asymptomatic with only a CT scan revealing bladder wall thickening	Thickening of the bladder wall	28.0	Bone, brain	Chemotherapy	NR	7	
	51	IDC/-/NR/+	Same as the primary lesion	Urgent urination	Bladder wall mass	5.8	Bone	Palliative treatment	NR	1	
	62	ILC/+/NR/-	Same as the primary lesion	NR	NR	3.4	Pleura	Endocrine therapy	NR	NR	

Table I. Continued.

First author (year)	Age, years	Primary breast lesion (pathology/ ER/PR/HER-2 status)	Metastases of the bladder (pathology/ ER/PR/HER-2 status)	First sign of bladder metastasis	Cystoscopic findings	Time from diagnosis of breast cancer to bladder metastasis, years	Incorporation of other site metastases	Treatment for breast cancer after bladder metastasis	Treatment outcome	Survival or follow-up time after bladder metastasis, months	(Refs.)
	66	IDC/+/NR/NR	Same as the primary lesion	Hematuria	Bladder wall mass	6.0	None	Chemotherapy	NR	12	
	57	ILC/+/NR/-	Same as the primary lesion	Asymptomatic with only a CT scan revealing bladder wall thickening	Bladder wall mass	5.4	Bone, liver, skin	Chemoradiotherapy	NR	12	
	67	IDC/+/NR/-	Same as the primary lesion	Asymptomatic, with only a CT scan revealing bladder wall thickening	Bladder wall mass	3.8	Ampullar region	Chemoradiotherapy	NR	4	
	68	IDC/+/NR/-	Same as the primary lesion	Asymptomatic, with only a CT scan revealing bladder wall thickening	Bladder wall mass	8.2	Pelvis	Chemotherapy	NR	2	
	77	IDC/+/NR/-	Same as the primary lesion	Hematuria	Bladder wall mass	6.2	Bone	NR	NR	NR	
	54	ILC/+/NR/-	Same as the primary lesion	Asymptomatic, with only a CT scan revealing bladder wall thickening	Bladder wall mass	4.3	Bone, liver	Chemotherapy	NR	>5	

Table I. Continued.

First author (year)	Age, years	Primary breast lesion (pathology/ ER/PR/HER-2 status)	Metastases of the bladder (pathology/ ER/PR/HER-2 status)	First sign of bladder metastasis	Cystoscopic findings	Time from diagnosis of breast cancer to bladder metastasis, years	Incorporation of other site metastases	Treatment for breast cancer after bladder metastasis	Treatment outcome	Survival or follow-up time after bladder metastasis, months	(Refs.)
	74	ILC/+/NR/-	Same as the primary lesion	Asymptomatic, only revealed a bladder wall mass by CT scan	Bladder wall mass	9.0	Bone	Chemotherapy	NR	>5	
Gitau *et al* (2020)	54	ILC/+/+/-	NR	Abdominal distension, hematuria, ascites	Multiple masses in the bladder	7.0	Bone, skin	Chemotherapy	Ineffective	9	(37)
Khan *et al* (2021)	63	IDC/+/+/-	IDC/+/+/NR	Lower abdominal pain, hematuria	Thickening of the bladder wall	17.0	None	Targeted therapy + endocrine therapy	Effective	NR	(12)
Mohammed *et al* (2021)	80	ILC/+/+/-	Same as the primary lesion	Urinary incontinence	Thickening of the bladder wall	4.0	None	Endocrine therapy	Effective	24	(29)
Wang *et al* (2022)	65	IDC + ILC/NR/NR/NR	ILC/NR/NR/NR	Hydronephrosis of the right kidney	No abnormal	4.0	Bone	NR	NR	NR	(35)
Present study	58	IDC/+/+/-	Same as the primary lesion	Uronephrosis	Bladder wall mass	8.0	Bone	Endocrine therapy + targeted therapy	Effective	>9	-

IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2; NR, not reported; CT, computed tomography.

Table II. Clinical characteristics of patients with breast cancer and bladder metastasis.

Clinical characteristics	Value
Sex, n (%)	
Female	55 (100.00)
Median age (range), years	65 (40-91)
Median time from diagnosis of breast cancer to bladder metastasis (range), years	5.6 (0-28)
Median survival or follow-up time after diagnosis of bladder metastasis (range), months	9 (0.5-60)
Complete pathological records of primary lesions, n	44
IDC (%)	23 (52.3)
ILC (%)	18 (40.9)
IDC + ILC (%)	3 (6.8)
Pathological consistency between primary and metastatic lesions	Consistent rate
Pathology was reported in all cases (n=36)	36 (100.0)
ER was reported in all cases (n=37)	33 (89.2)
PR was reported in all cases (n=30)	25 (83.3)
HER-2 was reported in all cases (n=20)	20 (100.0)
Pathology/ER/PR/HER-2 status was reported in all cases (n=11)	9 (81.8)
Report the combined metastasis site in detail, n	46
Bone (%)	20 (43.5)
Liver (%)	7 (15.2)
Lymph node (%)	7 (15.2)
Lung, n (%)	5 (10.9)
Brain or meninges, n (%)	5 (10.9)
Elsewhere, n (%)	7 (15.2)

infiltration by adjacent tumor types such as colorectal, cervical and prostate carcinomas (28,51).

Due to the rarity of bladder metastasis from breast cancer, there is a dearth of large-scale cohort studies and epidemiological data pertaining to this particular form of malignancy. Previous investigations have primarily focused on postmortem examinations for determining incidence rates, which range between 0.06 and 7% (19,38,52,53).

Including the present case, a total of 55 cases were included in the present literature review. The main clinical characteristics observed were as follows: All patients were female, with a median age of onset at 65 years and a median interval time of 5.6 years between breast cancer diagnosis and the development of bladder metastasis. Previous study have reported that bladder metastasis in breast cancer predominantly originates from breast ILC (19). However, the findings of the present study revealed that bladder metastasis caused by IDC accounted for 52%, while ILC accounted for 40.9%. As more case reports accumulate, this conclusion may gain further validity and may also be influenced by the higher incidence rate of IDC in breast cancer (46,54-57) between the primary tumor and metastases. According to the National Comprehensive Cancer Network guidelines (58), it is recommended that pathological biopsies be performed for precise guidance in treating metastatic lesions. Roulot *et al* (57) demonstrated that the concordance rates of ER, PR and HER2 between primary breast cancer and metastatic lesions were 80, 67 and 92%, respectively. Similarly, Santinelli *et al* (59) reported that the concordance rate of HER2 between primary breast cancer and metastatic lesions was 71.4%. The case described in the present study exhibited a notable pathological consistency between the primary breast lesion and bladder metastasis, consistent with the majority of cases included in the present study. The present study demonstrated a perfect 100% concordance with regard to the HER2 status, along with substantial concordance in ER (88.9%) and PR (83.3%). These findings provide valuable insight for guiding treatment decisions in patients for whom obtaining another biopsy is not feasible.

The symptoms caused by bladder metastases vary from asymptomatic manifestations to gross hematuria, obstructive uropathy and renal failure (16,20) metastasis (40). The present literature review indicated that urinary symptoms, including frequent urination, urgency, dyspnea, urinary incontinence, nocturia and gross hematuria, were the predominant clinical manifestations; however, the patient in the present case report did not exhibit any apparent urinary symptoms upon diagnosis; only hydronephrosis was found during the regular review, and a further examination confirmed bladder metastasis. A minority of patients initially presented with symptoms such as lower back pain or edema in the legs or ankles. In a small number of cases, no apparent urinary symptoms were exhibited and only an abnormal bladder signal was detected by a CT examination. Notably, these clinical manifestations do not differ from those observed in other types of bladder tumors. Furthermore, cystoscopy revealed similar findings to those observed in other types of bladder tumors, most commonly the thickening of the bladder wall and masses on the ureteral orifice.

The primary treatment for breast cancer with bladder metastases involves a comprehensive therapy tailored to the tumor size, clinical features and pathological immuno-typing of the metastases. The cases reported in the present study spanned from 1970 to 2022 (35,38), with the majority of the earlier cases managed with chemotherapeutic interventions due to the absence of established molecular classifications for breast cancer (30,31,38,40). Subsequently, commencing from 2000 onwards, alongside radiotherapy and chemotherapy, endocrine therapy and anti-HER2 therapy, were also incorporated (12,15,16,20,22,24,29,32,36,41,45). The patient in the present case report was diagnosed with bladder metastasis in 2021 and received a range of novel therapeutic agents, including palbociclib and fulvestrant.

It has been reported that bladder metastases from breast cancer are associated with worse prognosis than bone metastases (60,61) This disparity may be attributed to the fact that bladder metastases are typically diagnosed synchronously with or subsequent to other metastases. In the present study, the highest incidence of combined bladder metastases with other sites was observed in the bones (43.5%), followed by the liver, lymph nodes, lungs, brain and other sites. In the present study, the median time from the diagnosis of bladder metastasis until mortality or the end of follow-up was only 9 months (ranging from 0.5 to 60 months), which was potentially influenced by incomplete data reporting. Some patients were still alive at the time of the reporting of the case but were subsequently lost to follow-up.

In conclusion, bladder metastasis from breast cancer is a rare phenomenon that currently lacks well-defined epidemiological and pathological characteristics. However, the utilization of advanced diagnostic methods and imaging techniques in recent years has contributed to an increased number of reported cases. Previous studies have reported bladder metastasis from breast cancer; however, these studies are limited by small sample sizes and a lack of comparative analysis between primary and metastatic lesions in terms of pathology. The present study provides a comprehensive summary of the distinctive features associated with bladder metastasis in patients with breast cancer. In summary, bladder metastasis mainly originates from IDC, the median time from breast cancer diagnosis to bladder metastasis is 5.6 years, the pathological subtypes and immunohistochemical classifications of ER, PR and HER2 exhibit a significant concordance between them, and the median time from the diagnosis of bladder metastasis until mortality is 9 months. The primary breast cancer in the present patient case was identified as IDC, and the ER, PR and HER-2 subtypes of both the breast lesions and bladder metastases were concordant, aligning with the findings from the literature. The time interval between the diagnosis of breast cancer and the onset of bladder metastases in this patient was 8 years. Furthermore, the OS time after the diagnosis of bladder metastasis was 18 months, which is significantly longer than has been reported in the literature. This discrepancy could potentially be attributed to the utilization of new targeted therapies.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

TK contributed to the conception and the design of the study. HZ and TK wrote the manuscript and were involved in analysis and interpretation of data. DL and LC obtained and analyzed the patient information and contributed to manuscript drafting and critical revisions of the intellectual content. YZ and XZ treated the patient and performed the literature review. YG conducted cystoscopy. ML performed the histological examination of the tumor. HL, DL, LC and TK confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Third People's Hospital of Zhengzhou (ethical approval no. SY20230067). The patient provided initial written informed consent to participate.

Patient consent for publication

Written informed consent was obtained initially from the patient for publication of the data and images in this case report.

Competing interests

The authors declare that they have no competing interests.

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