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CASE REPORT

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Bladder metastasis from primary breast cancer: a case report and literature review

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Breast cancer is the most common malignancy in woman. The urinary bladder is an unusual site for metastasis from primary tumors of the breast, especially when it is the only organ involved. We present the case of a female patient with known breast cancer stage T2N3M0 who developed isolated bladder metastasis five years after the primary diagnosis. We reviewed the literature for similar cases and discussed the clinical presentation, pathophysiology, and prognosis of this entity.

Key Words: breast cancer ‹› metastasis ‹› urinary bladder

INTRODUCTION

Breast cancer, first described as early as 3000 B.C. by Edwin Smith Papyrus of Egypt, comprises 23% of all female malignancies (excluding non–melanomatous skin cancer) [1, 2]. In 2008, the number of deaths from breast cancer totaled 460,000 patients; it is a global concern accounting for 14% of all cancer deaths in females [3]. It is the most common invasive cancer in women with an incidence that ranges between 19.3 per 100,000 in Eastern Africa to 89.7 per 100,000 in Western Europe [4, 5]. The mortality in breast cancer patients is attributed to metastatic disease [3, 6]. It is known to metastasize to numerous organs including lymph nodes, lung, bone, liver, skin, kidneys, brain, adrenal, thyroid, and heart [3, 6, 7, 8]. Breast cancer metastasizing to the urinary bladder has only been reported sporadically totaling 41 cases in the English medical literature [3, 9–13]. Bladder metastasis from breast cancer as the only organ involved is very rare, with only eight cases reported worldwide [3, 11, 12, 14]. We herein present a patient who presented with bladder metastasis from breast cancer with the bladder being the only organ involved.

CASE REPORT

A 64–year–old female patient, a non–smoker known to have hypertension, diabetes mellitus, dyslipidemia, supraventricular tachycardia, and osteoporosis was diagnosed in 2005 with left breast intraductal carcinoma. She underwent a modified radical mastectomy with lymph node dissection. Ten out of 23 nodes were positive; she was staged as T2 (4 cm) N3 M0 disease. Receptors were positive for estrogen and progesterone, but negative for Her2. The patient was treated with eight cycles of chemotherapy, adriamycin, cytoxan,and taxol and 25 sessions of radiation therapy (total dose of 50 grays), and completed a 5–year treatment with an aromatase inhibitor. She had no evidence of disease until March 2010, when she presented to our clinic with recurrent urinary tract infections and urinary incontinence that failed

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Table 1.

	Reference/ year	GU symptoms	Finding on cystoscopy	Primary tumor to mets	Site in bladder	Bladder as only mets	Other organ involvement	Bladder mets to death	Chemotherapy used before bladder mets	Breast/ Bladder ER/PR	Breast tumor subtype	Treatment for bladder metastasis
1	Ganem and Batal. 1956	Gross Hematuria	Large tumor	10 yrs	Left Lateral wall	No	Bone, skin	>12 mo	Stilbesterol	NR	NR	NR
2	Perez–Mesa et al. 1965	Gross hematuria, frequency, dribling	Ulcerating tumor mass	2 yrs	Posterior wall	No	Bone, LN	NR	Fluoxymesterone	NR	NR	NR
3	Perez–Mesa et al. 1965	Gross hematuria, urinary frequency	Defined tumor mass	18 yrs	Infiltrated Tumor	No	LN, bone, omentum	12 mo	5–Fluorouracil	NR	NR	NR
4	Grabstald et al. 1969	Hydronephrosis	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
5	Pontes & Oldford 1970	Hematuria, low back pain	Tumor mass	1 yr	Right Ureteral orifice	No	Widespread	2 mo	Stilbesterol	NR	NR	Chemotherapy
6	Pontes & Oldford 1971	Back Pain	Cauliflower tumor mass	4 yrs	Right lateral wall	No	LN, retroperitoneum	1 mo	Estrogen	NR	Poorly anaplastic	Radiation
7	Schapira et al. 1980	Gross hematuria, Suprapubic pain	Telangiectasia and whitish plaque	5 yrs	Left lateral wall	No	NR	NR	NR	NR	NR	Radiation
8	Haid et al. 1980	Gross hematuria	Irregular sessile tumor	5.5 yrs	NR	No	Bone, Brain, meninges, Liver	1 mo	Hydrocortisone	NR	NR	NR
9	Haid et al. 1981	Frequency, nocturia, urge incontinence	Mucosal nodularities, restricted capacity	2.5 yrs	Adherent vaginal wall	No	Skin, pelvis	1 yr	DES	NR	NR	NR
10	Haid et al. 1982	Microscopic hematuria, abnormal cytology	Not performed	2.5 yrs	NR	No	Bone, meninges, lung, liver, peritoneum	1	Tamoxifen	NR	NR	Chemotherapy
11	Mairy et al. 1982	None	NR	9 mo	ExtraLuminal on partial cystectomy	No	Skin, bone	Alive >14 mo	NR	NR	NR	NR
12	Haid et al. 1983	Left adnexal mass	Walnut–size Tumor	3 yrs	Left ureteral orifice	No	LN, Pelvis	Alive >7 mo	Methotrexate, 5–FU, prednisone, L–phenylalanine	NR	NR	Radiation+ Chemotherapy
13	Mairy et al. 1983	Frequency, dysuria, incontinence, polyuria	Swollen mass	Same time	Left lateral wall	No	Bone, endometrium, skin	Alive >13 mo	NR	NR	NR	NR

	Reference/ year	GU symptoms	Finding on cystoscopy	Primary tumor to mets	Site in bladder	Bladder as only mets	Other organ involvement	Bladder mets to death	Chemotherapy used before bladder mets	Breast/ Bladder ER/PR	Breast tumor subtype	Treatment for bladder metastasis
14	Silverstein et al. 1987	Frequency, urgency, nocturia, abdominal pain	Smooth, hard raised immobile lesion	14 yrs	Right lateral wall	Yes	None	2 yr	No	NR +/NR	NR	NR
15	Silverstein et al. 1988	Gross hematuria, dysuria	Extensive nodularity	7 mo	Right lateral wall/ trigone	No	Brain, Bone	5 yr	Cyclophosphamide, prednisone,5 FU	–/– NR	NR	NR
16	Rigatti et al. 1991	Renal colic, microscopic hematuria	Exophitic mass	5 yrs	Right perimeatal	No	LN	NR	Cyclophosphamide, methotrxate,5 FU	NR	NR	NR
17	Rigatti et al. 1992	Irritative symptoms, incontinence	Small elevated reddened area	13 yrs	Lateral wall	No	LN, lung	NR	Tamoxifen, medroxyprogesterone	NR	NR	NR
18	Berger et al. 1992	Microscopic hematuria	Abnormal lesion	NR	Right Lateral/ posterior wall	Yes	None	NR	5–FU, cyclophosphamide, MitomycinC, doxorubicin, vinblastine, megestrol acetate	–/– NR	IDC	NR
19	Berger et al. 1993	Urinary retention, vaginal mass,gross hematuria	Abnormal lesion	6 yrs	NR	No	Supraclavicular node, bone, brain	<1 yr	Tamoxifen, methotrexate, 5–FU, cyclophosphamide	NR	NR	Radiation + Chemotherapy
20	Berger et al. 1994	Gross hematuria	Not performed	5.7 yrs	NR	No	Retroperitoneum, liver, SB/ LB	<1 yr	cyclophosphamide, tamoxifen, methotrexate, prednisone, vincristine, 5–FU	+/– NR	ILC	Chemotherapy
21	Williams et al. 1992	Frequency, nocturia, hydronephrosis	Large tumor mass	30 yrs	Trigone	NR	NR	NR	NR	NR	NR	NR
22	Schneidaue et al. 1995	Flank pain, gross hematuria, dysuria	Diffuse bullous edema	4 yrs	Base, posterolateral wall	No	Meninges	NR	Cyclophosphamide, methotrexate, 5–FU	NR	NR	NR
23	Lucas et al. 1996	Macroscopic hematuria	Large hypervascular	2.8 yrs	NR	No	Skin, lung, brain	<1 yr	Vindesine, mitomycin, tamoxifen	NR	NR	Radiation
24	Elias et al. 1999	Urgency	Few small polyps	5 yrs	Left lateral wall	Yes	None	Alive >1 yr	Tamoxifen	+/+ –/+	IDC	Hormonal therapy
25	Poulakis et al. 2001	Frequency, urgency, nocturia	Multiple invasive tumor	5 yrs	NR	Yes	Bladder recurrence	Alive >5 yrs	Tamoxifen	+/+ +/+	NR	NR

	Reference/ year	GU symptoms	Finding on cystoscopy	Primary tumor to mets	Site in bladder	Bladder as only mets	Other organ involvement	Bladder mets to death	Chemotherapy used before bladder mets	Breast/ Bladder ER/PR	Breast tumor subtype	Treatment for bladder metastasis
26	Feldman et al. 2002	Gross hematuria	Irregularities	10 yrs	Left lateral wall	No	Ovary	Alive >9 mo	Cyclophosphamide, doxorubicin, 5–Fu, Tamoxifen	–/– +/ NR	ILC	Radiation
27	Choudhary et al. 2003	Mixed Urinary incontinence	Atrophic hemorrhagic trigone	18 yrs	Trigone	Yes	None	Alive >8 mo	NR	NR +/NR	NR	NR
28	Soon et al. 2004	Mixed Urinary incontinence	Poorly compliant bladder	NR	Right side	Yes	None	NR	NR	NR	ILC	Hormonal therapy
29	Auprich et al. 2004	Gross hematuria, urge incontinence	Two large tumors	2 yrs	NR	No	Bone	NR	NR	NR	NR	NR
30	Lawrentschuk et al. 2005	Nocturia	Abnormal lesion	NR	NR	NR	NR	NR	NR	+/– +/–	ILC	NR
31	Gatti et al. 2005	NR	Ulcerated mass	5 yrs	NR	NR	NR	NR	NR	NR	IDC+ILC	Chemotherapy
32	Lawrentschuk et al. 2006	Groin pain, hydronephrosis	Abnormal lesion	NR	NR	NR	NR	NR	NR	+/+ +/–	iLC	NR
33	Zagha et al. 2006	NR	Ulcerated mass	8 yrs	NR	NR	NR	NR	NR	NR	NR	Surgery + hormone
34	Ryan et al. 2006	Urinary incontinence	Rigid infiltrating mass	NR	Posterior wall	No	NR	NR	NR	Nr +/–	NR	NR
35	Foster et al. 2006	Back Pain, malaise	Excessive nodular tumor	NR	Trigone	No	NR	NR	NR	+/+ +/+	NR	NR
36	Lin et al 2007	NR	Irregular mucosa and nodular lesions	3 yrs	NR	NR	NR	NR	NR	NR	NR	Chemotherapy
37	E. Vulcano et al. 2010	Urinary frequency and nocturia	Irregular lesion of the bladder dome	6 yrs	Dome	Yes	None	2 yrs	NR	NR/+ NR/–	ILC	Chemotherapy + hormonal therapy
38	Kamlesh et al. 2011	Fever with chills, bilateral pedal edema, oliguria and hydronephrosis	Thick irregular bladder wall with no definitive mass lesion	Same time	Diffuse	NR	None	6 mo	NR	NR/+ NR/–	ILC	Chemotherapy

	Reference/ year	GU symptoms	Finding on cystoscopy	Primary tumor to mets	Site in bladder	Bladder as only mets	Other organ involvement	Bladder mets to death	Chemotherapy used before bladder mets	Breast/ Bladder ER/PR	Breast tumor subtype	Treatment for bladder metastasis
39	Xiao et al. 2012	Difficult urination, hydronephrosis	Fixed bladder neck obscuring orifice	NR	Trigone, bladder neck	Yes	Neck, liver, lung	0.5 mo	NR	NR/+ NR/+	ILC	NR
40	Xiao et al. 2012	Difficult urination, hematuria	Mass obscuring ureteral orifice	NR	Trigone, posterior wall	No	None	1 mo	NR	NR/+ NR/+	ILC	NR
41	Xiao et al. 2012	NR	Nodular lesion	NR	Bladder neck, periurethra	NR	NR	NR	NR	NR/+ NR/+	Inflammatory	NR
42	Abou Ghaida et al. 2013	Frequency, dysuria, incontinence, hydronephrosis	Lesions	5 yrs	Diffuse	Yes	None	1 yr	Adriamycin, Cytoxan, Taxol	+/+ +/–	IDC	Chemotherapy

Abbreviations: GU – genitourinary, NR – not reported, mets – metastasis, LN – lymph node, SB – small bowels, LB – large bowels, ILC– invasive lobular carcinoma, IDC – invasive ductal carcinoma, ER – estrogene receptors, PR – progesterone receptors

to resolve with antibiotics alone. Her symptoms progressed and she developed severe disabling dysuria and suprapubic pain. She also reported intermittent bouts of bilateral flank pain radiating to her groin area.

Workup included a computed tomography (CT) scan of her abdomen and pelvis, which showed diffuse thickening of the urinary bladder wall with surrounding fat streaking of the pelvis and retroperitoneum (Figure 1). There was evidence of mild right hydroureteronephrosis with no evidence of obstructing urinary tract calculi (Figure 1). Cystoscopy showed inflammatory changes and suspicious bladder wall thickening in multiple areas. Transuretheral resection of bladder tumor (TURBT) for suspicious lesions was performed.

Pathology showed an unremarkable bladder mucosa, but a submucosal nest of carcinoma cells was found. The tumor was CK7 and CK20 negative, consistent with primary breast carcinoma. The cells were plasmacytoid with marked nuclear pleomorphism, frequent mitotic figures and multiple foci suggestive of lymphovascular invasion were present. The tumor cells were positive for estrogen receptor and E–cadherin; they were negative for progesterone receptors. This is consistent with breast ductal carcinoma (Figure 2).

Chest CT scan and bone scan were performed as part of the full work–up and failed to show any evidence of other distant metastasis. The patient

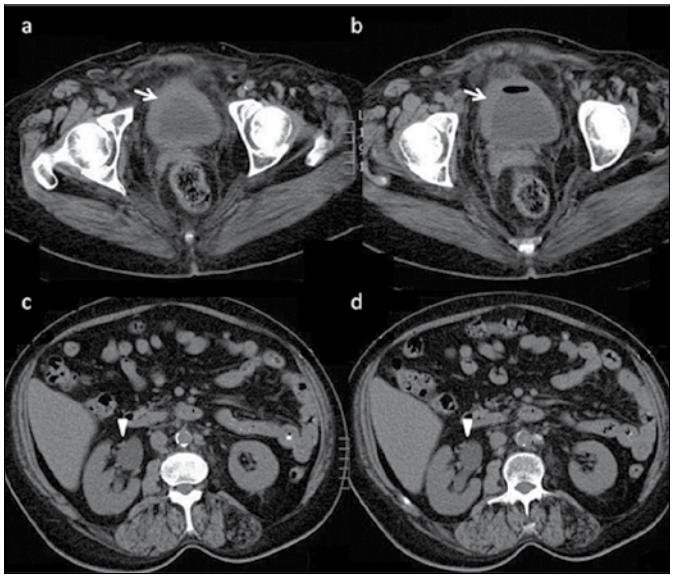

Figure 1. *Axial CT scan of the abdomen and pelvis without contrast. A, B. Diffuse thickening of the urinary bladder wall (arrows) with surrounding fat streaking of the pelvis. A pocket of gas is noted C, D. Mild right hydroureteronephrosis (arrowheads).*

was started on adriamycin, cyclophosphamide, and zometta. Follow–up re–TURBT was not performed. One week after receiving the first cycle of chemotherapy, the patient developed hematuria and clot retention. Several attempts of irrigation failed so

the decision was made to perform cystoscopy in order to fulgurate all bleeders. The cystoscopy identified a large clot in the bladder, which was removed and all bleeding areas were fulgurated. No gross evidence of residual tumor or recurrence was identified. Symptoms were relieved. Chemotherapy was continued and was complicated by neutropenia. The patient was clinically stable and tolerated the treatment. However, a few days after the third chemotherapy cycle she developed severe dyspnea and was found to have pneumonia that progressed to septic shock. The patient passed away from cardiorespiratory arrest one year after the diagnosis of the bladder metastasis.

DISCUSSION

Until 2012, 41 cases of bladder metastasis from breast cancer have been reported and they were mostly associated with systemic dissemination and multiple organ involvement. Only eight cases of solitary bladder metastasis from primary breast cancer have been documented and our case represents the ninth in the English medical literature [3, 11, 12, 14] (Table I, in bold). Most cases were diagnosed by cystoscopy and biopsy. Macroscopically, bladder metastasis may appear as a mass, irregular lesion, mucosal nodularity, abnormally thickened bladder wall, or plaque with telangiectasias. Any area of the urinary bladder can be involved. In our case, cystoscopy was performed based on the suspicious CT scan findings, and it revealed an abnormal bladder wall thickening and inflammation, which were both subsequently biopsied. Multiple sites of the urinary bladder were involved by carcinoma on pathology.

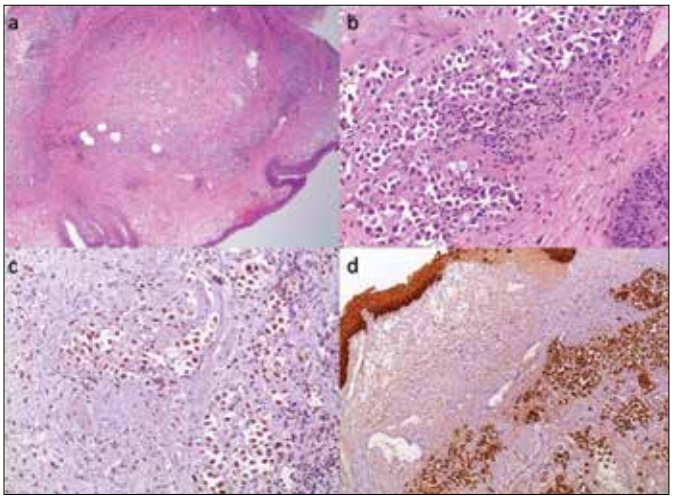

Figure 2. *A. H&E sections of the urinary bladder biopsy revealing a dense submucosal infiltrate (mag. 40x). B. The cells are cohesive, plasmacytoid with an abundant eosinophilic cytoplasm and eccentric nucleus (mag. 400x). The cells demonstrate positive immunostaining with anti–estrogen receptor (ER) antibody (C, mag. 400x) and anti–cytokeratin–7 (CK–7) antibody (D, mag. 200x).*

The breast primary tumor subtype was invasive intraductal carcinoma while in the previously published reports, the most common histology of the breast primary was invasive lobular (10 out of the 15 cases where the breast cancer subtype was determined).

Bates and Baithun reported 4.5% incidence of secondary bladder metastasis among all bladder cancer [9, 15], with secondary metastasis to the bladder from breast cancer being approximately 3% [16, 17]. When autopsy and pathology are used as mainstay for diagnosis, the incidence ranges from 0% to 7% [18]. Bladder metastasis from previously diagnosed breast cancer is reported in the literature to vary from 2% to 14% [3]. The most common primary tumors metastasizing to the bladder are: stomach, lung, skin/melanoma, and breast [19].

Symptomatic secondary bladder involvement from breast cancer is detected at late stages. It is only when the mucosa is involved by the disease will symptoms become clinically detectable. Metastasis involves the outer layer of bladder wall and progresses inward towards the mucosa [18]. Since mucosal involvement is the last stage of metastatic invasiveness into the bladder, the prognosis is very poor with a mean survival of two to three years, although a 5–year survival of two patients out of the 41 was reported in the literature [14, 20]. As a consequence, early stages of breast cancer metastasizing to the bladder are unapparent clinically, and detection of the disease remains a diagnostic challenge.

The most common findings in patients with secondary bladder metastasis are lower urinary tract symptoms (LUTS), flank or abdominal pain, hydronephrosis, and the painless hematuria that is in many cases the most common initial symptom (microscopic being more frequent than gross) [19]. Hematuria as a sign of bladder involvement following primary breast cancer is considered sensitive, but not specific for tumor metastasis. Gross hematuria with a history of breast cancer needs to be thoroughly investigated, keeping in mind the side effects of cyclophosphamide as treatment of the primary breast cancer, regardless of time or duration of treatment. However, our patient did not present with hematuria. Instead, she complained from recurrent urinary tract infections and urinary incontinence. Suprapubic and bilateral flank pain was later the major disabling symptom that warranted the investigation through CT scan imaging.

Ca 15–3 is one method to follow up breast cancer recurrence or metastasis [21], but strong evidence

are lacking on its clinical usefulness. The positron emission tomography (PET) scan has been showed to have increasing usage after suspecting bladder involvement in a breast cancer patient; however, its cost effectiveness is yet to be determined [22].

Breast metastasis to the bladder has been shown to have a worse prognosis than metastasis to bone [16]. The time interval between primary tumor diagnosis and detection of metastasis is highly variable between 0 month and 30 years with an average of 6.2 years (Table 1). Bladder metastases in our patient were identified five years after the initial diagnosis of primary breast carcinoma. Conduction of the proper investigations prevented the delay in the diagnosis of the metastatic disease. The patient survived one year from the time she first presented with urinary symptoms, and there was no evidence that her death was related to the bladder metastasis.

Only 8% of all breast cancer is lobular carcinoma [19], however, it is the most common type of breast cancer type involving the bladder (33% of secondary bladder metastasis) followed by ductal carcinoma, which accounts for the majority of primary breast cancer (66%) and metastasizes mostly to the lung parenchyma [19]. One hypothesis is that lobular carcinoma is of the serosal type, which gives it a predilection to spread to the gastrointestinal and gynecological systems [23]. It is part of the seeding soil hypothesis: the interaction of tumor with specific host factors in the metastasized organ [18]. The strongest predictor is lymph node involvement in the primary disease. Another culprit is concomitant steroid therapy, which is thought to be due to exacerbation of the immunosuppressive effect [19].

Estrogen, progesterone, and Her2 receptors are the three main receptors studied in breast cancer. Bladder metastasis from primary breast cancer was also subject to receptor studies [24]. Discrepancy between receptors is not uncommon between the primary and the secondary tumor (reported between 30 and 39%) [24]. Bladder metastases from our case were positive for estrogen receptors, which was also true for the patient's known primary cancer of the breast. However, progesterone receptors were only present in the malignant breast cells and not the secondary bladder metastasis. One hypothesis is that the polyclonicity of breast tumor cells is affected by treatment modalities (hormonal therapy may select some and suppress others), which manifests itself later in case of bladder metastasis [17]. It has been shown that if receptors convert from positive in the breast to negative in the bladder, it is associated with decrease survival [17, 24]. Even with receptor–negative secondary bladder metastasis, a trial of anti–receptor therapy has been used with promising results in controlling disease [24].

Reported cases of bladder metastasis were managed through surgery, chemotherapy, radiotherapy, hormonal therapy, or a combination of those. In our patient, chemotherapy was initiated after the TURBT and continued for three cycles. Neutropenia and the resultant complications went against the completion of the therapeutic plan.

CONCLUSIONS

We report a rare case of breast cancer with solitary urinary bladder metastasis that was diagnosed several years after the initial presentation. Secondary malignancies of the bladder are difficult to distinguish from non–transitional cell primary bladder cancer. A high level of suspicion and extensive investigation are warranted if a known primary cancer already exists. We emphasize the need to be more aware of the possible metastatic nature of every urinary symptom that shows in a breast cancer patient.

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