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...
| 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 | Chemo-therapy 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, dribbling | 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 | | | | | | | | | | | |
| 5 Pontes & Oldford 1970 | Hematuria, low back pain | Tumor mass | 1 yr | Right Ureteral orifice | No | Wes- spread | 2 mo | Stilbesterol | NR | NR | Chemo-therapy |
| 6 Pontes & Oldford 1971 | Back Pain | Cauliflower tumor mass | 4 yrs | Right lateral wall | No | LN, retroperitoneum | 1 mo | Estrogen | Poorly anaplastic | | Radia- tion |
| 7 Schapira et al. 1980 | Gross hematuria, Suprapubic pain | Telangiectasia and whith plaque | 5 yrs | Left lateral wall | No | NR | NR | NR | NR | Radia- tion |
| 8 Haid et al. 1980 | Gross hematuria | Irregular sessile tumor | 5.5 yrs | NR | No | Bone, Brain, meninges, Liver | 1 mo | Hydrocorti- sone | 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, perito- neum | 1 | Tamoxifen | NR | NR | Chemo-therapy |
| 11 Mairy et al. 1982 | None | | 9 mo | | No | Skin, bone | Alive >14 mo | | 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-phenylala- nine | NR | NR | Radiation+ Chemo-therapy |
| 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 |
| 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 | Chemo-therapy 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 |
| 16 Rigatti et al. 1991 | Renal colic, microscopic hematuria | Exophytic mass | 5 yrs | Right perineal | No | LN | NR | Cyclophosphamide, methotrexate, 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 | Cyclophosphamide, 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 | –/– | 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 + Chemo-therapy |
| 20 Berger et al. 1994 | Gross hematuria | Not performed | 5.7 yrs | NR | No | Retropitoneum, liver, SB/LB | <1 yr | Cyclophosphamide, tamoxifen, methotrexate, prednisone, vincristine, 5–FU | +/– | NR | ILC | Chemo-therapy |
| 21 Williams et al. 1992 | Frequency, nocturia, hydronephrosis | Large tumor mass | 30 yrs | Trigone | NR | 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 hypervas- cular | 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 | Chemo-therapy 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 | +/- | +/- | Radiation |
| 27 Choudhary et al. 2003 | Mixed Urinary incontinence | Atrophic hemorrhagic trigone | 18 yrs | Trigone | Yes | None | Alive >8 mo | NR | NR | NR |
| 28 Soon et al. 2004 | Mixed Urinary incontinence | Poorly compliant bladder | NR | Right side | Yes | None | NR | NR | NR | Hormonal therapy |
| 29 Auprich et al. 2004 | Gross hematuria, urge incontinence | Two large tumors | 2 yrs | NR | No | Bone | NR | NR | NR | NR |
| 30 Lawnrentschuk et al. 2005 | Nocturia | Abnormal lesion | 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 Chemo-therapy |
| 32 Lawnrentschuk et al. 2006 | Groin pain, hydro-nephrosis | Abnormal lesion | NR | NR | NR | NR | NR | +/- +/- | ILC | NR |
| 33 Zagha et al. 2006 | NR | Ulcerated mass | 8 yrs | 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 |
| 36 Lin et al 2007 | NR | Irregular mucosa and nodular lesions | 3 yrs | NR | NR | NR | NR | NR | NR | Chemo-therapy |
| 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 | Chemo-therapy + 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 | Chemo-therapy |
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 (Figure 1). There was evidence of mild right hydronephrosis with no evidence of obstructing urinary tract calculi (Figure 1). Cystoscopy showed inflammatory changes and suspicious bladder wall thickening in multiple areas. Transurethral 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 was started on adriamycin, cyclophosphamide, and zometa. 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

| 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 | Chemo-therapy used before bladder mets | Breast/Bladder ER/PR | Breast tumor subtype | Treatment for bladder metastasis |
|----------------|-------------|-----------------------|----------------------|----------------|---------------------|------------------------|---------------------|-------------------------------------|------------------|-----------------|-------------------------------|
| Xiao et al. 2012 | Difficult urination, hydronephrosis | Fixed bladder neck obscuring orifice | NR | Neck, bladder neck | Trigone, bladder neck | Yes | Neck, liver, lung | 0.5 mo | NR | NR/+ | ILC | NR |
| Xiao et al. 2012 | Difficult urination, hematuria | Mass obscuring ureteral orifice | NR | None, bladder neck | Trigone, posterior wall | No | None | 1 mo | NR | NR/+ | ILC | NR |
| Xiao et al. 2012 | NR | Nodular lesion | NR | Neck, bladder neck | Bladder neck, periurethra | NR | NR | NR | NR | NR/+ | Inflammatory | NR |
| Abou Ghaida et al. 2013 | Frequency, dysuria, incontinence, hydronephrosis | Lesions | 5 yrs | Diffuse | Yes | None | 1 yr | Adriamycin, Cytoxan, Taxol | +/+ +/+ | IDC | Chemo-therapy |

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 — estrogen receptors, PR — progesterone receptors

**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 hydronephrosis (arrowheads).
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. 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

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).
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 polyclonality 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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