



Case Report

Urinary bladder metastasis from primary breast cancer, a rare and challenging diagnosis. A case report and literature review

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ABSTRACT

Introduction: and Importance: Liver, lung, bone and brain are usual sites for breast cancer metastases. However, colorectal, prostate and cervical tumors may directly invade the urinary bladder (UB), but hematogenous spread from distant organs like the breast, is extremely rare and may indicate poor prognosis.

Case presentation: Here we describe the case of a 78-year-old female patient who was diagnosed with de novo metastatic breast cancer; initially to the bone and pleura with effusion, and then to the brain. Five years after her initial diagnosis, she presented with urinary symptoms and bilateral hydronephrosis. Work up showed diffuse thickening of the UB with no invasion from nearby structures; biopsy confirmed metastatic carcinoma of breast origin.

Clinical discussion: Adenocarcinoma of the UB is uncommon. Distinguishing primary adenocarcinoma of the UB from secondary involvement is often challenging. When encountered, involvement by a secondary tumor, either by direct extension or distant metastasis, should be considered. Immunohistochemical stains are essential in reaching an accurate diagnosis.

Conclusions: Breast cancer rarely metastasizes to the urinary bladder and prognosis is usually poor. Detailed medical history, imaging, and immunohistochemical studies on biopsy specimen should help reach accurate diagnosis.

1. Introduction

Breast cancer continues to be the most commonly diagnosed cancer among women worldwide [1]. Despite recent advances in early detection and the introduction of many new anti-cancer therapies [2], breast cancer remains a leading cause of cancer-related mortality among women. Most of these deaths are related to wide-spread metastases to vital organs such as the lung, liver and brain [3].

Most urinary bladder (UB) tumors are primary; very few are metastatic from other organs like stomach, melanoma, lung and more rarely the breast [4,5]. Direct extension, however, is more commonly encountered from tumors affecting nearby organs such as colon, rectal, prostate and cervix. Tumor extension, or peritoneal deposits, may result

in hydronephrosis and renal impairment. Regardless of the mechanism of involvement, both direct extension of the tumor to the bladder and hematogenous spread are associated with poor prognosis.

Here, we report a case of metastatic breast cancer to the UB that was diagnosed by cystoscopy following a thorough investigations for unexplained bilateral hydronephrosis. The updated 2020 consensus surgical case report (SCARE) guidelines were strictly followed while reporting our case [6].

1.1. Case Presentation

A 78-year-old female was diagnosed at an outside institution with de novo metastatic breast cancer to the bone 6 years earlier. A biopsy of the

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left breast mass revealed a grade-III invasive ductal carcinoma (IDC), estrogen (ER), progesterone receptors (PR) and human epidermal growth factor receptor-2 (HER2) were all positive. Staging imaging studies, back then, showed extensive bone metastasis with multi-level vertebral involvement and fractures, but no cord compression and no visceral metastasis noted. She underwent a multi-level kyphoplasty at L2, L3, and L4 vertebrae, and a biopsy from L4 confirmed the breast as the primary tumor. Palliative radiotherapy to L2-L5 was given along with hormonal therapy with letrozole, calcium/vitamin-D supplements and zoledronate infusion. During the course of her illness, she was treated with chemotherapy to control disease progression with malignant pleural effusion and then was maintained on fulvestrant and trastuzumab. Both kept her, other than the bone metastasis, disease-free. Two years later, she presented with headache and dizziness, work up showed multiple large supra- and infratentorial metastatic brain lesions for which she received whole brain radiation therapy (WBRT). Restaging imaging studies showed no disease elsewhere, so she was kept on the same treatment. Her course was also complicated by pulmonary embolism for which she was anticoagulated with low molecular weight heparin (LMWH) that was further complicated by bilateral subdural hematomas. A bilateral burr holes evacuation was performed, anticoagulation was stopped and an inferior vena cava (IVC) filter was placed. During the last two years, follow up indicated an increase in number and size of brain metastasis for which she had multiple treatments with stereotactic radiation therapy (SRT) to these brain lesions.

Recently, patient developed urinary symptoms including urgency and frequency. Renal ultrasound showed thickening of the urinary bladder wall and bilateral mild to moderate hydronephrosis. Cystoscopy revealed no tumors within or invading the bladder. Bilateral double J-stents were inserted, and random biopsies of the bladder wall revealed clusters and individual tumor cells in the lamina propria (Fig. 1a). The tumor cells were strongly and diffusely positive for GATA binding protein 3 (GATA-3) (Fig. 1b), focally positive for gross cystic disease fluid protein-15 (GCDFP-15) (Fig. 1c), positive for both ER and PR (Fig. 2a and b), respectively, and negative for p63 immunostain, thus confirming the mammary origin of the metastatic tumor. HER2 over expression was equivocal (score 2+) by immunohistochemistry (IHC) but negative by fluorescence in situ hybridization (FISH). Pelvic MRI showed no masses invading the bladder, but confirmed the diffuse thickening of the bladder wall, Fig. 3a and b. Positron emission tomography (PET) scan showed prominent UB wall thickening along with hypermetabolic metastatic process involving multiple sclerotic bone lesions, the right pleura, and mediastinal lymph nodes.

2. Discussion

Metastatic tumors to the UB are rare, the first reported case was in 1950 on an autopsy study performed on 1000 consecutive cases of malignant epithelial tumors at the Montefiore Hospital, New York City diagnosed between 1943 and 1947 [6,7]. Four (2.4%) of the 167 included cases with primary breast cancer had UB metastasis. Since then, there had been few reported cases, and was mostly due to local extension [8–10]. In a retrospective study of 6289 bladder tumors, 282 (4.5%) were characterized as secondary metastases and 7 (2.5%) of them were of primary breast origin; majority (n = 6, 85.7%) were detected only on post-mortem examination [5]. However, another study that reported on 19 patients with breast cancer and UB metastasis, showed that all patients were diagnosed following urinary symptoms that mandated cystoscopy and biopsy [11].

In another study, the clinicopathologic features of secondary bladder tumors in a cohort of 83 patients were analyzed, the tumors involved the bladder via direct extension from adjacent organs in 42 (50.6%) patients while another 41 (49.4%) had distant metastasis. Gynecologic tumors (n = 25), colon/rectum (n = 5) and breast (n = 4) were the most common sites of secondary metastasis encountered among females, while prostate and colorectal cancers were the most common primary

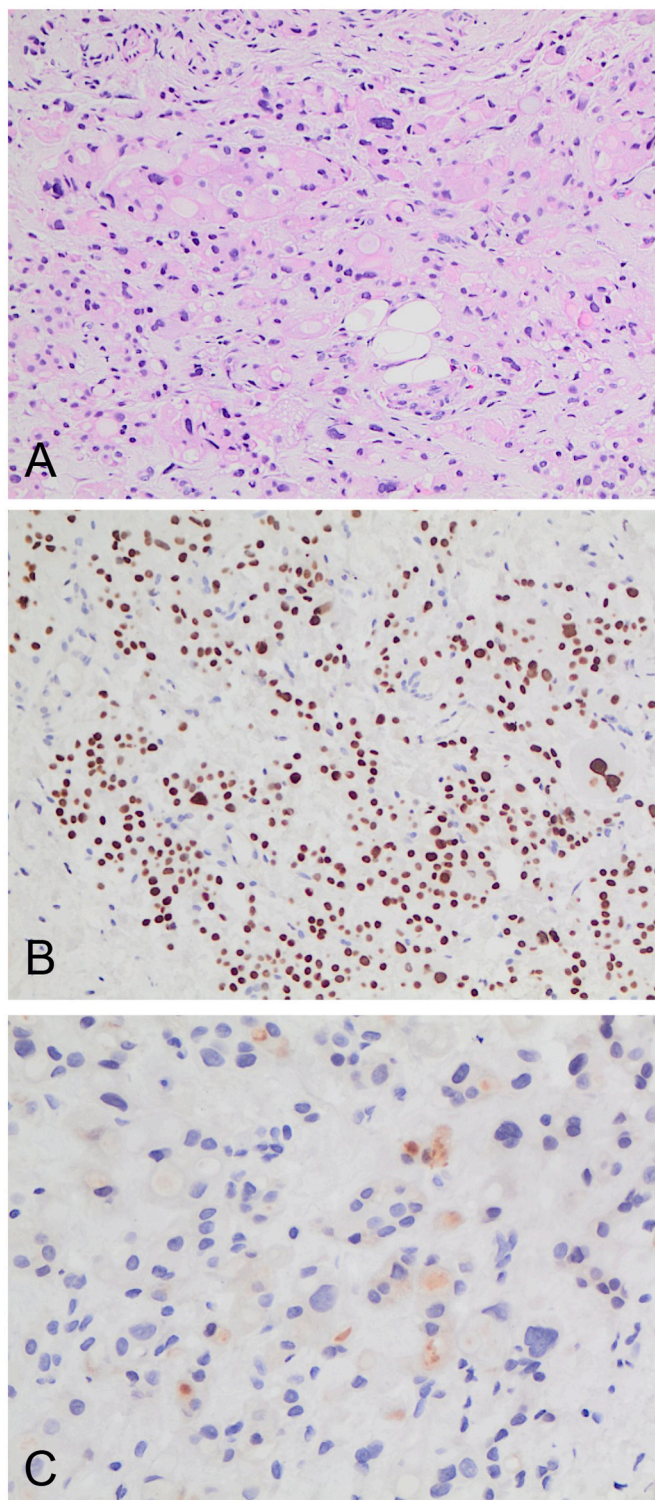


Fig. 1. Metastatic mammary carcinoma to urinary bladder. (A) Hematoxylin and eosin (H&E), 200X. (B) GATA-3 immunohistochemical stain, 200X. (C) GCDFP-15 immunohistochemical stain, 400X.

tumors that metastasize to the bladder among male patients [12].

Though most of breast cancer originates from the ducts (invasive ductal carcinoma), it is the less common subtype, invasive lobular carcinoma (ILC) that accounts for 5–15% of all breast cancers [13], that is better known for its unusual sites of metastasis, including the UB [14]. Invasive lobular carcinoma tends to spread to serosal surfaces, including the peritoneum, and this pattern of spread probably accounts for the

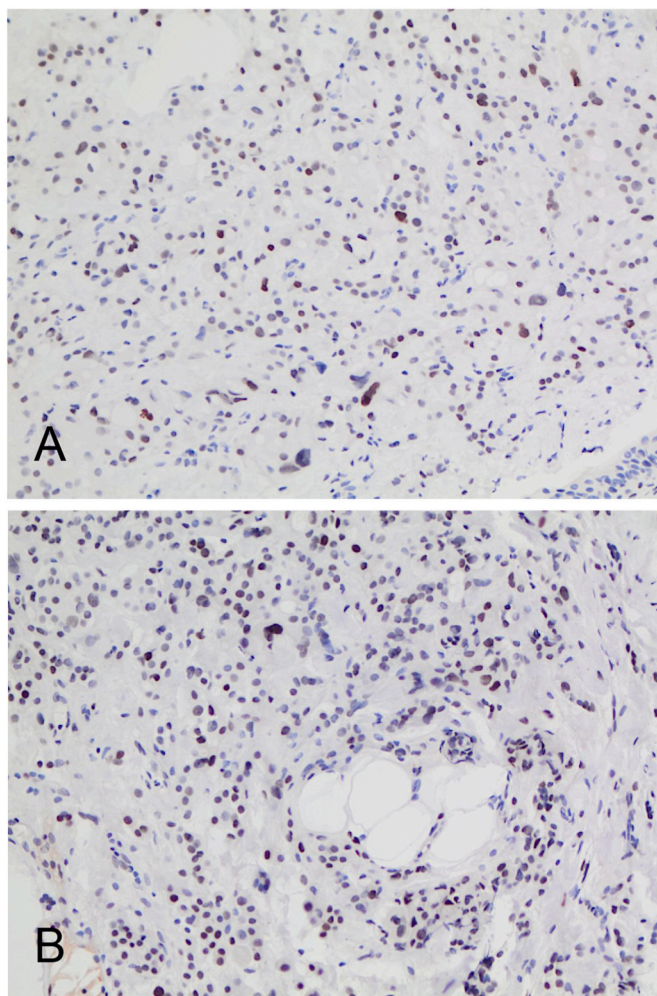


Fig. 2. Hormonal receptors immunohistochemical stain. (A) Estrogen receptors (ER) immunohistochemical stain, 200X. (B) Progesterone receptors (PR) immunohistochemical stain, 200X.

majority of breast cancer metastasis to the UB.

Urinary tract obstruction (UTO) is a commonly encountered problem among males, but not in females, and is considered an important cause of renal impairment and even failure in patients with cancer. Obstruction may occur at any level in the urinary tract; from the kidney and the ureter, down to the bladder and the urethra. Clinical manifestations related to UB metastasis can be variable and range from totally asymptomatic, like the ones diagnosed in autopsy studies, up to gross hematuria and renal failure [15].

Due to the frequently encountered discrepancies in receptor status between the primary tumor and the metastatic disease [16], rechecking the receptor status may alter treatment plan as illustrated in our case; contrary to the primary tumor, urinary bladder metastasis was HER2-negative. There is no sufficient data to guide physician about the prognosis of UB metastasis, though it can be poor [17].

Primary adenocarcinoma of the UB is uncommon, accounting for approximately 0.5–2% of all malignant bladder tumors [18,19]. Distinguishing primary adenocarcinoma of the UB from secondary involvement is often challenging. Whenever an adenocarcinoma involving the UB is encountered in a biopsy or resection, detailed review of the medical history is very essential. In this setting, the differential diagnosis includes glandular differentiation in urothelial carcinoma, primary UB adenocarcinoma, urachal adenocarcinoma and involvement by a secondary tumor either by direct extension or distant metastasis.

Immunohistochemical stains are essential in reaching an accurate

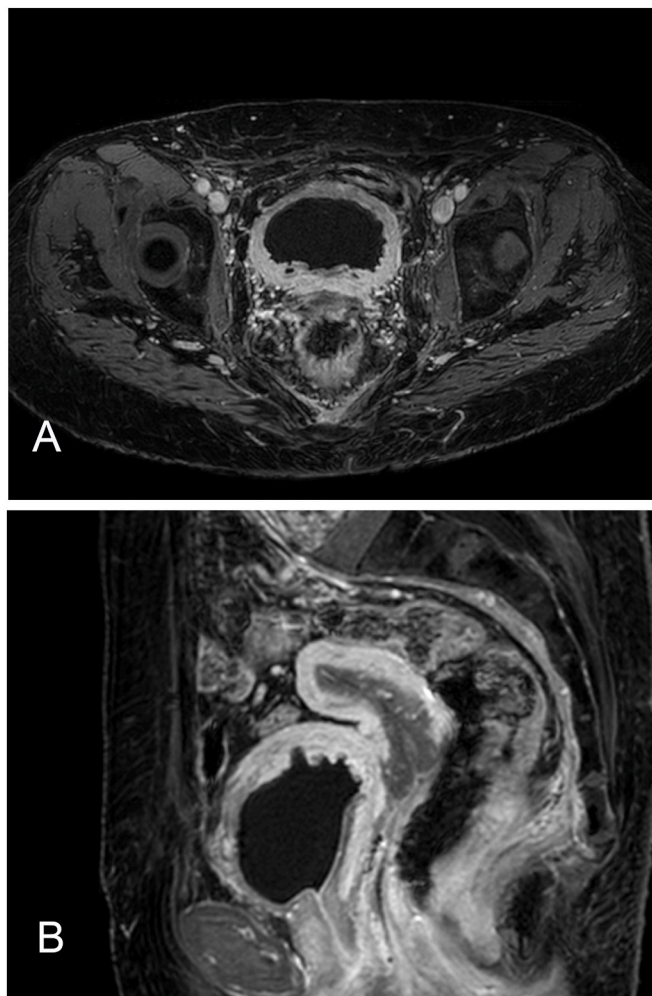


Fig. 3. Pelvic MRI showing diffuse thickening and enhancement of the fundus and posterior wall of the urinary bladder with swelling of the urothelium; (A) Axial view (B) Coronal view.

diagnosis, a panel of stains that includes ER, PR, GATA-3 and GCDFP-15 can be helpful in this setting. Although GATA-3 immunohistochemical stain is considered a marker with high sensitivity and specificity for primary breast carcinoma and urothelial carcinoma, the sole positivity of this stain is not sufficient to render a diagnosis of metastatic breast carcinoma when the differential diagnosis includes primary adenocarcinoma of the UB. The expression of GATA-3 in primary adenocarcinoma of UB is variable and depends on the subtype of adenocarcinoma [20,21]. In their study, Ellis et al. found the expression of GATA3 in primary adenocarcinoma of the UB to be strong and diffuse in adenocarcinoma with signet ring cells, as compared to negative staining in conventional type adenocarcinoma. In addition, none of the primary adenocarcinoma of the UB, regardless of the subtype, expressed ER or PR by immunohistochemistry [20]. In our case, the tumor cells were arranged individually and in clusters, but did not exhibit signet ring cell morphology and were positive for GATA-3, ER, PR and GCDFP-15 stains, confirming the diagnosis of metastatic breast carcinoma.

3. Conclusions

Breast cancer, even when the disease is extensive, rarely metastasizes to the urinary bladder. Hematuria, renal impairment and hydronephrosis may be encountered with bladder metastasis. Careful assessment of the pathology specimen with immunohistochemical stains should help reaching accurate diagnosis.

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Informed consent

Written informed consent was obtained from the patient's daughter for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

RAR, RAM, MA, OK, HA researched literature and wrote the first draft of the manuscript. MA, SE, RG were involved in case summary, gaining ethical approval and patient's consent. OJ described and wrote the pathology part. HA supervised the whole project. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Data availability

Data will be made available upon reasonable request.

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Not commissioned, externally peer reviewed.

Ethical approval

The publication of this case report was reviewed and approved by the ethics committee [Institutional Review Board (IRB)] at King Hussein Cancer Center.

Reference: 21 KHCC 177N.

Consent

Ethics committee was obtained from the IRB at King Hussein Cancer Center.

Additional, consent to publish this case report was obtained from patient's daughter. The following statement is written at the end of manuscript:

"Written informed consent was obtained from the daughter for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request".

Registration of research studies

1. Name of the registry: Research Registry (www.researchregistry.com)
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Guarantor

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Declaration of competing interest

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