Bladder metastasis from inflammatory breast cancer presenting with hematuria and hydronephrosis

Halle E. Foss, MD,[1] Jessica Bulafka, BS,[1] Nneamaka Nwaoduah, MD,[2] Mihir S. Shah, MD[1]

[1]Department of Urology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, USA
[2]Department of Pathology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, USA

FOSS HE, BULAFKA J, NWAODUAH N, SHAH MS. Bladder metastasis from inflammatory breast cancer presenting with hematuria and hydronephrosis. *Can J Urol* 2023;30(6):11747-11751.

We report a rare case of a 56-year-old Ukrainian female with inflammatory breast cancer (IBC) who underwent neoadjuvant chemoradiation and left radical mastectomy with her clinical course complicated by disease recurrence with bone and bladder metastases 2.5 years after her initial diagnosis. We highlight the presentation and diagnosis of genitourinary involvement of metastatic IBC, which has not previously been described in the literature.

Key Words: inflammatory breast cancer

Introduction

Inflammatory breast cancer (IBC) is a rare and aggressive disease that is distinct from the more common ductal and lobular morphologies of breast cancer. IBC represents only 2%-4% of breast cancer in the United States and, at the time of diagnosis, approximately 30% of patients have metastatic disease.[1] Involvement of the urinary tract in IBC disease progression has not previously been described. Here we present a 56-year-old Ukrainian female with IBC who underwent neoadjuvant chemotherapy and radiation prior to mastectomy, experienced disease recurrence followed by salvage chemotherapy and hormonal therapy, and subsequently developed a bladder mass three and a half years after her initial diagnosis.

Accepted for publication November 2023

Address correspondence to Dr. Mihir Shah, Department of Urology, Thomas Jefferson University Hospital, 1025 Walnut Street, Suite 1100, Philadelphia, PA 19107 USA

Case presentation

The patient is a 56-year-old Ukrainian woman who was diagnosed with IBC after presenting with tenderness, skin dimpling, and nipple inversion of the left breast. Punch biopsy confirmed IBC stage IIIb (T4dcN1aM0) with biomarker stains positive for both estrogen and progesterone receptors, but negative for HER2 (ER+/PR+/HER2-). She received neoadjuvant treatment with four cycles of dose-dense doxorubicin and cyclophosphamide, plus 12 weekly treatments of paclitaxel. Prior to surgical intervention she also received a course of radiation (51 Gy at 1.5 Gy BID) due to partial response to chemotherapy. She subsequently underwent left modified radical mastectomy approximately 10 months after diagnosis. Post-surgical pathology showed complete response in the breast and skin, but identified two lymph nodes positive for metastatic carcinoma, and she was placed on Anastrozole for maintenance therapy.

Approximately 18 months after mastectomy, a bone scan was obtained due to new rib and lower back pain which revealed multiple enhancing lesions consistent with widespread osseous metastasis. A biopsy of the right posterior ilium confirmed metastatic mammary carcinoma (ER+/PR+/tissue insufficient for HER2 testing). The patient was then started on fulvestrant (ER antagonist) and Palbociclib (CDK4/CDK6 inhibitor), and underwent multiple rounds of palliative radiation to the ilium, sacrum, and lumbar spine over the following year.

Six months after diagnosis of her bone metastases (approximately 3 years after her initial treatment), she developed new onset gross hematuria and presented for urologic evaluation. Although her gross hematuria lasted only 2 days and resolved without intervention, she also complained of intermittent suprapubic discomfort and increased urinary frequency not associated with a urinary tract infection. A computed topography (CT) scan of the abdomen and pelvis was obtained which revealed moderate left-sided hydroureteronephrosis with a delayed nephrogram and a partially circumferential, mass-like mural thickening up to 1.5 cm involving the bladder base and left bladder wall, Figure 1A, 1B. Other findings included left adnexal nodularity at the site of the ureteral transition point and a bulky-appearing cervix and vagina adjacent to the bladder mass. Urine cytology was collected and showed atypical cells suspicious for high grade carcinoma. She subsequently underwent cystoscopy with transurethral resection of bladder tumor (TURBT) which demonstrated a 3 cm nodular mass that encompassed the left lateral wall, trigone, and bladder neck and obscured the left ureteral orifice. The left ureteral orifice was identified upon resection and a left ureteral stent was placed at this time. Gynecologic oncology concomitantly performed a pelvic exam under anesthesia which revealed a grossly normal appearing

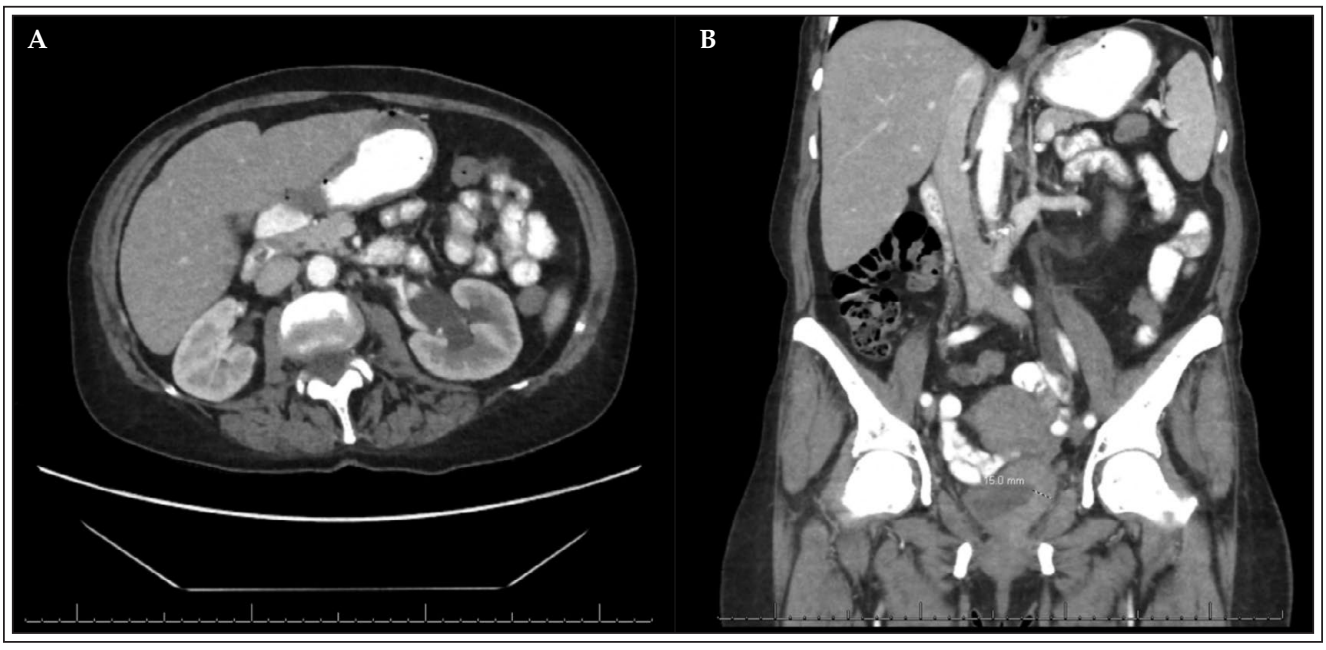

Figure 1. Contrast-enhanced CT of the abdomen and pelvis. **A)** Axial view demonstrating left-sided hydronephrosis and asymmetric thickening of the left lateral bladder wall and **B)** coronal view showing better characterization of bladder wall thickening, measuring up to 1.5 cm.

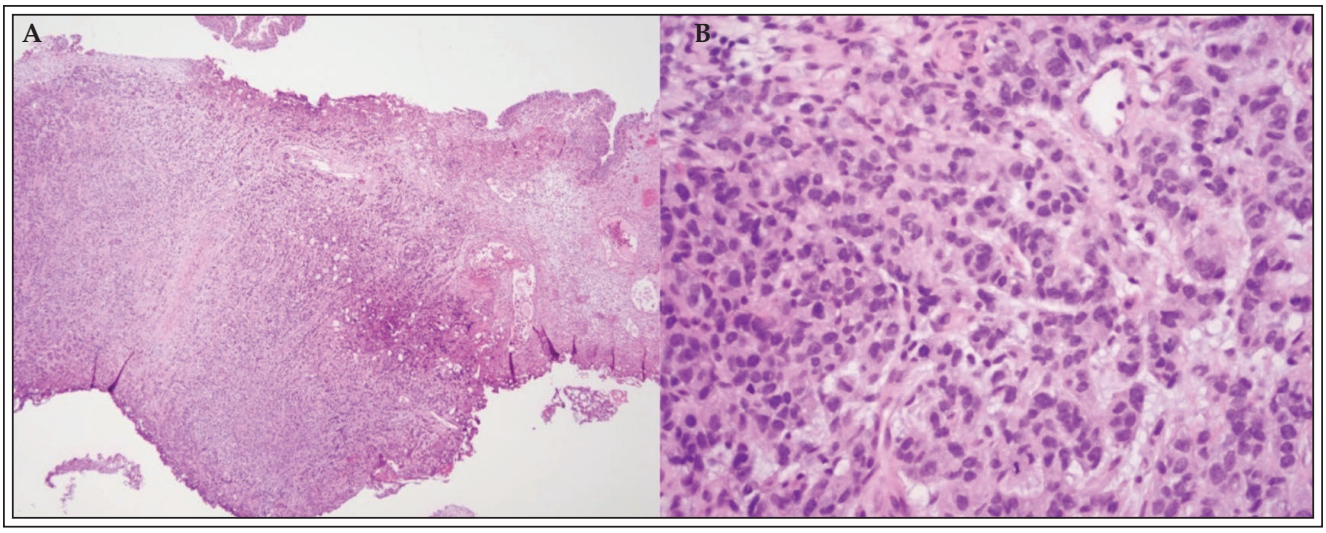

Figure 2. Hematoxylin and eosin stain of bladder biopsy specimen showing infiltrative malignant poorly differentiated epithelioid clusters with overlying unremarkable urothelial mucosa **A)** 40x magnification, **B)** 400x magnification.

vaginal canal and cervix. Pathologic analysis of the bladder specimen confirmed metastatic carcinoma of mammary origin, Figure 2A, 2B. Immunohistochemical stains demonstrated ER positive 70%, PR trace positive 5%-10%, and equivocal staining for HER2, Figure 3A-3E. However, follow up fluorescence in-situ hybridization (FISH) testing was negative for HER2 gene amplification, consistent with her initial breast pathology.

Given progression of her disease on fulvestrant and Palbociclib, she was transitioned to weekly paclitaxel chemotherapy with palliative intent. Unfortunately, her most recent imaging with CT and bone scan show persistent osseous disease and progression of additional liver metastases.

Discussion

Recent review of literature has demonstrated up to 65 cases of primary breast cancer with urinary bladder metastasis (UBM) described between 1950 to 2019.[2] The first known cases were found only during autopsy studies, but over the past several decades, cases of symptomatic UBM in patients with a history of breast cancer have become more prevalent. Among these, UBMs originating from infiltrating lobular carcinoma (ILC) tend to be more frequent than those from intraductal carcinoma (IDC).[2] This pattern has been attributed to the higher rate of multiple metastases from ILC than IDC. It has also been observed that ILC tends to metastasize to serosal surfaces, such as the peritoneum and gastrointestinal tract, more often than IDC.[3]

Unlike IDC and ILC which are diagnosed based on histologic morphology, IBC is a clinical diagnosis with a variable histologic presentation. Dermal lymphatic invasion on skin biopsy is a classic pathognomonic finding, but not necessary for diagnosis. It is theorized that lymphatic dissemination of tumor emboli may contribute to the development of distant metastases, as well as the characteristic tumor cell clusters that are dispersed throughout the stroma rather than a discreet tumor mass.[4] IBC tends to have lower ER and PR expression and a higher rate of HER2 positivity than non-IBC mammary carcinomas. Approximately 30% of IBC is triple negative (ER-/PR-/HER2-), compared to 15% of non-IBC breast cancers.[1,4]

Given its aggressive nature and overall greater disease burden of metastasis, one would expect the occurrence of UBMs among IBC patients to match or exceed that of non-inflammatory cohorts, but to the authors' knowledge, no cases of UBM from IBC have been described. One explanation could be that the relatively poor prognosis of IBC precludes patients from forming UBMs. The median overall survival among IBC patients is about 4 years, compared to 13 years in non-inflammatory breast cancer cohorts.[3] UBMs have been described occurring 1 month to up to 30 years from time of breast cancer diagnosis.[2] A thorough review of 19 cases of UBM by Feldman et al found an average time from breast cancer to UBM diagnosis of seven and a half years.

UBMs are most often preceded by metastases to the bone, liver, and/or lung, with only a handful of

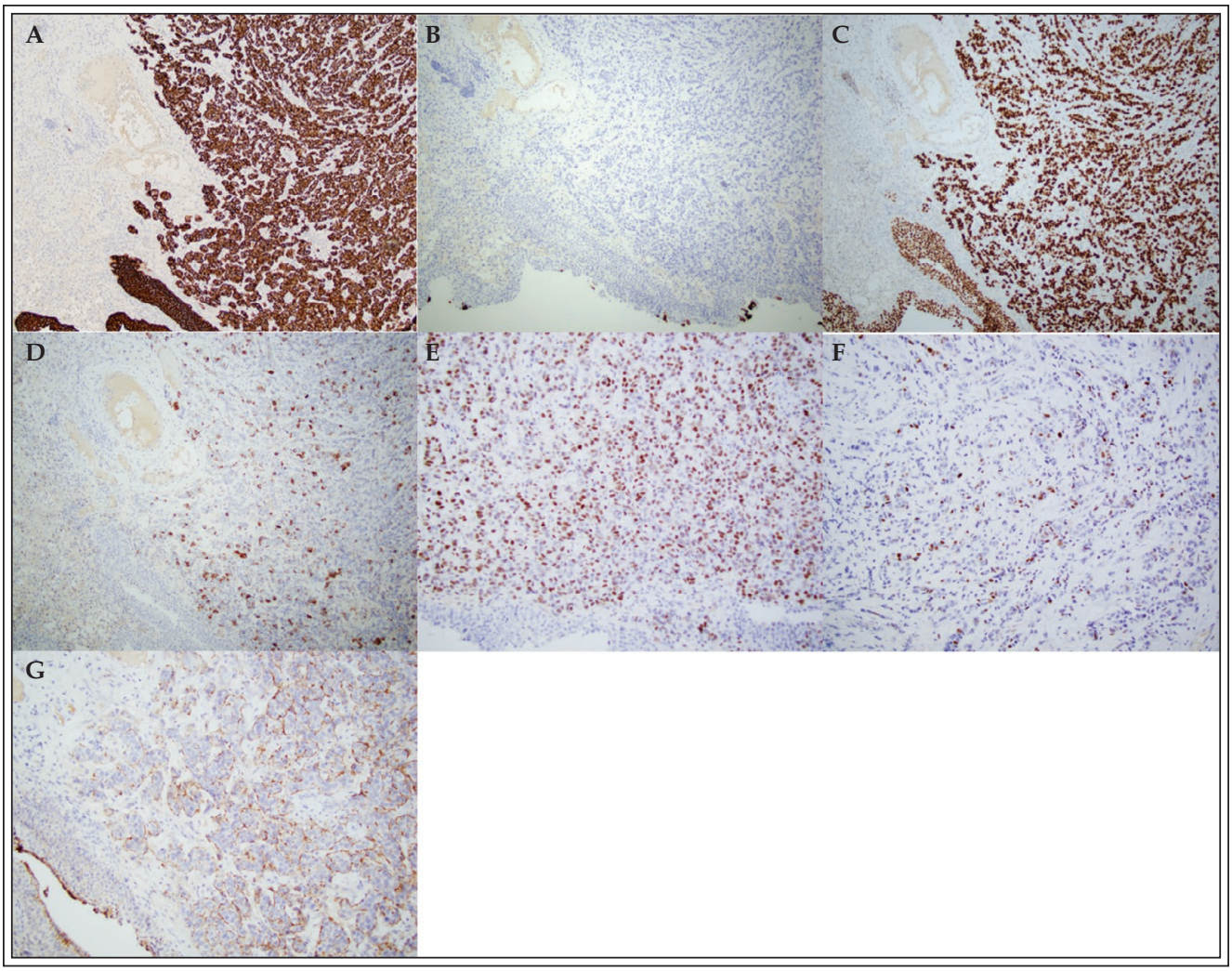

Figure 3. Immunohistochemical panel of bladder biopsy specimen. **A)** CK7 positive, **B)** CK20 negative (note positive umbrella cells in urothelium for internal control), **C)** GATA3 positive, **D)** GCDFP15 positive, **E)** ER positive (70%), **F)** PR positive (5%-10%), **G)** HER2 equivocal (2+). FISH studies were negative for HER2 gene amplification.

case reports to date describing an isolated metastasis to the bladder.[5,6] There are two theorized mechanisms of breast cancer spread to the bladder—implantation of tumor emboli in the serosal surface and direct tumor extension from the retroperitoneum and surrounding structures.[5-7] Both mechanisms suggest an outside-in approach of tumor growth in which the luminal urothelium is the last to be affected by metastatic invasion.

Due to this growth pattern, most UBMs are not identified until full-thickness invasion of the bladder wall. The most common presenting symptoms of UBMs are urinary frequency and hematuria.[2,5-7] Hydronephrosis can also be present on imaging, as seen in our patient, when the UBM involves the ureteral orifice. The outside-in growth of UBMs can pose a diagnostic challenge since irritative voiding symptoms may present due to invasion of the muscularis propria without involvement of the urothelium. Such a case was described by Feldman et al in which contrast urography and cystoscopy failed to reveal any mucosal abnormalities in a patient with hydronephrosis and hematuria, and ultimately a transurethral bladder biopsy performed based on CT findings alone yielded the diagnosis of UBM.

Tissue diagnosis of UBM from breast cancer via immunohistochemistry can also be challenging because many of the common tumor markers used in detecting carcinoma of mammary origin (GATA3, CK7/20, and p63) are also present in urothelial

carcinoma. Estrogen-receptor positivity has been demonstrated in up to 38% of urothelial carcinomas and 57% of non-tumor bladder tissue on metanalysis.[8] Perhaps the most high-yield marker for breast cancer metastasis to the bladder is gross cystic disease fluid protein 15 (GCDFP15) which has a positive predictive value of 98%-99%. The sensitivity of GCDFP15 ranges from 50%-74%, so it is best used in combination with mammaglobin which is a less specific marker, but more sensitive.[9] Hormone receptor and HER2 expression of the primary breast cancer differs from the receptor status of the metastasis in up to 36% of cases described, and patients whose metastases have a newly negative receptor status have been shown to have a poorer prognosis.[10] In our case the HER2 expression on immunohistochemistry came back equivocal and required further analysis via FISH, which ultimately confirmed the UBM as HER2 negative.

In conclusion, the case presented is unique in that the primary breast cancer which metastasized to the bladder was of the inflammatory subtype, a clinical presentation yet to be described in literature. Aside from the relatively aggressive nature of the metastasis, our case shared many characteristics with previously described cases of UBMs from ductal and lobular carcinomas of the breast. Irritative voiding symptoms, hematuria, and hydronephrosis are common but highly non-specific presenting symptoms of UBMs. In women with a history of breast cancer, regardless of how remote, a thorough evaluation including urine cytology and cystoscopy is warranted. In the event of normal-appearing mucosa on cystoscopy it is prudent to perform a thorough analysis of abdominopelvic CT imaging and proceed with imaging-informed biopsy if necessary. Immunohistochemical analysis of the UBM should include markers that are highly specific for breast cancer, such as GCDFP15/mammaglobin, as well as confirmation of hormone receptor and HER2 status. □

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