


Hormone Receptor Positive/HER2 Negative Breast Cancer With Isolated Bladder Metastasis: A Rare Case

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Abstract

Breast cancer is the most common cancer diagnosed in women in North America. Hormone receptor positive (HR+) and HER2 negative (HER2-) breast cancers account for at least 60% to 70% of all breast cancer cases. They usually metastasize to lymph nodes, bones, liver, lungs, and brain. Urinary bladder is a very unusual site for metastatic HR+/HER2- breast cancer and occurs in only 2% of all metastatic disease. In this article, we present a case of a 63-year-old female with locally advanced breast cancer who underwent mastectomy, adjuvant chemotherapy, radiation, and hormonal therapy. She was in remission for almost 17 years and subsequently presented with hematuria and lower abdominal pain. Cystoscopy was performed, which showed evidence of bladder wall thickening. Histopathology showed metastatic HR+/HER2- breast cancer consistent with her history of breast primary. Imaging studies did not show any other evidence of metastatic disease. She was started on cyclin D kinase 4/6 inhibitor, palbociclib, in combination with an aromatase inhibitor, letrozole. This is an exceedingly rare case of HR+ and HER2- breast cancer with metastasis to the urinary bladder. The late onset of recurrence with bladder metastasis makes this case very unique and to our knowledge only few similar cases have been reported in the literature.

Keywords

breast cancer, hormone receptor positive, bladder metastasis

Introduction

Globally, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer deaths in women. In the United States, breast cancer is also the most diagnosed cancer but the second most common cause of cancer deaths in women.¹ Common sites for breast cancer metastasis includes lungs, liver, lymph nodes, bones, and brain parenchyma, whereas metastasis to the thyroid, heart, adrenal gland, spleen, and urinary bladder are relatively uncommon. Secondary bladder cancer is very rare and comprises only 2% of all bladder tumors and most of them are found at autopsy.^{2,3} Direct infiltration from malignancies in the surrounding structures like colon, rectum, prostate, and cervical cancer occur more frequently.⁴ We present here a case of a 63-year-old African American female with locally advanced breast cancer who underwent mastectomy, adjuvant chemotherapy, radiation, and hormonal therapy. She was in remission for almost 17 years and subsequently presented with hematuria and lower abdominal pain. Cystoscopy and biopsy showed breast cancer metastasis to the urinary bladder.

Case History

A 63-year-old African American female was diagnosed with locally advanced invasive ductal carcinoma of the right breast (estrogen receptor-positive [ER+], progesterone receptor-positive [PR+], and HER2-). She underwent neoadjuvant chemotherapy with docetaxel and cyclophosphamide (TC) × 4 cycles followed by bilateral mastectomy. Five out of 8 lymph nodes were positive for metastases. She underwent local radiation and was started on tamoxifen thereafter. Treatment was changed to letrozole once she became postmenopausal. She finished a total 10 years of adjuvant hormonal therapy. She lost to follow-up thereafter

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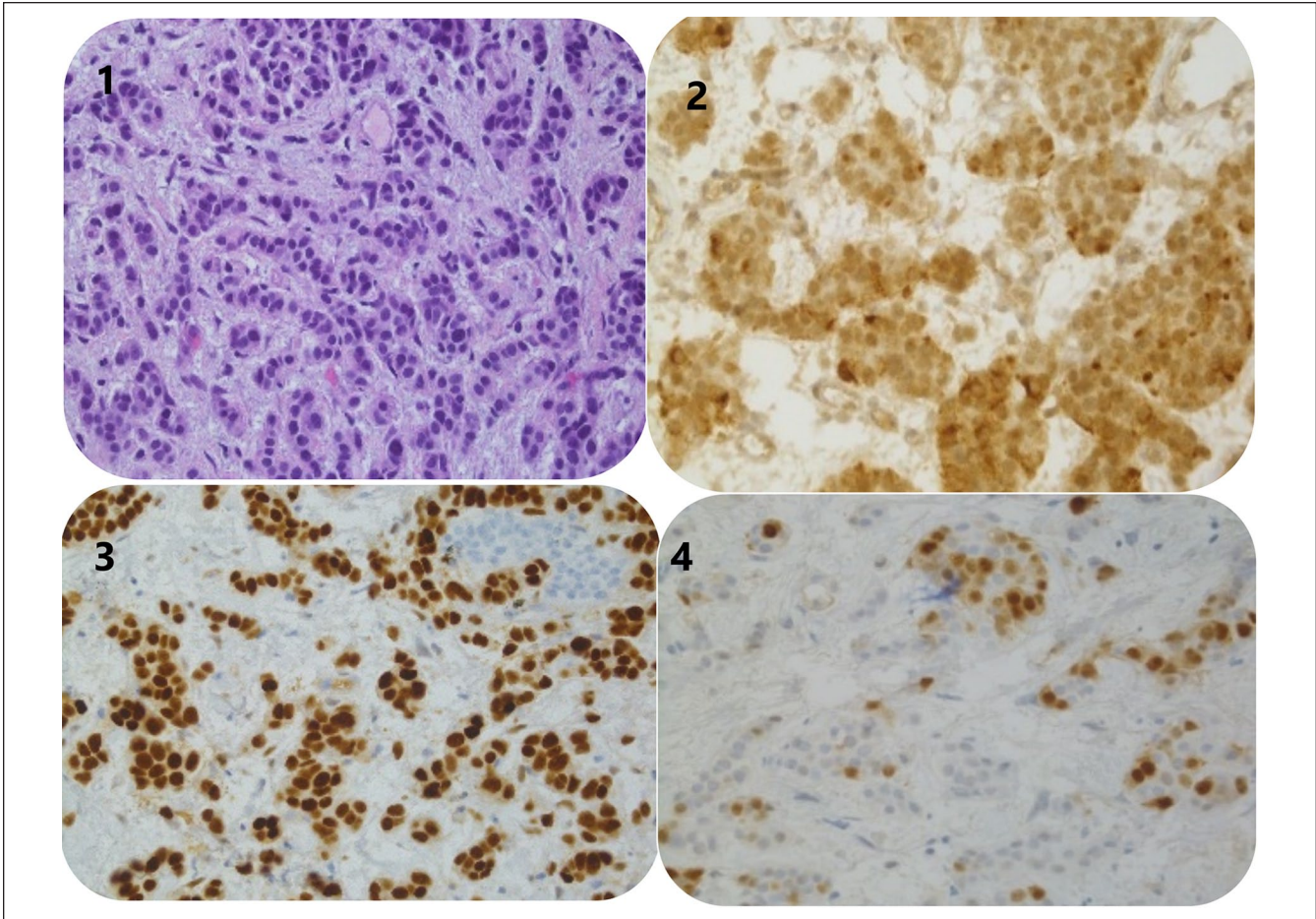


Figure 1. (1) Metastatic carcinoma cells from the breast cells infiltrating urinary bladder (hematoxylin-eosin 400 \times). (2) Gross cystic disease fluid protein-15 immunostaining is positive in the tumor cells, confirming breast cancer. (3) Estrogen receptor shows >90% positivity with strong nuclear staining. (4) Progesterone receptor immunostaining is positive with weak to moderate intensity in about 15% of tumor cell nuclei.

and 17 years after her initial diagnosis of breast cancer presented with lower abdominal pain and gross hematuria. Imaging with computed tomography (CT) scan of the abdomen/pelvis with contrast was performed and showed an enhancing lesion at the anterior aspect of the urinary bladder. She was referred to the urology clinic and cystoscopy was performed which showed thickening of urinary bladder wall and transurethral resection of bladder tumor was performed. Histopathology came back significant for metastatic breast cancer, consistent with her hormone receptor-positive (HR+) primary breast cancer (Figure 1). CT chest with contrast did not show evidence of other sites of metastases. Her laboratory results including complete blood counts and complete metabolic panel were within normal limits. She was started on letrozole and palbociclib. Her tumor markers (Ca 27.29) on the initial diagnosis of recurrence were 362.6 U/mL and decreased to 159.5 U/mL after 6 months of treatment. The hematuria initially resolved. However, follow-up CT scans showed mass-like lesion in the bladder dome, as well as right upper lobe lung nodule and right lobe thyroid nodule.

Repeated cystoscopy showed persistence of breast cancer metastasis. This was complicated by right hydro ureter secondary to ureteral urothelial invasion. She underwent stenting of the right ureter. The patient had several admissions after the second cystoscopy for recurrent hematuria and underwent multiple subsequent cystoscopies. Patient's systemic treatment was intermittently held due to several reasons including noncompliance and multiple hospital admissions due to similar and cardiac-related issues from severe aortic stenosis requiring transcatheter aortic valve replacement. She subsequently developed a left orbital metastasis.

A recent positron emission tomography CT scan showed no other sites of visceral metastases. At the time of this writing, it was planned to start another endocrine therapy with or without targeted therapy.

Discussion

According to the American Cancer Society, breast cancer is the most common type of cancer in American women with

an estimated incidence of 281 550 new cases in 2021.⁵ Metastasis to the urinary bladder is an uncommon location for HR+ breast cancer with an incidence ranging from 1.2% to 7%.⁶ Historically, the first autopsy report with bladder metastasis was published in 1950.³

The duration between initial tumor diagnosis and identification of metastatic disease is highly variable with an average of 6.2 years.^{7,8} Metastases from breast carcinoma can occur even when the primary tumor is <0.125 cm in size, as dissemination of the tumor occurs soon after vascularization of the primary tumor.⁹ Our patient was in remission for 17 years before being diagnosed with isolated urinary bladder metastasis but subsequently progressed to lung and orbital metastases.

Metastasis initially starts with involvement of the outer layer of bladder wall and progresses inward toward the mucosa. Therefore, symptoms of bladder involvement manifest at a later stage when mucosa is involved.¹⁰ Common initial symptoms include flank pain, dysuria, or both. Other symptoms include increased urinary frequency, urgency, or incontinence, as evident in our patient. Only 39% of patients in this review experienced hematuria.⁴ Our patient initially presented with lower abdominal pain and gross hematuria, and subsequent cystoscopy and biopsy revealed urinary bladder metastasis from breast cancer.

The pathophysiology of breast cancer metastasis to urinary bladder remains uncertain for the most part. It is proposed that either venous emboli implantation into the bladder serosa or direct extension from retroperitoneal involvement might be responsible for bladder involvement.⁷

Due to discrepancy in the receptor status of primary breast tumor and bladder metastasis, histology and immunohistochemistry with staining for ER, PR, and HER2 is crucial.^{7,11} An important histological marker, gross cystic disease fluid fibrous protein-15 (GCDFF-15 or BRST-2) is present on breast cancer with apocrine features and is used to differentiate between breast and primary bladder tumors.¹² In our patient, the bladder metastasis tested positive for ER and PR receptors, GCDFF-15, and was negative for HER2.

Initial treatment of HR+ metastatic breast cancer usually starts with hormonal treatment, mainly anti-estrogens. Local resection is mainly reserved for diagnostic purposes and amelioration of local symptoms as it is not curative. ER+ and PR+ tumors are responsive to hormone therapy with longer disease-free survivals than their HR- counterparts.¹³

In patients with previously untreated ER+, HER2- metastatic breast cancer, aromatase inhibitor letrozole in combination with CDK4/6 inhibitor, palbociclib resulted in significantly longer progression-free survival than that with letrozole alone.¹⁴ Similarly, several other combinations of CDK4/6 inhibitor and aromatase inhibitors have been approved in the frontline setting for metastatic HR+ breast cancer.¹⁵

The prognosis of bladder involvement with breast cancer is generally very poor with a mean survival of 2 to 3 years.¹⁶

In general, breast cancer with metastasis to the bladder has poor outcomes than breast cancer with metastasis to bone.¹⁷ Our patient initially responded to letrozole and palbociclib as evidenced by reduction in CA 27.29 tumor marker after 6 months of treatment. However, she subsequently progressed with bladder recurrence and left orbital metastases.

Conclusion

Breast cancer is the leading cause of cancer-related deaths in women worldwide. Metastatic HR+ breast cancer to urinary bladder is exceedingly rare and confers poor outcomes. However, newer agents and targeted therapy may improve outcome. The late onset of bladder metastasis as evident in our patient highlights the crucial role of regular follow-up after definitive treatment of HR+ early-stage breast cancer patients.

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

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