

Case Report

Hematuria in breast cancer: don't forget bladder metastases!

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Summary

The bladder is a rare site for breast cancer metastases, and only occasional reports are present in the literature. Most cases coexist with synchronous metastases elsewhere, but isolated cases of a single metastatic localization in the urinary bladder have been reported. The most common symptoms of a metastatic localization of breast cancer to the urinary bladder are hematuria and voiding dysfunction. Herein we present three cases of urinary bladder metastasis from breast carcinoma, all presenting with gross hematuria as the only symptom. After a review of the relevant literature, we discuss the clinical and histological characteristics unique to our cases, highlighting potential clinical and pathological diagnostic pitfalls and differential diagnoses.

Key words: breast cancer, bladder, hematuria, metastasis, differential diagnosis

Introduction

Breast cancer is the leading cause of cancer morbidity and mortality in women ¹. With 1.7 million new diagnoses and 0.5 million deaths per year, every minute three women are diagnosed with breast cancer and one dies because of it ¹. Metastases, in particular, are responsible for much of the mortality associated with breast cancer ^{2,3}. Despite advances in screening programs and diagnostic techniques, a number of breast cancers are still diagnosed at an advanced stage (III/IV), especially in developing countries ⁴.

The most frequent metastatic sites are the lung, liver and bone, but metastases in numerous other sites have been observed ³. The urinary bladder is a rare site for breast cancer metastases, with only about 65 reports published to date ². However, its frequency ranges from 1% to 7% in large autopsy series ^{5,6}.

Bladder metastases from breast cancer are often encountered in cases of widespread disease ⁷, but they can rarely represent the first site of metastasis. Herein we present three distinct cases of breast cancers which metastasized to the urinary bladder. All our cases presented with isolated hematuria as the only symptom and only histologic evaluation of the trans-urethral biopsy allowed the final diagnosis.

CASE 1

A 70-year-old woman presented to our institution with painless gross hematuria. Her medical history was significant for breast carcinoma resected 15 months prior with negative surgical margins and negative sen-

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tinel lymph node biopsy. The pathological examination revealed a high-grade invasive ductal breast carcinoma with focal expression of neuroendocrine markers (synaptophysin and CD56); estrogen receptor (ER) and progesterone receptor (PgR) were positive, while human epidermal growth factor receptor (HER2) was negative. The final pathologic stage was pT1 G3 pN0. A contrast-enhanced computed tomography highlighted a lesion of the bladder wall, confirmed by cystoscopy (diameter: 1.5 cm). The lesion was resected and submitted for pathological examination. Histological examination of the lesion showed that the bladder wall was diffusely infiltrated by a carcinoma with a solid and glandular pattern (Fig. 1, left). Scattered mitoses (often

atypical), neoplastic emboli and areas suggestive of urothelial in situ carcinoma (CIS) were also evident (Fig. 1, right). The cells were positive for pan-cytokeratin (AE1/AE3), CK 8/18, ER, PgR, chromogranin and focally for synaptophysin, but were negative for CK20, HER2 and p63. Interestingly, ER and PgR were positive in the apparent CIS component, which was in fact pagetoid involvement of overlying transitional urothelium (Fig. 1, right). After 3 months, fine-needle aspiration biopsy (FNAB) of an enlarged supraclavicular lymph node was performed as previously described and revealed a metastasis from breast carcinoma⁸⁻¹¹. The patient died after one year with multiple bone metastases.

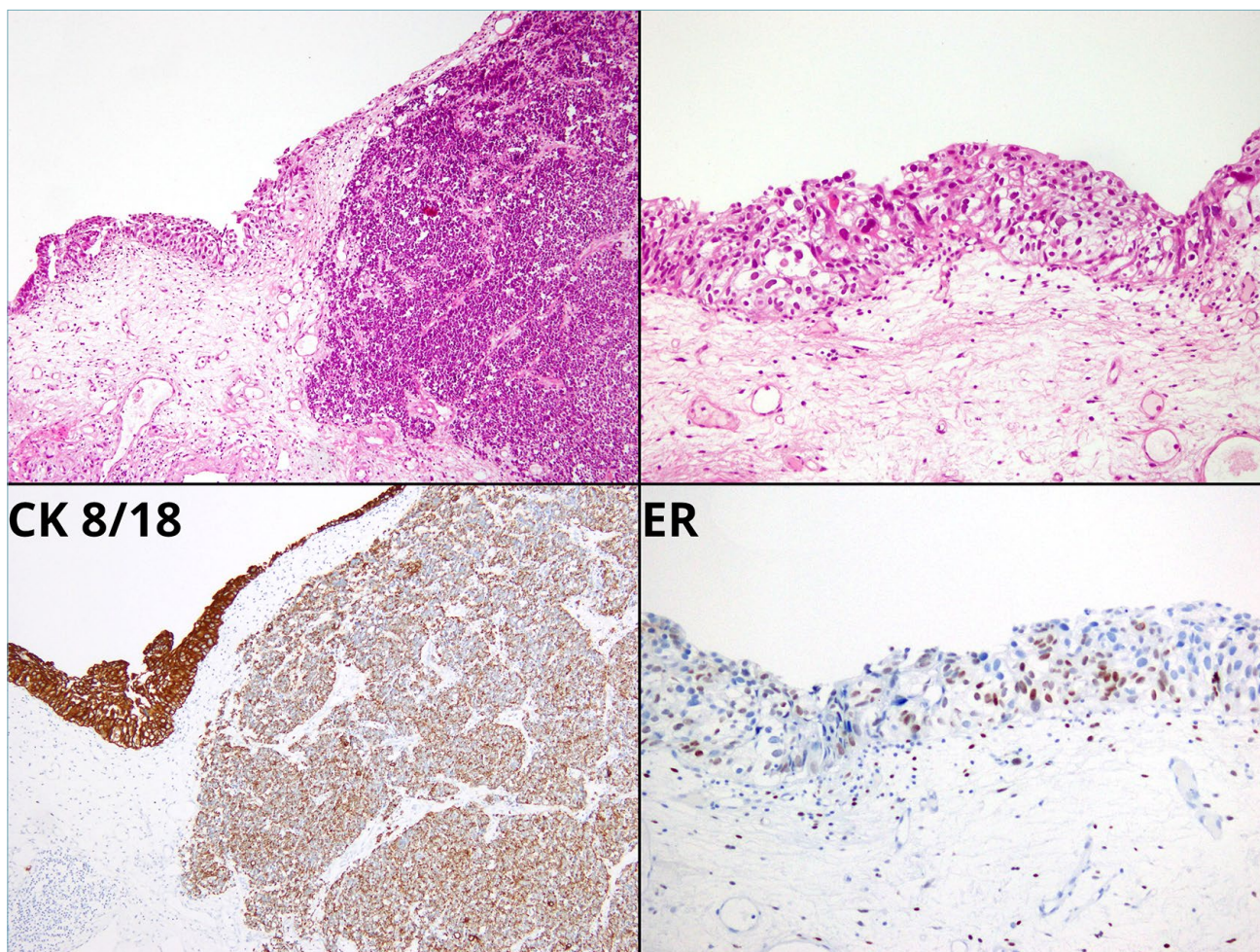


Figure 1. Bladder involvement by metastatic high-grade breast cancer with a neuroendocrine component. Left: the tumor diffusely infiltrated the bladder wall, sometimes reaching as far as the surface and causing ulceration. Residual urothelium is visible on the left. Cytokeratin 8/18 (bottom left) was strongly positive in urothelium and weakly positive in the tumor. Right: pagetoid involvement of urothelium mimicking CIS. Immunohistochemistry for ER shows that the neoplastic cells are ER-positive. Stains: hematoxylin and eosin (top) and peroxidase-diaminobenzidine (bottom); magnifications: 100x (left) and 200x (right).

CASE 2

An 85-year-old woman presented to our institution with painless gross hematuria. Her medical history was significant for a medullary carcinoma of the breast (pT2 G3 pN0) resected 21 months prior (Fig. 2). Immunohistochemically the tumor was negative for ER, PgR, and HER2 (triple negative).

The patient underwent cystoscopy with transurethral resection of the tumor. Histological examination of the lesion showed the presence of a carcinoma with a solid syncytial growth pattern composed of large epithelial cells with moderate to marked nuclear pleomorphism, prominent nucleoli and frequent karyorrhexis (Fig. 2, inset). A large number of mitoses and atypical giant cells were also evident with a diffuse lymphoplasmacytic and histiocytic infiltrate in the stroma. The urothelium showed diffuse squamous metaplasia. The cells were positive for pan-cytokeratin (AE1/AE3) and CK 8/18, but were negative for CK 20, ER, PgR, HER2 and p63. A total-body computerized tomography excluded other sites of metastasis. After four years the patient was alive and free of disease.

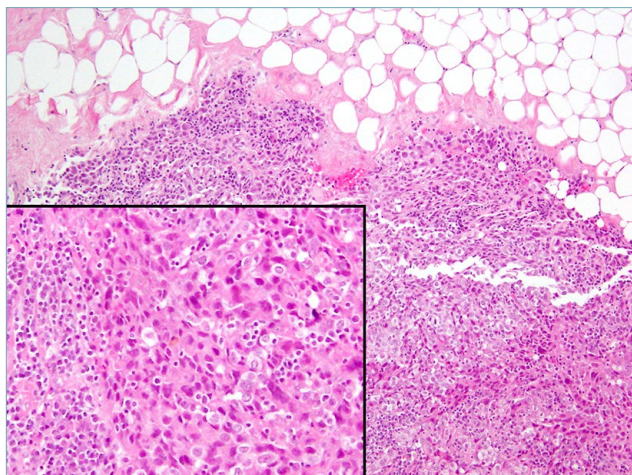


Figure 2. Medullary carcinoma of the breast. The large atypical epithelioid cells show a syncytial growth pattern, prominent nucleoli and frequent karyorrhexis. Inset: corresponding bladder metastasis showing a very similar histologic appearance. Hematoxylin and eosin, 100x (inset: 200x).

CASE 3

A 60-year-old woman presented to our institution with painless gross hematuria. Her medical history was significant for a pT1 N3 lobular breast carcinoma resected 11.5 years prior which had already metastasized to the pleura and stomach.

Trans-urethral bladder biopsy showed bladder mucosa infiltrated by a poorly differentiated single cells. Immunohistochemistry showed positivity for pan-cytokeratin (AE1/AE3), ER (60%), PgR (30%), and negativity for e-cadherin and HER2. The Ki-67 proliferation index was 30%.

Discussion

Metastases to the urinary bladder are rare and can sometimes mimic other more common entities, which makes them exquisitely tricky to diagnose^{12,13}. Even worse, invasive lobular carcinoma of the breast can metastasize to the bladder without forming a discrete mass, requiring a high degree of suspicion and skill to diagnose¹⁴. Because of their rarity, bladder metastases from breast cancer can represent a diagnostic dilemma. The most common presenting symptoms of bladder metastases from breast cancer are hematuria and voiding symptoms, as in our cases. However, most cases present in the context of widespread metastatic disease, while single metastases (as in our first two cases) are exceptional^{14,15}. One of our cases (#3) presented with the bladder metastasis 11.5 years after the diagnosis of the primary tumor. This is not unusual, as metastases after as many as 30 years have been reported².

Due to striking morphological similarity, our first case could have been misdiagnosed as a high-grade urothelial carcinoma with a neuroendocrine component and involvement of adjacent urothelium (CIS)¹⁶. In the differential diagnosis of primary urothelial tumor versus secondary metastatic involvement, involvement of the adjacent urothelium by CIS favors primary urothelial origin¹². However, in our case even this clue harbored a risk of misdiagnosis because the metastatic breast cancer infiltrated the overlying urothelium in a pagetoid fashion mimicking CIS.

In our second case, the differentiation between a primary high-grade urothelial neoplasm and metastatic breast cancer is even harder because the primary breast tumor was triple-negative. In cases like this, the absence of immunoreactivity for markers of urothelial carcinoma and the clinical history are of paramount importance for reaching the correct diagnosis.

In case of suspected breast cancer, a correct diagnosis is based on immunohistochemical confirmation with an appropriate panel including the expression of CK 7, CK 18, CK 19, CK 20, GCDPF-15, and ER/PgR. Urine cytology can help because metastatic cells, especially when the bladder lesion is ulcerated, can be found in urine¹⁷. However, caution should be exercised because cases with a high tumor burden can show metastatic cells in the urine without obvious urinary tract metastases¹⁸.

One interesting thing to note is that in all our cases, the lesions reproduced morphologically and immunohistochemically the primary tumor. Numerous authors report that metastatic breast cancer (to the bladder or elsewhere) can sometimes show a different immunohistochemical phenotype than the primary tumor, especially after hormonal therapy^{2,15}.

Hematuria in a breast cancer patient can be traced back to various causes, including cystitis (which is more frequent after cytotoxic chemotherapy), direct chemotherapy-induced toxicity (e.g. cyclophosphamide), or generic adverse drug reactions. Additionally, other common causes of hematuria like urolithiasis can also be responsible. Finally, one should be sure that the symptom reported as hematuria is indeed of urinary origin and not abnormal uterine bleeding, which would be very concerning in elderly patients or those being treated with tamoxifen.

The treatment of metastatic breast cancer relies on chemotherapy and hormonal therapy. Local resection (metastasectomy) can be performed to improve local symptoms, particularly in case of hematuria. The prognosis of patients with bladder metastases from breast cancer is unfortunately very poor, and most cases of bladder metastases are in fact a manifestation of a disseminated disease^{2,7,15}.

In conclusion, although rare, the possibility of a secondary bladder involvement by a breast cancer should be considered in patients with a history of breast cancer presenting with urinary symptoms. For clinical differential diagnosis, the physician should consider and rule out cystitis, chemotherapy-induced hematuria, urolithiasis and abnormal uterine bleeding. For pathological differential diagnosis, an appropriate immunohistochemical panel is always necessary. The examination of the biopsy by an expert urologic pathologist and a high degree of suspicion are of paramount importance to reach the correct diagnosis.

CONFLICTS OF INTEREST

The Authors declare no conflict of interest.

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None.

ETHICAL CONSIDERATION

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

AUTHORS' CONTRIBUTION

AC: conceptualization, drafting of the manuscript, ed-

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