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## Not everything is as it seems: a rare form of metastatic breast cancer

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### Abstract

Breast cancer is the most prevalent cancer and the leading cause of cancer-related death among females worldwide. Despite all therapeutic advances, metastatic breast cancer is still associated with a median overall survival of 3 years. Alongside this condition, bladder metastases of solid neoplasms are rarely observed. In this setting, the secondary bladder tumors with an origin in breast cancer occur in 2.5% of cases in some series. The authors report the case of a 68-year-old female with stage IV breast cancer (bone metastasis) treated with anastrozole, who presented with peripheral edema and renal failure with a creatinine clearance of 12.5 mL/min. After hospital admission, the patient was diagnosed with new liver lesions and bladder involvement with bilateral hydronephrosis. She was submitted to bilateral percutaneous nephrostomies with improvement in renal function. There was a high suspicion of primary bladder tumor in this patient who was a previous smoker, with a family history of high-grade bladder carcinoma (her mother). Liver and transurethral biopsies were performed, and histological examination was consistent with breast cancer metastases. The patient started treatment with capecitabine and denosumab, remaining clinically stable after 3 months of treatment. This case report underlines the diagnostic challenges of bladder metastases in a patient with multiple risk factors for bladder cancer and without evident clinical symptoms. Even though this is a rare entity, the close surveillance of metastatic breast cancer is important in order to allow early detection of new metastatic sites and their treatment to preserve the quality of life in these patients.

**Keywords:** Breast Neoplasms; Hydronephrosis; Urinary Bladder Neoplasms

### INTRODUCTION

In 2018, worldwide, breast cancer presented an estimated age-standardized incidence and mortality of 46.3 and 13.0 per 100,000 inhabitants, respectively.<sup>1</sup> Breast cancer is the most prevalent cancer and the leading cause of cancer-related death in females across the globe. Despite all the recent therapeutic advances, metastatic breast cancer is still associated with poor prognosis with a median overall survival of 3 years, and a 5-year survival rate of approximately 25%.<sup>2</sup> Metastatic disease at the time of the initial diagnosis is not common in breast cancer, with an estimated prevalence of 6%.<sup>3</sup> The different breast

cancer subtypes have been associated with different patterns of metastatic disease. The most frequent locations of breast cancer metastatic disease are the bone, liver, and lung.<sup>4,5</sup> In this clinical case, we present a rare form of presentation of metastatic breast cancer.

### CASE REPORT

A 68-year-old female patient sought the emergency room complaining of a 4-day history of back pain radiating to the flank, which she associated

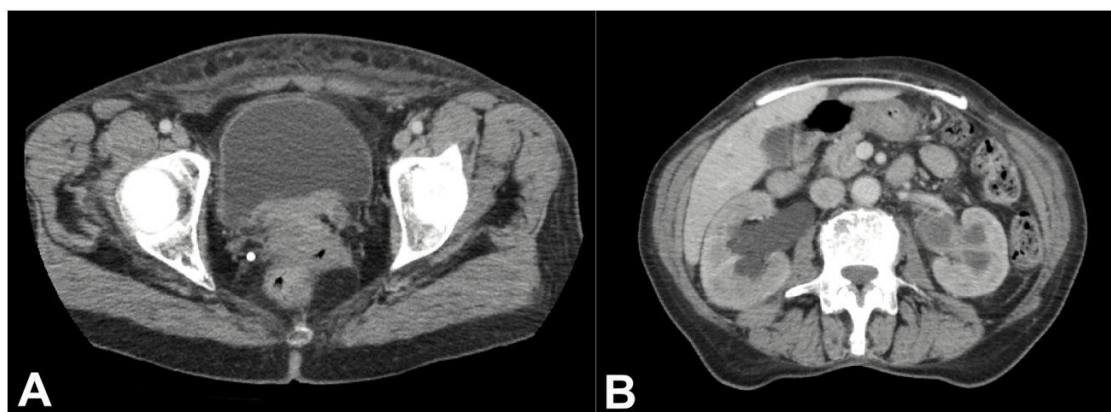
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with physical effort. Her past medical history included the diagnosis of rheumatoid arthritis, congestive heart failure with preserved ventricular function, and smoking (40 pack/years). She had undergone a mammogram every 2 years integrated into the national breast cancer screening scheme. Her living brother was diagnosed with Hodgkin lymphoma, and her mother, who had high-grade bladder urothelial carcinoma, had died at the age of 86. The diagnostic work-up included a spine computed tomography (CT) scan that showed diffuse morphologic and structural changes involving the posterior bodies and arches of the sacroiliac vertebrae with lytic lesions and discrete cortical erosions consistent with metastases. The thoracic, abdominal, and pelvic CT scan showed pleural effusion plus cervical and axillary adenopathy. The pleural effusion was consistent with transudate by biochemical analysis. The histological examination of the biopsied cervical lymph node was consistent with metastasis of breast cancer with positivity for CK7, CK19, CK20, E-cadherin, and estrogen receptors, but negativity for progesterone receptors and c-ErbB2. The ultrasound and mammography failed to show the primary breast cancer lesion. The patient was started on anastrozole and denosumab, and the disease remained stable for 17 months. By that time, she had started presenting peripheral edema and asthenia, but no concomitant urinary complaints such as dysuria, hematuria, or decreased urinary output. The analytic evaluation showed renal failure with creatinine clearance of 12.5 mL/min, hypocalcemia, and elevation of the tumoral marker Ca15.3 of 93 U/mL (previously 61 U/mL; reference range <30 U/mL). The physical

examination was normal except for the presence of lower limbs edema without other significant changes. The urinary tract ultrasound showed a vesical mass with 5 × 1.5cm and signs of invasion of both orifices of the ureters with consequent bilateral hydronephrosis. She was submitted to bilateral percutaneous nephrostomies with improvement in the renal function. The pelvic CT scan revealed a 5 cm lesion in the bladder floor (making it difficult to establish a cleavage plane with the vaginal dome), and multiple hepatic nodules consistent with metastases (Figure 1).

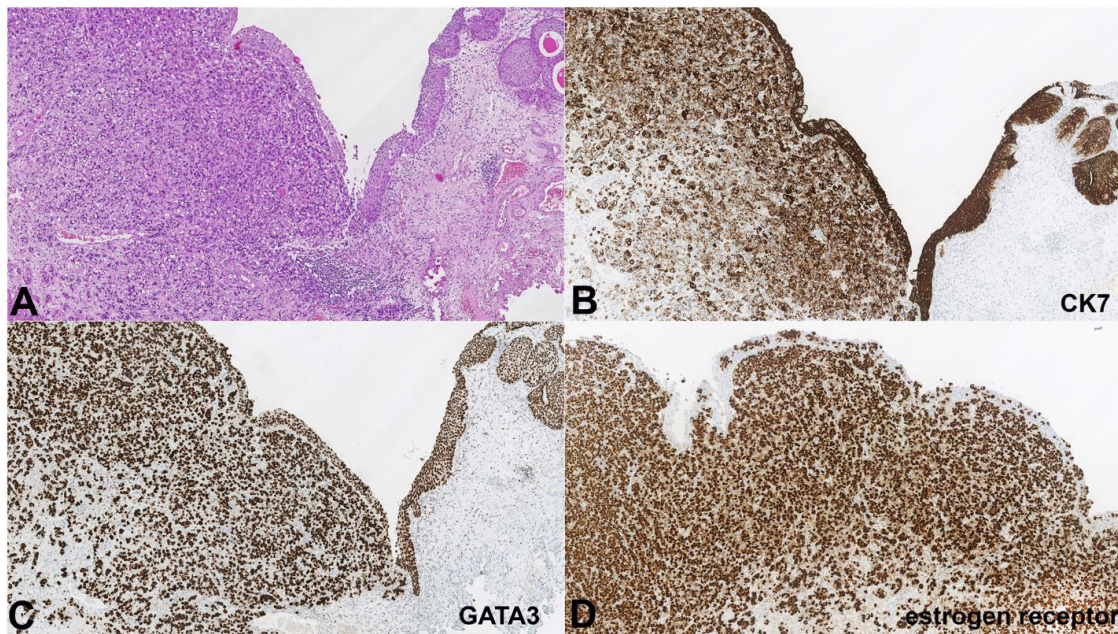
Due to the suspicion of bladder urothelial carcinoma, a liver biopsy and transurethral resection (RTU-V) of the bladder lesion were performed. During the RTU-V, both orifices of the ureters were not found due to the tumor invasion, and the lesion was partially resected. Histologic analysis of the liver biopsy was consistent with breast cancer metastasis with diffuse marking to CK7, estrogen, and progesterone receptors; and negative for CK20, CDX-2, TTF-1, c-ErbB2, and uroplakin III. Histologic analysis of the bladder biopsy showed tissue with the representation of mucosa, submucosa, and muscular tunica with neoplastic infiltration. The immunohistochemical study was characterized by the diffuse expression for CK7, estrogen receptors, and GATA3; and negative for CK20, p40 and uroplakin III, consistent with metastatic involvement of primary breast cancer (Figures 2 and 3).

The patient started treatment with capecitabine and denosumab, and remains clinically stable after 3 months of treatment with a decrease of the tumoral marker Ca15.3 to 72 (previously 93).

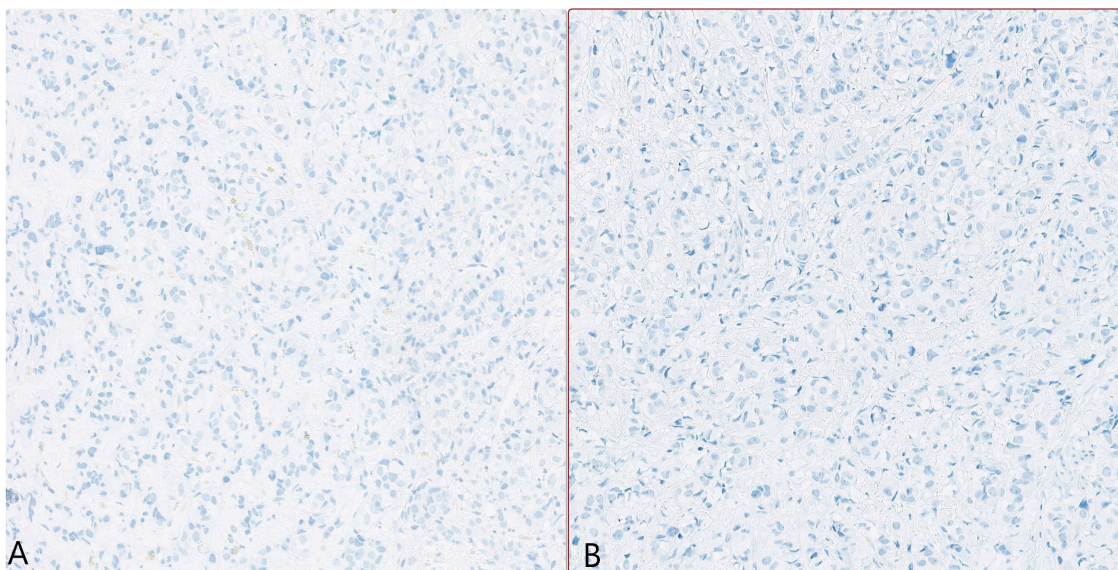


**Figure 1.** Computed tomography scan. **A** – Infiltrative lesion of the bladder floor, making it difficult to establish a cleavage plane with the vaginal dome, and infiltrating both orifices of the ureters. **B** – Bilateral hydronephrosis.





**Figure 2.** Photomicrographs of the biopsy specimen. **A** – Preserved urothelial mucosa (on the right) and mucosa involved by the neoplasm (on the left), with extensive involvement of the chorion by sheets or small nests of bulky neoplastic cells (H&E, 10X). **B** – Intense and diffuse expression of cytokeratin 7 by the neoplastic cell population on the left (10X). **C** – Intense and diffuse expression of GATA3 by the neoplastic cell population on the left (10X). **D** – Intense and diffuse expression of the estrogen receptors by the neoplastic cell population, and the absence of the ER expression by the residual surface urothelium (10X).



**Figure 3.** Immunohistochemical photomicrographs of negative staining for uroplakin III in a collection of neoplastic cells. **A** – Liver biopsy. **B** – Bladder biopsy.

## DISCUSSION

Occult breast cancer is extremely rare, accounting for 0.2% to 0.9% of all breast cancer cases.<sup>6,7</sup> It presents without a detectable primary cancer lesion whether on

a physical examination or an imaging examination such as ultrasound and mammograph. The initial symptoms of this entity include axillary lymph node metastasis, distant metastasis, nipple discharge, nipple dermatitis, papillary dermal edema, eczema, and skin retraction.<sup>8</sup>

The low incidence of occult breast cancer poses a diagnostic and therapeutic challenge even with the increasing availability of investigative techniques, such as mammography, ultrasound, and magnetic resonance imaging (MRI).<sup>9,10</sup> MRI and mammography can be used to detect non-occult breast cancer, but they are not sensitive for the diagnosis of occult breast cancer cases.<sup>11</sup> However, immunohistochemical staining of tumor tissue using breast-cancer-specific glycoprotein monoclonal antibodies is widely used for the diagnostic and prognostic evaluation of breast cancer.<sup>12</sup>

Particularly in this case, immunohistochemistry of the cervical lymph node biopsy pointed to breast origin, except for the expression of CK20, which may be an error. However, the lymph node biopsy could not be re-evaluated because it was processed in another laboratory.

Bladder secondary tumors from solid cancer are a rare entity. The retrospective study of Bates and Baithun<sup>13</sup> revealed that secondary tumors comprised 2.3% of surgical and 20% of postmortem cases in a series comprising 6,289 bladder tumors with the estimated prevalence of bladder secondary tumors of 4.5%. Most of the cases of bladder secondary tumors had their origin in adjacent organs as a direct invasion. The most common primary sites are the female genital tract, the prostate, and the lower gastrointestinal tract. Lymphatic or hematogenous metastatic spread to the bladder from distant primary tumors does occur but is much less common. In this setting, primary tumors of the stomach, skin, and lung are the most common places of origin of these distant metastases.<sup>13</sup> A recent systematic review conducted by Sanguedolce et al.<sup>14</sup> reported 54 cases of breast cancer with bladder metastasis. A retrospective study with 282 cases of secondary solid bladder tumors showed a prevalence of 2.5% of breast cancer metastasis.<sup>13</sup> Also, the analyses by Abrams et al.<sup>15</sup> found the incidence of 3.6% of secondary tumors of the bladder in a series of 1,000 autopsies of malignant epithelial neoplasms, and 4 cases (2.4%) of secondary bladder involvement with the origin in breast carcinoma. On the other hand, a study comprising 43 autopsies on patients with primary carcinoma of the breast did not find any case of bladder involvement.<sup>16</sup>

The metastatic involvement of the bladder may present a broad spectrum of symptoms; namely dysuria, urgency, lower abdominal or flank pain, and

gross or microscopic haematuria.<sup>17,18</sup> Less frequently, patients may be asymptomatic. The acute renal failure due to ureteral obstruction with hydronephrosis is a rare complication due to metastatic breast cancer.<sup>19,20</sup> Winston et al.<sup>21</sup> conducted a retrospective review of 57 CT scans of patients with metastatic lobular breast cancer and identified 6 patients (11%) with hydronephrosis as a complication caused by infiltration of the retroperitoneum.

In this specific case, the patient presented with peripheral edema and asthenia, secondary to renal failure due to hydronephrosis caused by a vesical mass. Further study showed hepatic nodules as well. Both the vesical mass and a hepatic nodule were biopsied, and both biopsies were consistent with the diagnosis of breast cancer metastasis, as was evident in the immunohistochemical analysis: CK7, estrogen, and progesterone receptors; and negative for CK20, CDX-2, TTF-1, c-ErbB2, and uroplakin III for the hepatic biopsy and diffuse expression for CK7, estrogen receptors, and GATA3; and negative for CK20, p40, and uroplakin III for the vesical biopsy. The absence of simultaneous staining for CK7 and CK20, which is typical in 65% cases of urothelial carcinomas, positive staining for estrogen receptors and negative staining for uroplakin III confirmed the diagnosis of liver and bladder metastasis of breast cancer.

The treatment of metastatic breast cancer may comprise a combination of chemotherapy and hormonal treatment depending on the intrinsic characteristics of the tumor and its clinical features. The transurethral resection of the lesion may improve symptomatology and allow catheterization of the ureters. However, in some cases, percutaneous nephrostomy is needed, as it was in our case report. Radiotherapy has its role as a hemostatic measure and as a local disease control.

The patients with bladder metastases usually have other metastatic sites and tend to have a poor prognosis.<sup>22</sup>

Our case exemplifies a rare form of metastatic breast cancer. The presence of risk factors, such as smoking tobacco, a family history of bladder cancer along with a failure of imaging study, and a lack of clinical symptoms, challenged the diagnosis of our case. It is essential for clinicians to be aware of urinary symptoms in breast cancer patients, as well as the early recognition of disease progression, and the necessity of rapid institution of measures to preserve the quality of life in these patients.



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