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<th><strong>Title</strong></th>
<th>Metastatic carcinoma of breast in the urinary bladder</th>
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<td><strong>Author(s)</strong></td>
<td>Wong, MH; Yiu, MK; Ho, KL</td>
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Introduction

Carcinoma of the breast is the commonest malignancy in Hong Kong women, and in 2009 it was ranked third as a cause of cancer mortality. The life-time risk for Hong Kong women is 1 in 19 and risk of consequential death 1 in 101. Evidently, 5% of the cases present as metastatic disease, common sites being lymph nodes, lung, liver, and bone. Metastases to other solid organs such as the urinary bladder are uncommon but have been reported sporadically. Patients with urinary bladder metastasis have very limited survival (about 1 month to 2 years). We present the first reported case of carcinoma of breast with metastasis to urinary bladder in Hong Kong, with a structured review of this entity.

Case report

An 83-year-old woman, with a history of left breast cancer and modified radical mastectomy performed more than 30 years earlier, presented in 2006 with a skin nodule on right chest wall. Biopsy of the right chest wall nodule showed metastatic adenocarcinoma which was oestrogen receptor (ER) positive, progesterone receptor (PR) positive, and c-ERBB2 negative. Metastatic workup revealed diffuse metastases to right chest wall, left breast, left axillary lymph node, bone, adrenal gland, and peritoneal deposit. She received serial hormonal therapy including letrozole and exemestane together with radiotherapy to bony metastasis. Follow-up imaging with positron emission tomography–computed tomography (PET-CT) showed stabilisation of disease and fine-needle aspiration cytology of the left breast lesion only showed mild epithelial hyperplasia. Five years after the diagnosis of metastases, she presented with anaemic symptoms and volunteered a 2-week history of gross haematuria. The CT revealed a contrast-enhancing mass arising from left lateral wall of the urinary bladder. Flexible cystoscopy showed a 25 mm x 25 mm erythematous patch on the left lateral wall with an irregular surface (Fig), which was biopsied with haemostasis achieved by cautery. Histology revealed irregular, solid nests and trabeculae of round-to-polygonal tumour cells. Rare glandular lumens lined by cells possessing a moderate amount of eosinophilic cytoplasm were also noted. On immunohistochemical staining, the tumour cells were positive for CK-7, and negative for CK-20 and GCDFP (gross cystic disease fluid protein). Moreover, ER and PR stains were avidly taken up while the C-ERBB2 score was 2 (ie equivocal). Haemostasis was achieved with electrocautery and no further haematuria was observed. The latest PET-CT showed an interval increase in metabolic activity in most of the metastases, including that in the urinary bladder. The patient continues to receive chemotherapy and hormonal therapy and is currentlyalive more than 6 years since the diagnosis of metastasis.

Discussion

Urinary bladder secondaries are rare and account for 2% of all bladder neoplasms; most are discovered at autopsy. Known primaries include gastric cancer, melanoma, as well as breast and lung cancer. In a recent clinicopathological study of 11 patients with metastatic lesions in the urinary bladder, most were in women and frequently breast cancer (3/11). Breast cancer commonly metastasises to lymph nodes, lung, liver and bone, whilst it rarely involves the brain, adrenals, spleen, thyroid, heart, or urinary bladder. In 1980, Haid et al reported a patient with urinary bladder metastases from breast carcinoma, although...
autopsy reports date back to 1956. To date, there have been at least 40 reported cases of metastatic breast cancer to the bladder.

One postulated mechanism of secondary bladder tumours is from emboli that traverse the pulmonary circulation without causing lung metastasis, but do so upon reaching the urinary bladder haematogenously. Other possible mechanisms are through lymphatic or direct retroperitoneal invasion.

The most common presenting symptom was urinary frequency and gross haematuria. Other presentations include difficulty in voiding, incidental finding on imaging, and/or ureteral obstruction or even urinary incontinence. Less-common findings include pelvic mass and bilateral hydronephrosis, and renal failure. Patients can present concomitantly with the primary tumour, or as a late metastasis, with time lapses exceeding 30 years. Our case demonstrates one of the longest time lapses between treatment of the primary tumour and presentation with a metastasis (more than 30 years). Rarely the diagnosis of breast cancer is made after bladder metastasis is discovered. As in our patient, most cases will have widespread metastases. However, a solitary metastasis to the urinary bladder has also been reported.

Diagnostic workup requires direct visualisation of the bladder mucosa by cystoscopy, and histological confirmation of a specimen obtained by means of cup biopsy or transurethral resection. Cystoscopic findings vary and include solid tumour, non-specific inflammatory patches, and thickened bladder wall with intact overlying mucosa (Fig). Upper urinary tract imaging is indicated when there is evidence of renal impairment suggesting obstructive nephropathy. Screening by means of magnetic resonance imaging or PET-CT may reveal other metastases.

Although ductal breast carcinoma is more common than the lobular subtype, infiltrating lobular carcinoma accounts for the majority of metastases to the bladder. The latter tends to occur as a diffuse thickening of mucosa rather than a discrete nodule. To differentiate histological variants of primary bladder tumour from secondaries, absence of bladder mucosa alterations/lesions can be helpful. There may also be unusual monomorphic growth patterns without accompanying conventional urothelial carcinoma features, and the tumour can appear to invade towards the luminal surface from the outside.

Additional means of avoiding diagnostic confusion is the utilisation of immunohistochemical staining for various markers. Common screening markers include cytokeratin, CK-7, CK-18, CK-19, CK-20, as well as ER/PR expression for tumours of suspected endometrial and breast origin. Other typical urothelial markers include p63, Ker903, thrombomodulin, GATA3, and CKs5/6. Other markers to screen for cancers include prostate-specific antigen for prostate, thyroglobulin for thyroid, uroplakin III for urothelium, and HepPar 1 for hepatocellular origin.

Treatment of metastatic breast cancer involves a combination of chemotherapy and hormonal treatment, mainly anti-oestrogens. Local resection is mainly reserved for diagnostic purposes and amelioration of local symptoms. It is not curative, as the deposit is muscular rather than mucosal, and ER- and PR-positive tumours are more responsive to hormone therapy than their negative counterparts that have longer disease-free survivals. However, not uncommonly the ER/PR status of the metastatic lesion differs from that of the original tumour, and one study reported that the discordance rate was as high as 24%. Patients whose tumour status changed from positive to negative (positive/negative) have...
shorter median survivals than positive/positive or negative/negative patients.\textsuperscript{13} In our case the original ER/PR status was unknown as the primary treatment was performed more than 30 years ago. Also, HER2-positive breast cancer tends to be more aggressive and less responsive to hormone treatment than other breast cancers. In cases of obstructive uropathy, percutaneous drainage via ureteric catheterization should be performed to optimise renal function before initiation of chemotherapy. In terms of survival, there are reports of survival for more than 5 years after diagnosis of bladder metastasis, but most patients die within 1 year.\textsuperscript{5} Our case is currently alive and receiving further hormonal manipulation.

The urinary bladder is an uncommon site of metastasis from breast cancer. Although routine screening of the lower urinary tract is not warranted for all patients, women with a history of breast cancer who present with urinary symptoms should be investigated to exclude such a bladder lesion. However, if the presence of a metastasis is confirmed, early initiation of appropriate treatment is warranted.

References

1. Hong Kong Cancer Registry. Hospital Authority; 2009.