CASE REPORT

Breast cancer metastasis to the bladder: a literature review

Adam M Kase,¹ David Menke,² Winston Tan^{3,4}¹Department of Internal Medicine, Mayo Clinic's Campus in Florida, Jacksonville, Florida, USA²Department of Pathology, Mayo Clinic's Campus in Florida, Jacksonville, Florida, USA³Department of Hematology, Mayo Clinic's Campus in Florida, Jacksonville, Florida, USA⁴Department of Oncology, Mayo Clinic's Campus in Florida, Jacksonville, Florida, USA**Correspondence to**
Dr Adam M Kase,
kase.adam@mayo.edu

Accepted 16 June 2018

SUMMARY

Given the prevalence of breast cancer and the mortality associated with metastatic disease, it is imperative for physicians to not only be aware of common sites but also of rare metastatic destinations such as the bladder. A postmenopausal woman with a medical history of stage 2 invasive ductal carcinoma, oestrogen receptor/progesterone receptor positive and human epidermal growth factor receptor 2 negative, in remission for 9 years, presented to her primary care physician with concerns of increased urinary urgency, frequency and incontinence. The patient underwent cystoscopy with biopsy of an area of granulation tissue. Biopsy revealed adenocarcinoma consistent with breast primary. The common sites of metastases from breast cancer are lung, bone and liver. This case is unique where breast cancer was found to metastasise to the bladder. It is important for physicians to consider further investigation when a breast cancer survivor develops urinary symptoms even without haematuria.

BACKGROUND

In the USA, 12% of women will develop invasive breast cancer over their lifetime and almost 90% of all females diagnosed with breast cancer will still be alive after 5 years.¹ This leads to a substantial number of breast cancer survivors who are at risk for recurrence. The most common sites of breast cancer metastases are bone, lung, liver and brain. Very few cases have been reported in the literature of metastatic breast cancer presenting with urinary symptoms. A literature review was performed which revealed under 50 cases reported of breast cancer metastasising to the urinary bladder. Here we report our own case and analysis of reviewed literature.

CASE PRESENTATION

A postmenopausal woman with a medical history of stage 3 invasive ductal carcinoma, oestrogen receptor (ER)/progesterone receptor (PR) positive and human epidermal growth factor receptor 2 (HER2) negative, was presented. In 2004, she had a right-modified radical mastectomy and elective left mastectomy for her multifocal right infiltrating ductal carcinoma; stage 3a, T1c, N2a and M0. She only completed five cycles of 5-fluorouracil, epirubicin and cyclophosphamide along with radiation due to toxicity and febrile neutropenia requiring hospitalisation. She was in remission for 87 months when she presented to her primary care

physician with urinary concerns. In February 2012, the patient experienced an increase in urinary urgency, frequency and incontinence over the past few months and denied haematuria or dysuria. Urinalysis and cytology were ordered and were completely negative. At that time, she was referred to urogynaecology who prescribed physical therapy as patient requested the least invasive therapy available. After her appointment, she did not pursue physical therapy and her symptoms of urinary incontinence worsened over a 6-month period. In November 2012, she returned to urogynaecology who performed a cystoscopy which revealed several areas of granulation tissue prompting biopsy. CT scans were also performed which revealed diffuse bladder wall thickening most notably on the left and posterior walls (figure 1), and bone metastasis (T8 and T12 vertebral bodies and right frontal calvarium) were present without evidence of lung or liver metastasis. *Biopsy of the bladder:* pathology results showed metastatic adenocarcinoma consistent with a breast primary infiltrating the bladder submucosa. Focal tumour cells showed targetoid mucin. Immunostains were positive for gross cystic disease fluid fibrous protein-15 (GCDFFP-15, also known as BRST-2) and ER (figure 2) and negative for PR. HER2 stains were 1+. The patient was started on fulvestrant for her metastatic disease. After 2–3 months of treatment, her urinary symptoms completely resolved and her bone metastases were stable for approximately 2.5 years. Her disease progressed after nearly 3 years of treatment with fulvestrant with new metastases at T5 and T10 transverse processes and extension to the rectosigmoid and anorectal regions. Fulvestrant was discontinued and paclitaxel was initiated. Unfortunately, the patient had a cerebral vascular accident, further progression of disease and neuropathy which led to the discontinuation of paclitaxel. In December 2015, she began palbociclib, but only tolerated for 2 months. The patient decided to discontinue all chemotherapy and pursue hospice care in July 2016. The patient passed away in October 2016 secondary to pulmonary haemorrhage.

DISCUSSION

For the year of 2016, it was estimated that 246 660 new cases of invasive breast cancer will be diagnosed in women and there are 2.8 million breast cancer survivors in the USA.² The most common sites of breast cancer metastases are bone, lung, liver and brain. Breast cancer is the primary source of metastases to the bladder in approximately 8.5%

To cite: Kase AM, Menke D, Tan W. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-222031

Figure 1 CT scan showing diffuse bladder wall thickening most notably on the left and posterior wall.

of cases.³ The most common primary tumours metastasising to the bladder are colon, prostate, rectum and cervix.⁴ A literature review was completed for documented cases of breast cancer that metastasised to the bladder. The literature search was completed using PubMed from 1956 through 2016 and 46 cases were documented, not including our case presented here.

Based on this literature review, patients with metastatic breast cancer to the bladder experience a wide range of symptoms (table 1).^{5–37} Only 21% of patients reported either (or both) flank pain or dysuria. A large number of patients experienced changes in voiding (44.7%). The voiding changes included a combination of increased urinary frequency, urgency or incontinence, as seen in our patient. Only 39% of patients in this review experienced haematuria. All patients, regardless of cancer history, with complicated urinary incontinence should be considered for cystoscopy, upper tract imaging or urodynamics.³⁸ Complicated urinary incontinence is classified by recurrent urinary incontinence or associated with pain, haematuria, recurrent urinary

Table 1 Percentage of patients with the following presenting symptoms at the time of diagnosis of metastatic disease

Symptoms	Percentage
Changes in voiding	44.7
Haematuria	39
Dysuria or flank pain	21

tract infection or voiding symptoms. Additional modalities for characterising bladder involvement include CT scans which will show thickened bladder wall, as demonstrated in this review of 15 of the 21 cases and other findings including hydroureteronephrosis. During cystoscopy, 19 of the 32 cases (59%) revealed a defined tumour or nodular area. The remaining cases showed areas of inflamed mucosa or areas of granulation tissue, as seen in our patient. With clinical suspicion for bladder cancer, cystoscopy is mandatory for tissue sampling and confirmation of diagnosis.

Cancers of unknown primary origin offer challenges to the investigator and a clear pathological diagnosis is achieved in only 30% of cases, of which, breast cancer is the primary origin 4% of the time.³⁹ Immunohistochemistry is valuable in defining the tumour lineage. The usual markers for breast cancer include GATA binding protein 3 (GATA3) (82%), ERs (80%), PRs (65%), BRST-2 (50%) and mammaglobin (50%). However, it is well known that primary bladder cancers can also express ERs and GATA3. ER beta and GATA3 is found in the urothelium in up to 77% and 78% of bladder cancer cases, respectively.³⁹ ERs are important in cellular growth and differentiation in the mammary glands and tumorigenesis in bladder cancer. In this literature review, where the original breast cancer ER status was reported, 12 of the 17 (71%) cases were oestrogen positive before metastases. The bladder tumour biopsy was oestrogen positive in 16 of the 18 cases (89%). The best approach to differentiate breast versus bladder primary is to test the tissue for gross cystic disease fluid fibrous protein-15 (GCDFF-15, also known as BRST-2). This antigen is expressed by breast carcinomas with apocrine features. The receptor status of breast cancer is known to transform. In our review, 5 of the 12 (42%) cases had concordant ER/PR status where both statuses were reported for the breast tumour and bladder metastasis. A change from positive ER status to negative status is associated with significant shorter median survival.⁴⁰ Knowing the receptor status of the tumour is necessary in developing a treatment plan.

For patients who are receptor positive, hormone therapy with selective ER modulators, aromatase inhibitors or HER2-directed therapy can be initiated for patients with metastatic breast cancer. Endocrine therapy can range from ER modulators to aromatase inhibitors. In our patient, fulvestrant was initiated without transurethral resection of bladder tumour since isolated tumours were not available for resection. Our patient had 32 months of progression-free survival and lived for 47 months after metastatic disease was diagnosed. Of the 28 patients where length of survival was known, 53.6% had a 1-year survival, 10.7% had a 3-year survival and 3.6% had a

Figure 2 Urinary bladder biopsy revealing metastatic adenocarcinoma consistent with breast primary infiltrating the submucosa, (A) H&E staining (600 $\times$). (B) Cytokeratin staining (100 $\times$). (C) BRST-2 positive staining (100 $\times$). (D) H&E staining (100 $\times$).

Table 2 Survival comparison for breast cancer metastasising to bladder and bone

	1-year survival (%)	3-year survival (%)	5-year survival (%)
Bladder metastasis (n=28)	53.6	10.7	3.6
Bone metastasis (n=2427)	52	26.4	13

Table 3 Median time from breast cancer diagnosis to metastasis

	Median time (months)
Bladder metastasis (n=35)	81.1
Bone metastasis (n=2427)	22.2

5-year survival. The 1-year survival, 3-year survival and 5-year survival of patients with breast cancer bone metastases is 52%, 26.4% and 13%, respectively (table 2).⁴¹ This may suggest that bladder metastasis from a breast primary has a worse prognosis than bone metastasis. However, may also be a surrogate of widespread disease leading to worse outcomes. In this review, the median time from breast cancer diagnosis to diagnosis of bladder metastasis is 81.1 months (ranging anywhere from 0 to 264 months), compared with the diagnosis of bone metastasis with a median time of 1.85 years or 22.2 months (table 3).⁴¹ This suggests that bladder metastases present or occur late, possibly secondary to the overlooked symptoms of metastatic disease to the bladder.

In conclusion, our case is an unusual presentation of metastatic breast cancer, notable with regard to the length of response to hormone therapy. This literature review reveals the level of difficulty that is present in diagnosing metastatic breast cancer to the bladder, not only because of the ubiquitous symptoms that develop but also because of the similarities between primary bladder cancer and metastatic breast cancer when it comes to hormone receptor expression. The prognosis of these patients is poor, but may be improved if early detection is achieved. Because of the number of breast cancer survivors, it is imperative that urinary symptoms of these patients are investigated fully in order to diagnose metastatic disease to the bladder.

Learning points

- All patients, regardless of cancer history, with complicated urinary incontinence should be considered for cystoscopy, upper tract imaging or urodynamics.
- It is important for physicians to consider further investigation when a breast cancer survivor develops urinary symptoms.
- Only 39% of patients in this literature review experienced haematuria as a symptom of metastatic disease to the bladder.
- The best approach to differentiate breast versus bladder primary is to test the tissue for gross cystic disease fluid fibrous protein-15 (also known as BRST-2).
- This literature review suggests that bladder metastasis from a breast primary has a worse prognosis than bone metastasis.

Contributors AK was the primary author and lead investigator in acquiring data and performing the literature review. DM provided manuscript revisions/intellectual guidance with his area of expertise and approval of the final version of the manuscript to be published. WT was responsible for the development of literature design and interpretation/analysis of the literature. He offered assistance with revisions and approval of the final manuscript version for publication.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 National Cancer Institute. Cancer Stat Facts: Female Breast Cancer. SEER Cancer Statistics, 1975–2009 (*Vintage 2009 Populations*) and SEER 18 2006–2012. <https://seer.cancer.gov/statfacts/html/breast.html>
- 2 American Cancer Society. Breast Cancer. 2016 <http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-key-statistics> (updated 5 Jan 2017).
- 3 Velcheti V, Govindan R. Metastatic cancer involving bladder: a review. *Can J Urol* 2007;14:3309–14.
- 4 Bates AW, Baithun SI. Secondary neoplasms of the bladder are histological mimics of nontransitional cell primary tumours: clinicopathological and histological features of 282 cases. *Histopathology* 2000;36:32–40.
- 5 Ganem EJ, Batal JT. Secondary malignant tumors of the urinary bladder metastatic from primary foci in distant organs. *J Urol* 1956;75:965–72.
- 6 Perez-Mesa C, Pickren JW, Woodruff MN, et al. Metastatic carcinoma of the urinary bladder from primary tumors in the mammary gland of female patients. *Surg Gynecol Obstet* 1965;121:813–8.
- 7 Grabstald H, Kaufman R. Hydronephrosis secondary to ureteral obstruction by metastatic breast cancer. *J Urol* 1969;102:569–76.
- 8 Pontes JE, Oldford JR. Metastatic breast carcinoma to the bladder. *J Urol* 1970;104:839–42.
- 9 Haid M, Ignatoff J, Khandekar JD, et al. Urinary bladder metastases from breast carcinoma. *Cancer* 1980;46:229–32.
- 10 Silverstein LI, Plaine L, Davis JE, et al. Breast carcinoma metastatic to bladder. *Urology* 1987;29:544–7.
- 11 Rigatti P, Broglia L, Montorsi F, et al. Breast cancer metastases of the urinary bladder. *Int J Tissue React* 1991;13:159–63.
- 12 Berger Y, Nissenblatt M, Salwitz J, et al. Bladder involvement in metastatic breast carcinoma. *J Urol* 1992;147:137–9.
- 13 Williams JR, Stott MA, Moisey CU. Bilateral hydronephrosis secondary to breast carcinoma metastasising to the bladder. *Br J Urol* 1992;69:97–8.
- 14 Schneidau T, Stroumbakis N, Choudhury M, et al. Metastatic breast cancer to the bladder. *Int Urol Nephrol* 1995;27:297–300.
- 15 Lucas B, Simon H, Malhaire JP, et al. Métastase vésicale d'un cancer du sein. *Presse Med* 1996;25:732.
- 16 Elia G, Stewart S, Makhuli ZN, et al. Metastatic breast cancer diagnosed during a work-up for urinary incontinence: a case report. *Int Urogynecol J Pelvic Floor Dysfunct* 1999;10:39–42.
- 17 Poulakis V, Witzsch U, de Vries R, et al. Metastatic breast carcinoma to the bladder: 5-year followup. *J Urol* 2001;165:905.
- 18 Feldman PA, Madeb R, Naroditsky I, et al. Metastatic breast cancer to the bladder: a diagnostic challenge and review of the literature. *Urology* 2002;59:138.
- 19 Choudhary M, Ahmed AA, Williamson JG. Sole bladder metastasis from breast cancer. *J Obstet Gynaecol* 2003;23:212.
- 20 Aufrich M, Augustin H, Ruppert A, et al. Bladder metastasis of bilateral breast cancer as first manifestation of metastatic spread: case report (Abstract). *BJU International* 2004;305.
- 21 Soon PS, Lynch W, Schwartz P. Breast cancer presenting initially with urinary incontinence: a case of bladder metastasis from breast cancer. *Breast* 2004;13:69–71.
- 22 Gatti G, Zurrida S, Gilardi D, et al. Urinary bladder metastases from breast carcinoma: review of the literature starting from a clinical case. *Tumori* 2005;91:283–6.
- 23 Lawrentschuk N, Chan Y, Bolton DM. Metastatic breast cancer to the bladder. *Breast J* 2005;11:143.
- 24 Ryan PD, Harisinghani M, Lerwill MF, et al. Case 6-2006: A 71-year-old woman with urinary incontinence and a mass in the bladder. *N Engl J Med* 2006;354:850–6.
- 25 Forster J, Agrawal V, Ananthan AJ, et al. Breast carcinoma metastasizing to the urinary bladder presenting as bilateral hydronephrosis treated with ureteral stenting and chemotherapy. *Urol Oncol* 2006;24:33–5.
- 26 Lin WC, Chen JH. Urinary bladder metastasis from breast cancer with heterogeneous expression of estrogen and progesterone receptors. *J Clin Oncol* 2007;25:4308–10.
- 27 Zagha RM, Hamawy KJ. Solitary breast cancer metastasis to the bladder: an unusual occurrence. *Urol Oncol* 2007;25:236–9.
- 28 Ramsey J, Beckman EN, Winters JC. Breast cancer metastatic to the urinary bladder. *Ochsner J* 2008;8:208–12.
- 29 Massoud W, Ferlicot S, Hajj P, et al. Metastatic breast carcinoma to the bladder. *Urology* 2009;74:785–6.
- 30 Vulcano E, Montesano M, Battista C, et al. Urinary complications from breast cancer metastasis: case report and review of the literature. *G Chir* 2010;31:243–5.
- 31 Luczyńska E, Pawlik T, Chwalibóg A, et al. Metastatic breast cancer to the bladder case report and review of literature. *J Radiol Case Rep* 2010;4:19–26.
- 32 Shah KG, Modi PR, Rizvi J. Breast carcinoma metastasizing to the urinary bladder and retroperitoneum presenting as acute renal failure. *Indian J Urol* 2011;27:135–6.
- 33 Xiao GQ, Chow J, Unger PD. Metastatic tumors to the urinary bladder: clinicopathologic study of 11 cases. *Int J Surg Pathol* 2012;20:342–8.
- 34 Ghaidi RA, Ayoub H, Nasr R, et al. Bladder metastasis from primary breast cancer: a case report and literature review. *Cent European J Urol* 2013;66:177–84.
- 35 Nieder C, Pawinski A. A case of recurrent breast cancer with solitary metastasis to the urinary bladder. *Case Rep Oncol Med* 2014;2014:1–3.

- 36 Cormio L, Sanguedolce F, Di Fino G, *et al.* Asymptomatic bladder metastasis from breast cancer. *Case Rep Urol* 2014;2014:1–3.
- 37 Al Ibraheemi AA. Case report of metastatic invasive breast lobular carcinoma to the urinary bladder. *Int J Hematol Oncol Stem Cell Res* 2016;10:51–5.
- 38 Bettez M, Tu leM, Carlson K, *et al.* 2012 update: guidelines for adult urinary incontinence collaborative consensus document for the canadian urological association. *Can Urol Assoc J* 2012;6:354–63.
- 39 Winston T. *Metastatic cancer with unknown primary site workup*: Medscape, 2016. <http://emedicine.medscape.com/article/280505>
- 40 Lower EE, Glass EL, Bradley DA, *et al.* Impact of metastatic estrogen receptor and progesterone receptor status on survival. *Breast Cancer Res Treat* 2005;90:65–70.
- 41 Cetin K, Christiansen CF, Sværke C, *et al.* Survival in patients with breast cancer with bone metastasis: a Danish population-based cohort study on the prognostic impact of initial stage of disease at breast cancer diagnosis and length of the bone metastasis-free interval. *BMJ Open* 2015;5:e007702–8.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow