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ORIGINAL ARTICLE

Metastatic breast carcinoma to the urinary bladder—a report of 11 cases including a tumor to tumor metastasis

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Abstract

Metastatic breast carcinoma to the urinary bladder is rare. Eleven cases of metastatic breast carcinoma to the bladder are described in this report, including one case with a tumor to tumor metastasis. The patients ranged from 51 to 83 years of age. The time intervals between the diagnosis of primary breast cancer and the occurrence of bladder metastases ranged from 41 to 336 months. There were seven cases of invasive ductal carcinoma and four cases of invasive lobular carcinoma. In one case, a lobular carcinoma of the breast metastasized to a concurrent squamous cell carcinoma of the bladder. The immunophenotypic status of estrogen receptor and Her2 expression of the metastatic carcinomas were all concordant with the primary tumors. In nine patients with follow-up available, seven patients died of the disease ranging from 1 to 23 months after the diagnosis of the bladder metastasis and two patients were alive at 5 months of follow-up. To date, this report is the largest single series of patients with breast carcinoma metastatic to the bladder. It is the first reported instance of lobular carcinoma of the breast metastasizing to a squamous cell carcinoma of the bladder.

Keywords Metastasis · Breast carcinoma · Bladder · Tumor to tumor metastasis

Introduction

Breast cancer is the most frequently diagnosed malignancy in women and remains the leading cause of death for cancer in women despite increased awareness, screening programs, and advanced therapies; this is due to the great metastatic potential of this tumor [1]. The urinary bladder is considered an unusual site of breast cancer metastasis. Such an occurrence has rarely been reported in the literature, and it may be a source of diagnostic and therapeutic pitfalls. The phenomenon of tumor-to-tumor metastasis in patients with multiple primary tumors is extremely rare [2–4]. Breast carcinoma metastatic to a second primary carcinoma of the urinary bladder has not been previously described.

In this article, we report 11 cases of breast carcinoma metastatic to the urinary bladder, including a case of lobular carcinoma of the breast metastatic to a concurrent squamous cell carcinoma of the bladder. We further review the reported cases of bladder metastasis from breast cancer with the aim of identifying pathologic features that may help pathologists to make the correct diagnosis and thus appropriately guide clinical management of this rare event.

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Materials and methods

The 11 cases were all obtained from BC Cancer Agency tumor registry, spanning the years from 1997 to 2018. Clinical data including patients' demographics, initial presentation, cystoscopic findings, and follow-up were collected from the clinical notes. All histology slides from each case were reviewed to confirm the diagnosis and identify additional pathology findings.

Results

Clinical presentation

The clinical information is summarized in Table 1. The patients were all female, ranging from 51 to 83 years of age at the time of bladder metastasis. The time intervals between the diagnosis of primary breast cancer and the occurrence of bladder metastases ranged from 41 to 336 months. Six cases were asymptomatic, being diagnosed by imaging techniques performed as part of the routine follow-up for breast carcinoma. Two patients had painless hematuria and one had urinary urgency, while another patient presented as renal failure. At the time of cystoscopy, eight patients were found to have mass lesions in the bladder, one showed bladder wall thickening, and another patient, who had renal failure, was found to have a ureteral obstruction. One patient had no information on clinical presentation or cystoscopic findings.

Pathological and immunohistochemical features

In seven cases, pathologic analysis of the bladder tumor demonstrated moderately to poorly differentiated pleomorphic carcinoma cells arranged in solid nests involving the wall of the urinary bladder (Fig. 1a, b). Involvement of muscularis propria by the carcinoma cells was seen in most cases (Fig. 1c). Metastatic carcinoma involving urothelial mucosa with ulceration is also seen (Fig. 1d). Foci of lymphovascular permeation and perineural invasion were noted. Immunohistochemical studies demonstrated positivity for GATA3 (Fig. 1e), estrogen receptor (ER) (Fig. 1f), and mammaglobin in the carcinoma cells. In these cases, the pathologic features were consistent with metastatic invasive ductal carcinoma (IDC) from the breast.

In three cases, the carcinoma cells were arranged in a linear manner as columns of cells, with separate areas of solid sheets of discohesive cells (Fig. 2a, b) and with areas of carcinoma cells infiltrating between the smooth muscle fibers of the muscularis propria (Fig. 2a). Some carcinoma cells had prominent intracytoplasmic vacuoles. Immunohistochemical studies demonstrated loss the expression of E-cadherin (Fig. 2c) and positivity for ER (Fig. 2d), gross cystic disease fluid protein (GCDFP) (Fig. 2e), and mammaglobin (Fig. 2f) in the carcinoma cells. In these cases, the pathologic features were consistent with metastatic lobular carcinoma (ILC) from the breast. There were no associated overlying papillary urothelial proliferation or urothelial carcinoma in situ (CIS) identified in any of the cases.

In case 11, the pathology of the transurethral resection of the bladder tumor demonstrated an invasive moderately differentiated squamous cell carcinoma involving the muscularis propria. There was a second population of carcinoma cells morphologically distinct from the squamous cell carcinoma. The tumor cells in this second population were discohesive

Table 1 Clinical presentations of breast carcinoma metastatic to the bladder

Case no.	Age	Sex	Subtype	Biomarker of the primary	Presentation	Cystoscopic finding	Interval (M)	Biomarker of the metastases	Other metastasis	Therapy	Follow-up (M)	Outcome
1	57	F	IDC	ER−, HER2+	Renal failure	Urinary obstruction	97	ER−, HER2+	Bone	Chemoradiation	23	DOD
2	83	F	IDC	ER+, Her2−	Found by CT	Thickened bladder wall	336	ER+, Her2−	Bone, brain	Chemo	7	DOD
3	51	F	IDC	ER−, HER2+	Urinary urgency	Mass	69	ER−, HER2+	Bone	Palliative	1	DOD
4	62	F	ILC	ER+, Her2−	n/a	n/a	41	ER+, Her2−	Pleura	Hormonal	n/a	n/a
5	66	F	IDC	ER+	Hematuria	Mass	73	ER+		Chemo	12	DOD
6	57	F	ILC	ER+, Her2−	Found by CT	Mass	65	ER+, Her2−	Bone, liver, skin	Chemoradiation	12	DOD
7	67	F	IDC	ER+, Her2−	Found by CT	Mass	45	ER+, Her2−	Ampullary	Chemoradiation	4	DOD
8	68	F	IDC	ER+, Her2−	Found by CT	Mass	98	ER+, Her2−	Pelvic	Chemo	2	DOD
9	77	F	IDC	ER+, Her2−	Hematuria	Mass	74	ER+, Her2−	Bone	n/a	n/a	n/a
10	54	F	ILC	ER+, Her2−	Found by CT	Mass	52	ER+, Her2−	Bone, liver	Chemo	5	AWD
11	74	F	ILC	ER+, Her2−	Found by CT	Mass	108	ER+, Her2−	Bone	Chemo	5	AWD

F female, *ILC* invasive lobular carcinoma, *IDC* invasive ductal carcinoma, *M* month, *AWD* alive with disease, *DOD* dead of disease

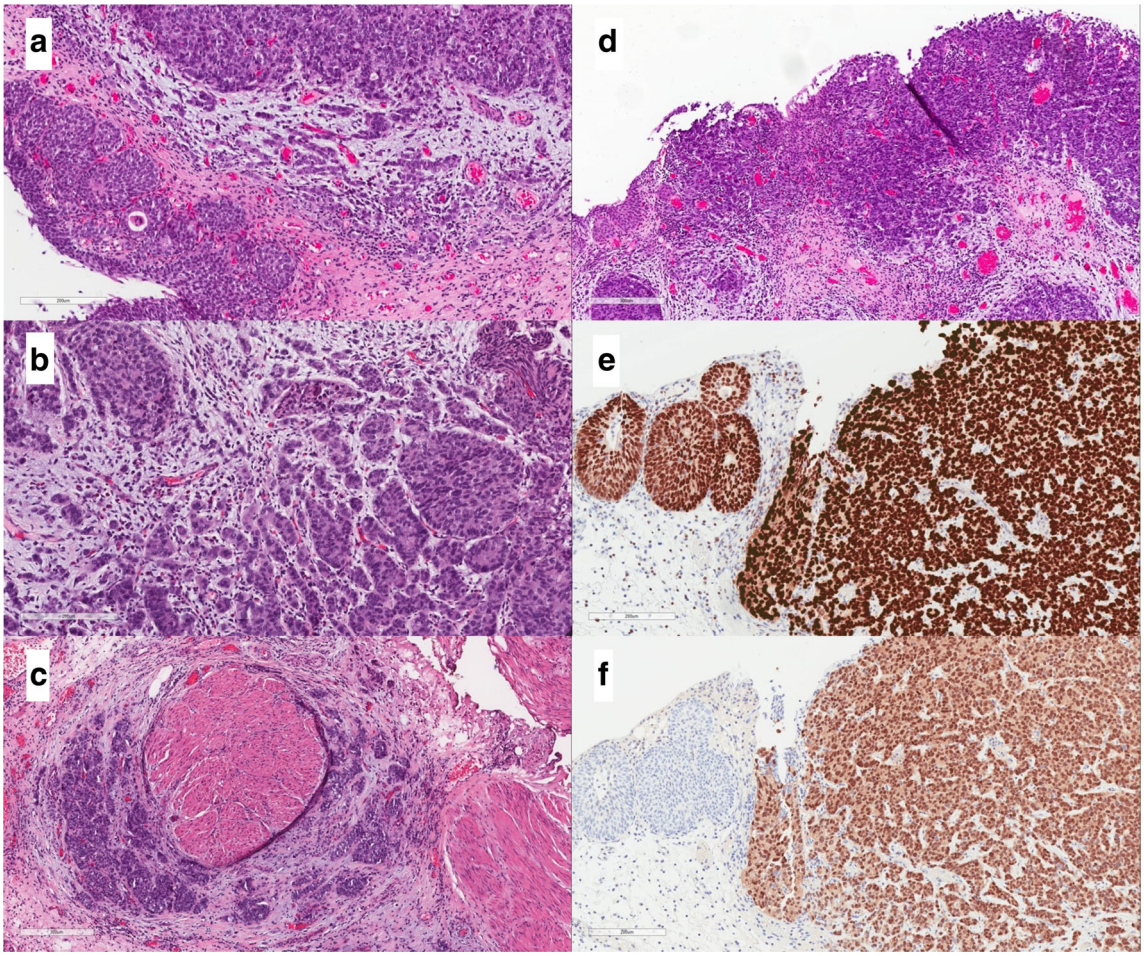

Fig. 1 Invasive ductal carcinoma of the breast metastatic to the bladder. **a** Low-power view demonstrates invasive carcinoma involving the wall of the urinary bladder. **b** At high-power magnification, there are moderately to poorly differentiated pleomorphic tumor cells arranged in solid nests. **c** Tumor cells involve muscularis propria. **d** Metastatic carcinoma involves urothelial mucosa with ulceration. **e** The immunohistochemical stain for GATA3. Note the carcinoma cells and the overlying urothelial cells are both positive for GATA3. **f** the carcinoma cells are positive for estrogen receptor (ER). Note the negative stains for ER in benign urothelial cells

and plasmacytoid in appearance with intracytoplasmic vacuoles (Fig. 3a, b). The immunohistochemical stains demonstrated positivity for ER (Fig. 3c) and mammaglobin (Fig. 3d) in this second population, supporting the diagnosis of ILC of the breast metastatic to a squamous cell carcinoma of the bladder.

All the metastatic tumors were tested for ER and Her2 protein expression, except one patient, in 1997, was tested for ER only. The ER/her2 statuses for all the metastatic tumors were concordant with that of the primary tumors (Table 1).

Treatments and follow-up

Ten of the 11 patients were found to have metastatic breast carcinoma in other anatomic sites. Bone metastases were found in seven patients, and metastases were found to the liver in two patients, to the pelvis in one patient, to the brain in one patient, to the ampulla in one patient, and to the skin in one patient. In nine patients with follow-up, eight patients received chemotherapy or chemoradiation, and one patient received palliative care. Seven patients died of their metastatic disease ranging from 1 to 23 months after the detection of the bladder metastasis. Two patients, both with 5 months of follow-up, were alive with disease at the time of review. In the 7 patients with additional bone metastasis, one of them died from extensive skeletal metastasis and severe anemia/sepsis, and 3 of them died from other events (acute renal failure, bowel obstruction etc.).

Discussion

Bladder metastases from breast cancer are very uncommon, with only 55 cases having been reported in the literature. Some of them were identified in autopsies as incidental findings, while most of the rest were identified either because of urinary symptoms or by image studies during breast cancer follow-up [5–9]. On the other hand, breast cancer represents the primary site in about 2.4% of cases of all bladder

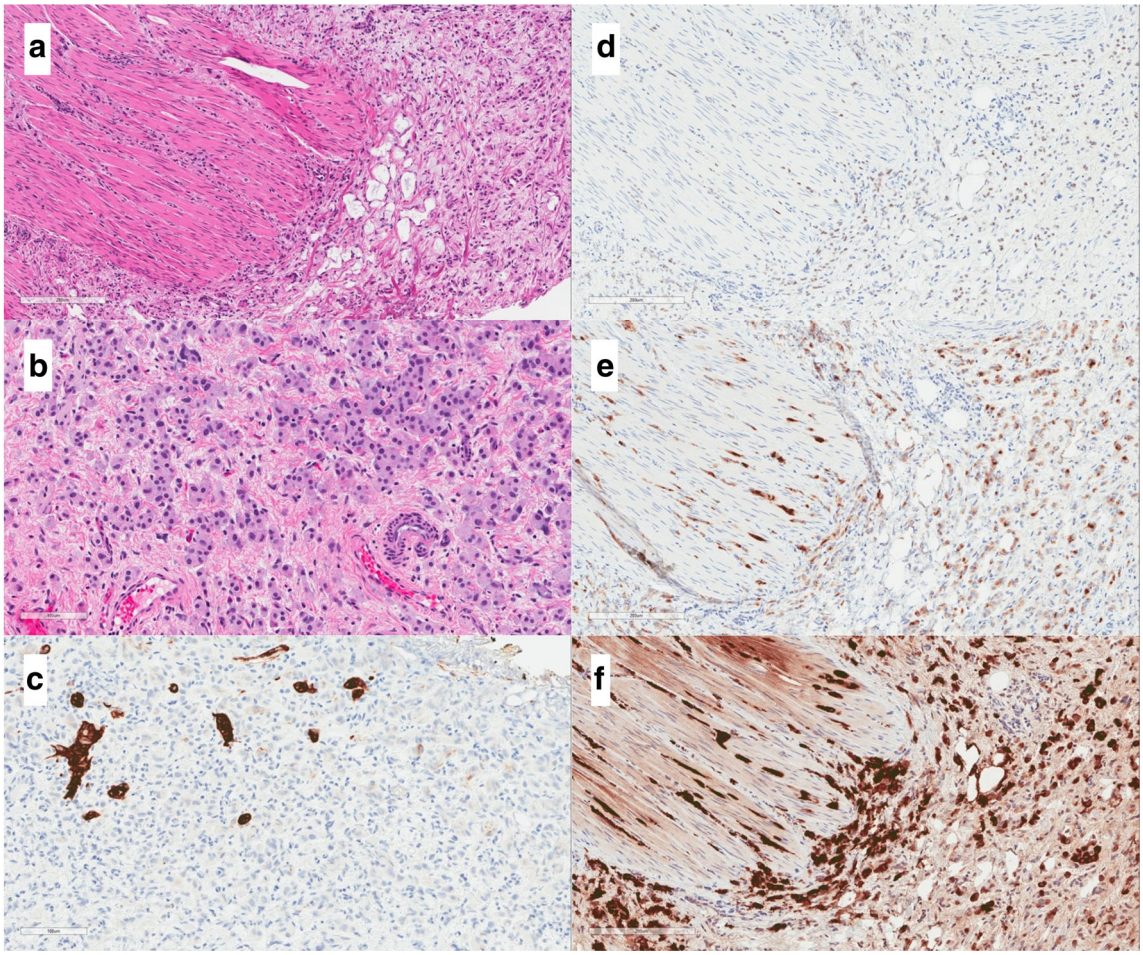

Fig. 2 Invasive lobular carcinoma of the breast metastatic to the bladder. **a** Low-power view demonstrates invasive carcinoma involving the lamina propria and infiltrating into the muscularis propria of the wall of the urinary bladder. **b** High-power view demonstrates the tumor cells arranged in linear manner as single-cell files and in separate areas as solid sheets of discohesive cells. **c** Loss of E-cadherin expression. **d** The carcinoma cells are positive for ER. **e** The carcinoma cells are positive for GCDFP. **f** The carcinoma cells are positive for mammaglobin

metastases, according to a large series of surgical and postmortem material [10–13]. Recently, Xiao et al. described primary breast carcinoma in three out of 11 cases of bladder metastases [14]. The current report, with 11 of the cases, comprises the largest series of breast carcinoma metastatic to the bladder and brings the total number of reported cases to 66.

The occurrence of tumor-to-tumor metastasis is extremely rare [2–4]. Postulated reasons include the hostile microenvironment the tumors create for other cells [2], biological and antigenic differences between cancer cells and normal cells [15, 16], and the nutritional competition for cellular growth [17, 18]. Carcinomas of the lung are the most common donors in tumor-to-tumor metastasis, followed by carcinomas of the breast, gastrointestinal tract, prostate, and thyroid. The most frequent recipient tumor is renal cell carcinoma (RCC), followed by meningioma and thyroid tumor [16]. Our case 11 is the first reported case of breast carcinoma metastatic to a bladder carcinoma.

The distant metastatic pattern of ILC differs significantly from that of IDC, as it tends to occur as a diffuse thickening of mucosa rather than a discrete nodule. Moreover, IDC often metastasizes to the lung, liver, bone, and brain, whereas ILC tends to spread to the gastrointestinal tract, genitourinary tract, peritoneum, retroperitoneum, and leptomeninges [19–21]. In our series, there were four cases (36%) of ILC involving the bladder, with the prevalence consistent with the previous study by Feldman et al. [22] and much higher than the overall prevalence of ILC in breast carcinoma [20]. It was postulated that breast cancer metastasizes to the bladder via retroperitoneal involvement, due to minute viable tumor emboli that pass through the pulmonary circulation without establishing a lung metastasis and subsequent spread to the urinary bladder by hematogenous transport [8]. This mechanism would explain the increased incidence of ILC metastasizing to the bladder.

The clinical presentation of metastatic breast carcinoma involving the bladder may vary, ranging from painless hematuria (microscopic being more frequent than gross hematuria) as the most common, to stress and urge incontinence, urinary frequency and nocturia, difficulty in voiding, and back pain [14, 23–25]. In fact, some cases are asymptomatic, as seen in six

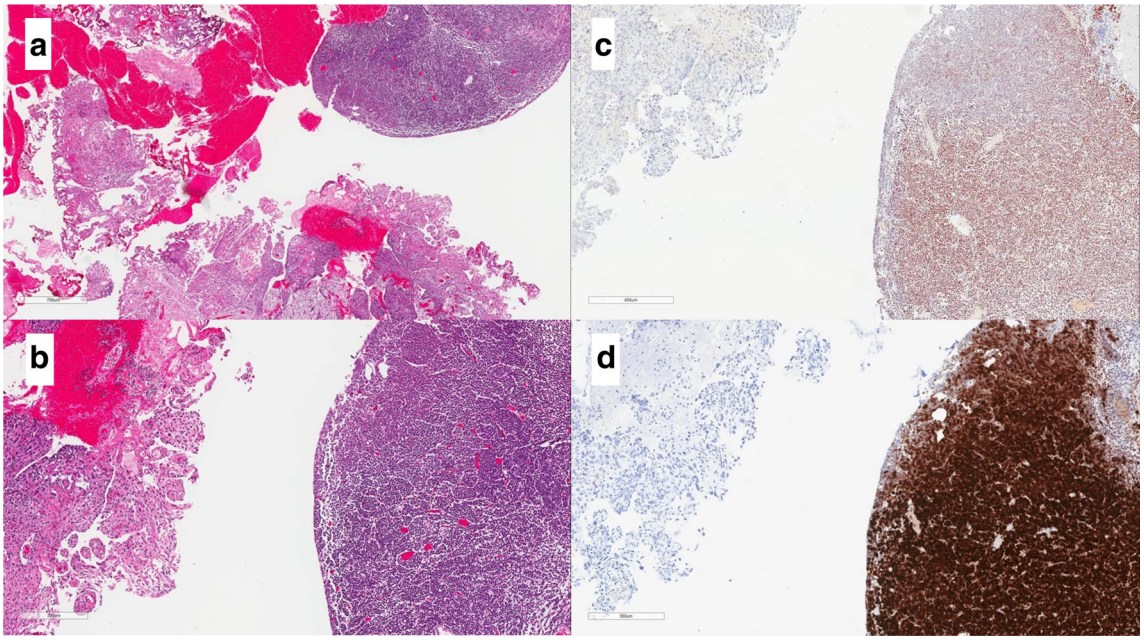

Fig. 3 Lobular carcinoma of the breast metastatic to the squamous cell carcinoma of the bladder. **a** The transurethral resection of the bladder tumor demonstrates moderately differentiated squamous cell carcinoma (left lower part), with a second population of morphologically distinct carcinoma cells (right upper part). **b** The carcinoma cells in the second population are discohesive and plasmacytoid in appearance with intracytoplasmic vacuoles. **c** The immunohistochemical stain demonstrates the positivity for ER in this second population. **d** The immunohistochemical stain demonstrates the positivity for mammaglobin in this second population

of the 11 cases in this report, which were discovered upon imaging studies performed on routine follow-up of this neoplasm [26, 27]. Unfortunately, urine cytology may turn out to be negative if the mucosal lining has not been involved. Detrusor involvement may also lead to ureteral obstruction and renal failure, as seen in case 1 in our series. In another series, the ureteral obstruction was found in six (11%) of patients with breast cancer metastatic to the retroperitoneum [28].

In cases of metastatic breast carcinoma involving the bladder, the differential diagnosis obviously includes variants of urothelial carcinoma such as the micropapillary, lymphoepithelioma-like, and plasmacytoid variants of urothelial carcinoma [29]. The relative infrequency of primary adenocarcinoma of the bladder also causes the dilemma whether bladder adenocarcinoma represents a primary or secondary process [10]. Obtaining a proper clinical history is always important. Urothelial carcinoma is usually associated with overlying papillary urothelial proliferation or flat carcinoma in situ. In metastatic carcinoma to the urinary bladder, the presence of unusual monomorphic growth patterns without accompanying conventional urothelial carcinoma features and the appearance of tumor cells invading towards the luminal surface from the outside may be of help [30]. Ancillary studies such as immunohistochemistry, to include, for example, immunostains for ER and progesterone receptor (PR) and uroplakin [29–31], will help to arrive at a correct diagnosis, but they should be used with caution. According to Amin [31], concurrent staining for CK7 and CK20 is typical of urothelial carcinoma cells in 65% of cases, while as many as 37% urothelial carcinoma may lack CK20 expression, which is the common phenotype of breast carcinoma cells. It is important to be aware that some bladder-associated markers such as 34betaE12, thrombomodulin, and GATA3 are also expressed in breast carcinoma [14]. In most cases, positive staining for ER and PR allows one to identify breast carcinoma metastatic to the bladder and not mistake it for urothelial carcinoma. Nevertheless, not all cases of breast cancer express ER and PR. In such cases, the differential diagnosis between primary bladder cancer and a secondary breast carcinoma metastasis to the bladder may rely on other immunohistochemical markers, including GCDFP-15, which has high specificity but low sensitivity [26], and mammaglobin, which is more sensitive than GCDFP in our experience. The commonly used markers for urothelial carcinoma and breast carcinoma are summarized in Table 2. In our study, all bladder metastases showed the same ER and Her2 expression status as the primary tumors. However, it has been reported that hormone receptors (ER, PR) and Her2 expression may differ between primary and metastatic tissues, with discordance rates ranging from 24 to 39% [20, 22, 25, 30, 32].

Patients with bladder metastases from breast cancer tend to have a very limited survival (between 1 month and 2 years), although there are reports of survival for more than 5 years [33–36]. In the literature review from Kase et al., the 28 previously reported patients, where length of survival was known, had 53.6% 1-year survival, 10.7% 3-year survival, and 3.6% 5-year survival [9], which were worse than the 1-year, 3-year, and 5-year survivals of patients with breast

Table 2 Immunohistochemical markers in urothelial carcinoma and breast carcinoma

	Urothelial carcinoma	Breast carcinoma
GATA3	+	+
Thrombomodulin	+	+
34betaE12	+	– (+ in metaplastic)
p40	+	– (+ in metaplastic)
p63	+	– (+ in metaplastic)
CK5/6	+	– (+ in metaplastic)
Uroplakin	+	– (+ in apocrine Ca)
CK7	+	+
CK20	+/–	–
ER	–	+/–
PR	–	+/–
Mammaglobin	–	+/–
GCDFP-15	–	+/–
E-Cadherin	– in plasmacytoid variant	– in lobular carcinoma

cancer bone metastases (52%, 26.4%, and 13%, respectively) [37]. However, it may be a surrogate of widespread disease leading to worse outcomes. In our series, ten of 11 patients developed metastases to other sites, predominantly to the bone (seven patients). Seven patients died of metastatic breast carcinoma, with follow-up ranging from 1 to 23 months after the detection of bladder metastasis. Two patients with a follow-up of 5 months remained alive with the disease. Two patients were lost to follow-up. These findings are consistent with those in the literature [33–36]. In the 7 patients with additional bone metastasis, only one of them died from extensive skeletal metastasis and severe anemia/sepsis, and 3 of them died from other events. Although there was only a limited number of cases, it seems that the mortality from the bone metastasis largely depends on the extensiveness of the bone involvement.

Conclusion

Bladder metastases from breast cancer are rare, with most cases detected years after the initial diagnosis of primary breast cancer. They are usually associated with metastases to other sites. Apart from asymptomatic cases incidentally diagnosed by follow-up imaging studies, most cases present with urinary voiding symptoms. Pathologic diagnosis requires awareness of the previous history of breast cancer, careful attention to morphological detail, and the use of immunohistochemical studies to distinguish this entity from primary invasive urothelial carcinoma. The prognosis is usually poor, with rare patients surviving more than 5 years.

Author contributions Gang Wang conceived and designed the study, collected data, and wrote, edited, and reviewed the manuscript. Chen Zhou, Christopher Conklin, Malcolm Hayes, Carlos Villamil, Avrum Ostry, and Edward Jones collected data and edited and reviewed the manuscript. All authors gave final approval for publication. Gang Wang takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Compliance with ethical standards

The current study was approved by the institutional review board of the University of British Columbia.

Conflict of interest The authors declare that they have no conflict of interest.

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