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URINARY BLADDER METASTASES FROM BREAST CARCINOMA: REVIEW OF THE LITERATURE STARTING FROM A CLINICAL CASE

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Bladder metastases from solid tumors are rare. Breast carcinoma cells seldom spread to the urinary bladder. We report the case of a patient with invasive breast carcinoma who developed a breast recurrence followed by bone and urinary bladder metastases. Starting from this clinical case we review the available literature on this issue. Only few cases of urinary bladder metastases from primary breast cancer have been reported, although the case reports have increased in recent years. Patients with breast cancer presenting with urinary symptoms should be examined for possible bladder metastases.

Key words: breast carcinoma, distant metastases, urinary bladder metastases.

Introduction

Urinary bladder metastases from solid tumors represent 2% of all bladder neoplasms. About 2.5% of these metastatic cancers affecting the urinary bladder arise from primary breast lesions[1,2]. Breast cancer commonly metastasizes to the lung, bone, liver, lymph nodes and skin; less frequently it involves the brain, adrenal glands, ovary, spleen, pancreas, kidney, thyroid and heart[3-7]. There are reports on unusual sites of breast cancer metastases; the urinary bladder is considered one of these unusual sites.

Case report

A 49-year-old premenopausal woman was admitted to the Senology Division of the European Institute of Oncology in January 1996 with a left breast lump highly suspicious for malignancy. The patient had already undergone partial resection of the left breast and left axillary dissection in another center in 1985, with a diagnosis of invasive ductal carcinoma. She had received interstitial brachytherapy with no adjuvant drug treatment.

The family history of the patient revealed no other cases of breast carcinoma. As for previous pharmacological treatments, the patient had experienced two atrial flutter episodes (in 1983 and in 1996) and had been treated with mexiletine chloride (2 cpr/day). She had never been exposed to HRT or other hormonal treatment.

On admission, physical examination showed nipple retraction but no signs of skin infiltration. There was no nipple discharge. The patient underwent bilateral mammography showing no lesions in either breast, while breast ultrasound showed a 3 cm hypoechogenic mass. Fine-needle aspiration cytology was performed but was not conclusive.

The patient underwent a simple left mastectomy and reduction mastoplasty of the right breast after intraoperative confirmation of malignancy in the left breast. The histological finding in the left breast was invasive lobular carcinoma G1, pT3, ER-negative, PgR 50%, and Ki-67 10%. Lobular carcinoma *in situ* was found in the right breast specimen.

In November 1996 the patient underwent surgical resection for a local disease recurrence to the skin; this was followed by radiotherapy. In February 1997 she underwent a total right mastectomy for ductal carcinoma *in situ*. A diagnosis of bone metastases was made in October 1999 (vertebral metastases to T4-T7) and treatment with local radiotherapy, pamidronate and six cycles of 5Fluorouracile, vinorelbine, folinic acid (FLN) was started.

After the patient complained of dysuria in February 2001, CT scan and ultrasonography showed right hydroureteronephrosis. The patient underwent cystoscopy, ureteropyelography, stenting and transurethral resection. The pathological report documented urinary bladder metastases from breast carcinoma. Chemotherapy with 5-FU (continuous infusion) and vinorelbine was given, followed by an oral regimen of cyclophosphamide and methotrexate. This resulted in good remission of disease in the bladder.

In January 2002 there was progression of disease in the urinary bladder. The patient underwent six cycles of capecitabine leading to a temporary decrease in tumor marker levels followed by progression of disease in the bone. Radiotherapy (T10-L1) was then performed. In June 2002 a gemcitabine/vinorelbine regimen was ad-

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Table 1 - Patients with metastasis to the urinary bladder

Reference	N pts	Symptoms	Cystoscopy	Breast cancer to bladder metastasis (months)	Other sites of metastasis	Bladder metastasis to death (months)	Medication before bladder metastasis
Ganem & Batal[1] (1956)	1	Gross hematuria	Large tumor mass	120	Bone, skin	Alive >12	Stilbestrol
Perez-Mesa *et al*.[14] (1965)	2	Gross hematuria, frequency, dribbling	Ulcerating tumor mass	26	Bone, lymph nodes	Not stated	Fluoxymestrone
		Urinary frequency, gross hematuria	III-defined tumor mass	216	Lymph nodes, bone, omentum	12	5-Fluorouracil
Grabstald *et al*.[17] (1969)	1	Hydronephrosis	Not known	Not known	Not known	Not known	Not known
Pontes & Oldford6 (1970)	2	Hematuria, low back pain	Tumor mass	12	Widespread	2	Stilbestrol
		Back pain	Cauliflower tumor mass	48	Lymph nodes, probably retroperitoneal	1	Estrogen
Haid *et al*.[7] (1980)	4	Gross hematuria	Irregular sessile tumor mass	66	Bone, brain, meninges, liver,	1	Hydrocortisone
		Frequency, nocturia, urge incontinence	Mucosal nodularity	32	skin, pelvis	13	DES
		Microhematuria	Not performed	32	Bone, meninges, lung, liver, peritoneum, bone marrow	1	Tamoxifen
		Abdominal mass	Walnut-size tumor mass	38	Lymph nodes, pelvis	Alive >7	Methotrexate, 5-fluorouracil, prednisone, levophenil-alanine
Mairy *et al*.[13] (1982)	2	None	Not known	9	Skin, bone	Alive >14	Not known
		Frequency, dysuria, incontinence	Not known	Concurrently	Bone, endometrium, skin	Alive >12	Not known
Silverstein *et al*.[25] (1987)	2	Frequency, nocturia, urgency, abdominal pain	Smooth, raised, hard, immobile lesion	168	Bone	24	None
		Gross hematuria, dysuria	Extensive nodularity	7	Brain, bone	5	Cyclophosphamide, prednisone, 5-fluorouracil
Rigatti *et al*.[22] (1991)	2	Renal colic, microhematuria	Exophytic mass	63	Lymph nodes	Not stated	Cyclophosphamide, methotrexate, 5-fluorouracil, tamoxifen, medroprogesterone
		Irritative bladder symptoms, urinary incontinence	Small elevated and reddened area	164	Lymph nodes, lung	Not stated	Tamoxifen
Berger *et al*.[11] (1992)	3	Microhematuria	Abnormal lesions	Not stated	None detected	Not stated	5-fluorouracil, cyclophosphamide, doxorubicin, mitomycin C, vinblastine, megestrol acetate
		Urinary retention, vaginal mass, gross hematuria	Abnormal lesions	72	Supraclavicular node, bone, brain	<1	Tamoxifen, methotrexate, 5-fluorouracil, cyclophosphamide
		Gross hematuria	Not performed	69	Liver, retroperitoneum, small and large bowel	<1	Cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen, methotrexate, prednisone, vincristine
Williams *et al*.[16] (1992)	1	Frequency, nocturia, hydronephrosis	Large tumor mass	360	Not stated	Not stated	Not stated
Schneidau *et al*.[15] (1995)	1	Flank pain, dysuria, gross hematuria	Diffuse bullous edema	>48	Meninges	Not stated	Cyclophosphamide, methotrexate, 5-fluorouracil
Lucas *et al*.[24] (1996)	1	Macroscopic hematuria	Tumor mass	34	Skin, lung, brain	1	Vindesine, mitomycin, tamoxifen
Lund *et al*.[26] (1997)	1	Not known	Not known	Not known	Not known	Not known	Not known

(Segue)

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Reference	N pts	Symptoms	Cystoscopy	Breast cancer to bladder metastasis (months)	Other sites of metastasis	Bladder metastasis to death (months)	Medication before bladder metastasis
Elia *et al*.[12] (1999)	1	Stress, urge incontinence	Small polyps	62	None detected	Alive >12	Tamoxifen
Poulakis *et al*.[20] (2001)	1	Frequency, urgency and nocturia	Multiple invasive tumors	60	Bladder recurrence 1 year after first bladder metastasis	Alive >60	Tamoxifen
Feldman *et al*.[19] (2002)	1	Gross hematuria	Normal	Not stated	Ovary	Alive >9	Cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen
Choudhary *et al*.[21] (2003)	1	Hydronephrosis	Atrophic, hemorragic trigonal area	216	None	Alive >8	None reported
Auprich *et al*.[27] (2004)	1	Intermittent gross hematuria, urge incontinence	Two large tumors	2	Bone	16	Not known
Total	28						

ministered, resulting in minimal bladder response and progression of bone disease. The patient was given weekly docetaxel. Urinary bladder remission was good, while the bone situation was not evaluated.

The patient was admitted to our Institute in December 2002 with a diagnosis of pulmonary embolism, disseminating intravascular coagulation, hyperammonemia and liver dysfunction. She died 12 days later.

Review of the literature and discussion

Secondary urinary bladder tumors can be subdivided into:

- metastases by direct extension from a primary focus in an adjacent organ;
- metastases by ureteral or renal pelvis spread;
- metastases from lymphoma or leukemia;
- metastases by lymphogenous or hematogenous spread from a primary focus in a distant organ[1].

The commonest primary tumors in case of bladder metastasis involve the stomach, lung, skin (melanoma) and breast[1,2]. This kind of spread of tumor cells is not a common clinical occurrence and could be due to minute viable tumor emboli that pass through the pulmonary circulation without establishing a lung metastasis and subsequently reach the urinary bladder by hematogenous transport[1,6,8,9]. Other possible routes are extension from retroperitoneal involvement or dissemination through the lymphatic or arterial circulation[6].

In 1950, an analysis of 1000 autopsies showed four cases of bladder metastases in 167 patients affected by metastatic breast carcinoma[10]. In a retrospective study Bates and Baithun[2] found 282 secondary urinary bladder metastases in a series of 6289 bladder tumors (about 4.5% of all bladder tumors detected). Seven cases of primary breast cancer were found; bladder metastases were detected post-mortem in six of these seven cases and all of them had metastasized widely. Histology was available in six cases; all of them were poorly differentiated invasive ductal carcinomas. The advanced stage of the primary tumors at autopsy and the high prevalence of widespread metastases indicate that secondary bladder tumors are typically late complications of disease and have a poor prognosis[2,11,12].

In patients with a history of breast cancer, even subtle urinary symptoms should be thoroughly evaluated. Awareness among clinicians of this metastatic route in breast cancer patients should be heightened; it may be helpful to look for hematuria or even mild urinary symptoms in these patients[12]. Clinical presentation may range from the most common hematuria to back pain or irritative voiding symptoms, such as urgency, hematuria or dysuria[1,6,11,13-15]. On rare occasions, urinary metastases from breast cancer presented with hydronephrosis[16,17].

Some authors have associated the likelihood of developing bladder metastases with the presence of positive lymph nodes[7] or with steroid therapy[18]. Patients who have been administered steroids may develop unusual metastases due the possible influence of the immunosuppressive effect of steroids.

In patients receiving cyclophosphamide, macroscopic hematuria may be dismissed as cystitis secondary to chemotherapy[7]. The evaluation of a patient with a history of breast cancer in whom hematuria develops should include at least cystoscopy and biopsy of any suspicious lesion. Feldman *et al*.[19] stated that evaluation should include also imaging studies. They described a case with negative cystoscopy findings, despite strong evidence of bladder involvement from the patient's symptoms and CT scans.

Table 1 lists the 28 cases of urinary bladder metastases due to breast cancer reported in the literature[17,26]. In most of the reported cases the urinary bladder involvement was part of systemic spread. Only four cases of isolated bladder metastasis have been described[12,20-22]. Relatively long periods of time elapsed between the initial diagno-

sis of breast cancer and urinary bladder involvement.

Soon *et al*.[23] described a case of urinary bladder metastases detected before the diagnosis of invasive ductal carcinoma. This patient was treated with tamoxifen and had stable bladder disease 22 months after diagnosis. She had a history of urinary incontinence. The authors concluded that in patients with a history of breast cancer and urinary symptoms the possibility of bladder metastases should be carefully evaluated, and that urinary incontinence might be, as in the case described, the first sign of breast cancer.

Survival after the onset of distant metastases is relatively short, even if Poulakis *et al*.[20] in 2001 reported a patient with breast cancer and urinary bladder involvement still alive at five years from diagnosis. Appropriate treatment and follow-up may improve the prognosis of patients with solitary bladder metastases.

Conclusions

Bladder metastases from primary breast cancer have been reported occasionally in the literature, but the number of reports have increased in the last decades, probably due to the improved survival. Some authors believe that this diagnosis will be made with increasing frequency if it is more actively sought[7].

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