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Bladder Metastases from Breast Cancer: Managing the Unexpected. A Systematic Review

Keywords

Bladder · Metastasis · Breast cancer · Pathology · Oncology

Abstract

Breast cancer (BrC) has the highest incidence among females world over and it is one of the most common causes of death from cancer overall. Its high mortality is mostly due to its propensity to rapidly spread to other organs through lymphatic and blood vessels in spite of proper treatment. Bladder metastases from BrC are rare, with 50 cases having been reported in the last 60 years. This review aims to discuss some critical points regarding this uncommon condition. First, we performed a systematic review of the literature in order to draw a clinical and pathological profile of this entity. On this basis, its features in terms of diagnostic issues, imaging techniques, and survival are critically examined. Most bladder metastases from BrC are secondary lobular carcinoma, which mimic very closely the rare variant of urothelial cancer with lobular carcinoma-like features (uniform cells with an uncohesive single-cell, diffusely invasive growth pattern); thus, immunohistochemistry is mandatory to arrive at

a correct diagnosis. This article summarizes the current knowledge regarding the incidence, clinical presentation, diagnosis, prognosis, and treatment of bladder metastases in patients with BrC.

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Introduction

Breast cancer (BrC) is the most frequently diagnosed malignancy in women according to the latest epidemiology reports, with an estimated 1.67 million new cancer cases diagnosed worldwide (25% of all cancers) [1]. Incidence rates show variability across different countries, reflecting discrepancies in early diagnosis and in the entity of risk factors; the highest rates have been recorded in more developed countries, from Northern America to Australia/New Zealand as well as Northern and Western Europe [1]. BrC also 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 tumour. The urinary

bladder is considered an unusual site of BrC metastasis and such a spread, which has rarely been reported in literature, may be a source of diagnostic and therapeutic pitfalls.

In this article, we reviewed the reported cases of bladder metastasis (BM) from BrC with the aim of identifying clues that could help pathologists to reach the correct diagnosis and guide clinicians in planning treatment.

Methods

To proceed with the review, we electronically searched the PubMed, Medline and Google Scholar databases, between 1950 and 2017, using the following keywords: “bladder metastasis,” “breast cancer,” “pathology,” and “oncology.” All case reports, case series and review articles were systematically examined, and data regarding epidemiology, histotypes, route and pattern, signs and symptoms, diagnostic workup, pathology features, hormonal status, management and outcome was analytically reported.

Epidemiology

BMs from solid tumours are rare, accounting for up to 4.5% of all bladder neoplasms [2–4], though incidence rates as high as 14% have been reported [5]. Most BMs are due to the direct extension from another pelvic neoplasm, such as cervical, prostate and colon cancer. Metastases from distant organs are extremely rare and have been reported sporadically, the most common being stomach, lung and skin (melanoma) [6, 7].

BMs from BrC are extremely rare, with only 54 cases having been reported in literature, most of them having been identified only in old autopsy series. In 1950, a large series on 167 metastatic BrCs displayed BM only in 4 patients (2.4%) [3]. In 1967, Goldstein [8] identified 4 (1.2%) cases of BM after reviewing 341 autopsy cases of patients who died of advanced BrC. Pontes and Oldford [9] found 6 (7%) cases of BM among 85 autopsies of people dying from widespread BrC. Hagemester et al. [10] evaluated 166 autopsies of patients who died of BrC and found 8 (4.8%) cases of BM, none of which was clinically suspected. However, in a review of autopsy reports of 43 people who died from metastatic BrC, Saphir and Parker did not report any BM [11]; similarly, Warren and Witham found no BM in their series of 162 BrC cancer metastases [12].

On the other hand, BrC represents the primary site in about 2.4% cases of all BMs, according to a large series of surgical and postmortem material [2, 13]. In an autopsy

series of 142 cases of BM, only 3 (2.1%) arose from BrC [14]. In another series of 2,502 bladder specimens including bladder tumours, non-neoplastic vesical lesions associated with bladder tumours, and other pathological processes resembling a tumour, only 9 cases of BrC metastatic to the bladder were found [15]. More recently, 7 cases of primary BrC were found among 282 BMs [2], whereas Xiao et al. [16] described breast primaries in 3 out of 11 cases of BM.

In our opinion, such lack of metastases in very early studies may be due to several causes, that is, (1) missed examination of breast masses during autopsy, and (2) absence of screening and early diagnosis programs.

Histotype, Route and Pattern

BrC is a histologically heterogeneous disease. Infiltrating ductal carcinoma (IDC), the most common histologic subtype, accounts for approximately 90% of BrCs [17], whereas infiltrating lobular carcinoma (ILC), the second most common type of cancer, accounts for the remaining 10% of BrCs [18, 19]. Although ILC accounts only for 10% of BrCs, its incidence is twice that of invasive cervical cancer and equal to that of ovarian cancer and thus affects a large number of women [20]. The results of an epidemiologic study suggest that the incidence of ILC is increasing in postmenopausal women [21], possibly due to hormone replacement therapy in this population.

The histopathologic and mammographic appearance of ILC is different from that of IDC, since the first is characterized by small round cells that infiltrate the breast stroma in a single-file (“Indian-file”) pattern and tend to surround benign mammary ducts and lobules in a targetoid fashion, without forming glandular aggregates [17, 19]. This type of infiltration through the breast parenchyma typically does not destroy the anatomic structure or incite substantial connective tissue response; for such reason, ILC often fails to form a distinct mass in the breast, and its early detection by physical examination or mammography may be challenging, frequently resulting in locally advanced disease at the first diagnosis. In addition, ILC tends to have a multifocal, multicentric distribution and is found to occur in both breasts [17, 22].

Approximately 3–10% of all BrC patients have metastatic disease at their initial diagnosis; recurrent disease or metastasis occurs in approximately 30% of patients during follow-up after initial treatment [23–26]. 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 gastrointestinal tract, genitourinary tract, peritoneum, retroperitoneum, and leptomeninges [19, 27, 28]. In a review of 19 cases of BMs from BrC, Feldman et al. [7] found that 33% of the cases with available histologic subtypes were ILC, which is much higher than the 10% prevalence of reported in other series [29], and anyway higher than IDC [27].

Borst and Ingold reviewed 2605 cases of BrC, 13.8% of which were ILC and 86.2% were IDC. They noted that 3.1% of ILC metastasised to the peritoneum-retroperitoneum compared with 0.6% of IDC and this was statistically significant [19]. Pontes and Oldford [9] postulated that BrC metastasizes to the bladder via retroperitoneal involvement. This kind of spread of tumour cells is not a common clinical occurrence and could be due to minute viable tumour emboli that pass through the pulmonary circulation without establishing a lung metastasis and subsequently reach the urinary bladder by hematogenous transport [8, 9, 12, 30]. This mechanism would explain the increased incidence of ILC metastasizing to the bladder. It has been postulated that in ILC loss of E-cadherin, the cell-to-cell adhesion molecule, may decrease the adhesiveness of cells and facilitate the metastasis process [31].

Another hypothesis regarding metastatic spread is that ILC is of the serosal type, which gives it a predilection to spread to the gastrointestinal and gynaecological systems [32]. In fact, lung parenchyma metastases have been more common with IDC, while metastases to the bone, meninges, and peritoneal/retroperitoneal structures are more common with ILC [33].

Some authors have associated the likelihood of developing bladder metastases with the presence of positive lymph nodes at first diagnosis of the primary disease or with steroid therapy [5, 34, 35]. Patients who have been administered steroids may develop unusual metastases due to the possible influence of the immunosuppressive effect of steroids.

Signs and Symptoms

Patient complaints are rare until the tumour penetrates the mucosal lining, which usually is a late event after metastasis has occurred. Therefore, the number of clinical reports is not a good indicator of true incidence because many metastases may not be apparent if they are confined to the serosal or muscular layers [36].

As a matter of fact, some cases are asymptomatic, being diagnosed only by imaging techniques carried in routine follow-up of this neoplasm [37, 38]. Clinical presentation may vary, ranging from the most common painless hematuria (microscopic being more frequent than gross), stress and urge incontinence, urinary frequency and nocturia, difficulty in voiding, and back pain [16, 32, 35, 39]. Gross hematuria with a history of BrC needs to be thoroughly investigated, since haematuria among patients receiving cyclophosphamide, a common cytotoxic drug used in adjuvant settings, may be easily dismissed as cystitis secondary to chemotherapy, leaving the metastatic bladder spread undiagnosed [40]. Voiding symptoms, particularly the irritative ones, may occur earlier than hematuria due to detrusor involvement. Bladder ultrasound and CT scanning may display bladder wall thickening. 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; few cases of BM from BrC have been reported to present with symptomatic hydronephrosis and renal failure [5, 7, 9, 30, 32, 36, 37, 41–50]. In one series, ureteral obstruction was found in 6 (11%) of patients with BrC metastatic to the retroperitoneum [51]; another series [52] reported as many as 24 patients with ureteral obstruction secondary to metastatic BrC.

Diagnostic Workup

Bladder ultrasound remains the first-line diagnostic procedure in patients with BrC and voiding symptoms. In case of negative findings and persistent symptoms, CT scans become imperative also in view of the poor performance of urine cytology in this setting. Magnetic resonance imaging or PET-CT may be useful in revealing other metastatic sites rather than better depicting a bladder one [53, 54]. As a matter of fact, magnetic resonance imaging could help in precise local cancer staging and in the exclusion of adjacent structure involvement (i.e., uterus and adnexa). PET/CT has increasingly been used in the imaging evaluation of patients with bladder neoplasms; however, its cost effectiveness in a BrC patient is yet to be determined [55]. Recently, 11C-choline has been claimed as a new effective tracer for the bladder wall, as it lacks urinary excretion [56].

It is worth mentioning that patient assessment should include serum CA15-3 testing, as it remains the most sensitive tumour marker in BrC follow-up. Its main function is to monitor patient response to treatment and watch for

cancer recurrence [57]. In patients with no concomitant benign disease, which might elevate CA15-3, progressive elevation of the marker strongly suggests BrC relapse [58]. As for BMs from BrC, one report [35] revealed, at urinary symptoms onset, slight elevation of this marker; the bladder lesion was detected 3 months later, due to a further increase of CA15-3. Nine months after the first elevation, CA15-3 was almost 10 times higher.

Once the bladder lesion is visualized, cystoscopy and cold-cup biopsy or, better still, transurethral resection of the lesion is mandatory to obtain a definite diagnosis. Cystoscopic findings vary and include solid tumour, non-specific inflammatory patches, abnormally thickened bladder wall with intact overlying mucosa, irregular lesion, mucosal nodularity, or plaque with telangiectasias [53, 54]. Since the disease usually originates in the detrusor muscle, biopsies are recommended even in the case of negative cystoscopic findings.

Pathology

The possibility of a BrC metastasis should be raised when the bladder neoplasm presents with an epithelial infiltration in the form of cords or individual cells involving the lamina propria, with no associated overlying papillary urothelial proliferation or “flat” CIS. In such cases, the differential diagnosis should also include rare variants of UC, that is, the micropapillary, lymphoepithelioma-like and plasmacytoid variants of UC [59, 60]. Obtaining a proper clinical history and information on the use of immunohistochemistry, for example, antibodies to oestrogen and progesterone receptors, uroplakin and thrombomodulin (see below) [59, 61, 62], will help to arrive at a correct diagnosis. Secondary lobular carcinoma of the breast mimics very closely the rare variant of UC with lobular carcinoma-like features [59]. Similarly to breast lobular carcinoma, this lesion shows areas where the tumour is composed of uniform cells with an uncohesive single cell, diffusely invasive growth pattern. In some areas the tumour cells are arranged in linear manner as single-cell files and in separate areas as solid sheets of uncohesive cells. In all of the cases, some tumour cells show prominent intracytoplasmic vacuoles. In addition to this pattern, some cases show typical TCC or CIS. It is important to recognize this rare variant to avoid a misdiagnosis of metastatic lobular carcinoma of the breast, especially in small biopsies [63]. Moreover, the presence of unusual monomorphic growth patterns without accompanying conventional urothelial carcino-

ma features, and the appearance of tumour cells invading towards the luminal surface from the outside may be of help [61].

The relative infrequency of primary adenocarcinoma of the bladder causes the dilemma whether bladder adenocarcinoma represents a primary or secondary process [2]. Mostofi et al. [63] have proposed several guidelines for such differentiation. If the adjacent mucosa contains polypoid formation, Brunn's nests, or glandular or mucous metaplasia, a primary bladder lesion is likely.

Immunohistochemistry is an indispensable adjunct in the correct diagnosis of metastatic tumours in all sites. In order to disclose an unknown primary, current algorithms suggest the first step be the assessment of CK7/CK20 expression [64]. According to Amin [62], concurrent staining for CK7 and CK20 is typical of UC cells in 65% cases, while as many as 37% UCs may express lack CK20 expression, which is the common phenotype of BC cells. Also, bladder-associated markers such as high-molecular weight cytokeratin 34betaE12, thrombomodulin and GATA3 are expressed in BrC [16]. In most cases, a positive staining for ER and PR may allow the differential diagnosis between primary bladder adenocarcinoma and BM from BrC to be relatively simple. Nevertheless, not all cases reported in the literature showed BM having the same ER and PR status of the primary BrC. In such cases, apart from the few morphological tips suggested by Mostofi et al. [63], the differential diagnosis between primary and secondary bladder cancer relies on other immunohistochemical markers, particularly GCDFP-15, which has high specificity but low sensitivity [38].

Hormonal Status

Some authors reported differences in hormonal (ER, PR) and HER2 expression between primary and metastatic tissues, with discordance rates ranging from 24 to 39% [7, 19, 39, 43, 61, 65–68]. Interestingly, patients whose tumour status changed from positive to negative (positive/negative) have shorter median survivals than positive/positive or negative/negative patients [43, 65, 69]. Anyway, even with receptor-negative secondary BM, a trial of anti-receptor therapy has been used with promising results in controlling disease [65].

The putative mechanisms of the heterogeneous ER and PR expression in the primary tumour and metastatic lesions in the same patient include the following conditions: the BrC cells are polyclonal; and ER and PR expres-

sion may shift after endocrine therapy, due to the elimination and growth of ER- and PR-positive or negative cells or due to gene mutations [43, 65].

Management and Outcome

BM from BrC may occur as late as 30 years after the initial diagnosis of the primary tumour, with a mean time of 90 months having been calculated in a large series [7]. However, it is worth mentioning that there is the possibility of BM being present at the time of first diagnosis of BrC, like in the case reported by Shah et al. [42] whereby acute renal failure due to ureteral obstruction was the presenting sign. Two further cases reported concurrent detection of BM and primary BrC [37, 39]. Rarely the diagnosis of BrC follows the diagnosis of BM [7].

In any case, transurethral resection of the vesical lesion serves diagnostic purposes, for ameliorating urinary symptoms, and to facilitate ureteral stenting in case of ureteral obstruction. Otherwise, ureteral obstruction requires percutaneous nephrostomy to achieve normalization of renal function, thus making the patient suitable for further administration of systemic chemotherapy.

While local radiotherapy should be considered because of its ability to stop hematuria [70, 71] and to provide local disease control, treatment of BM from BrC involves a combination of chemotherapy and hormonal treatment, mainly anti-oestrogens. ER- and PR-positive tumours are more responsive to hormone therapy than their negative counterparts that have longer disease-free survivals [43].

Patients with BM from BrC tend to have a very limited survival (between 1 month and 2 years), although there are reports of survival for more than 5 years [6, 53, 72, 73].

In the study by Xiao et al. [16], 7 of the 11 patients had a known history of other metastases besides the bladder. This is likely due to the fact that in the vast majority of BM cases, metastases to other organs were also present. Lin and Chen [43] reported a case in which BM was the only metastatic site. This patient relapsed 3 years after the initial diagnosis of ER negative Her-2 positive ductal carcinoma. Primary systemic therapy was given and the patient was alive at the time of writing (2 years).

Finally, one patient with lobular cancer developed simultaneous BM and local recurrence of her BrC 6 years after initial BrC diagnosis [35]; she received chemotherapy but, unfortunately, survival was not reported.

Conclusions

BMs from BrC are rare but the literature reveals an increase of such occurrence over the last few years, probably also due to better imaging techniques. Most cases are diagnosed years after the diagnosis of primary BrC and are associated with other metastatic sites; most are due to IDC rather than ILC. Apart from asymptomatic cases incidentally diagnosed by imaging techniques, particularly follow-up CT scans, most cases present with voiding symptoms. Serum CA15-3 may also be useful. Once imaging techniques identify a bladder lesion in a patient with a BrC history, transurethral resection should be warranted. Pathologic diagnosis relies on immunohistochemical studies to distinguish this entity from its main confounder, namely, infiltrating UC. Chemotherapy and hormonal treatment represent the standard therapy, with radiotherapy being used only to control bladder bleeding. The prognosis is usually poor unless BM represents the only metastatic site.

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