Vulvar metastasis from breast cancer

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Malignant tumors of the vulva are rare, with only a few reported cases in the literature. The authors present a case of vulvar metastasis in a 57-year-old woman with breast cancer. They concur that metastatic disease of the vulva is an uncommon manifestation of breast cancer; however, a high level of suspicion and further workup are needed to differentiate primary malignancy of the vulva from metastatic disease or treatable cancers such as breast cancer.

Metastasis to the vulva is an uncommon occurrence. The primary tumor is usually of a gynecologic origin. The breasts are one of the nongynecologic primary sites of vulvar metastasis.

Case history

A 57-YEAR-OLD WOMAN presented with a right breast mass. A biopsy revealed invasive lobular carcinoma in situ. Subsequent lumpectomy showed infiltrating lobular carcinoma (both solid and cribriform type) associated with diffuse lobular carcinoma in situ. Axillary lymph node dissection revealed 22 lymph nodes involved with metastatic disease. Hormone receptor analysis showed a tumor that tested positive for estrogen 90% and for progesterone 5%. There was no evidence of HER2/neu overexpression.

She received adjuvant chemotherapy with 4 cycles of doxorubicin and cyclophosphamide followed by 4 cycles of paclitaxel. She underwent a mastectomy for persistent tumor in the breasts, followed by radiation treatment to the chest wall and the axillae. She was subsequently started on tamoxifen (20 mg/d).

Two years after the presentation of the breast mass, she had a biopsy-proven local recurrence on the chest wall, and the next month, noticed a painless lump in the left labium. CT scan of the pelvis revealed a 1.5-cm contrast-enhancing lesion arising from the labial fold. PET scan showed tracer activity in the region of the labia (Figure 1). No other metastatic focus was identified. A biopsy of the labial mass was reported as invasive lobular cancer, morphologically similar to her primary breast cancer (Figure 2). No normal breast tissue or intralobular or ductal component was reported. The tissue tested positive for epithelial membrane antigen and keratin and negative for HMB45 and S100 protein. Hormone receptor analysis was positive for estrogen and negative for progesterone receptors.

Hormonal treatment was changed to anastrozole (Arimidex). She continued to develop skin and subcutaneous nodules in the axillae, upper extremities, and neck. For the past year, her condition has been stable with third-line hormonal manipulation with exemestane (Aromasin).

Discussion

Malignant vulvar tumors are rare, constituting less than 1% of all malignant lesions in women.[1] They account for 3%–5% of malignant tumors of the female genital tract.[1] Metastasis to the vulva is also uncommon, constituting only 5%–8% of all vulvar tumors, with few case reports and series in the literature.[1–3]

The most common histology seen in the vulva is squamous cell carcinoma, followed by melanoma. Although adenocarcinomas are usually the result of metastatic disease, primary adenocarcinomas can occur from the ectopic mammary tissue in the vulva or from Bartholin's gland.[4]

A majority of the primary tumors causing vulvar metastasis were reported from the female genital tract.[5,6] The cervix is the most common primary site, followed by the vagina, endometrium, and ovaries.[1,4,6] Nongynecologic primary sites are uncommon; the reported sites are the breasts, lungs, kidneys, rectum, and lymphoma. Metastasis from breast cancer also most frequently involves the regional lymph nodes. The common distant sites are the lungs, bone, liver, and brain. Although involvement of the female reproductive organs is rare, the usual sites are the ovaries and uterus.[6–8]

A synchronous or metachronous primary tumor

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Lobular carcinoma of the breast: a 'sneaky' cancer

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If a woman with breast cancer develops a metastasis to an unusual site, such as the vulva as described in the case above, most of us would shake our heads and mutter, "That's sneaky lobular cancer for you." Invasive lobular carcinomas represent about 10% of all primary breast cancers. Unlike the more common invasive ductal carcinoma, lobular carcinoma is likely to present as an ill-defined thickness in the breast rather than a well-defined mass. This fact contributes to its larger size at diagnosis. A recent series from the Baylor College of Medicine Breast Cancer database of 4,140 patients with invasive lobular carcinoma showed that 14% of the tumors exceeded 5 cm, compared with 9% of invasive ductal carcinomas.[1]

Pathologic examination of the breast mass shows small cells infiltrating through the stroma in a single file. There is little desmoplastic reaction, explaining the fact that screening mammography and physical examination may not detect these cancers at an early stage. The nondescript appearance of the malignant cells may allow small lymph node metastases to be missed on pathologic examination. Consistent with their appearance, lobular carcinomas are likely to have a low S-phase fraction and to lack human epidermal growth factor-2 overexpression. The estrogen receptor is almost always positive.

Limited response to neoadjuvant chemotherapy

We are not surprised when neoadjuvant chemotherapy, which may be highly successful in treating a high-grade ductal carcinoma, does not "melt away" a typical lobular cancer, as in the patient described in the accompanying case. In the M. D. Anderson Cancer Center experience, only 3% of the 122 patients with stage II or III invasive lobular cancer treated with primary (neoadjuvant) chemotherapy attained a pathologic complete response. This result compared with a pathologic complete response rate of 15% in 912 patients with invasive ductal carcinoma.[2]

The patient discussed in this case report had 22 positive nodes at the time of the original diagnosis, 2 years prior to her presentation with skin and vulvar metastases. Because of this finding, adjuvant chemotherapy was prescribed, with AC-T (Adriamycin [doxorubicin] and cyclophosphamide followed by Taxol [paclitaxel]) given every 3 weeks. Although most of us would have treated her with a similar program, we could also argue that chemotherapy would do little to improve her prognosis. Women with a large tumor burden (more than 20 positive nodes and a tumor > 5 cm) have a poor prognosis, despite adjuvant chemotherapy.[3] In addition, women with estrogen-receptor–positive breast cancer derive less benefit from adjuvant chemotherapy than do women with estrogen-receptor–negative disease.[4]

Patterns of metastasis

Should this woman have been followed more closely for the development of metastases? As our patients finish their adjuvant therapies, they ask us whether we will be ordering tests to screen them for metastatic disease. "How will you know if the cancer has spread?" is a question we often hear. When we explain that the evidence-based American Society of Clinical Oncology (ASCO) guidelines for the follow-up of a woman with breast cancer are basically to take a history and to perform a periodic physical examination, including pelvic examination as well as follow-up mammograms,[5] our patients are puzzled. It is difficult for them to understand that there is no survival benefit linked to the diagnosis of an asymptomatic metastasis. In this case, the ASCO guidelines served the patient well by detecting the first recurrence on the chest wall and within a month a 1.5-cm vulvar mass, which also proved to be metastatic lobular carcinoma. This was part of a systemic recurrence, with the rapid development of disseminated skin and subcutaneous metastases within a few months despite changes in endocrine therapy.

What determines the pattern of metastasis in breast cancer? Invasive lobular breast cancer, like invasive ductal cancer, can metastasize to any organ or site in the body. However, certain patterns are more common to lobular carcinoma. For example, unusual metastases to the peritoneum, gastrointestinal tract, and ovaries occur more frequently with lobular carcinoma

than with ductal carcinoma.[1] The peritoneal metastases may lead to a "linitis plastica" type of involvement of the stomach or to asymptomatic hydronephrosis. Involvement of the bladder and the uterus, if found in a woman with breast cancer, is usually associated with lobular cancer. In one series of patients with metastatic breast cancer, carcinomatous meningitis was associated almost exclusively with lobular carcinoma.[6]

The reason for the differences in the clinical picture of lobular and ductal carcinomas from the time of presentation to the time of metastasis is not known. There has been interest in the adhesion molecule e-cadherin and its role in tumor behavior. Lobular carcinoma, in contrast to ductal carcinoma, lacks immunohistochemical staining for e-cadherin.[7] We can hypothesize that this lack of e-cadherin keeps the lobular cancer cells from "clumping together" and facilitates the single-file infiltrative pattern in the breasts and the tendency to metastasize in a sheet-like fashion, such as on the peritoneal surface.

New areas of breast cancer research

There are two new areas of breast cancer research that may enhance our understanding of the biology of metastases. The first addresses the genetic predisposition of breast cancer cells to seek certain sites for metastasis.[8,9] The second addresses the need to prepare a metastatic site before the malignant cells arrive.[10]

The first area, exemplified by the work of Minn et al[8] at Memorial Sloan-Kettering Cancer Center, deals with the tissue tropism of breast cancer metastasis. They hypothesize that the site of metastasis is not random but is genetically programmed into the original cancer cells. Using a human breast carcinoma cell line, they injected the cells into immunodeficient mice and isolated cells from lung and bone metastases. Microarray analysis of cells from these two different sites had distinct signatures. Knockdown studies of three of the genes associated with lung metastases led to decreased lung metastatic activity. The lung metastasis signature defined by these experiments was applied to a clinical cohort of breast cancer patients with known metastases and was predictive of the presence or absence of lung metastases. This work is exciting for clinicians, as it may open new doors for tailored adjuvant therapy and may lead to more targeted therapies for metastatic disease.

A second area of innovative research in metastatic breast cancer involves the initiation of the premetastatic niche by vascular endothelial growth factor receptor-1 positive hematopoietic bone marrow progenitors.[10] These cells leave the bone marrow in response to a humoral signal from the primary tumor and home to a site, eg, the lymph nodes or lungs, where they initiate a niche where metastases can settle. Although the majority of the experiments described by Kaplan et al[10] from Weill Medical College of Cornell University were performed in mice, the investigators describe similar niches in human tissue as well. Tumor-specific growth factors upregulate fibronectin in resident fibroblasts of the niches in preparation for the metastatic cells. The location of these niches is specific for certain tumor types. This unique mechanism may also contribute to the distinct metastatic pattern of lobular carcinoma. The concept of targeting the cellular or humoral components of the premetastatic niche and thus preventing metastases is an exciting area for clinicians to follow.

Conclusion

The oncologist who cares for patients with a history of breast cancer, particularly lobular cancer, realizes that the disease can recur in any location at any time after a primary diagnosis. Why are vulvar metastases so rare? The biology of the vulva should be similar to the skin and subcutaneous tissue elsewhere in the body. Oncologists should continue to report and to study rare metastases. With the new techniques available, these studies may help to elucidate the basic biology of metatases and ultimately lead to better treatment options for our patients with breast cancer.

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FIGURE 1 Positron emission tomography scan showing tracer activity in the region of the labia.

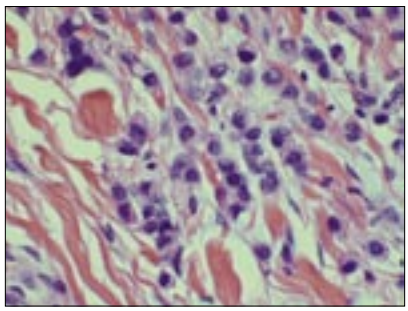

FIGURE 2 Indian file pattern of invasive lobular carcinoma. Hematoxylin and eosin.

of the orthotopic and ectopic breast tissue in the vulva has been reported.[1,3] Primary mammary cancer has been seen in supernumerary breast tissue in the vulva.[1,3] Even though they are rare, malignant vulvar tumors should be differentiated from isolated metastatic disease to the vulva, since local treatment includes aggressive radical surgery for the primary tumor in the vulva. They can be differentiated by identifying the primary breast tissue and malignancy in the vulva, especially if there is an in situ component, and ruling out primary orthotopic breast cancer.[1,3,6] In patients with a history of breast cancer, diagnosis of a vulvar tumor is made by histology, morphologic correlation with a primary breast tumor, and confirmatory staining for hormone receptors and HER2/neu overexpression.[1,8–10]

Both ductal and lobular carcinomas of the breasts with metastasis to the vulva have been reported.[3,4] However, an autopsy study reviewing the metastatic pattern of breast cancer found that infiltrating lobular carcinoma was associated with a greater propensity to involve the internal genital organs than were invasive ductal lesions.[1,4,6] Although involvement of the vascular space has been suspected, the real etiology of this metastatic phenomenon is not clear.

The most common presenting feature is a vulvar nodule or mass, followed by pain and ulceration.[1,4,8,9] The common site of metastasis is the labium majus.[4] Metastasis to the clitoris has been reported from urologic and/or gastrointestinal primary tumors.[4]

Treatment of primary breast cancer of the vulva is similar to that of primary orthotopic breast cancer.[3] Metastatic disease also can be managed similarly, depending on the prognostic factors and the extent of disease.[11]

The American Society of Clinical Oncology has recommended that patients with breast cancer undergo a pelvic examination and a Pap smear at regular intervals.[1,11] Careful, routine gynecologic surveillance along with vigilance about unusual metastatic sites can help to facilitate the detection and treatment of uncommon manifestations of breast cancer.

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