

Case Report

Breast cancer metastasis to the vulva 20 years remote from initial diagnosis: A case report and literature review

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1. Introduction

Breast cancer is the most common malignancy affecting women in the United States, with an estimated 232,670 new cases and 40,000 deaths in 2014 (National Cancer Institute, 2015). The two most common histologic subtypes of invasive breast cancer are ductal and lobular. Invasive ductal carcinoma (IDC) accounts for 60–75% of all tumors, while invasive lobular carcinoma (ILC) accounts for 10–15% of all tumors. Cancer of the vulva, by contrast, is relatively uncommon, accounting for less than one percent of all cancers in women. Metastatic disease to the vulva is even less common, representing 5–8% of all vulvar cancers (Neto et al., 2003).

Both lobular carcinoma and ductal carcinoma of the breast can be metastatic to common sites such as the liver, bone, and lung. ILC, in particular, is known to have a distinct metastatic pattern with a higher frequency of metastasis to sites such as the peritoneum, hollow viscera, and internal reproductive organs. Metastasis may occur remote from the time of original breast cancer diagnosis by several years in patients who are relatively asymptomatic. Such case reports demonstrate a greater prevalence of pre-menopausal patients with hormone receptor-

positive disease, although the role of selection bias in the literature is unclear (Abu-Rustum et al., 1997; Bigorie et al., 2010; Lamovec and Bracko, 1991; Ferlicot et al., 2004).

We present the case of a 57-year-old female with an isolated, asymptomatic vulvar metastasis of ILC of the breast, greater than 21 years following her initial breast cancer diagnosis. This represents the longest interval between primary breast cancer and vulvar recurrence in the literature to date.

2. Case presentation

The patient originally underwent a left modified radical mastectomy in April 1993 at the age of 36. Surgical pathology revealed mixed ductal and lobular carcinoma, estrogen and progesterone-receptor positive, with 7 of 38 axillary lymph nodes positive for disease. She underwent adjuvant chemotherapy in the form of doxorubicin for four cycles, followed by a triple regimen of cyclophosphamide, methotrexate, and 5-fluorouracil for eight cycles. This was followed by Tamoxifen therapy, which the patient voluntarily discontinued after 2 months. She also received adjuvant radiation therapy to the chest wall and left supraclavicular area.

She had no evidence of disease for nearly 10 years, with surveillance mammography consistently negative for recurrence in the remaining breast. In January 2003 she presented to her primary care physician with a complaint of abdominal bloating. The following month she underwent a diagnostic laparoscopy, revealing a large amount of chylous ascites, an approximately 8 cm right adnexal mass, and carcinomatosis of virtually all peritoneal surfaces. The decision was made to proceed with trans-abdominal hysterectomy, bilateral salpingo-oophorectomy, appendectomy, staging, and radical debulking. Surgical pathology returned with diffusely metastatic carcinoma, 8 of 13 lymph nodes positive for disease, with histologic features consistent with lobular carcinoma of the breast. Pathologically, cancer morphology was noted to be similar to that seen in prior breast carcinoma specimen from 1993. Postoperatively the patient was initiated on chemotherapy with Taxotere and Xeloda, with subsequent transition to Arimidex maintenance chemotherapy. She underwent surveillance with serum tumor markers CA 27–29 and CT scans of the chest, abdomen, and pelvis. The patient was offered BRCA 1/2 testing, which had not been widely available at the time of her primary breast cancer, but declined.

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In early 2014, laboratory studies began to demonstrate a gradual rise in serum CA 27–29 levels. PET scan from May 2014 failed to demonstrate any abnormal metabolic activity of the chest, abdomen, or pelvis. In July 2014 the patient presented to her Gynecologic Oncologist complaining of a palpable right-sided labial mass. Physical exam revealed a pea-sized nodule of the right labium majora deep to the skin. The patient underwent excision of the right labial mass. Intraoperative findings included a firm, approximately 0.5 cm mass of the right labium majora, not involving the overlying skin. Final surgical pathology returned with metastatic lobular carcinoma of the breast. Postoperatively, the patient was initiated on chemotherapy with multiple agents, and developed signs of metastatic disease including ascites, pleural effusion, inguinal lymphadenopathy, and lesions of the thoracic and lumbar spine.

3. Pathologic analysis

3.1. Modified radical mastectomy of the left breast, 1993

Microscopic examination demonstrated a moderately-differentiated infiltrating mixed ductal and lobular carcinoma (Fig. 1). The tumor cells were arranged with rare tubule development, high nuclear pleomorphism, and rare mitotic activity. The cells were arranged in nests and cords of single infiltrative cells with targetoid appearance, characteristic of a lobular carcinoma. Atypical ductal hyperplasia was seen focally. Metastatic carcinoma involved 7 of 38 axillary lymph nodes, with extra-capsular extension of carcinoma. Tumor cells were estrogen and progesterone receptor positive.

3.2. Transabdominal hysterectomy, bilateral salpingo-oophorectomy, staging, appendectomy, and radical debulking, 2003

Examination of the ovaries, fallopian tubes, uterine serosa, lymph nodes, appendix, and omentum showed extensive involvement by metastatic carcinoma. Histologic features were suggestive of a lobular carcinoma of the breast, with pleomorphic tumor cells arranged in nests and cords of single cells with absent glandular formation. Cells had oval pleomorphic nuclei containing small nucleoli and moderate quantities of polygonal shaped cytoplasm. Some of the cells had intracytoplasmic clear areas resulting in a targetoid appearance. This morphology is similar to that seen in the prior breast specimen from the original 1993 mastectomy. The tumor cells were positive for estrogen receptor. The pelvic fluid obtained at surgery was noted to be positive for malignant cells consistent with adenocarcinoma.

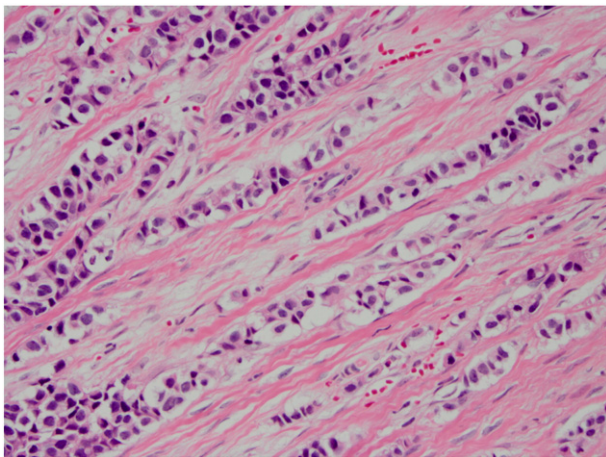


Fig. 1. 1993 H&E 400 \times . The mixed ductal and lobular carcinoma of the breast primary is arranged in nests and single-file cords with nuclear pleomorphism and rare mitotic activity.

3.3. Excision of right labial mass, 2014

Microscopic examination of a right labial mass revealed soft tissue with focal areas of infiltrative carcinoma arranged in cords of single cells (Fig. 2). Perineural invasion was present. Immunohistochemistry was strongly positive for CAM 5.2 and estrogen receptor. Tumor cells were negative for CD68. This immunophenotype and morphology are consistent with the known breast primary.

In a prior case report by Perrone et al., criteria were suggested for differentiating primary versus metastatic breast-like carcinoma in the vulva (Perrone et al., 2009). They suggest that primary breast-like carcinoma of the vulva should have normal breast tissue within the specimen, and an in situ component. Conversely, metastatic breast carcinoma of the vulva would lack those two components, and be found in a patient with a known history of a breast carcinoma. Additionally, metastatic disease would have a similar histologic subtype, hormonal receptor status, and immunohistochemical pattern. When applying these diagnostic criteria to our case, we feel confident in identifying the tumor as a metastatic breast carcinoma to the vulva.

4. Literature review

The differences in metastatic spread between IDC and ILC have been well documented. One retrospective autopsy study of 261 patients found no difference in spread to common sites including the liver, bone, and pleura. ILC was more likely to spread to uncommon sites including the peritoneum, retroperitoneal structures, hollow viscera, uterus and ovaries, leptomeninges, and myocardium. These metastases were noted to be clinically silent for prolonged periods of time (Lamovec and Bracko, 1991).

Another retrospective analysis evaluated 109 patients treated for ILC with subsequent development of metastatic disease, compared to a control group of 2749 patients with IDC. The ILC group was noted to have more frequent metastases to the bone, peritoneum, ovaries, gastrointestinal tract, adrenal glands, gall bladder, pancreas, kidney, bladder, and eyelid (Ferlicot et al., 2004).

Neto et al. reported in 2002 on 66 cases of metastatic disease to the vulva occurring at M.D. Anderson Cancer Center over a 57-year time frame. 43.9% of cases were of non-gynecologic origin, including four breast primaries (6.0% of all cases). The histologic subtypes of these cases included one ductal carcinoma, one lobular carcinoma, one cystosarcoma phyllodes, and one poorly differentiated carcinoma (Neto et al., 2003).

We reviewed PubMed for all dates using the terms *breast cancer recurrence*, *breast cancer metastasis*, *breast cancer vulva*, *metastatic cancer vulva*, and *vulvar cancer*. Including our case, a total of 20 published

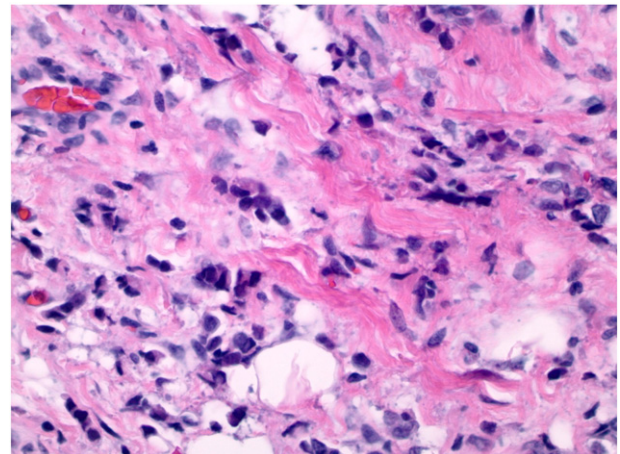


Fig. 2. 2014 H&E 400 \times . The right labial mass shows focal areas of pleomorphic infiltrative carcinoma arranged in cords of single cells.

Table 1

Case reports of breast cancer metastatic to the vulva.

Author	Year	Age	Histology	Interval (months)
Perrone et al. (2009)	1964	78	Comedocarcinoma	66
Perrone et al. (2009)	1973	36	Ductal carcinoma	33
Perrone et al. (2009)	1982	61	Undifferentiated	12
Perrone et al. (2009)	1988	N/A	N/A	N/A
Perrone et al. (2009)	1996	48	Ductal carcinoma	7
Perrone et al. (2009)	1997	61	Ductal carcinoma	4
Menzin et al. (1998)	1998	53	Lobular carcinoma	Synchronous
Sindico et al. (1998)	1998	79	Ductal carcinoma	144
Porzio et al. (2001)	2001	67	Ductal carcinoma	168
Miliaras (2002)	2002	45	Ductal carcinoma	12
Neto et al. (2003)	2003	65	Ductal carcinoma	24
		48	Lobular carcinoma	84
		47	Undifferentiated	60
		53	Cystosarcoma pylloides	48
Valenzano Menada et al. (2003)	2003	49	N/A	132
Sheen-Chen et al. (2004)	2004	32	Lobular carcinoma	40
Perrone et al. (2009)	2008	72	Ductal carcinoma	Synchronous
Papaioannou et al. (2010)	2010	93	Lobular carcinoma	156
Julien et al. (2012)*	2012	68	Ductal carcinoma	72*
Alligood-Percoco	2014	57	Lobular carcinoma	255

* Julien et al. (2012), case report of a 6-year delayed clitoral metastasis of IDC, interval in months not provided.

reports have documented metastasis of breast cancer to the vulva, including 9 cases of IDC, 5 cases of ILC, 2 cases of undifferentiated carcinoma, 2 cases that were not clinically described, 1 case of comedocarcinoma, and 1 case of cystosarcoma phyllodes (Table 1). The time interval between initial breast cancer diagnosis and vulvar metastasis, not including cases of synchronous diagnosis, ranged from 4 months to 255 months. Our case represents the longest reported interval. Cases of metastatic ILC to vulva had, on average, a longer interval to vulvar metastasis of 133.8 months, compared to 58.0 months for the IDC cases (Neto et al., 2003; Perrone et al., 2009; Menzin et al., 1998; Sindico et al., 1998; Porzio et al., 2001; Miliaras, 2002; Valenzano Menada et al., 2003; Sheen-Chen et al., 2004; Papaioannou et al., 2010; Julien et al., 2012).

5. Discussion

Breast cancer continues to pose a tremendous disease burden, as both the most common malignancy and the most common cause of cancer death in American women today. The differences in metastatic spread between ILC and IDC have been previously described, with ILC more prone to delayed metastasis, and metastasis to sites such as the peritoneum, hollow viscera, and internal reproductive organs. Metastatic spread of breast cancer to the vulva is exceedingly rare.

Embryologic development of the female reproductive tract involves formation and regression of the mammary ridge along the primitive "milk line", extending from the axilla to the groin region. Remnants of ectopic breast tissue can occasionally be found along this tract, including the vulva (Perrone et al., 2009). Rare cases have documented primary breast-like carcinoma in the genital region, thought to originate from this ectopic tissue. Our pathologic analysis has confirmed that this

case represents a delayed metastasis of primary breast ILC greater than 21 years after the primary diagnosis.

This case reinforces concerns regarding the risk for delayed metastasis in patients with ILC, particularly young patients with hormone receptor-positive disease. The existing literature suggests that these patients are at risk for delayed recurrence at distant metastatic sites. Counseling and surveillance of these patients should take this risk into consideration, with incorporation of routine physical examination including pelvic examination. Oncologists should assess the role for screening serum markers and imaging based upon the patient's unique clinical history. The duration of surveillance for ILC in remission is controversial. This case report as well as others cited here support long term, even indefinite follow-up, with hopes of finding metastatic disease as early as possible.

Conflict of interest statement

The authors have no conflicts of interest, financial or otherwise, to declare and we have completed the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.gore.2015.05.002>.

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