Primary Ectopic Breast Carcinoma of the Vulva: A Case Report

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Abstract

A 64-year-old woman presented to the Emergency Department with acute vomiting and moderate, sharp, diffused abdominal pain, and weakness. She reported chronic Bartholin's cyst for 1 year, which prompted gynecology consult. Investigations had revealed a primary breast carcinoma of the vulva. Surgical excision was performed, and pathology of the mass demonstrated estrogen receptor weakly positive (20%), progesterone receptor negative (< 1%), and HER2 oncoprotein positive (3+). PET/CT showed metastatic disease involving retroperitoneal, bilateral iliac chain and pelvic lymph nodes and the left T12 lamina. Mammogram showed no evidence of disease, and all her prior mammograms were negative. Due to the lack of standard treatment guidelines, the patient was managed utilizing the established breast cancer treatment guidelines. The purpose of this case report is to highlight the rarity of the diagnosis of primary breast carcinoma of the vulva and the importance of including this diagnosis in differential when evaluating patients with mass lesions of the vulva.

Introduction

Ectopic breast tissue is a common congenital condition found in 2% to 6% of women and 1% to 3% of males, which may develop along the embryologic mammary lines extending bilaterally from the axilla through the breast to the mons pubis (1, 2). The term *ectopic breast tissue* is used for both supernumerary and aberrant breast tissue. Supernumerary breasts have nipples, areolae or both with varied composition of glandular tissue, whereas an aberrant or accessory breast tissue has no organized secretory system and does not communicate with the overlying skin. The most common location for the accessory breast tissue is the axilla while other uncommon sites are infraclavicular, subscapular, epigastric and vulva (3). An accessory breast tissue is hormonally sensitive and may enlarge in response to pregnancy or exogenous hormones, and these tissues may also develop breast pathologies, including fibroadenoma, phyllodes tumor, Paget disease, and invasive adenocarcinoma (1, 2). Ectopic breast carcinoma is often not detected, or diagnosis is delayed until significant clinical symptoms due to lack of screening. We report herein a case of primary ectopic breast carcinoma of the vulva with distant metastasis to bones and lymph nodes in a postmenopausal woman.

Case Presentation

A 64-year-old obese, postmenopausal woman, gravida 1 para 1-0-0-1, presented to the Emergency Department with acute vomiting and moderate, sharp, diffused abdominal pain, and weakness. On physical exam, patient was febrile and tachycardic with diffuse abdominal tenderness. Her complete blood count with differential revealed neutrophilic leukocytosis. Blood culture grew group B *Streptococcus*. Computed tomography of abdomen and pelvis revealed several enlarged lymph nodes within the inguinal regions and iliac chains within the pelvis bilaterally (Figure 1). The patient was admitted for evaluation and management of her presenting symptoms.

Upon further investigation of unclear etiology of inguinal lymphadenopathy and bacteremia, patient reported chronic Bartholin's cyst for 1 year, which prompted gynecology consult. External examination of genitalia showed 3 cm x 4 cm firm left vulvar mass with irregular border superiorly with erythema. There was no fluctuance or drainage. On her hospital stay day 3, she was taken to the operating room for simple excision of vulvar mass for management of sepsis as suspected source of infection. Firm, non-mobile, non-necrotic, 3.5 cm x 4.5 cm vulvar mass on left labia majora was excised for biopsy.

Histopathologic evaluation reveals a 2.7 cm poorly differentiated infiltrative mass invading subcutaneous tissue, epidermis, and dermis with skin ulceration. Deep surgical

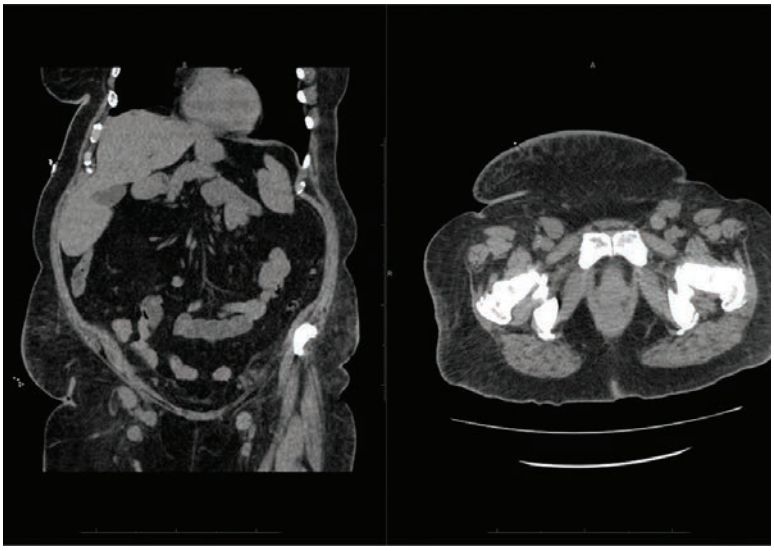

Figure 1. Computed tomography shows several enlarged lymph nodes within the inguinal regions and iliac chains within the pelvis bilaterally.

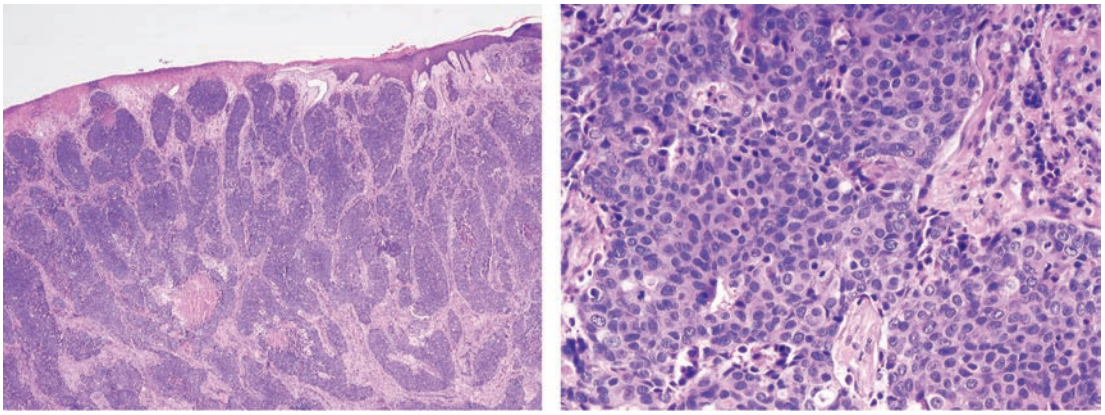

Figure 2. Hematoxylin and eosin stain of ulcerated skin with invasive tumor x20 magnification (left) and x200 magnification (right).

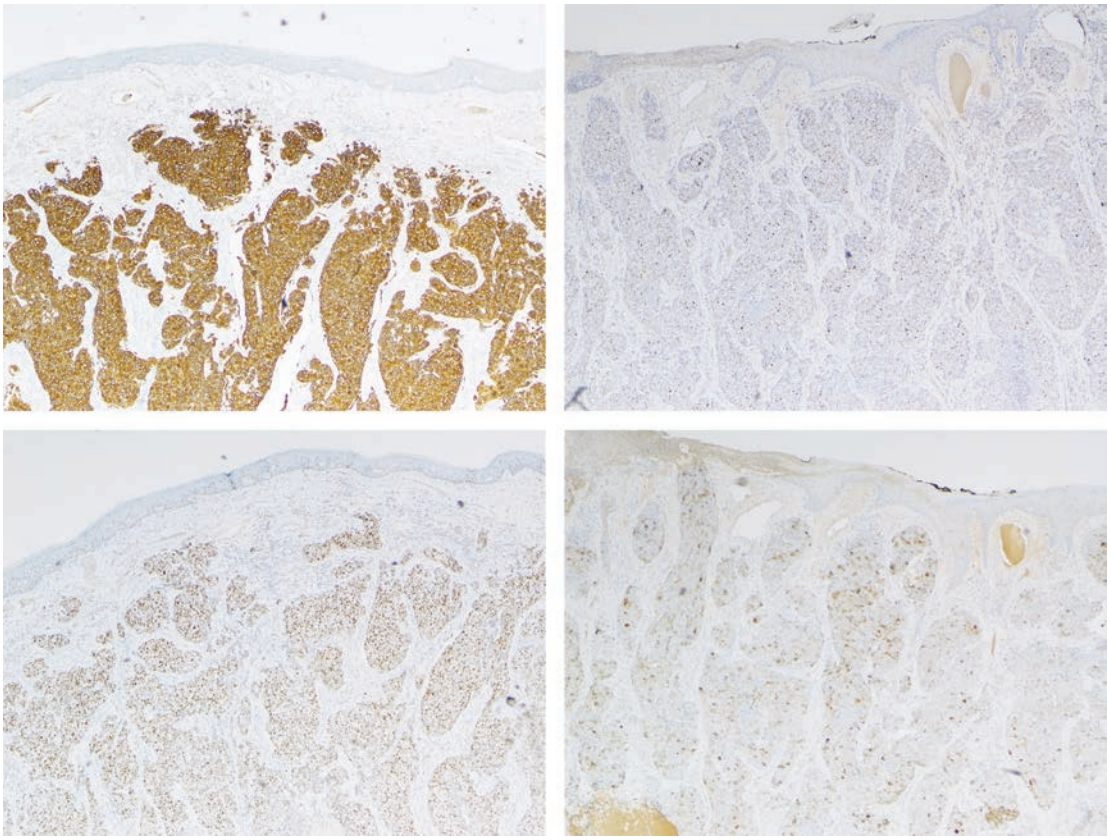

Figure 3. CK7 immunostain (top left), estrogen receptor immunostain (top right), GATA-3 immunostain (bottom left), and GCDFP-15 immunostain (bottom right) of invasive tumor x40 magnification.

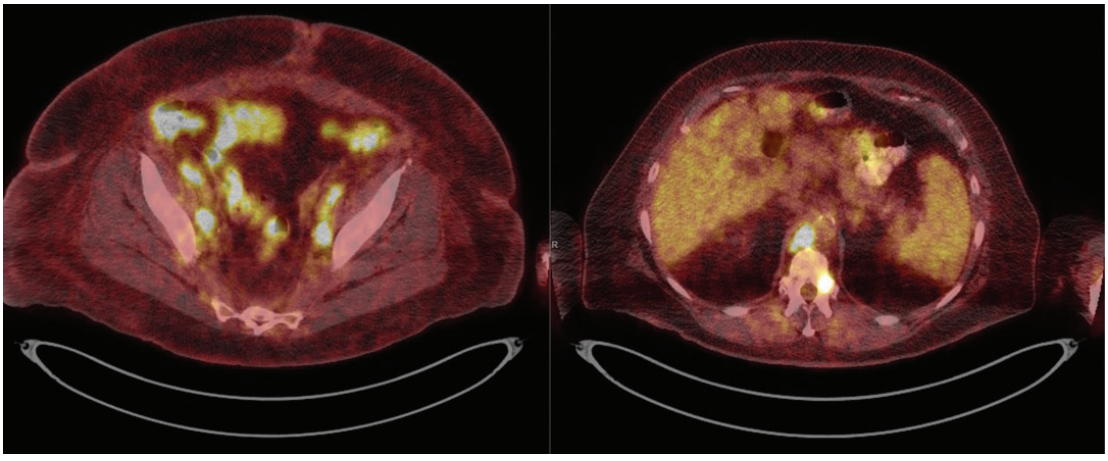

Figure 4. PET/CT scan shows multiple FDG avid bilateral iliac chain and pelvic lymph nodes (left) and left T12 lamina (right).

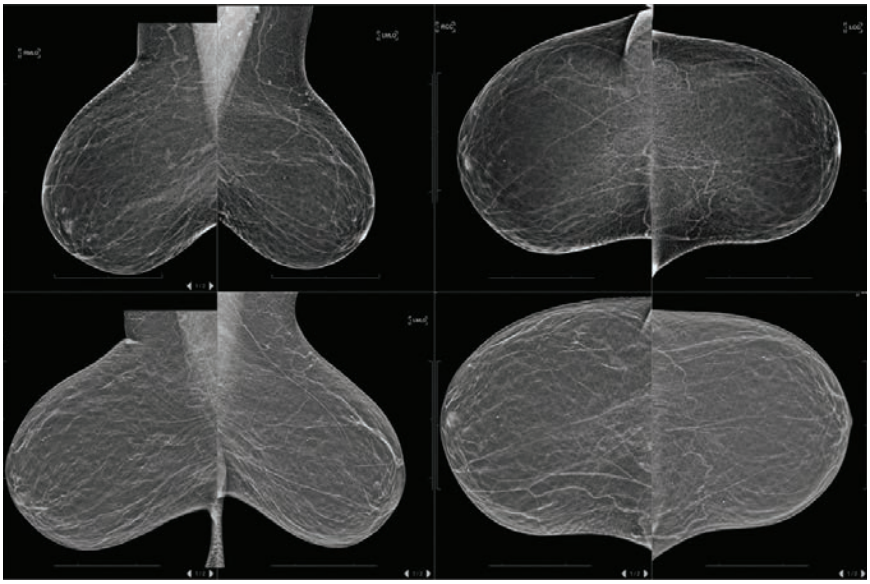

Figure 5. Mammography from 2019 (top) and 2020 (bottom).

margins were involved, and the mass comprises infiltrative sheets and clusters of malignant ductal epithelial cells with comedo-type necrosis. The tumor cells show markedly enlarged pleomorphic nuclei with vesicular chromatin and a distinct-to-prominent nucleoli (Figure 2). Myoepithelial cell layer is absent. The tumor shows the following immunophenotypic profile: CK7 and GATA-3 diffuse positivity; GCDFP-15 and estrogen receptor (ER) patchy positivity; BNC5 immunostain confirms a clonal ductal proliferation with loss of the myoepithelial cell layer; CK20, p40, CK5/6, uroplakin-II, mammaglobin, CD56, synaptophysin, and S100 immunostains are all negative; and p16 immunostain shows equivocal patchy staining. Therefore, usual markers of breast origin (CK7, GATA-3, GCDFP-15, and ER) are positive, while usual markers of melanocytic, neuroendocrine, and urothelial primaries are negative (Figure 3). Hence, the diagnosis of a primary ectopic breast carcinoma of the vulva, histologic grade 3 (poorly differentiated). The pathologic staging for this case is a pT1b pNX (for lesions more than 2 cm or any size with stromal invasion more than 1.0 mm, confined to the vulva and/or perineum; and regional lymph nodes cannot be assessed). Prognostic markers revealed: ER is weakly positive (20%), progesterone receptor (PR) is negative (<1%), and HER2 oncoprotein is positive (3+).

The tumor cells show the usual profile of an invasive ductal carcinoma of breast origin. Evaluation of receptor protein expression is performed by visual analysis of formalin-fixed paraffin-embedded immunostaining of the invasive tumor using FDA-cleared antibodies and protocols with estrogen receptor protein (Ventana SP1 antibody), progesterone receptor protein (1E2 antibody) and FDA approved HER2 oncoprotein (Ventana 4B5 antibody). ER protein expression is weakly positive with 20% nuclear positivity and 2+ average intensity score (range 0 to 3+). PR protein expression is negative with <1% nuclear positivity. Assay external control immunoreactivity is appropriate. No internal control was present in the analyzed tissue. False negative results may occur when no internal control ducts are present in tissue with negative reactivity in the tumor cells. Therefore, the results from specimens that are negative must be evaluated accordingly. HER2 oncoprotein expression is positive with 3+ average membranous intensity.

Positron emission tomography/computed tomography (PET/CT) scan was performed which showed multiple enlarged and fluorodeoxyglucose (FDG) avid retroperitoneal, bilateral iliac chain and pelvic lymph nodes most consistent with metastatic disease. Several indeterminate subcentimeter, mildly FDG avid bilateral subpectoral lymph nodes were visualized as well. Hypermetabolic osseous lesion involving the left T12 lamina is consistent with metastatic disease (Figure 4). There is an indeterminate 8 mm left upper lobe nodule with no abnormal FDG activity seen on CT, likely too small to be seen on PET. Mammogram showed no evidence of malignancy (BI-RADS Category 1), and past mammography from 2019, 2018, 2016 and 2014 were all negative (Figure 5). The patient has a history of hypertension, diabetes mellitus Type 2, dyslipidemia, iron deficiency anemia, osteoarthritis, rheumatoid arthritis, sleep apnea, chronic diarrhea, and nausea. Past surgical history includes Cesarean section, dilation and curettage, fluorescein angioscopy, bevacizumab injection, and retina treatment (photocoagulation). There is no significant family history of cancer.

The patient is being managed by a hematology oncology provider. A biopsy of lymph nodes or bone was requested but was not feasible. Initial treatment options were followed: chemotherapy with paclitaxel, trastuzumab and pertuzumab. A cycle is every 21 days with close monitoring of heart function. Echocardiogram was obtained prior to initiating the treatment to assess the baseline cardiac function which was within normal limits. Denosumab is given to prevent skeletal events with the plan for restaging every three to four cycles. Following the initiation of the treatment, Taxol was changed to Abraxane due to allergic reaction, even with oral high dose dexamethasone. A cycle is 21 days: 2 weeks on and 1 week off. The patient reported severe depression and anxiety, and she was referred to palliative care and support group. The patient also reported a new onset headache, which prompted CT scan of brain which was within normal limits. The patient declined MRI due to claustrophobia.

Discussion

At the fifth or sixth week of fetal development, an ectodermic thickening starts to form the mammary ridges, which extends bilaterally from the axilla to the groin along the milk lines. These ridges are not prominent in the human embryo and disappear over the following months, except for small portions that may persist in the pectoral region (5, 6). Ectopic breast tissue is persistent epidermal thickenings along milk line from axilla to perineum or vulva due to clusters of primordial breast cells that fail to involute. Ectopic breast tissue may be combinations of breast glandular tissue and nipple, and it occurs in 2% to 6%

of females and 1% to 3% of males. Almost any type of known breast pathology can occur in such ectopic breast tissue, and primary breast carcinoma arising from accessory breast tissue has been reported in 60% to 70% of all forms of ectopic breast tumor (4).

Primary carcinoma of the ectopic breast is relatively common at the axilla, while primary carcinoma arising from ectopic breast tissue in the vulva is extremely rare with an incidence of 4%. The predominant pathology is that of invasive ductal carcinoma, however, ductal carcinoma in situ, lobular carcinoma, mucinous adenocarcinoma, phyllodes tumors, and fibroadenomas have also been reported in ectopic breast tissue (7). Multiple cases of this rare malignancy have been reported in the English-language clinical literature; however, ectopic breast carcinoma is difficult to diagnose due to the late expression of pathologic symptoms.

In the absence of concurrent breast carcinoma, the lesion of primary vulvar origin can be categorized by the following: a morphologic pattern consistent with breast carcinoma, the presence of estrogen and progesterone receptors, and/or positivity for common breast cancer markers such as epithelial membrane antigen, carcinoembryonic antigen, and glandular keratins (8). For a diagnosis of this disease, a thorough metastatic workup is necessary including, but not limited to history, physical examination, and radiologic examination of the breasts, to confirm that the vulvar lesion is the primary site as opposed to a metastasis from a primary breast cancer. Although primary breast cancer of the vulva tends to metastasize early and to have a poor prognosis, definitive treatment guidelines have been unavailable. Currently, this type of cancer is stage and treated according to current tumor, node, metastasis (TNM)-based classification applicable to primary breast cancer. The treatment should consist of individualized combination of surgery, chemotherapy, monoclonal antibody therapy, radiation, and adjuvant endocrine therapy, as appropriate.

Conclusion

Primary breast carcinoma, arising from embryonic mammary ridge remnants, is an extremely rare histologic subtype of vulvar cancer; however, this should be included in differential diagnosis when evaluating patients with mass lesions of the vulva. Obtaining adequate tissue biopsy is essential in establishing a morphologic diagnosis, since diagnosis rests on the pathologic findings, with recognition of the characteristic histologic features and the presence of estrogen, progesterone and/or HER2 receptors and the extent of disease. Therapy should consist of an individualized combination of surgery, radiotherapy, chemotherapy, antiestrogen therapy, and monoclonal antibody therapy, like cancer of the orthotopic breast of similar stage. Owing to the rarity of this lesion, clinical trials to determine optimum treatment are not available, and management guidelines will rely on small series or case studies.

Acknowledgments

We thank the patient for allowing us to share her details and thank John S. Farrell, MD, Department of Radiology, Geisinger, for radiologic image acquisition.

Disclosures

Youngeun C. Armbuster, Paula Ronjon, Cletus Baidoo, and Waqarun N. Rashid declare that they have no conflict of interest.

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