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Primary breast cancer of the vulva: A case report and literature review

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Abstract

An elderly lady presented with a 2-year history of intermittent vaginal bleeding and later the development of a vulvovaginal mass. A core biopsy histology specimen from the mass and the left inguinal lymph node was suggestive of metastatic adenocarcinoma of breast origin. No breast lesion was detected on mammography, and axillary nodes were negative. The histopathologic features and the expression of GATA3, cytokeratin (CK)7, mammaglobin staining and estrogen and progesterone receptors led to a diagnosis of breast cancer originating from the ectopic mammary tissue in the vulva. Given the rarity of these lesions, and the lack of standard treatment guidelines, the management of the patient was extrapolated from the established breast cancer treatment guidelines. Radiotherapy and chemotherapy followed by hormone therapy with aromatase inhibitor were administered to this patient in the metastatic setting with good palliation.

Key words: breast cancer, carcinoma of the vulva, ectopic breast cancer.

Introduction

Ectopic breast tissue is reported to affect 2% to 6% of the general population[1]; this ectopic tissue is susceptible to the same physiological and pathological changes affecting the normally located breasts including malignancy. It may originate at any point in the so-called milk line, with a relatively higher incidence in the axilla, followed by the inframammary area.

Primary carcinoma arising from ectopic breast tissue in the vulva is extremely rare with an incidence of 4%.[2] To our knowledge, 28 cases of this rare malignancy have been reported in the English-language literature.

Case Report

A 76-year-old lady, Para 2–0–0–2, who had a hysterectomy for uterine prolapse with intramural fibroid in 2012 presented with a 2-year history of intermittent vaginal bleeding and presumed hematuria. She was a lifetime non-smoker, and her medical history was remarkable for hypertension and hypothyroidism with no history of cancer or breast disease and no family history of malignancy. She had an episode of heavy vaginal bleeding and hematuria in July 2014, followed by a second episode 4 months later.

Despite a thorough physical examination and investigations, no cause was identified for her bleeding. As a result of this, she became a recluse and had to wear multiple pads every day.

In March 2015, a CT scan of abdomen and pelvis revealed suspicious soft tissue thickening of the bladder wall suggestive of carcinoma. However, subsequent cystoscopy and biopsy only revealed mild chronic inflammation with no evidence of malignancy. In December 2015 she had a third episode of heavy vaginal bleeding with progressive swelling of the left leg, which was managed by the gynecologist

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as a case of moderate cyst-enterocele associated with vaginal atrophy. Further gastroenterology review and colonoscopy were negative. Subsequently, vaginal bleeding became continuous and she was referred again for further gynecological evaluation. Pelvic examination at that time showed a large pelvic mass with ulceration of the posterior vaginal wall, right inguinal lymph nodes and multiple subcutaneous vulval nodules. Initially, fine needle aspiration (FNA) biopsy of the groin node revealed poorly differentiated large cell metastatic carcinoma indicating a metastatic adenocarcinoma; an immunohistochemical (IHC) test was positive for cytokeratin (CK)7 and GATA3 while negative for CK20, Pax8, SOX10 and D2–40 with some positive staining to CK5/6. A second opinion was requested, and additional core biopsy from the vaginal mass and inguinal lymph node was suggestive of metastatic adenocarcinoma of breast origin. The IHC was consistent with breast cancer, being positive for estrogen receptor (90%) and progesterone receptor (80–90%). HER 2 was negative. Proliferation index Ki-67 was very high (80–90%) with positive GATA3, cytokeratin (CK) 7, and mammaglobin staining. These pathologic features were consistent with a breast cancer origin (Fig. 1). The patient's baseline CA 15.3 was 102 U/mL in April (normal range < 30 U/mL); other tumor markers including carcinoembryonic antigen (CEA) and CA125 were normal. Further investigation by pelvic MRI confirmed the presence of a perineal mass on the lower half of the vagina with bilateral inguinal and external iliac lymph node enlargement that explained the left leg lymphedema. A whole-body positron emission tomography (PET)-CT scan in search of a primary tumor elsewhere only showed an avid pelvic mass in the region of the vagina near the rectum with multiple nodes above and below the diaphragm, but no breast or axillary lesions or another non-nodal metastasis (Fig. 2). A clinical breast exam was negative and bilateral mammography and breast ultrasound showed normal fatty breasts with no suspicious lesions in the breasts or axillae. A breast MRI was not done due to cost. The case was discussed at the multidisciplinary meeting, and a diagnosis of primary adenocarcinoma of the ectopic breast tissue of the vulva was made. Following discussion with the patient and given her locoregional symptoms with multiple vulval nodules, constant per vaginum bleeding, right leg edema and the long natural history of her symptoms, it was decided to treat her with high dose VMAT (volumetric modulated arc therapy) radiation to a dose of 50.4 Gy in 28 fractions with a simultaneous integrated boost to the pelvic mass and inguinal nodes. Her radiotherapy commenced on March 7, 2016 and was completed on April 15, 2016. The bleeding stopped after 11 fractions and did not recur. The patient developed moist desquamation of the vulva, intermittent diarrhea and some nausea, but tolerated the radiotherapy remarkably well. In addition, her hemoglobin level dropped to 78 g/dL, requiring a blood transfusion. Given the high proliferation marker (Ki-67 of 80–90%) indicative of an aggressive and rapidly growing malignancy, hormonal therapy was initially considered, but given the extent of the disease it was considered that initial chemotherapy was a better systemic therapy option to control her metastatic disease. She was subsequently treated with six cycles of Abraxane (Paclitaxel protein-bound), which she tolerated well and resulted in a good clinical response. The CA15.3 continued to fall from 102 to 55 U/mL at the end of the chemotherapy course. A progress CT scan confirmed a partial response in the lymph nodes. The patient was then started on maintenance treatment with Femara (Letrozole) hormone therapy. Unfortunately, she presented 10 weeks later with acute obstructive uropathy from bilateral ureteral obstruction caused by enlarged retroperitoneal lymph nodes which were treated by bilateral stent insertion. Her case was discussed again in a multidisciplinary meeting and given the fact that her disease was quite aggressive with high Ki-67 of (80–90)%, the patient was restarted on Abraxane chemotherapy which she tolerated well. However, her disease continued to progress in the form of retroperitoneal lymph node enlargement with progressive bilateral ureteric obstruction and progressive renal impairment. Despite the multiple trials of antegrade, retrograde and finally nephrostomy tube insertion, her condition did not improve, and the patient died in January 2017.

Discussion

During the 5th week of gestation, an ectodermic thickening starts to form the mammary ridges on the ventral surface of the embryo. It extends bilaterally from the axilla to the groin along what is called the milk lines. The majority of these ridges would normally regress over the following months, leaving a paired tissue on the anterior chest which will form the normal pectoral breasts. On occasion, rudimentary tissue persists at any point along the milk line and gives rise to ectopic mammary tissue.[2] Ectopic breast tissue is reported to affect 2% to 6% of the general

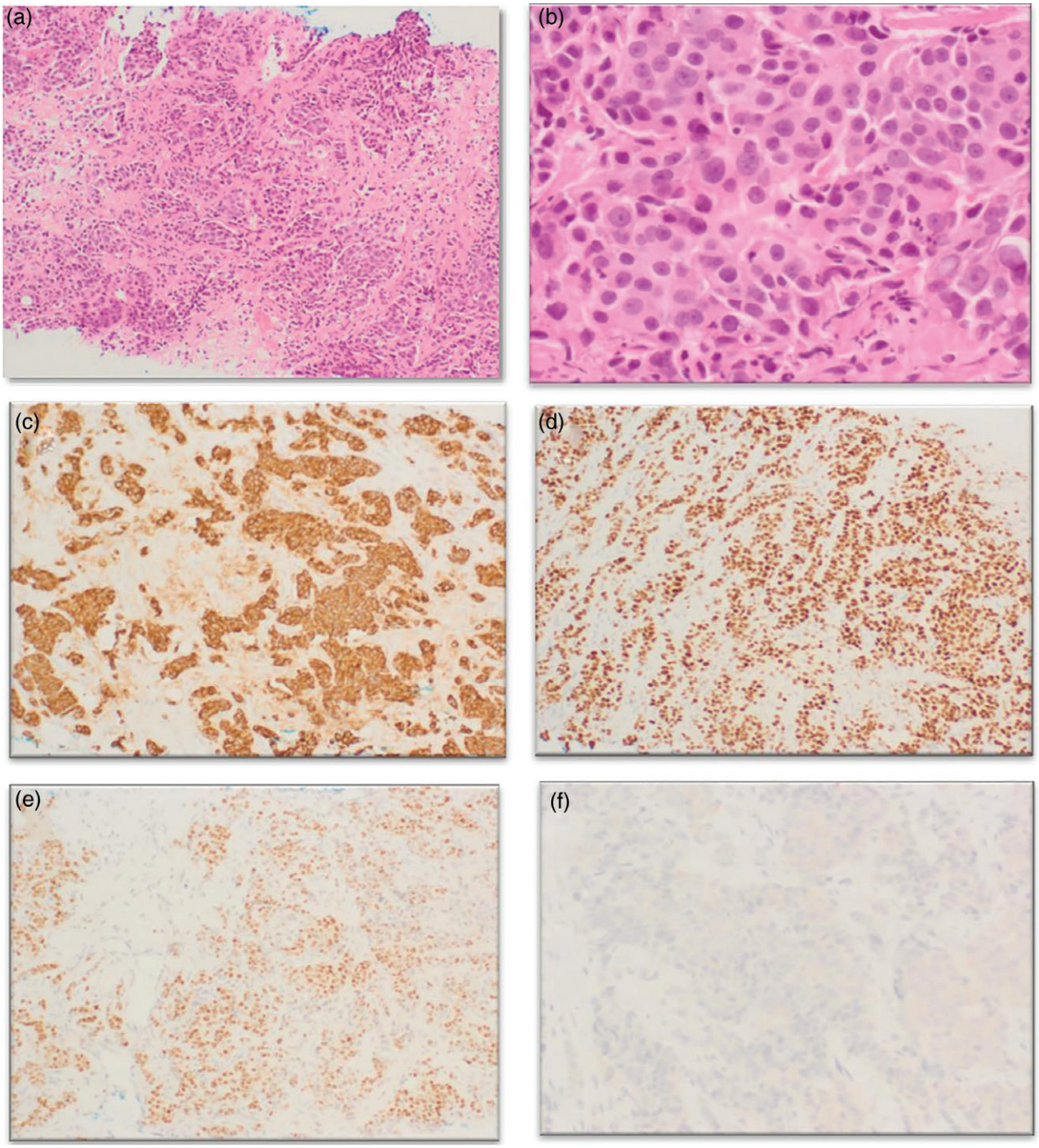

Figure 1 Hematoxylin and eosin stain of mammary type vulvar adenocarcinoma: (a) at ×100, (b) at ×400. Immunoperoxidase stains: (c) positive for cytokeratin7 (CK7), (d) positive for GATA3, (e) positive for ER, (f) negative for Pax8.

population[1]; this ectopic tissue is susceptible to the same physiological and pathological changes affecting the normally located breasts, including malignancy. Primary cancer of the ectopic breast is relatively common at the axilla, while exceedingly rare at the vulva with an incidence of just 4%.[3] We are reporting this curious case of primary cancer of the vulva that presents a clinicopathologic challenge to define whether the tumor is metastatic to or primary originating from the ectopic tissue in the vulva. The main presentation was an unexplained vaginal bleeding in a previously hysterectomized elderly lady without any initially visible local lesion, while the majority of the reported cases presented with a painless vulvar mass, ranging in diameter size from 1.5 cm to 20 cm.[4] To our knowledge, there have been 28 reported cases of primary breast carcinoma of the vulva[5–8] since the first documented case by Greene in 1935.[9] The age of the reported cases ranged from 45 to 82 years (mean: 62 years), which is consistent with normally located breast cancer. The most common clinical presentation was a painless, solitary nodule, arising most often in the labia majora.[10,11] Among the histological subtypes of primary breast cancer that can arise in the vulva, including infiltrating ductal, lobular, mucinous, mixed and carcinoma *in situ* (DCIS), invasive ductal carcinoma is the predominantly reported histology.[12–14] The following criteria have been proposed to

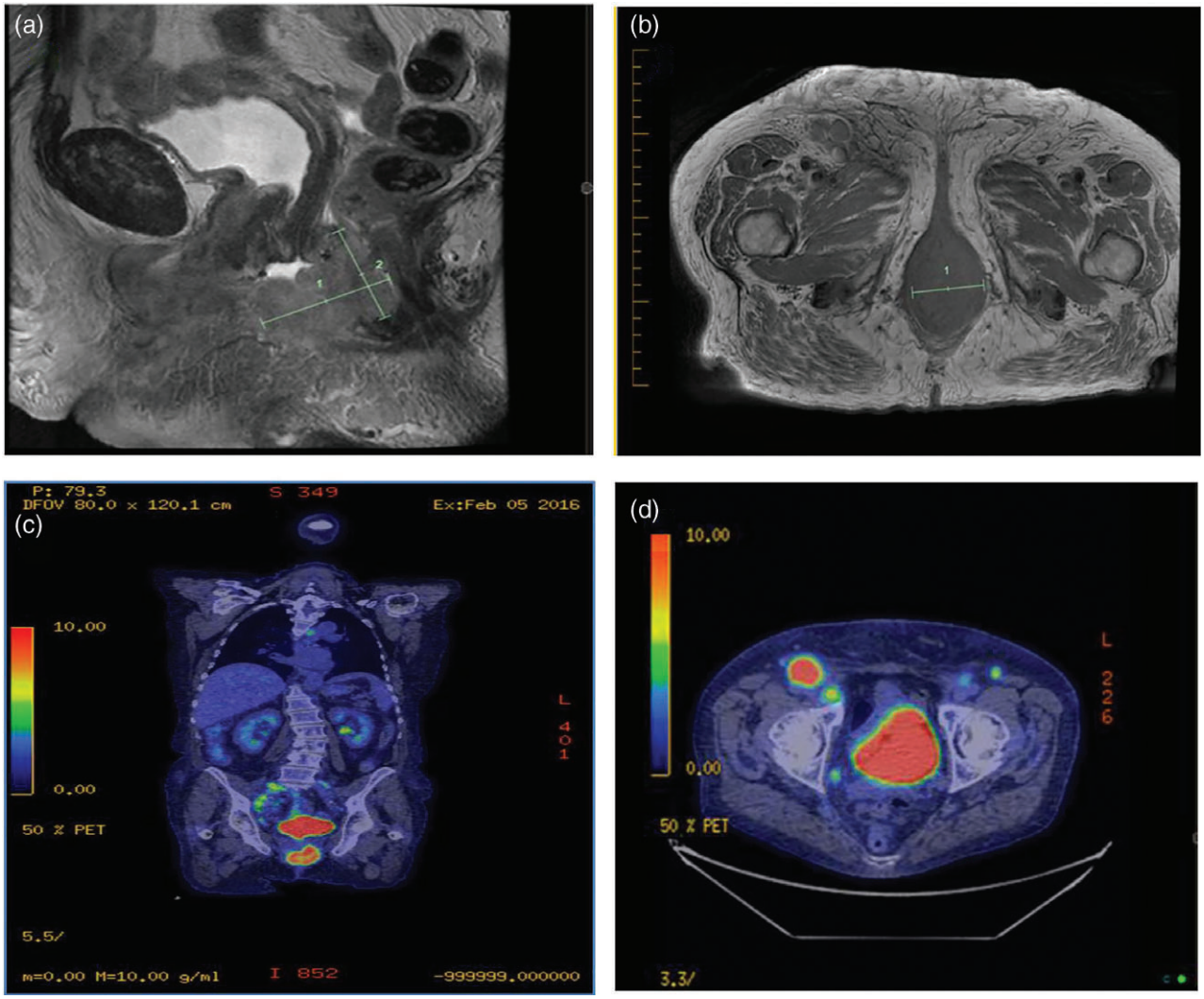

Figure 2 (a and b) Pelvic MRI showing a perineal mass on the lower half of the vagina (c) & (d) FDG PET scan shows an intensely avid pelvic mass, with multiples avid nodes above and below the diaphragm.

differentiate between primary and metastatic vulval cancer: (i) a histological pattern consistent with breast carcinoma; (ii) the positivity of ER and/or PgR; (iii) positive immunohistochemical test for common breast cancer-associated markers, and (iv) the presence of non-malignant breast tissue or carcinoma *in situ*.[10] In our case we relied on the histological pattern, common breast cancer markers and positivity for hormonal receptors to establish the diagnosis of primary breast cancer of the vulva.

Given the rarity of these lesions, and the lack of standard treatment paradigm, the management of carcinoma of the ectopic breast tissue is extrapolated from the established treatment guidelines of the normally located breast cancer. Treatment modalities have ranged from wide local excision for DCIS to radical vulvectomy with bilateral inguinal nodal dissection for invasive carcinomas.[6,11] Adjuvant therapies took the form of chemotherapy, radiation and hormonal therapy. For patients with ER-positive vulva cancer, adjuvant hormonal therapy has been used since it has been proven of survival benefit in ER-positive breast cancer.[11] The use of Trastuzumab (Herceptin) in HER2 positive cases has been reported only once in the literature.[14] The average survival for patients who did not receive adjuvant treatment was 1–4 months, with the longest reported survival was 48 months for IDC treated with adjuvant radiation and hormonal therapy.[15] The management of individual cases is tailored according to the histological type of the tumor and the lymph node status, which is the most important prognostic factor in vulvar cancer.

In conclusion, although primary ectopic breast cancer of the vulva is a rare clinical entity, this diagnosis should be considered when evaluating a patient with an undiagnosed vulval lesion. Pathologic and immunohistochemical tests combined with a thorough metastatic workup are essential to establish the diagnosis and exclude a metastatic breast cancer. Since most data on primary breast cancer of the ectopic vulva tissue rely on case reports and literature reviews, additional research is required to establish a management guideline for this rare malignancy.

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Disclosure

None declared.

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