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Case report

Primary breast cancer of the vulva with concurrent breast and endometrial cancers: A case report and literature review

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1. Introduction

Breast cancer is the most common cancer among women in the United States, with 266,120 estimated new cases in 2018 (Siegel et al., 2018). Ectopic breast tissue may be found anywhere along the milk line from the axilla to the vulva, although the exact histogenesis of vulvar mammary glands remains unclear. Cancers of ectopic mammary tissue are extremely rare and present unique challenges in diagnosis and management, especially in the context of concurrent breast cancer. We present a case of mammary-like adenocarcinoma of the vulva in a patient with concurrent breast and endometrial cancers. The diagnostic approach to concurrent breast, endometrial, and vulvar cancers is discussed.

2. Case presentation

A 69-year-old multiparous woman with newly diagnosed ductal carcinoma in situ (DCIS) of the right breast was referred for evaluation of postmenopausal bleeding and an asymptomatic left vulvar mass present for over 20 years. The patient reported no personal history of gynecologic cancer. Relevant family history includes a father with pancreatic cancer. Her body mass index was 41 kg/m^2.

A diagnostic mammogram of the right breast showed pleomorphic and linear calcifications spanning 8 mm in the anterior third of the outer central right breast. Stereotactic guided biopsy showed ductal carcinoma in situ, positive for estrogen and progesterone receptor. Repeat diagnostic mammography revealed no additional lesions. Endometrial biopsy showed well-differentiated endometrioid adenocarcinoma. Pap smear was negative for malignancy. Vulvar biopsy showed poorly differentiated adenocarcinoma. As additional stains of the vulvar biopsy were pending at the time of surgery, the working diagnosis at this time was metastatic uterine cancer. Computed tomography imaging of the chest, abdomen, and pelvis showed no other evidence of metastatic disease.

The patient underwent right breast lumpectomy by Breast Surgery as well as a robotic-assisted total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, sentinel lymph node mapping and aborted sampling, and a radical vulvar excision. Preoperatively, the patient declined inguinal lymph node sampling. On laparoscopy, there was no evidence of ascites. The uterus contained small fibroids, the fallopian tubes and ovaries were grossly normal, and all peritoneal surfaces appeared smooth. Poor exposure due to body habitus led to the decision not to pursue extensive sentinel lymph node sampling. A right sentinel node at the superior vesical artery was removed, but complete lymphadenectomy was not performed. The patient's post-operative course was complicated by right breast hematoma, which resolved without intervention, and vulvar pain. Vulvar cultures showed gram positive organisms and the patient was treated with oral trimethoprim/sulfamethoxazole with resolution of symptoms.

Surgical pathology showed DCIS of the right breast with negative margins, positive for estrogen and progesterone receptor; stage 1A well-differentiated endometrioid adenocarcinoma of the endometrium; and stage 1B, grade 3 primary mammary gland type adenocarcinoma of the vulva, positive for estrogen and progesterone receptor. The tumor was focally seen less than 1 mm from one margin, however two additional margins taken beyond these were negative. The patient declined re-excision of the vulvar lesion. Testing of the vulvar tumor using the Amsterdam 70-gene breast cancer gene signature showed a low risk of recurrence and no significant benefit from chemotherapy. After a multidisciplinary discussion, the patient declined adjuvant radiation therapy to the vulva and was treated with aromatase inhibitor therapy, anastrazole 1 mg orally daily, for both her breast and vulvar cancers. No adjuvant therapy was recommended for her stage 1A endometrial cancer. The patient is currently without evidence of disease 18 months after the initial diagnosis.

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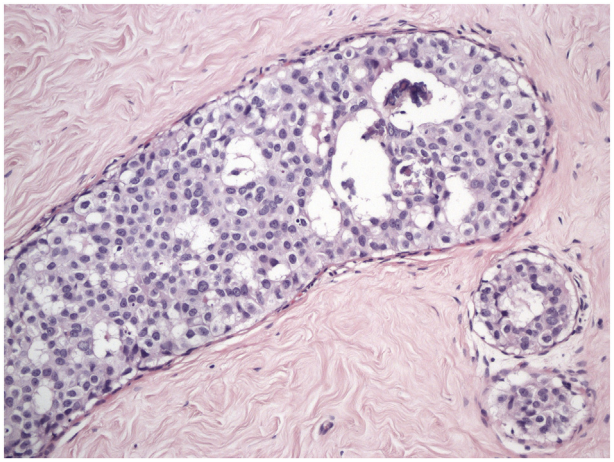

Fig. 1. Intermediate to high-grade ductal carcinoma in situ of cribriform and solid growth with moderate nuclear pleomorphism, prominent nucleoli, and microcalcifications (original magnification ×200).

3. Pathologic analysis

3.1. Right breast lumpectomy

Microscopic examination demonstrated DCIS spanning 16 mm (Fig. 1). The tumor cells were of intermediate to high nuclear grade, with both solid and cribiform types, showing calcifications and areas of necrosis. Margins were negative. The tumor cells were positive for estrogen and progesterone receptor.

3.2. Total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, sentinel lymph node sampling

Microscopic examination of the endometrium demonstrated well-differentiated endometrioid adenocarcinoma spanning 3 cm in diameter (Fig. 2). The tumor was minimally invasive in the myometrium and present superficially in adenomyosis, with less than 5% myometrial invasion. Parametrial edges and uterine serosa were negative. No lymphovascular space invasion was identified. Background endometrium showed atypical simple hyperplasia. Cervix, ovaries, and fallopian tubes were unremarkable. A right pelvic sentinel lymph node was negative. Immunohistochemical expression of DNA mismatch repair proteins MLH1 and PMS2 were lost in the tumor cells. MLH1 methylation testing was negative. Expression of MSH2 and MSH6 were retained, indicating a high likelihood of microsatellite instability and the need for genetic testing, which the patient declined.

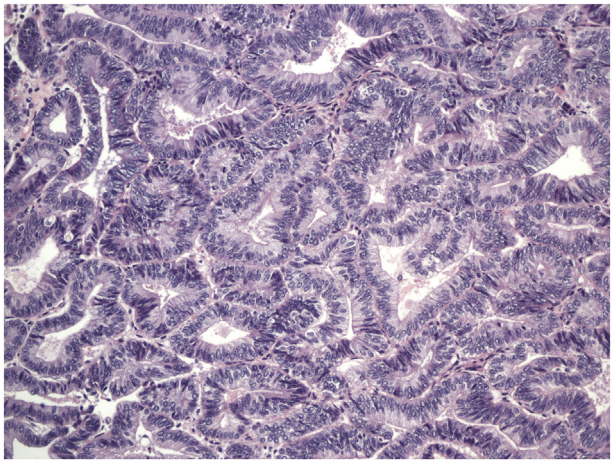

Fig. 2. Back-to-back, complex, and well-defined glands with minimal cytologic atypia characteristic of well-differentiated endometrioid adenocarcinoma (original magnification ×200).

3.3. Excision of left vulvar mass

Microscopic examination of the vulvar mass demonstrated high grade adenocarcinoma with apocrine features, spanning 4.6 cm, involving the entire dermis and extending into the subcutaneous adipose tissue (Fig. 3). Signet cells were noted on hematoxylin and eosin stains. The tumor demonstrated insidious infiltration circumferentially extending into the subcutaneous adipose tissue and was focally seen on the medial, lateral, and deep margins. Additional medial and deep margins were negative. No lymphovascular space invasion was identified.

Immunohistochemical stains of the tumor cells were positive for GATA3, mammaglobin, e-cadherin, AR, ER, and PR. The tumor was negative for BRST2, p63, CK5/6, and D2-40. Staining for HER2 was equivocal. Confirmatory in situ hybridization testing for HER2 was negative. The overall findings were consistent with a primary vulvar adenocarcinoma of mammary gland type.

4. Discussion

While primary breast-like cancer of the vulva is extremely rare, it has been increasingly described. A recent literature review identified approximately 28 cases of primary mammary adenocarcinoma of the vulva in the English language literature (Lopes et al., 2017). A population-based study from the Netherlands identified 5 such cases among 108 primary vulvar malignancies from 2000 to 2015, as well as 2 cases of secondary vulvar malignancies due to recurrent or metastatic breast cancer (van der Linden et al., 2017).

A breast-like vulvar lesion in a patient with concurrent breast cancer presents a diagnostic challenge. Histologic criteria for the diagnosis of primary mammary-like carcinoma of the vulva include morphology consistent with breast carcinoma, estrogen and/or progesterone receptor positivity, positivity for common breast cancer markers (such as CEA and glandular keratins), and the presence of adjacent carcinoma in situ or non-neoplastic ectopic breast tissue (Lamb et al., 2013). However, not all criteria may be present, and a thorough workup for orthotopic breast carcinoma is warranted (Perrone et al., 2009). In our patient, immunohistochemical staining and the absence of concurrent invasive breast cancer facilitated the diagnosis of primary mammary-like carcinoma of the vulva. Next-generation whole exome sequencing and copy number analyses may be useful in determining tumor lineage in when multiple sites of disease are present (Labidi-Galy et al., 2017).

There are no guidelines for the treatment of mammary carcinomas of the vulva. Treatments are often extrapolated from guidelines for orthotopic breast cancers of the same stage. Management has ranged from radical vulvectomy or wide local excision with adjuvant chemotherapy, radiation, or hormonal therapy; the role of sentinel inguinal lymph node sampling or lymphadenectomy remains unclear (Lopes et al., 2017). A recent case report demonstrated the use of whole-genome and transcriptome sequencing to identify a HER2+ mammary-like vulvar cancer and may provide opportunities for identifying therapeutic options (Grewal et al., 2017).

There are several reports of endometrial cancer metastasis to the vulva in patients with aggressive histologic types or extensive disease, with only one reported case of an isolated vulvar metastasis in early stage endometrioid carcinoma (Abdullah et al., 2014). Endometrial cancer metastasis was on the initial differential diagnosis as our patient's endometrial biopsy showed well-differentiated endometrioid adenocarcinoma and vulvar biopsy showed poorly differentiated adenocarcinoma. This diagnosis was excluded upon review of histopathology from the surgical specimens as previously discussed.

To our knowledge, this is the second case of concurrent DCIS and

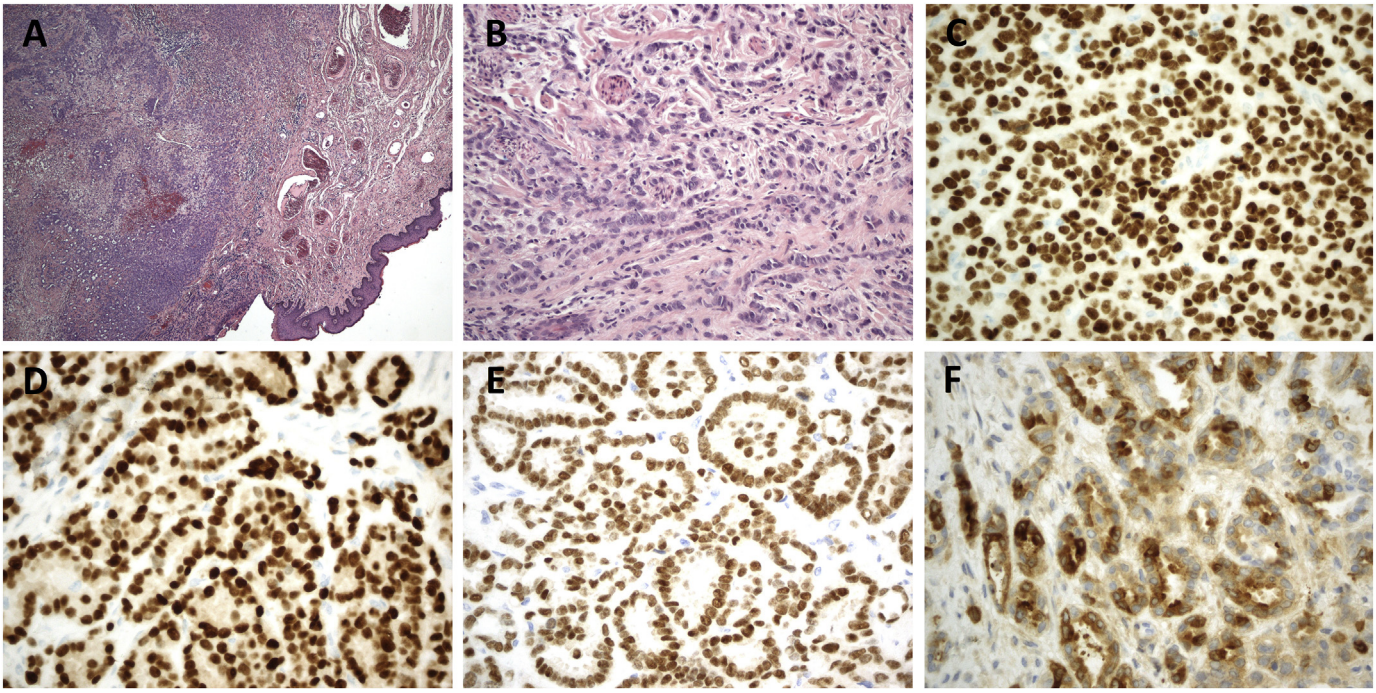

Fig. 3. Hematoxylin and eosin stain of vulvar excision showing dermal nodular and infiltrative lesion with overlying epidermis (A) and infiltrative pattern of single-file malignant cells with prominent nucleoli (B). The tumor cells demonstrate diffuse positivity for ER (C), PR (D), GATA3 (E), and mammaglobin (F). (Original magnification ×40 [A]; original magnification ×200 [C–F].)

primary breast carcinoma of the vulva and the first known case of concurrent breast, vulvar, and endometrial malignancies (Intra et al., 2006). Any diagnosis of multiple primary malignancies raises the question of underlying genetic predisposition. Interestingly, all three cancers in our patient were hormone-sensitive, and while class 3 obesity may have contributed to her disease, it is unlikely the sole factor. Several cases of synchronous breast and ectopic mammary cancers have been reported, lending credence to the hypothesis that mammary-like vulvar cancer is a further reflection of multicentric breast-related disease (Intra et al., 2006).

While certain syndromes confer an increased risk for endometrial cancer (e.g., Lynch, Cowden), the link between BRCA mutations and uterine cancer remains unclear. While our patient's endometrial cancer demonstrated mismatch repair deficiency, she declined recommended genetic testing due to religious beliefs. There is only one reported case of mammary-like vulvar cancer in a patient with hereditary breast and ovarian cancer (mutation 8765delAG on BRCA2) (Lamb et al., 2013). Another study found PIK3CA mutations in two mammary-like carcinomas of the anogenital region (Konstantinova et al., 2017). Further research is needed to clarify the role of these and other genes in the pathogenesis of mammary-like vulvar cancer. Next-generation gene sequencing may be useful in determining tumor lineage, guiding therapies, and potentially uncovering an underlying susceptibility to carcinogenesis.

Conflict of interest

There are no conflicts of interest to disclose for any of the listed authors.

Author contributions

M.S. and S.B. directed the case report. S.E. provided the interpretation of anatomic pathology. S.E. and S.L. designed the figures and figure legend. S.L. wrote the manuscript in consultation with M.S. and S.B.

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References

Abdullah, A., Seagle, B.-L.L., Bautista, E., Hansra, B.S., Samuelson, R., Shahabi, S., Jul 1, 2014. Vulvar metastasis of an early-stage well-differentiated endometrial cancer after minimally invasive surgery. J. Minim. Invasive Gynecol. 21 (4), 708–711.

van der Linden, M., Schuurman, M., Bulten, J., van der Aa, M., Massuger, L., de Hullu, J., 2017. Incidence and survival of glandular vulvar malignancies in the Netherlands. Gynecol. Oncol. 144 (3), 553–557.

Grewal, J.K., Eirew, P., Jones, M., Chiu, K., Tessier-Cloutier, B., Karnezis, A.N., et al., 2017. Detection and genomic characterization of a mammary-like adenocarcinoma. Cold Spring Harb Mol Case Stud. 3 (6) Nov [cited 2018 Feb 14]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5701302/.

Intra, M., Maggioni, A., Sonzogni, A., De Cicco, C., Machado, L.S., Sagona, A., et al., Feb 1, 2006. A rare association of synchronous intraductal carcinoma of the breast and invasive carcinoma of ectopic breast tissue of the vulva: case report and literature review. Int. J. Gynecol. Cancer 16 (S1), 428–433.

Konstantinova, A.M., Shelekhova, K.V., Imyanitov, E.N., Iyevleva, A., Kacerovska, D., Michal, M., et al., 2017. Study of selected BRCA1, BRCA2, and PIK3CA mutations in benign and malignant lesions of anogenital mammary-like glands. Am. J. Dermatopathol. 39 (5), 358–362.

Labidi-Galy, S.I., Papp, E., Hallberg, D., Niknafs, N., Adleff, V., Noe, M., et al., 2017. High grade serous ovarian carcinomas originate in the fallopian tube. Nat. Commun. 8 (1).

Lamb, A., Darus, C.J., Skripenova, S., Weisberg, T., Miesfeldt, S., 2013. Association of primary breast cancer of the vulva with hereditary breast and ovarian cancer. J. Clin. Oncol. 31 (13), e231–e232.

Lopes, A., St. Louis, J., Balancin, M.L., Nogueira-Rodrigues, A., LCFF, Silva, Paulino, E., et al., 2017. A Rare Presentation of Primary Breast Carcinoma in the Vulva: A Case Report and Literature Review.

Perrone, G., Altomare, V., Zagami, M., Vulcano, E., Muzii, L., Battista, C., et al., Jul 1, 2009. Breast-like vulvar lesion with concurrent breast cancer: a case report and critical literature review. In Vivo 23 (4), 629–634.

Siegel, R.L., Miller, K.D., Jemal, A., Jan, 2018. Cancer statistics, 2018. CA Cancer J. Clin. 68 (1), 7–30.