

Case report

Metachronous vulvar ectopic breast cancer, a case report and literature review

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1. Introduction

Ectopic breast tissue, which extends from axilla to groin, is a rare finding in the general population with an incidence of 1–2%. Ectopic breast tissue may respond to physiological stresses and hormonal stimulation and develop benign and malignant histopathologic changes similar to those seen in normal breast tissues, including invasive and in situ carcinoma (Kitamura et al., 1995). Although breast cancer is the most common malignancy in women, both metastatic and primary breast cancer arising from the vulva are extremely rare and only a limited number of cases have been published in the literature (Cokmert et al., 2014; Kitamura et al., 1995). Breast carcinoma may be present in the vulva as either a distant metastasis or as a primary carcinoma arising in ectopic mammary tissue. Differentiating synchronous or metachronous breast carcinoma in the vulva from a metastatic lesion can be challenging. Although there have been 30 previously reported cases of cancer arising in vulvar breast ectopic tissue, to the best of our knowledge, based on a Medline search with search terms including ‘vulvar breast cancer’, ‘ectopic breast cancer’, and ‘metachronous/synchronous breast cancer’, there have been only three previously reported cases of synchronous or metachronous vulvar ectopic breast cancer (Guerry and Pratt-Thomas, 1976; Intra et al., n.d.; Li et al., 2019)

(Supplementary Table 1). In this report we describe the challenges in diagnosis and management of a patient with primary carcinoma of the breast and vulvar ectopic breast tissue.

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.gore.2019.100515>.

2. Case report

Our patient is a 43-year-old Caucasian female who was initially diagnosed with nuclear grade 3 infiltrating ductal carcinoma with associated ductal carcinoma in situ of the right breast. Her tumor was noted to be strongly estrogen receptor (ER) positive, progesterone receptor (PR) negative, and Her2 positive by fluorescent in situ hybridization. One month after diagnosis she underwent a lumpectomy and sentinel node biopsy. All three sentinel nodes and two non-sentinel nodes were negative, consistent with a Stage I breast cancer. However, the posterior margin of the tumor was positive and she underwent re-excision later in the same month with subsequent negative tumor margins. After surgery, she was treated with 12 cycles of weekly Taxol and Herceptin over one year. Tamoxifen was started seven months after her diagnosis and was continued for one year.

Three months after discontinuation of Taxol and Herceptin, and

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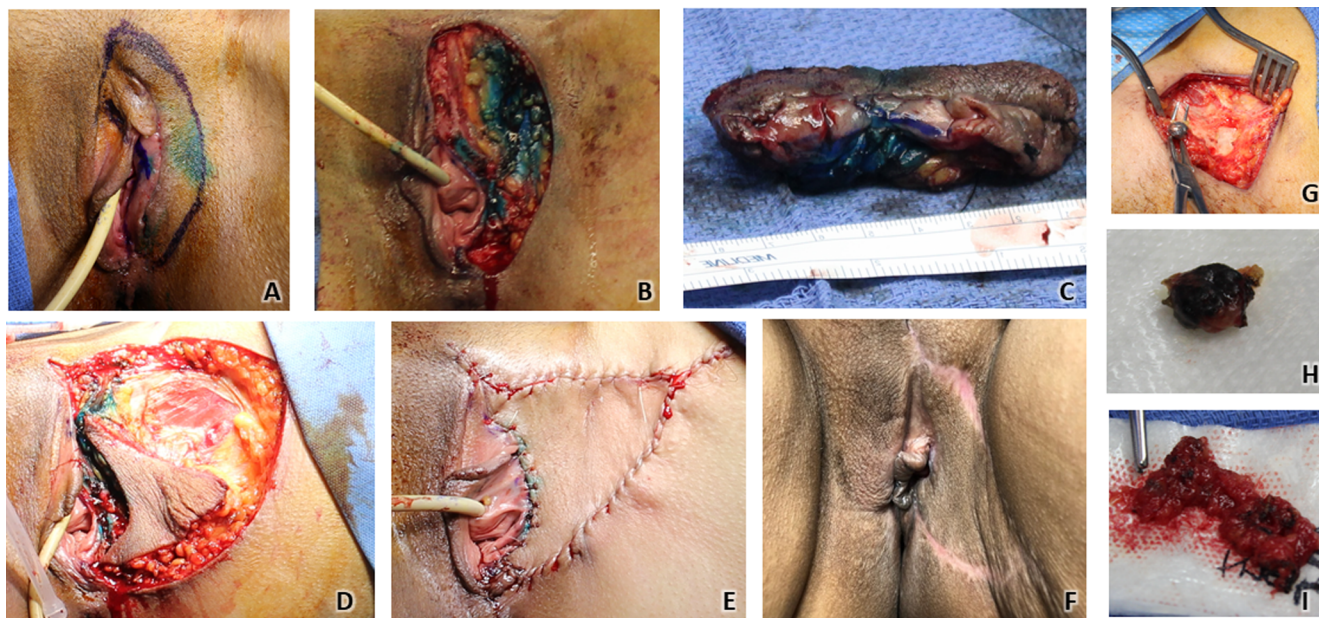


Fig. 1. Radical vulvectomy and repair, with lymph node dissection. A. Anatomy prior to radical vulvectomy. B. Surgical defect. C. Gross vulvar tumor, ultimately found to contain ectopic breast tissue and primary breast carcinoma. D. Repair in process using a 12 cm × 12 cm V to Y fasciocutaneous flap E. Repaired anatomy. F. Healed surgical site four months after repair. G. Lymph node dissection. H. Right sentinel lymph node, mapped with Isosulfan Blue, which was found to be positive for 4 mm focus of micro-metastasis. I. Left sentinel node, mapped with technetium.

17 months after her initial breast cancer diagnosis, the patient noted new vulvar lesions for which she was assessed by her primary obstetrician gynecologist and ultimately referred to gynecologic oncology. She was noted to have a nodular, subdermal lesion on the left labia majora and minora. Due to her history of breast cancer a metastatic workup was ordered, including CT chest, abdomen, and pelvis, with no evidence of metastasis. She underwent a left simple partial vulvectomy and reconstruction as well as dilation and curettage of the endometrium.

Initial pathology impression of the vulvar tissue was multifocal metastatic carcinoma consistent with known breast primary, but upon further review the vulvar tumor was noted to be Her2 amplified and ER and PR positive whereas the breast primary was ER positive but PR negative. In addition, the morphologic features of the carcinoma in the vulva were different from those of the patient’s primary breast carcinoma (Fig. 2). This discrepancy prompted reexamination of the tumor, revealing multifocal invasive carcinoma associated with rare foci of non-neoplastic ectopic breast lobules and ductal carcinoma in situ.

Immunohistochemical staining of the tumor was positive for GATA3, mammaglobin, and CK7; and was negative for CK20 (Fig. 3). The in situ component was positive for ER, PR, mammaglobin, P63, and Calponin (Fig. 4). This staining pattern is consistent with the presence of myoepithelial cells overlying an in situ carcinoma. The revised diagnosis was consistent with a primary poorly differentiated ductal carcinoma with pagetoid spread within the epidermal surface, arising from ectopic breast tissue in the vulva.

Surgical margins were positive after the initial surgery and a left radical hemi-vulvectomy and bilateral inguinofemoral sentinel lymph node biopsies were performed at the end of the next month without complication. The left vulva and clitoris were negative for residual disease. Due to the size of the tumor, the deficit required repair using a 12 cm × 12 cm V to Y fasciocutaneous flap (Fig. 1, A–D). Of note, intraoperatively, activity was detected in the left but not right sentinel lymph node using technetium. The right sentinel node, which was detected using Isosulfan Blue, was positive for a metastatic focus (Fig. 1, F and G). The remaining nodes were negative. PET CT was performed

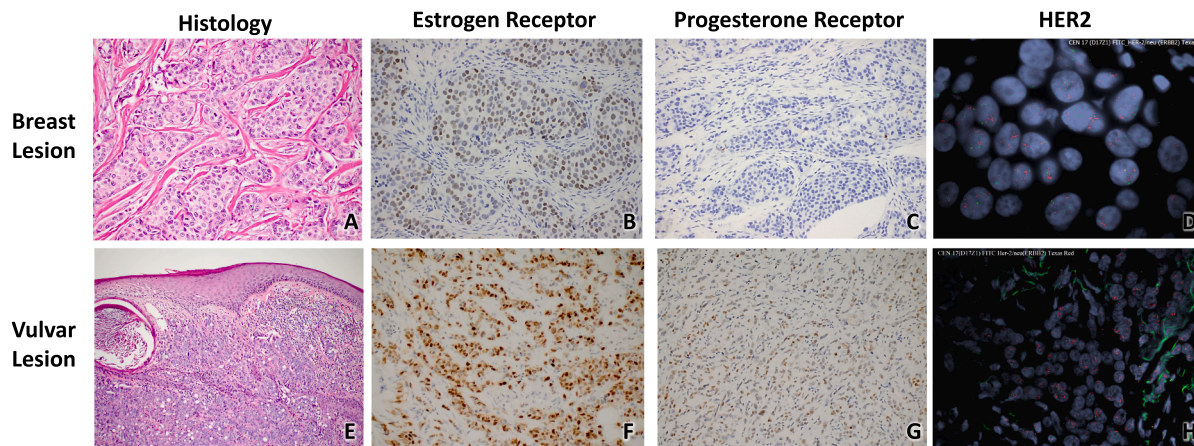


Fig. 2. Hormone receptor status of breast versus vulvar tumor. A-D Initial lesion in the breast, ER positive, PR negative, and HER2 positive. E-H Vulvar lesions, ER positive, PR positive, and HER2 positive. The two lesions have differing hormone receptor expression patterns.

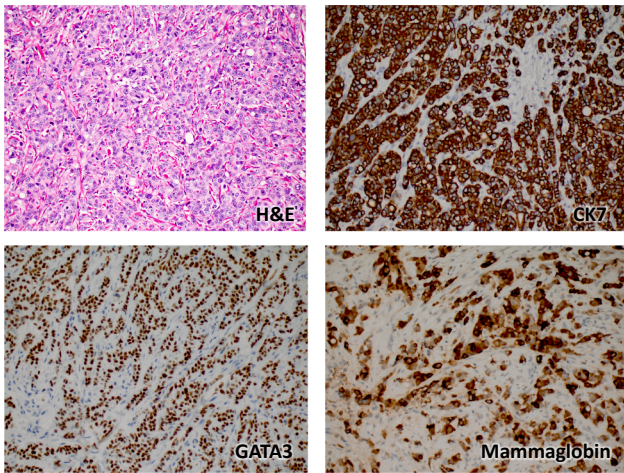


Fig. 3. Vulvar lesions is a breast carcinoma. Immunohistochemistry of the vulvar lesion was positive for CK7, GATA3, and Mammaglobin is consistent with a breast carcinoma. CK20 was negative (not pictured).

metastatic breast cancer rarely occur in ectopic breast tissue in the vulva. Differentiating primary versus metastatic vulvar lesions presents a diagnostic dilemma.

This diagnosis is primarily based on histopathologic patterns which include a morphology consistent with breast carcinoma, positive estrogen and/or progesterone receptor expression on immunohistochemical staining, immunostaining positive for additional common breast cancer associated markers including CK7, GCDFP-15, mammaglobin, and GATA3, as well as the presence of a non-neoplastic breast tissue or an in situ carcinoma component (Bogani et al., 2013; Fracchioli et al., 2006; Lamb et al., 2013; North et al., 2007).

Our patient has a history of right breast ductal carcinoma which was ER and HER2 positive but PR negative while her vulvar invasive ductal carcinoma was positive for ER, PR, and HER2. Due to the difference in hormonal receptor status it is unlikely that the vulvar tumor represents a metastasis. Furthermore, the vulvar tumor was associated with benign non-neoplastic breast lobules, and an in-situ component which was demonstrated by positive calponin and p63 immunostaining. The presence of a benign in-situ component is required for differentiating between a primary versus metastatic lesion.

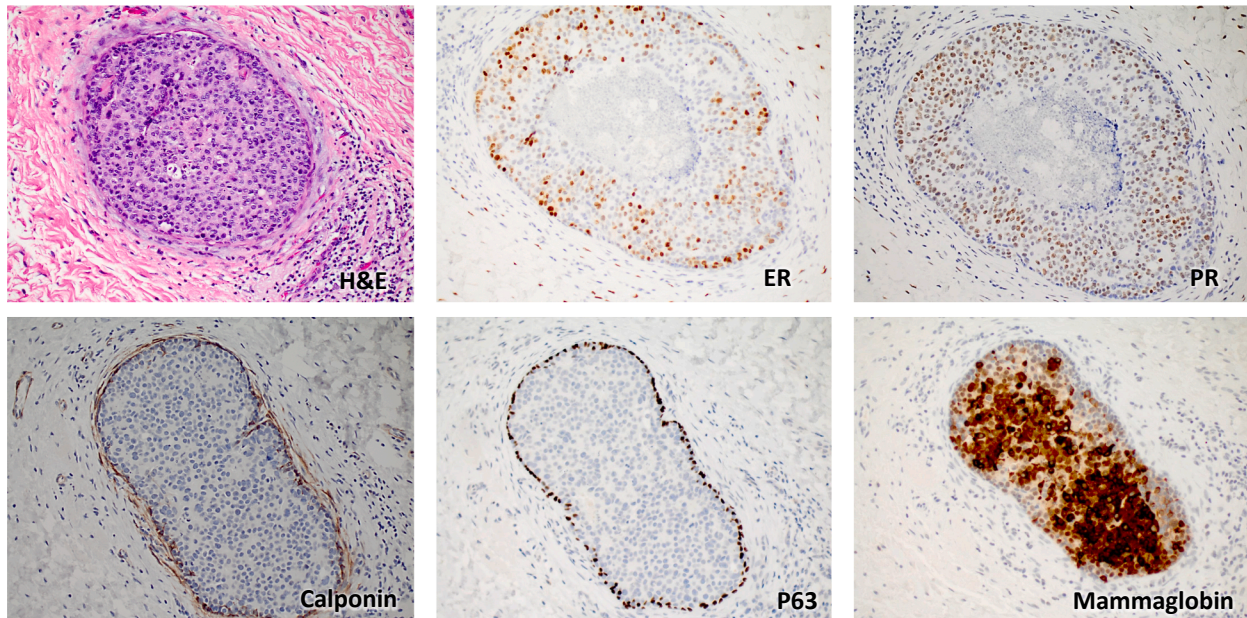


Fig. 4. Breast in situ component in the vulvar lesion. Immunohistochemistry of the in situ component was positive for ER, PR, and mammaglobin, which is consistent with a breast carcinoma. Calponin and P63 staining pattern is suggestive of an in situ component, suggesting that the vulvar lesion is a metachronous ectopic breast primary of the vulva and not a metastasis.

after the radical vulvectomy and was negative for evidence of metastasis. A left adnexal cyst was present and stable from previous imaging; there was no increased uptake. She is currently undergoing systemic chemotherapy using tamoxifen, doxorubicin, cyclophosphamide, and trastuzumab, with a recommendation for subsequent pelvic irradiation. At the three month mark she is tolerating treatment well.

3. Discussion

Ectopic breast tissue is a rare finding in the general population with an incidence of 1–2% (Kitamura et al., 1995). Tumors that arise in ectopic breast tissue, although rare, can have pathologies similar to tumors in the breasts, ranging from benign, noncancerous lesions to malignancies (Ishigaki et al., 2017; Kazakov et al., 2011). Approximately 60–70% of ectopic breast carcinomas occur in accessory breast tissue (Francone et al., n.d.; Marshall et al., 1994; Singer et al., 2001; Stomper et al., 2003; Venkatesan et al., 2009). Both primary and

Both metastatic and primary malignancies can occur in any anatomic location of the vulva, but there is a predilection for the labia majora. Most lesions present as a solitary mass. The majority of patients with a primary breast carcinoma in the vulva have a lymph node metastasis at the time of diagnosis, as was the case in our patient. Due to the rarity of the diagnosis there is no standard of care or management. Surgical management has varied from wide local excision to radical vulvectomy with bilateral inguofemoral lymph node dissection.

Adjuvant therapies utilized in previous cases include radiation, anthracycline-based chemotherapy, as well as hormonal therapy. Patients who did not receive adjuvant therapy had a median survival of 4 months whereas those who did had a median survival of 22 months with only one death reported in the literature (Lopes et al., 2018). In this case prognosis and treatment was impacted significantly by making the correct diagnosis. If the vulvar tumor had been a metastasis from the patient’s known breast primary, it would have represented a recurrent, stage IV, breast cancer, and a vulvar primary would represent a

Stage IIIB based on tumor size and regional nodal metastasis. This new primary ectopic breast cancer, even with regional nodal metastasis, represents a Stage IIB tumor (Lee et al., 2014; National Comprehensive Cancer Network, n.d.; Oh et al., 2017). The respective 5-year survival rates are approximately 20% for Stage IV breast cancer and 40% for Stage IIIB vulvar cancer versus over 90% for Stage IIB breast cancer, highlighting the importance of proper staging and of making this challenging diagnosis (“Cancer Statistics Review, 1975–2014 - SEER Statistics,” n.d.).

Author contributions

H.A., P.K, A.S., K.A., N.B., S.D., M.F., D.G., W.G., L.C., R.V., and V.A. contributed to authoring this manuscript including participation in literature review, writing, and editing. K.A., M.F., D.G., and V.A. participated in the surgical care of the patient, N.B. provided pathology consultation, and W.G. participated in oncologic management.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

References

- Bogani, G., Uccella, S., Cromi, A., Casarin, J., Donadello, N., Ghezzi, F., 2013. Primary mammary-like ductal carcinoma of the vulva: a case report and analysis of the literature. *Am. J. Dermatopathol.* 35, 685–687. <https://doi.org/10.1097/DAD.0b013e31828484c0>.
- Cancer Statistics Review, 1975–2014 - SEER Statistics [WWW Document], n.d. URL https://seer.cancer.gov/archive/csr/1975_2014/ (accessed 2.7.19).
- Cokmert, S., Demir, L., Akyol, M., Bayoglu, I.V., Can, A., Unek, I.T., Bolat, F.A., 2014. Clitoris metastasis from a retroperitoneal leiomyosarcoma: a case report. *World J. Clin. Oncol.* 5, 28–32. <https://doi.org/10.5306/wjco.v5.i1.28>.
- Fracchioli, S., Puopolo, M., Rigault De La Longrais, I.A., Scozzafava, M., Bogliatto, F., Arisio, R., Micheletti, L., Katsaros, D., 2006. Primary “breast-like” cancer of the vulva: a case report and critical review of the literature. *Int. J. Gynecol. Cancer* 16, 423–428. <https://doi.org/10.1111/j.1525-1438.2006.00364.x>.
- Francone, Elisa, Nathan, Marco J., Murelli, Federica, Bruno, Maria Santina, Traverso, Enrico, Friedman, Daniele, 2013. Ectopic breast cancer: case report and review of the literature. *Aesth. Plast. Surg.* 37 (4), 746–749. <https://doi.org/10.1007/s00266-013-0125-1>.
- Guerry, R.L., Pratt-Thomas, H.R., 1976. Carcinoma of supernumerary breast of vulva with bilateral mammary cancer. *Cancer* 38, 2570–2574.
- Intra, M., Maggioni, A., Sonzogni, A., DE Cicco, C., Machado, L.S., Sagona, A., Talakhadze, N., n.d. 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 (Suppl 1), 428–33. <https://doi.org/10.1111/j.1525-1438.2006.00237.x>.
- Ishigaki, T., Toriumi, Y., Nosaka, R., Kudou, R., Imawari, Y., Kamio, M., Nogi, H., Shioya, H., Takeyama, H., 2017. Primary ectopic breast cancer of the vulva, treated with local excision of the vulva and sentinel lymph node biopsy: a case report. *Surg. Case Rep.* 3, 69. <https://doi.org/10.1186/s40792-017-0343-x>.
- Kazakov, D.V., Spagnolo, D.V., Kacerovska, D., Michal, M., 2011. Lesions of anogenital mammary-like glands. *Adv. Anat. Pathol.* 18, 1–28. <https://doi.org/10.1097/PAP.0b013e318202eba5>.
- Kitamura, K., Kuwano, H., Kiyomatsu, K., Ikejiri, K., Sugimachi, K., Saku, M., 1995. Mastopathy of the accessory breast in the bilateral axillary regions occurring concurrently with advanced breast cancer. *Breast Cancer Res. Treat.* 35, 221–224.
- 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, e231–e232. <https://doi.org/10.1200/JCO.2012.45.5972>.
- Lee, J., Jung, J.H., Kim, W.W., Hwang, S.O., Kang, J.G., Baek, J., Kim, H.J., Park, J.Y., Jeong, J.Y., Lim, J.Y., Park, H.Y., 2014. Ductal carcinoma arising from ectopic breast tissue following microcalcification observed on screening mammography: a case report and review of the literature. *J. Breast Cancer* 17, 393–396. <https://doi.org/10.4048/jbc.2014.17.4.393>.
- Li, S., Schwartz, M., Everest, S., Blank, S.V., 2019. Primary breast cancer of the vulva with concurrent breast and endometrial cancers: a case report and literature review. *Gynecol. Oncol. Rep.* 27, 35–37. <https://doi.org/10.1016/j.gore.2018.12.005>.
- Lopes, A., St Louis, J., Balancin, M.L., Nogueira-Rodrigues, A., Silva, L.C.F.F., Paulino, E., Sá, B.S., Bukowski, A., Barbosa, E.M., Costa, R.L.R., Goss, P.E., 2018. A rare presentation of primary breast carcinoma in the vulva: a case report and literature review. *Clin. Breast Cancer* 18, e291–e294. <https://doi.org/10.1016/j.clbc.2017.06.004>.
- Marshall, M.B., Moynihan, J.J., Frost, A., Evans, S.R., 1994. Ectopic breast cancer: case report and literature review. *Surg. Oncol.* 3, 295–304.
- National Comprehensive Cancer Network, n.d. Breast Cancer (Version 4.2017) [WWW Document]. URL https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (accessed 10.12.19).
- North, J., Perez, D., Fentiman, G., Sykes, P., Dempster, A., Pearse, M., 2007. Primary breast cancer of the vulva: case report and literature review. *Aust. New Zeal. J. Obstet. Gynaecol.* 47, 77–79. <https://doi.org/10.1111/j.1479-828X.2006.00685.x>.
- Oh, S.W., Lim, H.S., Lee, J.S., Moon, S.M., Park, M.H., 2017. Invasive micropapillary carcinoma in axillary ectopic breast and synchronous ductal carcinoma in situ in the contralateral breast. *J. Breast Cancer* 20, 314–318. <https://doi.org/10.4048/jbc.2017.20.3.314>.
- Singer, C., Blankstein, E., Koenigsberg, T., Mercado, C., Pile-Spellman, E., Smith, S.J., 2001. Mammographic appearance of axillary lymph node calcification in patients with metastatic ovarian carcinoma. *Am. J. Roentgenol.* 176, 1437–1440. <https://doi.org/10.2214/ajr.176.6.1761437>.
- Stomper, P.C., Geradts, J., Edge, S.B., Levine, E.G., 2003. Mammographic predictors of the presence and size of invasive carcinomas associated with malignant microcalcification lesions without a mass. *Am. J. Roentgenol.* 181, 1679–1684. <https://doi.org/10.2214/ajr.181.6.1811679>.
- Venkatesan, A., Chu, P., Kerlikowske, K., Sickles, E.A., Smith-Bindman, R., 2009. Positive predictive value of specific mammographic findings according to reader and patient variables. *Radiology* 250, 648–657. <https://doi.org/10.1148/radiol.2503080541>.