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CASE REPORT

Metastatic Lobular Carcinoma Involving the Vulva as Initial Presentation of Disease in a Patient with Dense Breast Tissue

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Abstract

We present the case of a 72-year-old woman with dense breast tissue and no initial mammographic signs of malignancy, who presented with a vulvar mass that was discovered to be metastatic lobular carcinoma from the breast. This is the first example documented in the English literature of metastatic lobular carcinoma involving the vulva as the initial presentation of disease. This case report highlights the pathologic features of this uncommon entity and its diagnostic challenges.

Case Presentation

A 72-year-old woman presented with an isolated vulvar mass. Physical examination revealed a red nodule in her labia major a that was subsequently biopsied. Of note, the patient had had routine annual mammographic screening and no history of previous breast pathology but was status-post a bilateral reduction mammoplasty nine years prior. Ultimately, the woman died from her disease three years after presentation.

Histopathologic examination of the vulvar mass following incisional biopsy revealed a nodular aggregate of uniform, hyperchromatic, neoplastic cells infiltrating in single-file linear cords without secondary lumen formation. The nodular configuration of the tumor cells in the sub-mucosa favoured a metastatic process. Perineural involvement and a prominent circumferential onion-skinning pattern around the background non-neoplastic anogenital glands was noted (Figure 1). No *in situ* component was identified in the adjacent anogenital mammary-like glands.

Immunohistochemical stains were performed. The carcinoma was immunoreactive for estrogen receptor (ER) (70% of cells), progesterone receptor (PR) (30% of cells), and negative for E-cadherin, supporting the histologic interpretation of metastatic lobular carcinoma from the breast (Figure 2). A recommendation for additional evaluation of the breasts and a bone scan was made. A right breast mass was subsequently identified and biopsied. Histopathologic examination revealed invasive mammary carcinoma with mixed ductal and lobular features and atypical lobular hyperplasia. Review of the patient's previous mammography reports showed heterogeneously dense breast tissue with no evidence of malignancy.

Discussion

In the United States, breast cancer represents the most common malignancy diagnosed in women with an incidence of over 310,000 cases per year. Invasive lobular carcinoma (ILC) represents approximately 10% of all breast cancer diagnoses [1]. Secondary to an increased emphasis on mammographic screening, the incidence of invasive lobular carcinoma has increased over the past two decades [2]. However, in the setting of dense breast tissue, mammography has been observed to have both a decreased sensitivity for the detection of breast cancers as well as an increased interval cancer

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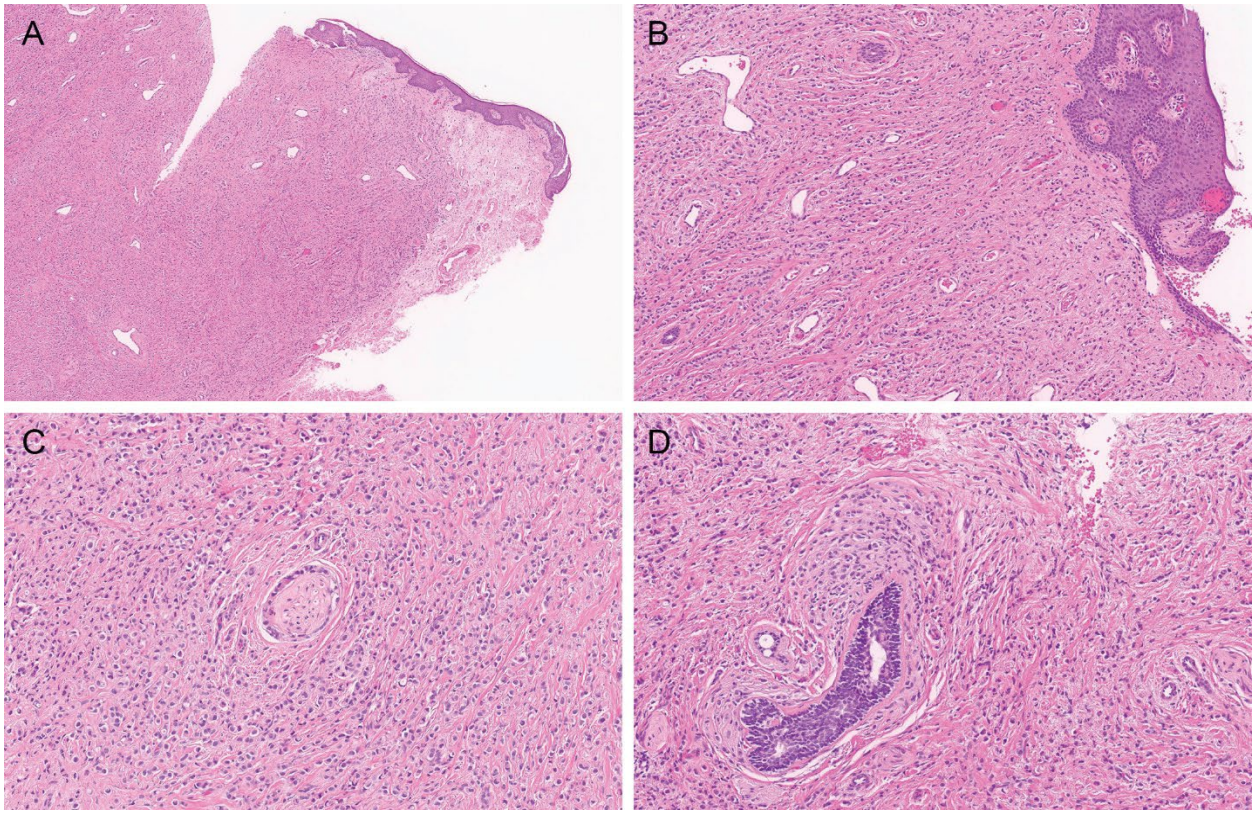

Figure 1: (A) Nodular growth of metastatic lobular carcinoma to the submucosa of the vulva H&E 4X magnification; (B) Cords of uniform tumor cells infiltrate in solid sheets and single file around vessels and non-neoplastic anogenital mammary like glands H&E 10X; (C) Perineural invasion of metastatic lobular carcinoma to the vulva, with some cells showing signet ring morphology H&E 20X; (D) Lobular carcinoma diffusely infiltrates around non-neoplastic anogenital gland in a concentric targetoid fashion H&E 20X.

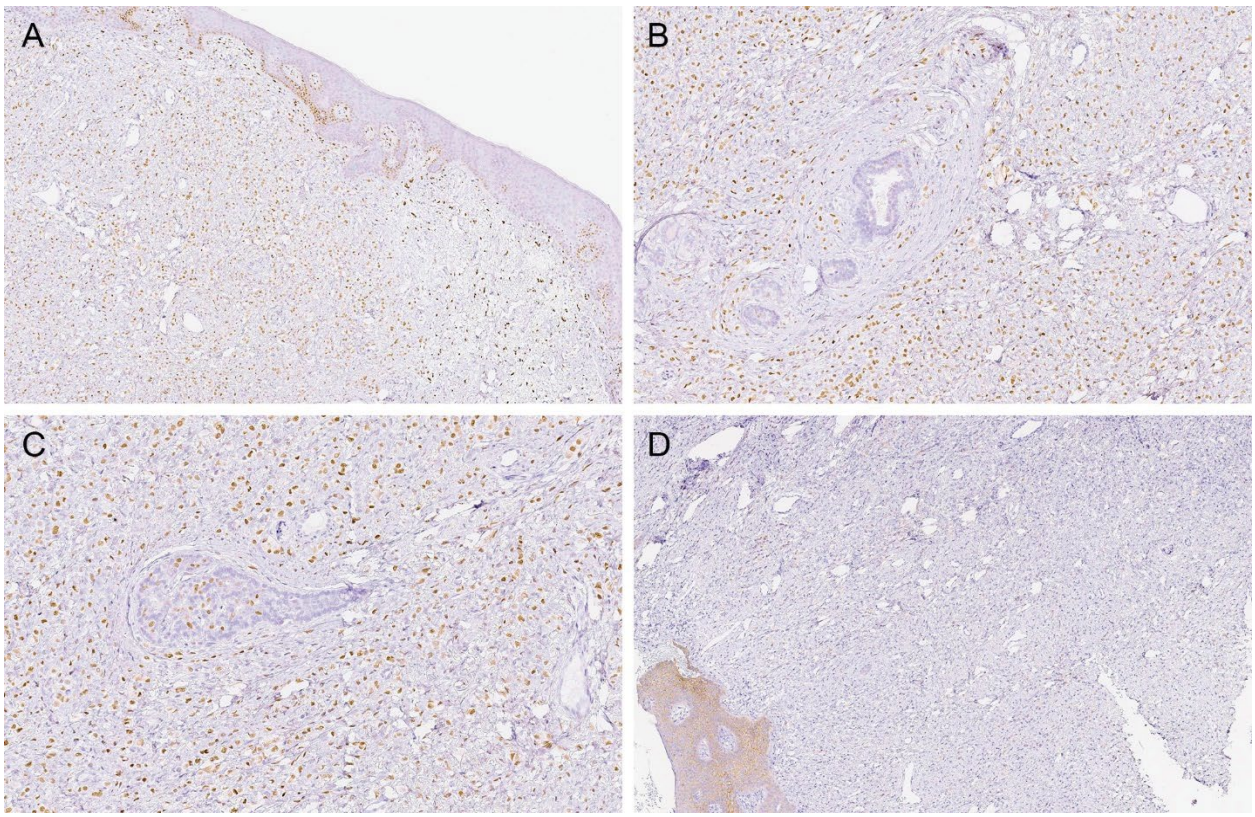

Figure 2: (A) Nuclear staining of estrogen receptor 4X; (B) Nuclear staining of estrogen receptor 10X; (C) Nuclear staining of estrogen receptor in both the tumor cells and occasional cells of anogenital mammary like glands as reported by Ro, et al. [15]; 20X (D) E-cadherin immunohistochemical stain showing faint staining in overlying squamous epithelium and negative staining in the metastatic lobular carcinoma, confirming the histologic impression 4X.

rate, as the opaque tissue on mammogram can mask malignancies. Additionally, dense breast tissue confers an increased risk of developing breast cancer when compared to patients with fatty breast tissue [3].

ILC presents a unique diagnostic challenge because of its ability to grow in a diffuse manner without significant tissue destruction or stromal response. Up to 30% of cases of ILC are not visualized on routine mammography. The sensitivity of mammography for the detection of ILC ranges from 57 to 81% [4]. Berg, et al. conducted a study in which the diagnostic accuracy of several imaging modalities in preoperative assessment of breast cancer as a function of tumor type and breast density were evaluated. Of the biopsy-proven ILCs, 11% were detected in dense breasts, 36% in heterogeneously dense breasts, 60% in breasts with minimal scattered fibro glandular density, and 100% in fatty breasts. Ultrasound, when used in conjunction with mammogram, can increase the sensitivity of ILC diagnosis to 93.2% [5]. This is helpful because current breast screening algorithms may employ mammography and ultrasonography together when a patient is symptomatic or has a palpable breast mass. Otherwise, only abnormal routine screening mammograms are followed up with additional studies [6]. In the Berg, et al. study, 28% of ILC cases were palpable.

Invasive lobular carcinoma has a propensity to metastasize to the bone, liver, gastrointestinal tract, gynecological tract, and lymph nodes [7,8]. Within the gynecological tract, metastases tend to favor the serosal surfaces of the ovary and uterus. Metastatic lobular carcinoma involving the vulva represents an exceedingly rare manifestation of breast cancer [9]. Unlike this case, metastases are typically detected following an established diagnosis of a primary breast carcinoma and can even present more than 20-years after an initial diagnosis [10]. Primary invasive lobular carcinoma arising in mammary-like glands of the vulva, while also incredibly rare, must be included in the differential diagnosis. The absence of a corresponding *in-situ* lesion is more supportive of metastatic disease rather than a vulvar primary [11,12]. Both primary and metastatic lobular carcinomas have identical immunohistochemical profiles with immunoreactivity for GATA3, ER, PR, and HER2 [13-15], and immunohistochemistry alone is not sufficient to distinguish between the two. Of note, three cases of primary lobular carcinoma of the vulva have been documented in the English literature, with E-cadherin confirmation reported in the case example by Matek, et al. [13,16,17], although no *in situ* component has been confirmed to date [18]. The differential diagnosis of a carcinoma involving the vulva should also include extra mammary Paget's disease, particularly when neoplastic cells are found within the epithelium. Metastatic lesions to the epithelium, however, tend to have a nested configuration rather than a mixture of nests and individual neoplastic cells within the epithelium, as seen in Paget's disease [19]. Moreover, the cells of Paget's disease are larger and less uniform than those of lobular carcinoma. As in this patient's case, if lobular carcinoma is identified on biopsy and associated with the anogenital glands of the vulva, a recommendation should be made for evaluation of the breasts to determine if a breast primary exists.

Invasive lobular carcinomas demonstrate a characteristic loss of E-cadherin by immunohistochemistry in the vast majority of cases. E-cadherin is a cell-to-cell adhesion molecule that is responsible for coupling cytoskeleton-associated desmosome proteins and has also been implicated in the suppression of tumor invasion and metastasis [20]. In most epithelial tissues, E-cadherin maintains a membrane-predominant staining distribution. This is particularly evident in ductal carcinoma and can be used to distinguish it from lobular carcinoma, which generally displays loss of E-cadherin staining [21]. However, even in examples of lobular carcinoma where membranous E-cadherin staining is retained, it is usually diminished and is usually associated with dysfunction of the E-cadherin adhesion protein. This aforementioned finding by Rakhma, et al. and others suggests that loss of function of the E-cadherin complex is integral to the behaviour of lobular carcinoma, including its tendency to invade tissues in a single file pattern and the promotion of metastasis [20].

Conclusion

Metastatic lobular carcinoma involving the vulva of patients with dense breast tissue presents a diagnostic challenge due to its rarity and subtle clinical presentation. Accurate diagnosis relies on histopathologic examination and confirmatory immunohistochemical stains to differentiate metastatic disease from primary vulvar malignancies. A nodular configuration in the submucosa without accompanying carcinoma *in situ* favours a metastasis. Rare cases of lobular type carcinoma arising in anogenital mammary-like glands of the vulva have been reported, but a breast primary should first be excluded examination of the breast by mammography and ultrasound. Identifying and reporting of similar cases is necessary to enhance understanding and management of this uncommon disease.

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