

## Breast-like Vulvar Lesion with Concurrent Breast Cancer: A Case Report and Critical Literature Review

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**Abstract.** In the current report, we describe an intriguing case of a breast-like cancer lesion located in the vulvar region in a woman lacking a remarkable past medical or family history of breast cancer but with concurrent breast cancer. Consequently, a differential diagnosis between a primary synchronous breast and vulvar cancer or a metastatic breast carcinoma to the vulva is a key point in terms of the clinical approach. In a review of the literature, 39 cases of breast-like cancer lesion have been described: 23 cases of primary infiltrating carcinoma of the vulva and 16 cases of vulvar metastases of breast carcinoma. To the best of our knowledge, this is the first report of a clinically synchronous vulvar metastasis from an invasive ductal carcinoma. The main diagnostic criteria for differential diagnosis between primary or metastatic breast-like vulvar carcinoma are also discussed.

Here we describe a case of a breast-like vulvar cancer lesion in a patient with a concurrent breast cancer. Metastases from breast cancer, the most common malignancy and the leading cause of cancer-related death in women, usually occur in the axillary lymph nodes, lungs, bone, liver and brain in descending order of frequency (1). Involvement of the female reproductive tract is rare. When it does occur, the ovaries and uterus are the most frequently reported sites (2). On the other hand, it has been proposed that ectopic breast tissue can occur anywhere along the primitive 'milk line', extending from the axilla to the vulva (3). Such ectopic tissue may undergo the same physiological and pathological processes found in the normal breast. In the present paper,

we discuss the differential diagnosis between primary breast-like carcinoma of the vulva and metastatic vulvar lesion of primary breast cancer on the basis of the literature review.

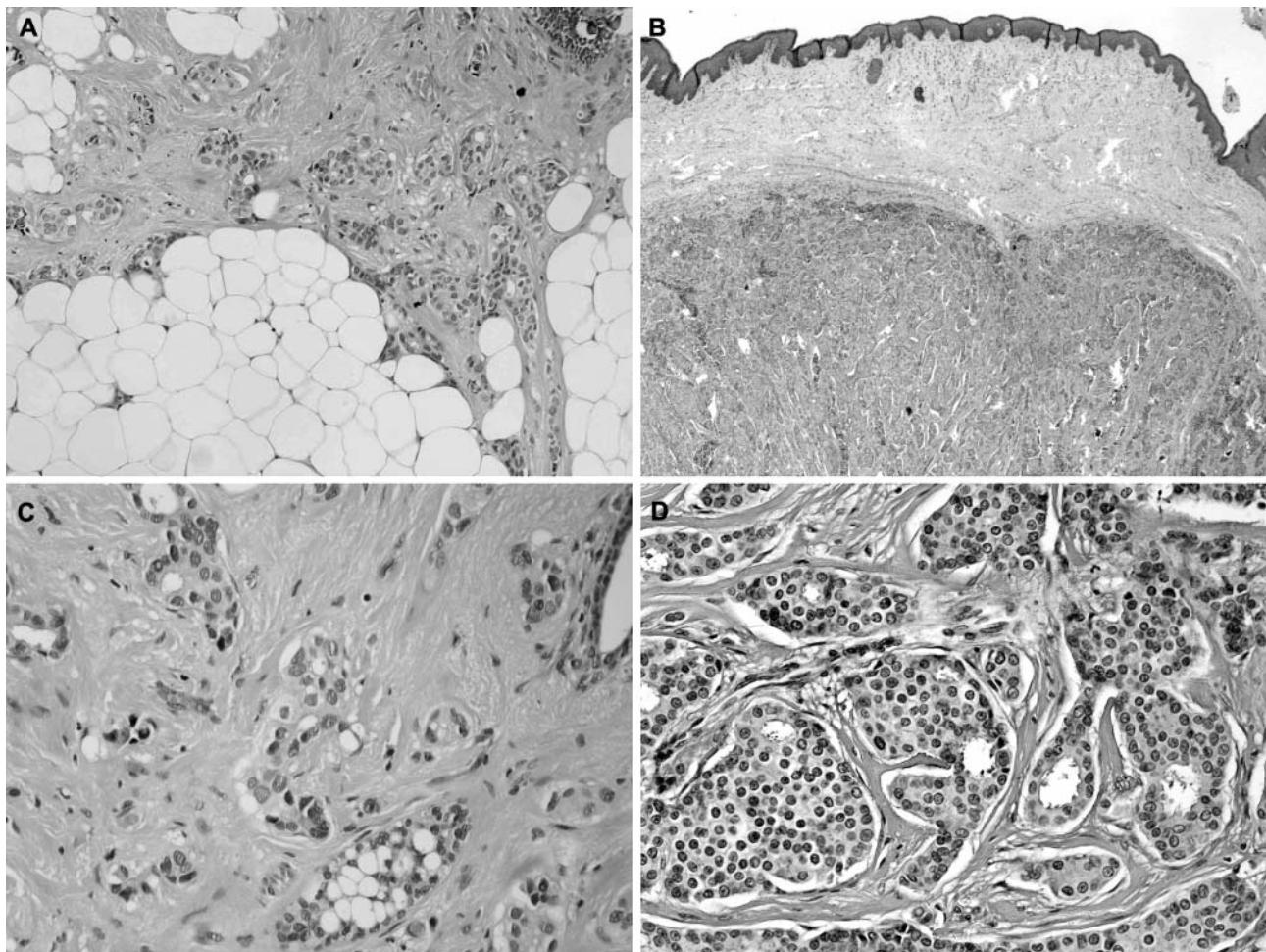
### Case Report

The patient was a healthy 72-year-old woman, without a remarkable personal or family medical history. She was admitted to our institution because of the appearance of a nodular tumefaction in the right labia majus of the vulva that enlarged over 5 months. She underwent surgical excision of this lesion and histological examination documented a carcinoma morphologically and immunophenotypically compatible with breast-like cancer. On the basis of these findings, the patient underwent further examination with bilateral mammography, which revealed a suspicious 10-mm left breast lesion between the upper quadrants. A fine-needle aspiration cytology confirmed the neoplastic nature of the lesion. A left breast superior quadrantectomy associated with ipsilateral sentinel lymph node biopsy revealed an invasive ductal carcinoma, which was sentinel lymph node-negative. Total body computed tomography scan with and without contrast medium, bone scintigraphy, chest X-rays and hepatic ultrasonography excluded distant metastases. Postoperative chemotherapy with six courses of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) was administered without complications. Given the positive oestrogen (ER) and progesterone (PGR) receptor status of the tumour, hormonal therapy with tamoxifen was started after chemotherapy. After 20 months from the initial diagnosis, the patient is free of disease.

Representative tumour blocks were cut at 3 µm thickness for standard histology and immunohistochemical studies. Immunohistochemistry was performed by the streptavidin-biotin method. The antibodies used were mouse monoclonal antibodies against cytokeratin 7 (clone OV-TL 12/30), cytokeratin 20 (clone Ks20.8), p53 protein (clone DO7), ER (clone 1D5), Ki-67 protein (clone MIB-1), PGR (clone 1A6) all from Dakocytomation, Denmark. Sections were incubated

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**Figure 1.** Histological findings. The breast lesion (A, C) was a well-differentiated invasive ductal carcinoma. The vulvar lesion (B, D) was covered by integral skin. Neoplastic cells can be seen arranged in cords with occasional areas of glandular differentiation appearing as tubular structures with central lumina morphologically consistent with a breast-like lesion. Original magnification: A, B  $\times 40$ ; C, D  $\times 400$ .

with LSAB2 (Dakocytomation). Immunohistochemical evaluation of HER-2/neu expression was performed using the HercepTest™ (Dakocytomation) according to the manufacturer's instructions. 3-3-Diaminobenzidine (DAB) was used for colour development and haematoxylin was used for counterstaining. Slides were examined by two investigators (G.P. and M.Z.) without knowledge of the corresponding clinicopathological data. ER, PGR, p53 and Ki-67 staining were categorized by the percentage of positively stained nuclei in a total of at least 1,000 tumour cells. The assessment of HER-2/neu overexpression was performed as recommended by the following HercepTest™ scoring guidelines: 0, no staining or <10% membrane staining; 1+, partial membrane staining in >10% of the tumour cells; 2+, weak or moderately complete membrane staining in >10% of tumour cells; 3+, strong complete membrane staining in >10% of tumour cells. A case was

considered positive if >10% of tumour cells showed complete membrane staining.

**Vulvar lesion.** The lesion presented a hard consistency, was approximately 3 cm in diameter and was covered by integral skin. Pathological examination revealed a carcinoma arranged in cords with occasional areas of glandular differentiation without skin involvement, morphologically consistent with a breast-like lesion (Figure 1 A, B). Careful histological examination of the specimen failed to reveal an *in situ* component or ectopic normal breast tissue. Immunohistochemistry showed positivity of the neoplastic elements for cytokeratin 7 and negativity for cytokeratin 20; ER and PGR were also positive (95% and 90% respectively) and the proliferative index (MIB-1) was 2%. The p53 positivity was <1% and Hercep test negative (score 0) (Figure 2 A, C, E).

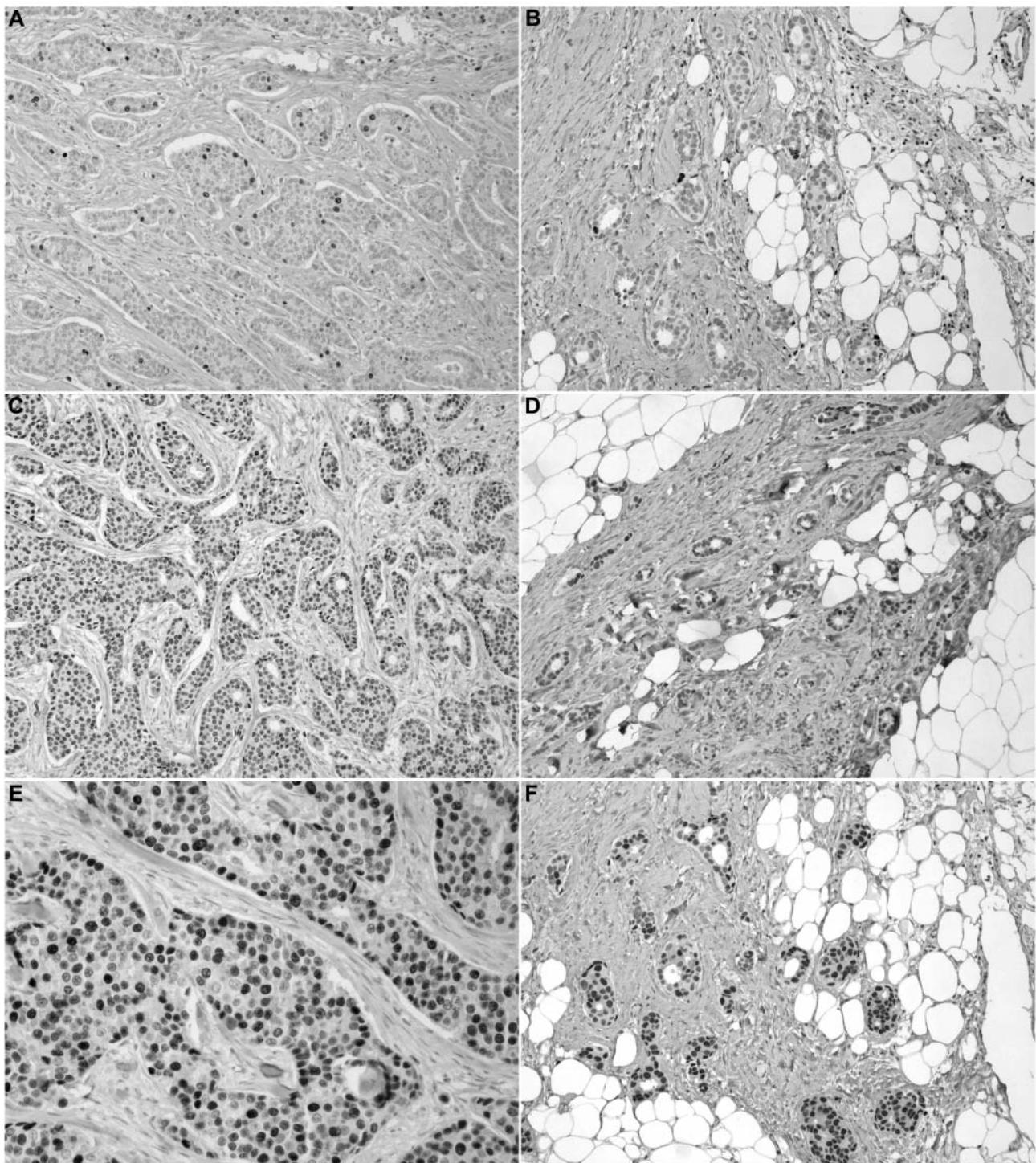


Figure 2. Immunohistochemistry. A, C, E Vulvar lesion; B, D, F: breast lesion. A, B: Ki-67; C, D: oestrogen receptor; E, F: progesterone receptor. As images show, similar immunohistochemical staining was found between vulvar and breast lesions suggesting a metastatic vulvar breast cancer. Original magnification: A-D, F:  $\times 200$ ; E:  $\times 400$ .

**Breast lesion.** A fine-needle aspiration cytology confirmed the neoplastic nature of the lesion. Left breast superior quadrantectomy, associated with ipsilateral sentinel lymph

node biopsy, revealed an invasive ductal carcinoma (grade 1, according to the Nottingham classification) (Figure 1 C, D). Immunohistochemistry showed positivity for ER and PGR in

Table I. Characteristics of breast-like carcinomas of the vulva collected from literature.

First author (ref no.)	Year	Patient's age (years)	Site	Histology	<i>In situ</i> component present
Greene (7)	1936	49	RL major	Adenocarcinoma	No
Hendrix (8)	1956	58	LL minor	Adenocarcinoma	No
Guerry (9)	1976	62	LL major	Ductal carcinoma	Yes
Guercio (10)	1984	49	LL major	Lobular carcinoma	No
Cho (11)	1985	70	RL major	Ductal carcinoma	No
Simon (6)	1988	60	RL major	Ductal carcinoma	No
Rose (12)	1990	68	RL major	Ductal carcinoma	Yes
Di Bonito (13)	1992	42	RL major	Ductal carcinoma	No
Bailey (14)	1993	65	RL major	Ductal carcinoma	No
Levin (4)	1995	62	Left paraclitorial	Ductal carcinoma	No
Kennedy (15)	1997	71	LL major	Lobular carcinoma	Yes
Erb-Gremillet (16)	1999	62	LL major	Adenocarcinoma	Yes
Irvin (17)	1999	64	Mons pubis	Adenocarcinoma	NA
Gorisek (18)	2000	81	LL major	Ductal carcinoma	No
Neumann (19)	2000	60	RL major	Lobular carcinoma	No
Piura (20)	2002	69	LL major	Ductal carcinoma	Yes
Chung-Park (21)	2002	47	RL major	Mucinous carcinoma	No
Ohira (5)	2004	82	LL major	Adenocarcinoma	NA
Intra (22)	2006	53	LL major	Ductal carcinomas	NA
Fracchioli (23)	2006	57	LL major	Ductal carcinoma	No
Martinez-Palones (24)	2007	49	RL major	Ductal carcinoma	No
North (25)	2007	49	Right paraclitorial	Adenocarcinoma	Yes
Tseung (26)	2008	49	RL major	Ductal carcinoma	Yes

RL: Right labium, LL: left labium; NA: not available.

95% and 92% of the neoplastic cells, respectively; the proliferative index (MIB-1) was 2%, p53 positivity was <1% and the Hercep test was negative (score 0) (Figure 2 B, D, F). Histological examination of the sentinel lymph node was negative for metastasis.

## Discussion

A diagnosis of breast-like cancer lesion located at the vulva is generally based on histopathological features (4), which nonetheless should be confirmed by the presence of oestrogen and/or progesterone receptors, and positivity for common breast cancer immunohistochemical markers because of its extremely rare occurrence (5). Here, we present the case of a breast-like cancer lesion located in the vulvar region in a woman lacking remarkable past medical or family history of breast cancer but with a concurrent breast cancer. Consequently, a differential diagnosis between a primary synchronous breast and vulvar cancer or a breast carcinoma metastatic to the vulva is a key point in terms of the clinical approach. In terms of primary breast cancer of the vulva, the majority of authors quote the ontogenetic theory of the mammary ridges, which are bilateral thickened ectodermal streaks wherein primordial breast tissue develops. This breast-like tissue of the vulva

responds to the hormonal influences of the menstrual cycle, pregnancy and lactation just as normally located breast glands do, and it is also subject to the same benign and/or malignant processes characteristic of thoracic breast tissue (6). To date, 23 cases of primary breast-like carcinomas have been reported in the English literature (Table I). Breast cancer metastasizes to the lymph nodes, lungs, bone and liver. Involvement of the genital tract *i.e.* the ovaries and uterus can occur but is uncommon in the vulva. To date, the literature reports 16 cases of vulvar breast cancer metastases. The time lapse of vulvar recurrence from the diagnosis of primary breast cancer ranged from 0-168 months (mean 55.6 months). In only one case was the vulvar metastasis clinically synchronous with primary breast cancer (Table II). It is not possible to make a clear-cut differentiation on histological or immunohistochemical grounds alone between a primary and metastatic breast cancer (37). However, several criteria have been proposed with the aim of distinguishing between a primary and metastatic vulvar lesion (32). The diagnosis of metastatic disease should be supported by identical histological, immunohistochemical and hormonal receptor status patterns shown by the breast cancer and the vulvar lesion. Furthermore, the diagnosis of vulvar metastasis is supported by the absence of *in situ* and/or normal breast

Table II. Characteristics of metastatic lesion to the vulva of breast cancer.

First author (ref no.)	Year	Patient's age (years)	Histology	Interval from primary diagnosis (months)
Covington (1)	1964	78	Comedocarcinoma	66
Dehner (27)	1973	36	Ductal carcinoma	33
Mader (28)	1982	61	Undifferentiated carcinoma	12
Cohen (29)	1988	NA	NA	NA
Patsner (30)	1996	48	Ductal carcinoma	7
Curtin (31)	1997	61	Ductal carcinoma	4
Menzin (32)	1998	53	Lobular carcinoma	Synchronous
Sindico (33)	1998	79	Ductal carcinoma	144
Porzio (34)	2001	67	Ductal carcinoma	168
Miliaras (35)	2002	45	Ductal carcinoma	12
Valenzano (36)	2003	49	NA	132
Neto (37)	2003	65	Ductal carcinoma	24
		48	Lobular carcinoma	84
		47	Undifferentiated carcinoma	60
		53	Cystosarcoma phyllodes	48
Sheen-Chen (38)	2004	32	Lobular carcinoma	40
Present	2008	72	Ductal carcinoma	Synchronous

NA: Not available.

Table III. Proposed clinicopathological criteria for differential diagnosis between primary and metastatic breast-like carcinoma localized to the vulva.

	Primary breast-like carcinoma of the vulva	Metastatic breast cancer to the vulva
Positive history of primary breast cancer	–	+
Presence of normal breast tissue in vulvar specimen	+	–
Presence of <i>in situ</i> breast carcinoma in vulvar specimen	+	–
Identical pathological histotype	–	+
Similar hormonal receptor status	–	+
Similar immunohistochemical pattern	–	+

cells in the vulvar specimen. Moreover, the presence of a positive history of primary breast cancer facilitates the diagnosis of a metastatic lesion. Table III summarises clinicopathological criteria for differential diagnosis between primary and metastatic vulvar breast cancer.

Nevertheless, these conditions are not always present, as for instance the contiguous *in situ* component. In fact, 11/17 cases of primary breast like carcinoma described did not show *in situ* carcinoma. Furthermore, metastatic tumours can exhibit some differences in hormonal receptor status from the primary cancer (34), probably resulting from the spontaneous mutations that may occur in the course of disease. Our patient had a clinically early breast lesion with a concurrent vulvar breast-like lesion. The diagnosis of a vulvar metastasis rather than a synchronous extramammary primary cancer is supported by the similar histological, immunohistochemical and hormonal receptor status patterns exhibited by the breast and vulvar lesions, as well as by the

absence of an *in situ* component and normal ectopic breast tissue in the vulvar specimen. To the best of our knowledge, this is the first reported case in the English literature of synchronous vulvar metastasis arising from a low-grade (G1) ductal breast carcinoma. Our report confirms that, as suggested by the American Society of Clinical Oncology, all patients with breast cancer should have a postoperative pelvic examination at regular intervals (39).

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