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CASE REPORT

Expression of the breast differentiation antigen NY-BR-1 in a phyllodes tumor of the vulva

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Abstract We describe a phyllodes tumor of borderline malignancy in the labium majus of a 49-year-old woman. The histogenetic origin of phyllodes tumors in the vulva is controversial. Strong immunoreactivity for NY-BR-1, a novel breast differentiation antigen, was demonstrated within the epithelial components of the phyllodes tumor. A similar expression pattern was observed in mammary-like glands of the vulva. These findings provide further evidence that phyllodes tumors of the vulva might derive from mammary-like glands in the labium majus or from ectopic breast tissue.

Keywords Vulva · Phyllodes tumor · NY-BR-1 · Mammary-like glands

Introduction

Mammary glands are modified apocrine glands arising along the mammary ridges, which appear on either side of the body in the fourth week of embryonal development, persisting only for a week. Remnants of these ridges can result in an arborising mesh of canals, giving rise to aberrant lactiferous ducts at anatomical sites other than the breast in the form of ectopic breast tissue. A fully formed mammary gland arising in the vulvar region was first described in 1872 by Hartung in a 30-year-old woman at the left labium majus. Since then, various benign and malignant variants of epithelial mammary tumors have been described, and ectopic mammary glands have been regarded as the tissue of origin of these neoplasms.

It has been reported that histologic changes in the ectopic breast tissue are, in general, similar to hormon-induced lesions in the breast occurring during puberty and early pregnancy [9]. Benign or malignant tumors of the vulva other then squamous neoplasms occur very rarely [20]. Whether proliferative processes mimicking breast lesions in the anogenital region evolve from remnants of the mammary ridges or originate from local adnexal structures, e.g. eccrine, sebaceous and apocrine glands of the skin, from mammary-like glands (MLGs) of the vulva, or whether they arise in neoplastically transformed ectopic breast tissue are still a question of debate.

In this report, we present a rare case of a phyllodes tumor in the vulva. We show that the recently described breast differentiation antigen NY-BR-1 is expressed in this tumor at an extramammary site as well as in MLGs of the vulva.

Clinical history

A 49-year-old hysterectomized, smoking (60 package years) but otherwise healthy perimenopausal patient presented with a rapidly growing mass at the labium majus near the clitoris on the right side. The patient was treated with 17-β-estradiole for menopausal symptoms. The symptoms were spotting and discharge. The lesion, which developed within 5 weeks, measured 3.7 cm in diameter and appeared sharply circumscribed. The tumor was excised surgically. A second resection was performed 2 months after the first tumor excision.

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Materials and methods

The surgical specimen was fixed in 4% buffered formalin and submitted entirely for histology. Two-micrometer sections from the paraffin-embedded tissue were taken for immunohistochemistry and haematoxylin and eosin (H&E) staining (Superfrost Plus, Menzel, Braunschweig, Germany). Immunostaining for mAb NY-BR-1 [21]; Ludwig Institute, New York) was performed on Ventana Benchmark (Ventana Medical Systems, Tucson, AZ) at a dilution of 1:400 (concentration, 2 μg/ml), MIB-1 (DAKO Diagnostics, dilution 1:20), CD34 (Serotec, dilution 1:50), estrogen receptor (6F11, Ventana dispenser), and progesterone receptor (1A6, Ventana dispenser).

Results

On gross examination, the specimen appeared as a polypoid firm lesion, with an uneven surface. The polyp was covered by normal epidermis. The cut surface was light gray, showing a firm sharply demarked tumor of 3.7 cm in diameter (Fig. 1).

The histological examination of the tumor revealed a subcutaneous mass consisting of a predominant stromal component, interrupted by leaf-like spaces lined by an epithelial component with bilayered epithelia consisting of myoepithelial and secretory cells, which directly harbored to the surface and covered the same one superficially. The surface of the tumor was focally ulcerated, without direct infiltration through neoplastic cells (Fig. 2).

The lining was predominantly composed of secretory (apocrine)-type epithelia and resembled mammary glandular epithelia. The secretory epithelial cells demonstrated a strong nuclear and cytoplasmatic immunoreactivity to NY-BR-1 and a 100% nuclear immunoreactivity for estrogen and progesterone receptors. No atypia or significant mitotic activity was present in the epithelial tumor component. The stroma was hypercellular with spindle-shaped, moderately pleomorphic cells with pale elongated nuclei and scanty cytoplasm. Focally, the mitotic activity of the stroma was increased (three to four mitoses per ten high-power fields, HPF). The proliferation index was 5% (MIB-1, Ki67). The neoplastic stroma demonstrated a stronger immunoreactivity for CD34 than the surrounding subcutaneous connective tissue. There was a small intraductal papilloma within the polypoid lesion. Overtly polymorphic stromal cells, necrosis or brisk mitotic activity exceeding ten mitoses per ten HPF were absent. Therefore, the tumor was diagnosed as a phyllodes tumor with "borderline" malignancy.

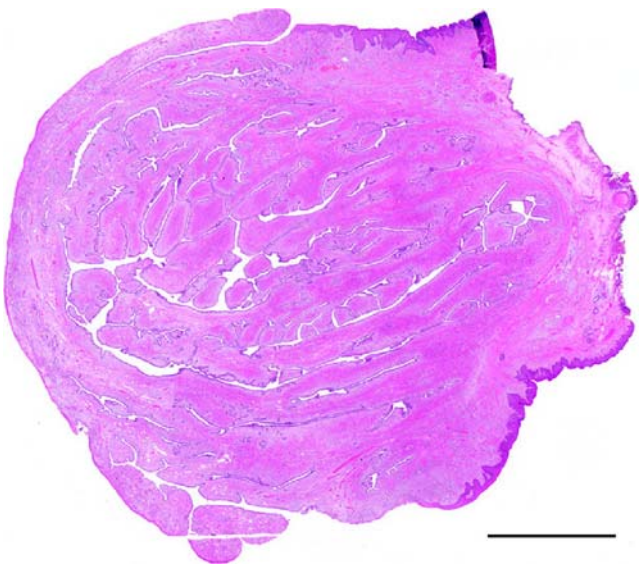

Fig. 1 Phyllodes tumor of the vulva. Overview (H&E). Typical leaf-like pattern (scale bar=1 cm)

Eccrine glands and MLGs were observed adjacent to the tumor. The latter also showed nuclear and cytoplasmic reactivity for NY-BR-1.

Because of the incomplete resection and the unpredictable behavior of "borderline" phyllodes tumors, a second resection was performed 2 months after the primary excision. The resection specimen contained MLGs, regenerative tissue with foreign body reaction but no remnants of the phyllodes tumor.

Discussion

In this report, we describe a phyllodes tumor of the vulva and discuss its histogenesis in the light of its expression of the novel breast differentiation antigen NY-BR1.

Various benign and malignant tumors resembling breast neoplasms have been described in the vulvar region [1–3, 5, 6, 8, 9, 15, 16, 20]. It has been suggested that these tumors derive from ectopic breast tissue or from MLG.

Cystosarcoma phyllodes of the breast, today preferentially named phyllodes tumor, was first described by Johannes Müller in 1838 [7]. According to our knowledge, five phyllodes tumors [4, 14, 17, 18] of the vulva and one phyllodes tumor of the perineum [13] have been reported. More than two dozen fibroadenomas of the vulva have been described, and it has been discussed whether these neoplasms arise from skin adherence glands or from ectopic mammary tissue.

The epithelial cells of the present tumor demonstrate strong cytoplasmic and nuclear NY-BR-1 immunoreactivity. NY-BR-1 is a novel mammary differentiation antigen. It was recently identified by SEREX analysis of a metastatic breast carcinoma patient [10–12]. The NY-BR-1 gene has been mapped to chromosome 10p11–12 and is composed of 37 exons. It encodes a peptide of Mr 150,000 to 160,000, which is regarded as a putative transcription factor. NY-BR-

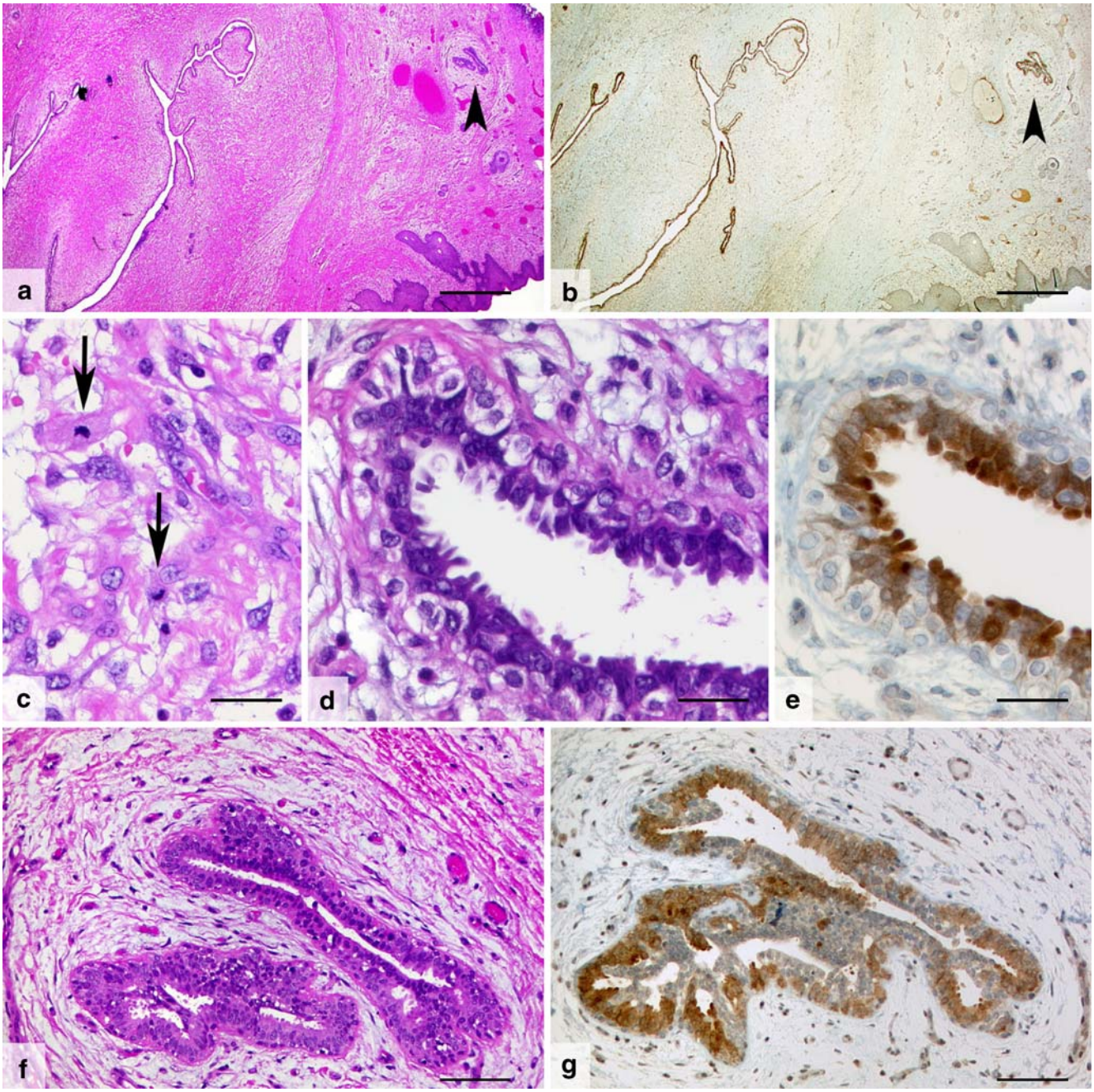

Fig. 2 Phyllodes tumor of the vulva. Histology and immunohistochemistry. *A–B* Mammary-like glands in the vicinity of the phyllodes tumor (*arrowhead*) HE (**a**) and NY-BR-1 immunohistochemistry (**b**; A–B scale bar=1 mm). *C–E* Detail of stroma with increased mitotic activity. *Arrows* indicate two mitoses in one HPF (**c**); Bilayered epithelium consisting of myoepithelial- and secretory-cell layers (**d**); NY-BR-1 immunoreactivity in cytoplasm and nuclei of secretory ductal cells (**e**; C–D scale bar=20 μm). Legend to figures: *F–G* MLG in the surroundings of the phyllodes tumor. HE (**f**) and NY-BR-1 (**g**; F–G scale bar=0.15 mm)

1 mRNA expression was found in a high percentage of breast cancers (84%) and normal breast tissue and at a much lower level in normal adult testis but not in other normal tissues [10]. We have recently demonstrated strong protein expression in mammary glands and in carcinomas of the breast using immunohistochemistry [21]. Our findings suggest that the novel monoclonal NY-BR-1 antibody can be used as a surrogate marker for tumors of breast origin.

The NY-BR-1 expression is a strong argument for a derivation of the phyllodes tumor of the vulva from MLGs or from ectopic breast tissue. Further evidence for a derivation of the phyllodes tumor from MLGs is its location at the inner side of the labium majus and the

prominent MLGs in the immediate surroundings. Van der Putte [19, 20] suggests that vulvar neoplasms resembling breast tumors most probably arise in MLGs. He observed that many of these lesions (a) greatly resemble but are not identical to corresponding lesions of the breast, (b) occur also in the perineum and around the anus but rarely elsewhere on the skin and (c) are elements of discussion concerning their derivation that focus on eccrine or apocrine glands or their precursor cells rather than on mammary tissue. He further argues that these features reflect basic elements of the MLGs that are directly related to eccrine glands and show apocrine metaplasia. Some MLGs reveal a mammary-type histology as the predominant feature.

The behavior of phyllodes tumors is difficult to predict by histology alone. In the breast, phyllodes tumors are classified into benign, borderline and malignant according to mitotic rate, nuclear pleomorphism and presence of necrosis.

Because of the increased mitotic activity, the tumor of our patient was classified as "borderline." After incomplete excision of the lesion, an additional resection was performed to prevent local recurrence.

In summary, we present a phyllodes tumor of the vulva with strong expression of the breast differentiation antigen NY-BR-1. MLGs of the vulva also express this antigen and were abundantly present in close vicinity to the tumor. Therefore, we speculate that at least some phyllodes tumors of the vulva are derived from such glands, although we cannot exclude that ectopic mammary glands are also the origin of such vulvar tumors.

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