Phyllodes Tumor of Vulva

A Brief Diagnostic Review

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• Phyllodes tumors of the vulva are rare proliferations that share morphologic similarities with breast neoplasms. Their histogenetic origin is elusive and may be associated with specialized mammary-like glands of the vulva. Because of their rarity, the clinical and pathologic features, classification, and therapy are not well defined, and their biologic behavior is difficult to predict by histology alone. Immunohistochemical expression of estrogen and progesterone receptors and breast markers provide further support for a common origin. Surgical resection is the current mainstay of therapy and is definitive in most cases.

(*Arch Pathol Lab Med*. 2014;138:1546–1550; doi: 10.5858/arpa.2013-0581-RS)

In 1872, Hartnug et al, as cited by van der Putte,[1] were the first to report mammary-like glands in the vulvar region. Since that first report, many different neoplastic conditions that show morphologic similarities to their breast counterparts have been reported in the vulva, including lactating adenoma,[2] pseudoangiomatous stromal hyperplasia,[3] fibroadenomas,[4–7] and mammary-type carcinomas.[8–10] Phyllodes tumors of the vulva are uncommon neoplasms, with only 10 previous cases reported, to our knowledge, on review of literature, which may be due to the rarity of this entity or to reporting under various names, such as *fibroadenoma*, *adenofibroma*, or variants of *mammary-like gland adenoma of the vulva*,[11] at the benign spectrum of the entity. The prognosis of this neoplasm is uncertain, with local recurrence being the most common complication.[12–14] However, none of the reports of this entity, to our knowledge, has yet shown evidence of metastatic potential associated with its breast counterpart, despite a case report showing phyllodes tumor of the vulva with histologic features suggestive of malignancy.[15]

In this report, we review the literature on clinical and pathologic findings of this rare entity. We also discuss the concepts regarding its etiology, differential diagnosis, and clinical implications.

Accepted for publication October 25, 2013.

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The authors have no relevant financial interest in the products or companies described in this article.

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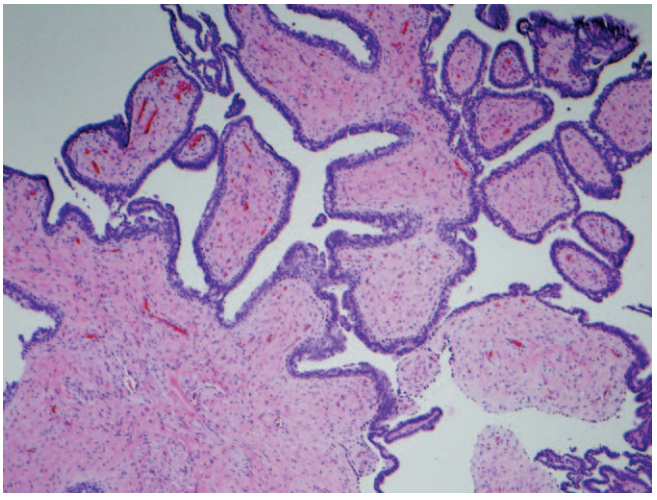

Figure 1. *Classic, leaflike architecture of phyllodes tumor projecting into cystic spaces. A thin bilayered epithelium covers the stromal projections (hematoxylin-eosin, original magnification ×40).*

PATHOGENESIS

There are 2 main theories to explain the presence of phyllodes tumors in the vulva. One claims its origin in ectopic breast tissue, and the other claims local adnexal structures: the specialized, anogenital, mammary-like glands. This latter theory is the most favored in recent, specialized publications.[1,16,17]

Supernumerary breast tissue deriving from the caudal remnants of embryonic milk ridges are thought to occur in the vulva and may be the source of the array of vulvar tumors that resemble their breast counterparts. However, that concept has been a matter of debate. van der Putte[17] challenged the concept of the origin in a milk ridge remnant by describing histologic features of anogenital glands and showing the normal presence of those structures mimicking mammary glands in the anogenital region. He further asserted that the primordia of the mammary glands did not extend beyond the axillary pectoral region in the human embryo. Further, because these mammary-like anal glands can show eccrine and apocrine features with frequent expression of estrogen and progesterone receptors, van der Putte[17] deduced they must be the origin of the various conditions and neoplasms with similar breast counterparts.[18] He also highlighted the histologic and ultrastructural differences based on simpler

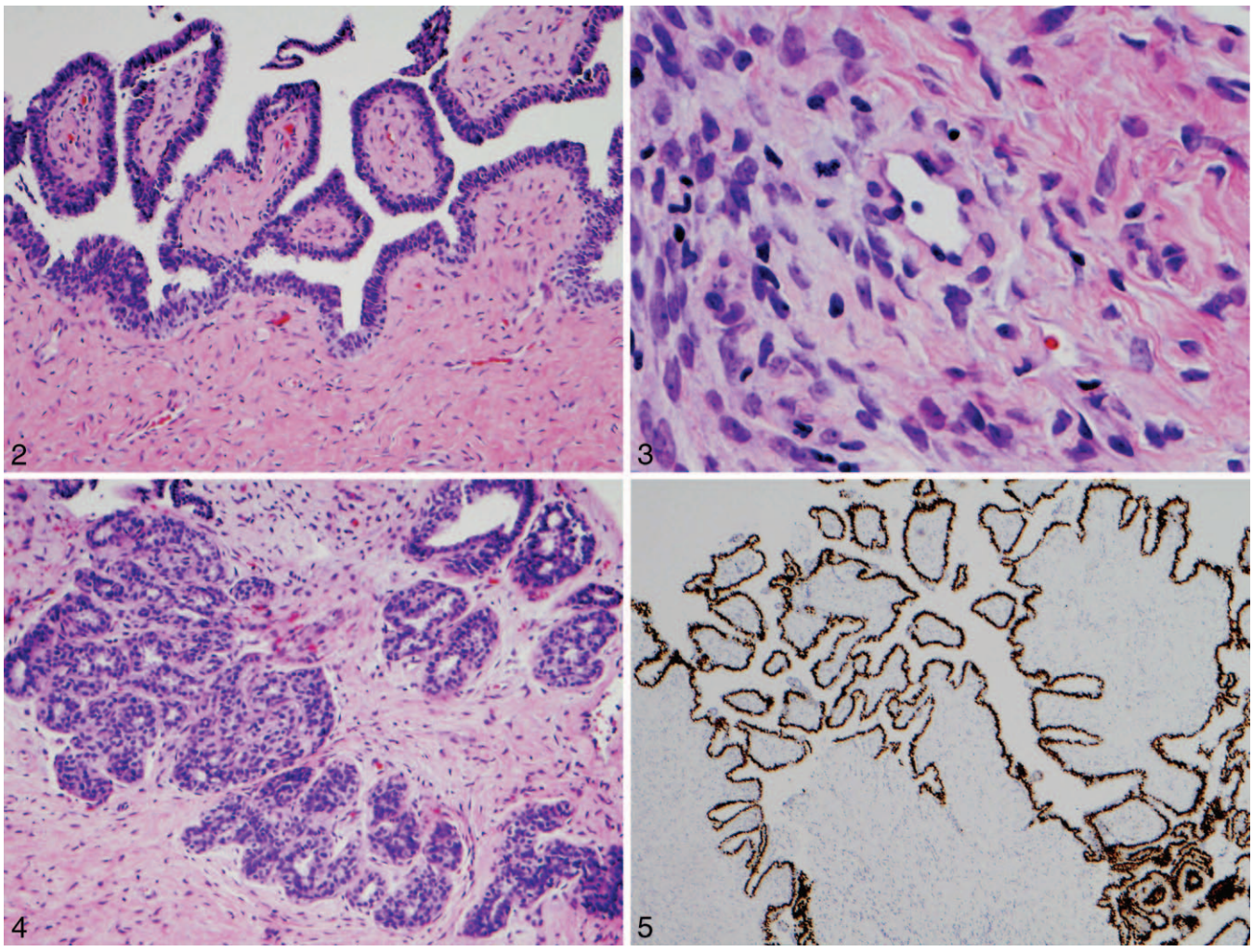

Figure 2. *Epithelium shows stratified cuboidal cells. A myoepithelial layer with overlying secretory type cells is shown (hematoxylin-eosin, original magnification ×100).*

Figure 3. *Highly cellular stroma (left part of the image) interfaces with an area of less cellular stroma (right side of the image). A mitotic figure can be seen in the upper left of the vascular space (hematoxylin-eosin, original magnification ×400).*

Figure 4. *Mammary-like, anogenital glands present in the area adjacent to the tumor. A lobular configuration with benign apocrine-type epithelium is present (hematoxylin-eosin, original magnification ×100).*

Figure 5. *Secretory epithelial cells are highlighted by estrogen receptor antibody. Stromal cells do not express estrogen (estrogen immunostain, original magnification ×40).*

gland configuration, different acinar epithelium, and the fewer electron-lucent secretory granules seen in mammary glands.[1]

Additional support for the theory for mammary-like anogenital glands being the origin of mammary-type neoplasms and conditions, including phyllodes, comes from reports of those entities in regions that are not part of the caudal milk line, including phyllodes of the perianal region,[3,13] prostate,[18,19] and seminal vesicle.[19,20]

Giger et al[20] demonstrated strong NY-BR-1 expression by the phyllodes tumor of the vulva with similar strong expression from nearby mammary-like anogenital glands, suggesting that the phyllodes tumor of the vulva likely originate from these glands. The involvement of hormones in the development of phyllodes tumors of the vulva is suggested by reports that correlate the appearance of tumor with the onset of puberty[14] and rapid growth during 17-β-estradiole treatment for menopausal symptoms.[20,21] The presence of similar tumors in prostate and seminal vesicles with a different immunohistochemical pattern suggest alternate mechanisms for these locations.[18,19]

CLINICAL FEATURES

The Table summarizes the clinical and pathologic characteristics of the previous cases reported in the literature. The patients' age ranged from 17 to 69 years, with most of the tumors located in the labium majus. Other locations included interlabial sulcus, mons pubis, and periclitoral sites. The tumors are usually solitary, with one report describing bilateral disease (case 1) and another with 3 separate nodules (case 2). Tumor sizes ranged from 0.7 to 6.6 cm at greatest dimension, and almost all cases were described as well-circumscribed tumors that were freely mobile and nontender to touch. Nulliparity was reported in 3 cases, but most cases did not include that information in the patient's history. Growth rate was variable, with some

Cases of Phyllodes Tumor of Vulva						
Case No.	Source, y	Grade	Age, y	Location	Clinical Information	Gross Findings
1	Tbakhi et al,[14] 1993	Benign	20	Labia majora	Pruritus, dyspareunia; multiple (n =5), bilateral, well-circumscribed, mobile, nontender; present since age 15 y; obese, G0P0	1–4 cm; cystic, filled with white-tan, soft, frondlike projections
2A	Tresserra, et al[23] 1998	Probably benign	39	Labium majus	Infertility; 2 cm, solid, painless nodule	White, soft, ovoid; 1.4 cm; cut surface foliaceous with elongated clefts
2B			17	Interlabial sulcus	Multiple (n = 3) with enlargement of vulvar nodule present for 2 y	3 ovoid nodules; 0.7–1.6 cm; cut surface with irregular clefts
3	Chulia et al,[24] 2001	Benign	34	Labium majus	Ulcerated, well-circumscribed, mobile; G0P0	Circumscribed with clefts; smooth-surfaced, rubbery nodule; 6 cm
4	Mariappan et al,[25] 2006	Probably benign	69	Interlabial sulcus	Nontender, nonulcerated, mobile, subcutaneous mass	Firm, pink, partially circumscribed mass; 3 cm
5	Giger et al,[20] 2007	Borderline	49	Labium majus	Rapidly growing mass; 5-wk development; undergoing postmenopausal estrogen treatment; well circumscribed	Polypoid, firm lesion; cut surface light gray; sharply circumscribed tumor; 3.7 cm
6	Hefferman et al,[12] 2010	Benign	39	Midline, superior to clitoris	Primary: vulvar discomfort, enlarging vulvar mass, nontender; Recurrence: at area of previous excision, painful	Primary: exophytic; lobulated with cauliflower-like appearance; tan homogenous cut surface; poorly delineated: 4 cm
7A	Kazakov et al,[13] 2010		38	Periclitoral	History of neurofibromatosis, mammary fibroadenomas	4-cm mass; fleshy polypoid appearance
7B			31	Labium majus	History of mammary fibrocystic disease	Solitary 2-cm nodule
8	Mannan et al,[26] 2010	Benign	18	Labium majus	Slow-growing, painless mass for 1 y; nontender, nonulcerated, freely mobile	Well-circumscribed, globular mass with frondlike masses projecting into small cystic spaces; 5.5 cm
9	Fu et al,[15] 2011	Malignant	61	Labium majus	Rapidly growing mass; 1 mo hx of postmenopausal bleeding, painful sensations in vulva; ulcerated, pedunculated mass G0P0	Exophytic mass with ulcerated surface and necrosis; pushing margins; 6.6 cm
10A	Ozbudak, et al[27] 2013	Benign	43	Anterior mons pubis	Firm nodule 1 y prior; 3 mo increase in size	Oval, white-yellow with cleftlike spaces; 4.7 cm
10B			50	Labium majus	Postmenopausal; 2 mo; painless mass	Similar to 10A; 3.2 cm

Abbreviations: EMA, epithelial membrane antigen; ER, estrogen receptor; G0P0, nulligravid–no pregnancies; HPFs, high-power fields; hx, history; NED, no evidence of disease; PASH, pseudoangiomatous stromal hyperplasia; PR, progesterone receptor; SMA, smooth muscle actin.

cases showing recent rapid growth and others being present without growth for years and discovered as an incidental finding. Recurrence was uncommon, with one case implicating positive margins as the culprit (case 6). Unusual clinical characteristics included ulceration (cases 3 and 9) and multiple tumors (cases 1 and 2B). Common gross findings included a homogenous, tan-white, firm, and well-delineated lesion with a cystic or solid-cut surface. Frondlike projections or a polypoid appearance with a pushing margin was also characteristic. Rarely, necrosis (case 9) and ill-defined margins (case 6) were seen.

HISTOPATHOLOGY AND IMMUNOHISTOCHEMISTRY

Phyllodes tumor of the vulva has histologic features similar to phyllodes tumor of the breast. All reports described the low-power appearance of a biphasic tumor with a leaflike architecture and fronds projecting into a cystic space (Figure 1). The characteristic frond growths were covered with a bilayered epithelium composed of a myoepithelial layer with a secretory-type outermost layer (Figure 2). Hyperplastic epithelium and pseudostratification were seen (case 6 and 7) but without overt malignant cytologic features.

The stroma was variably cellular, ranging in reports from low to high. Areas composed of bland spindled cells with tapered nuclei and indistinct cytoplasm in a collagenized background were admixed with areas of higher cellular density composed of larger cells with plump oval nuclei and scattered mitotic figures (Figure 3). Recurrent tumors usually showed higher stromal cellularity (cases 1 and 7), but cytologic atypia was absent. Mitotic count was usually low to absent, with a couple of cases reporting more than 1 to 2 mitosis per 10 high-power fields. Marked nuclear pleomorphism was uncommon (case 9), and condensation of stromal cells toward the lumen was rare (case 10). Heterologous elements were rare, and striated muscle differentiation has been reported (case 9). Stromal overgrowth, defined by the absence of the epithelial component in a ×40 microscopic field, was also rare (case 9). Adjacent tissue sometimes showed lobules of mammary-like glands (Figure 4).

Immunohistochemistry uniformly showed nuclear estrogen and progesterone receptor reactivity in the secretory epithelium (Figure 5), with smooth muscle actin and S100 staining in the myoepithelial cells as expected. BRST-2 and mammoglobin sometimes demonstrated patchy reactivity in the epithelial component. Stroma was consistently negative for estrogen and progesterone receptors and showed reaction with CD34, vimentin, and smooth muscle actin. Ki-67, when performed, ranged from 1% to 15%.

Grading

Because of its rarity, grading of phyllodes tumors of vulva has not been established, but the authors of previous case reports have classified those lesions as benign, borderline, or malignant based on a semiquantitative assessment of

Extended		
Microscopic Findings	**Immunohistochemistry**	**Follow-up**
Biphasic, leaflike architecture; fibrocystic changes; stroma, sparsely cellular	BRST-2 patchy positive in ducts and lobular units	Recurrence, 8 mo after excision, 2 more masses removed; more-cellular stroma
0 mitoses/50 HPFs; adjacent lobules of mammary-like glands		3 mitoses/50 HPFs; NED at 10 mo
Biphasic, leaflike architecture; bilayered epithelium; hypocellular stroma with variable collagen; rare mitoses; adjacent lobules of mammary-like glands; pseudocapsule	EMA$^+$, AE1/3 $^+$ epithelial cells; actin + myoepithelial cells	Excision; NED at 18 mo Excision; NED at 6 mo
Biphasic, leaflike architecture; hypercellular stroma; pushing margins; 1 mitosis/10 HPFs; adjacent lobules of mammary-like glands	Vimentin-positive, CD34$^+$, SMA$^+$, BCL2$^+$ stromal cells; AE1/3$^+$, CAM 5.2$^+$, ER/PR$^+$ BCL2$^+$ epithelial cells; 1% Ki-67 in stroma	Simple excision; NED at 18 mo
Biphasic, leaflike architecture; secretory-type epithelium; hypercellular stroma; <3 mitosis/HPF; pushing margins	Not reported	Simple excision; follow-up not provided
Biphasic, leaflike architecture; bilayered epithelium with secretory cells; hypercellular stroma	CD34$^+$ stromal cells; NY-BR-1$^+$, ER/PR$^+$ epithelial cells; 5% ki-67 in stroma	Simple excision; re-excision performed at 2 mo with NED
3–4 mitosis/10 HPFs; adjacent lobules of mammary-like glands		
Biphasic, leaflike architecture; hyperplastic bilayer epithelium; moderately cellular, bland stromal cells; no cellular atypia or necrosis; rare mitoses; adjacent lobules of mammary-like glands	ER/PR$^+$ in >50% of epithelial cells; positive BRST-2, mammoglobin focal in epithelial cells	Primary: wide, local excision with positive margins; Recurrence: 4 cm, wide, local excision with negative margins, NED
Biphasic, leaflike architecture; hyperplastic epithelium, with florid ductal hyperplasia; hypercellular stroma; 1–2 mitosis/10 HPFs; associated PASH	CK7$^+$, AE1/3$^+$, P53$^-$ BRST-2$^+$ ER$^+$, PR$^+$, mammoglobin-positive epithelial cells; CD34$^+$, vimentin-positive, weak SMA$^+$, desmin-positive in stroma	Simple excision; 12-cm recurrence 2 y later; higher stromal cellularity NED at 9 y NED at 4.5 y
Biphasic, leaflike architecture; bilayered epithelium; hypocellular spindle stroma; 1–2 mitoses/50 HPFs; no necrosis	ER/PR$^+$, BRST-2$^+$, AE1/3$^+$, NY-BR-1$^+$ epithelial cells; S100$^+$, SMA$^+$ myoepithelial cells	Simple excision; NED at 12 mo
Biphasic, leaflike, papillary; bilayered epithelium; hypercellular stroma with severe cytologic atypia; overgrowth; striated muscle differentiation; 12 mitosis/10 HPFs	ER/PR$^+$, BRST-2$^+$ epithelial cells; CD10$^+$, p63$^+$ myoepithelial cells; myogenin-positive, desmin-positive, SMA$^+$, h-caldesmon–negative in striated muscle component; 15% Ki-67 in stroma	Wide, local excision with clear margins; NED at 12 mo
Anogenital mammary –like glands present		
Biphasic, leaflike architecture; bilayered epithelium; hypercellular stroma with condensation around ducts; no mitotic activity	Not reported	Surgical excision; no follow-up data reported

stromal cellularity, cellular pleomorphism, and mitotic activity or on a Ki-67 index of the stroma, similar to that described in the breast.[20] Stromal overgrowth, defined as no epithelial component in a ×40 microscopic field, increased stromal cellularity with significant cytologic atypia, mitotic counts greater than 10 per 10 high-power fields, heterologous differentiation, and infiltrative growth pattern are features possibly suggestive of malignancy.[15]

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis for phyllodes tumor of the vulva is fibroadenoma. Although both neoplasms are relatively uncommon in the vulva, fibroadenoma is more common than the phyllodes tumor.[13] Overlapping features can be seen, and distinction between these entities can be problematic. Analogous to its breast counterparts, the main differentiating characteristics are the typical growth pattern, the tendency of phyllodes tumors to become cystic, the increased cellularity, cellular heterogeneity, and cytologic atypia in the stroma of the phyllodes tumor. The characteristic leaflike projections in phyllodes tumor, rarely described in fibroadenomas,[4,7] were the defining architectural feature present in all case reports.[13] The assessment of stromal cellularity is a second level of evaluation but an important prognostic consideration.[14]

A graver potential pitfall in the differential diagnosis is an extension of a Müllerian adenosarcoma of the cervix into the vulva.[21,22] Müllerian adenosarcoma is a biphasic lesion that may also present as a polypoid mass with a leaflike pattern and with histologic features that include periglandular stromal condensation, greater stromal cellularity, and increased mitotic activity.[22,23] One case of phyllodes tumor of the vulva showed increased cellularity, stromal overgrowth, and increased mitotic activity,[15] whereas stromal condensation was reported in a recurrent lesion.[13] Immunohistochemical stains may be useful in this differential because the sarcomatous component of Müllerian adenosarcoma shows reactivity for WT1, CD10, and estrogen and progesterone receptors,[22] whereas stroma of the phyllodes tumor in the vulva was nonreactive for the above markers. The typically bilayered epithelium of the phyllodes tumor may also be helpful in making the distinction.

The other 2 tumors lower in the differential diagnosis include papillary hidradenoma and syringoma. Although the papillary and cystic nature of both lesions may be grossly similar, papillary hidradenoma should be distinguishable from phyllodes because of the lack of a prominent stromal component. Chondroid syringoma may resemble phyllodes because of its biphasic nature, but the myxoid stroma, often with cartilaginous components, and the lack of a leaflike architecture should help with differentiation between the 2 entities.

THERAPY AND PROGNOSIS

The mainstay of therapy was surgical excision with clear margins. Recurrence was described in a lesion classified as benign, most likely related to prior incomplete resection,[12] but additional excision with clear margins was curative.

Therefore, close follow-up is warranted, irrespective of histologic categorization. Although the prognosis is still unclear because of the rarity of the tumor, no cases of metastatic phyllodes tumor of the vulva have been described.

In summary, phyllodes tumor of the vulva are fibroepithelial proliferations that most likely arise from anogenital, mammary-like glands in women, with striking morphologic homology to similar neoplasms occurring in the breast.

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