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Case Report

Angiomyofibroblastoma of the Vulva: A Large Pedunculated Mass Formation

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Angiomyofibroblastoma is a rare, usually small benign mesenchymal tumor that occurs in vulvar lesions of premenopausal women. A case of angiomyofibroblastoma that arose as a unique pedunculated and particularly large mass in the left vulva of a 48-year-old woman is presented herein. The patient had been aware of a gradually enlarged mass of 7 years' duration without any other gynecological symptoms or signs. The maximum dimension of the tumor measured 11 cm. The resected tumor was well circumscribed with a bulging and glistening cut surface. Histological examination revealed an admixture of irregularly distributed hypercellular and hypocellular areas with spindled, plump spindled, or plasmacytoid stromal cells and abundant venular or capillary-sized vessels. Stromal cells characteristically cluster around delicate vessels within an edematous to collagenous matrix. In the present case, intralesional adipose tissue was present throughout the tumor. There was no significant nuclear atypia, and mitotic figures were very sparse. There was little stromal mucin throughout the tumor. Immunohistochemically, the stromal cells were characterized by strong reactivity for vimentin and CD34, with focal reactivity for desmin and alpha smooth muscle actin. Both estrogen and progesterone receptors were diffusely expressed in the stromal cells. These histological findings are consistent with angiomyofibroblastoma and support the hypothesis that angiomyofibroblastoma originates from perivascular stem cells with a capacity for myofibroblastic and fatty differentiation.

Key words: angiomyofibroblastoma, vulva, adipose tissue, pedunculated mass

Angiomyofibroblastoma (AMFB) has been distinguished from aggressive angiomyxoma (AAM) by Fletcher *et al.* based on its different biological behavior [1]. AMFB is a rare mesenchymal neoplasm arising in the lower genital tract of middle-aged women, predominantly in the vulva [2–4], although a few cases of AMFB-like tumors in males have been reported that involve inguinal lesions, such as scrotum, perineum, or spermatic cord [5, 6]. Nowadays, AMFB is known to have distinct clinicopathologic features as a nonaggressive benign mesenchymal tumor [7, 8]. The histology of AMFB is characterized by bland-looking stromal cells and abundant small blood vessels. In addition, in some

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cases fatty differentiation of stromal cells is noted in relation to the cell origin [9].

The vulval AMFB presented here was found to show unique morphotypes, *i.e.* macroscopically large pedunculated mass formation and microscopically apparent fatty differentiation. AMFBs are usually well-circumscribed small lesions and do not form a pedunculated mass. To our knowledge, only 2 cases of AMFB with pedunculated mass formation have been reported in the English literature [1, 10]. The present study was based on the morphology and immunohistochemical profiles of AMFB in association with its histogenesis.

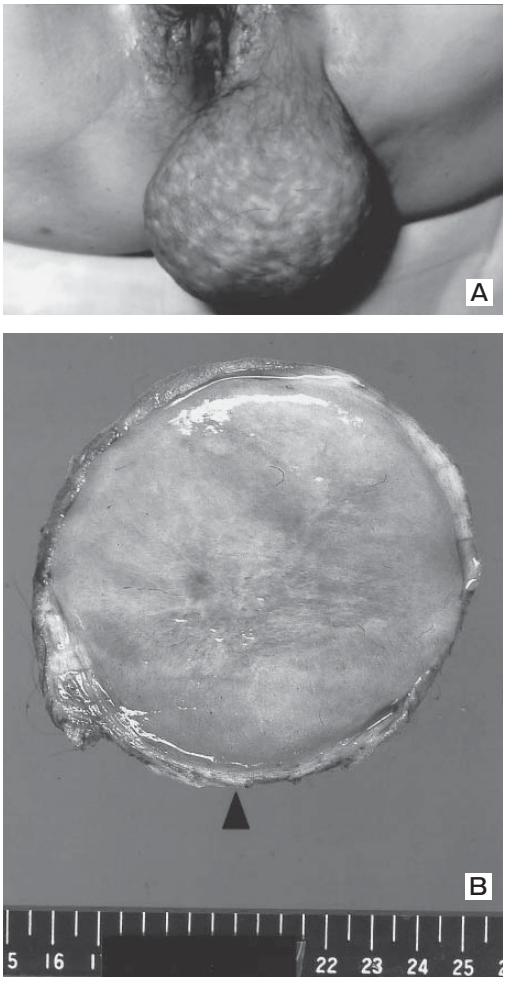

Fig. 1 **A**, The tumor shows a pedunculated large mass arising from the left vulva with a short stalk; **B**, A cut section of gross specimen, showing a well-circumscribed mass, bulging above the cut surface. The arrowhead shows the resected edge of the tumor.

Case Report

Clinical summary. A 48-year-old Japanese woman, gravida 0 para 0, presented with an asymptomatic large pedunculated mass, 11 cm across, having a short stalk arising from the lateral margin of the left labium majus pudendi (Fig. 1A); the patient had first noticed the tumor 7 years previously, as a red bean-sized subcutaneous nodule, and 4 years later, it became hen egg-sized. She ignored the mass, despite its gradual enlargement during her disease course. The patient had no medical and family history of note. On vaginal examination and ultrasonography imaging, the uterus and bilateral uterine adnexae showed no abnormalities. Inguinal lymph nodes were not swollen. Laboratory examination revealed no remarkable findings on admission. Tumor markers were not examined. The tumor gave a clinical impression of lipoma, and simple tumor excision was subsequently performed at the site of the stalk. There was no evidence of local recurrence or metastasis 3 years after surgery.

Pathological findings.

(1) Gross appearance. The surgically resected specimen was 360 g and contained a solid, elastic-soft tumor, $11 \times 9 \times 8$ cm in size, in the subcutaneous area. The tumor was well-circumscribed but non-encapsulated, and the cut-surface was homogenous, pinkish-gray, and glistening (Fig. 1B). Neither hemorrhage nor necrosis was noted, and the pedicle was not involved by the tumor.

(2) Microscopical appearance. The tumor was fixed with 15% formalin and embedded in paraffin. The sections were stained routinely with hematoxylin and eosin (HE), phosphotungstic acid hematoxylin (PTAH), argentaffin silver impregnation, alcian-blue and phyloxin methylene blue.

The vulvar tumor grew under tunica dartos labialis without tumor involvement. It was characterized by an admixture of irregularly distributed hypercellular and edematous hypocellular areas. The closely packed stromal cells in the hypercellular area were loosely dispersed in an edematous background containing thin wavy collagen fibers in the hypocellular areas (Fig. 2). Stromal cells were closely packed in the hypercellular areas. These cells had, in general, a small amount of faintly eosinophilic cytoplasm and a single round or ovoid nucleus with slightly coarse

chromatins and small or inconspicuous nucleoli. Cell borders were often indistinct. There was no significant nuclear atypia and less than one mitosis figure per 10 high-power fields. Slightly polygonal cells and binucleated cells were occasionally seen. A scattering of mast cells were observed, and slight lymphocytic infiltration was present. The hypocellular areas featured compact stromal cell aggregation, argentaffin fibers, and abundant, small thin-walled vessels as well as capillary-sized blood vessels. The shape of stromal cells is generally spindle, plump-spindle, or ovoid, and the cells are characteristically clustered around vessels within an edematous to collagenous matrix. Plasmacytoid and plump stromal cells tend to be arranged in small nests. The small vasculature is closely related to the stromal cells partly featuring a capillary-like pattern (Fig. 3). No stromal mucin was demonstrated anywhere. In both areas, spindle stromal cells with PTAH-positive slender cytoplasm were frequently seen. Furthermore, small clusters of mature adipocytes were found to exist in close association with the stromal cells and to be located in both hypercellular and hypocellular areas, including the center of the tumor (Fig. 4). As a whole, the adipocytic element occupied approximately 5% of the tumor. The nuclei of the adipocyte were somewhat plump, similar to those of stromal cells, with fine to slightly coarse chromatin and inconspicuous nucleoli. The superficial skin free from the tumor showed acanthosis and fibrous thickening of the dermis.

Immunohistochemical examination of the tumor on formalin-fixed paraffin-embedded sections was attempted using the avidin-biotin-peroxidase complex method with the following antibodies of commercial source (DAKO, Kyoto, Japan, and *Immunon, Pittsburg, PA, USA); anti-vimentin, anti-CD34, anti-desmin, anti-Factor VIII, anti-estrogen receptor (ER), anti-progesterone receptor (PR), anti-S-100 protein, anti-synaptophysin, anti-cytokeratin (AE1/AE3), *anti-alpha-smooth muscle actin (ASMA), and anti-Ki-67(MIB-1). The stromal cells revealed immunoreactive profiles for the anti-sera as follows (Fig. 5); staining for vimentin was diffuse and intense. An extensive population of stromal cells was positive for CD34, and factor VIII was focally and slightly positive. A minor population of stromal cells was reactive for desmin and ASMA. Nuclear ER and PR were demonstrated over almost the entire tumor

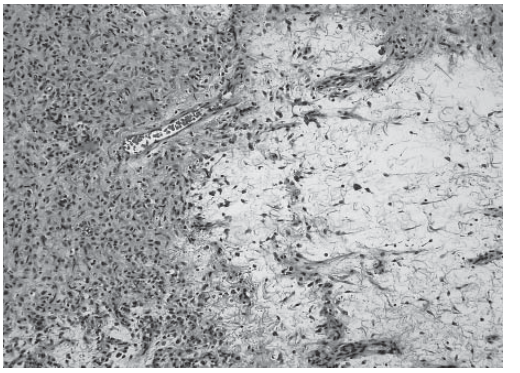

Fig. 2 The tumor is characterized by alternating hypercellular and hypocellular edematous areas.
The closely packed stromal cells in the hypercellular area were loosely dispersed in an edematous background containing thin wavy collagen fibers in the hypocellular areas.

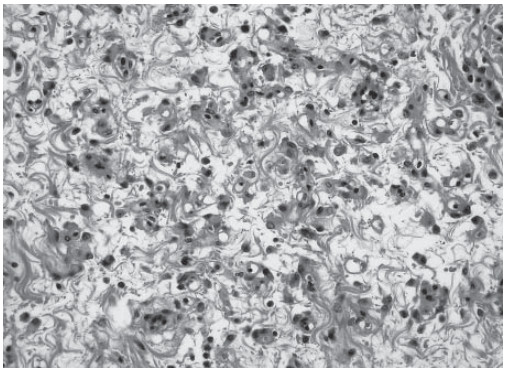

Fig. 3 Plump stromal cells tend to aggregate and demonstrate a capillary-like structure.

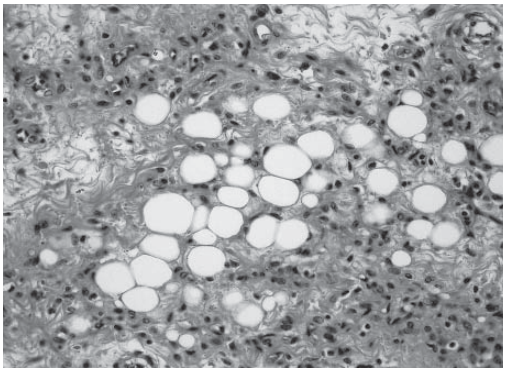

Fig. 4 Small clusters of mature adipocytes can be seen within the tumor.

area. S-100 protein, synaptophysin, and cytokeratin were not detected in the stromal cells. The intralesional mature adipocytes were immunoreactive for vimentin and S-100 protein but not for ER and PR. The MIB-1 labeling index was less than 1%.

Discussion

The large vulvar tumor reported herein is regarded as AMFB based on the following clinical and pathological aspects: 1) the tumor presented in the most usual site; 2) the histology disclosed typical features of AMFB such as the coexistence of hypercellular and hypocellular areas of nonatypical stromal cells intimately associated with small vasculature; and 3) there was no stromal mucin.

Most cases of AMFB measure less than 5 cm, and previously reported cases ranged from 0.5 cm to 13.0 cm in greatest diameter [1, 10]. The tumor usually exists as a sharply circumscribed mass in the subcutaneus tissue of the vulva and is less likely to be macroscopically polypoid [11]. To our knowledge, 2 cases of pedunculated AMFB have been reported in the English literature[1, 10]. One case involved a mass measuring 12×4 cm in size with an 8-year history, and the other a mass measuring $13 \times 12 \times 11$ cm with a 6-month history. It is worth noting that the reported cases of pedunculated AMFBs, including the present case, are extremely large as AMFB, and 2 of them contained adipocytes. In our case, the tumor gave a clinical impression of lipoma because the tumor presented as a well-circumscribed mass without infiltrative growth by ultrasonography imaging. Preoperative differential diagnosis included bartholin cyst, labial cyst, inguinal hernia, and mesenchymal tumors such as lipoma and liposarcoma. AMFB was not included because of the unusually large pedunculated mass formation with a stalk. Therefore, clinicians and surgical pathologists should be aware that a large AMFB can form a vul-

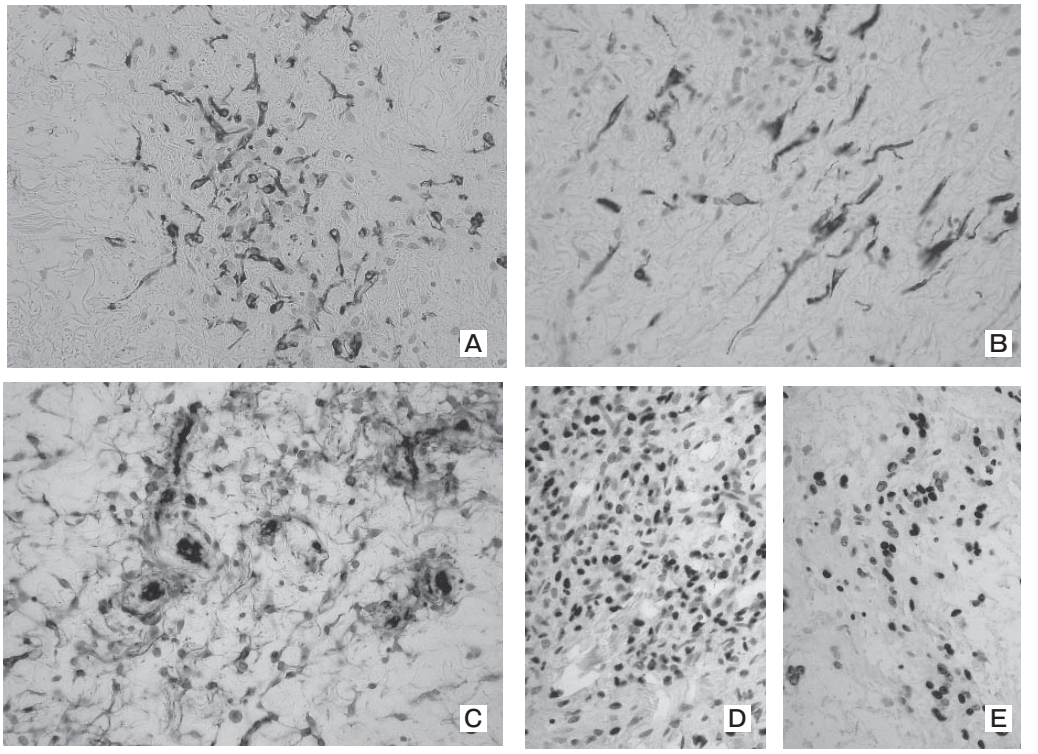

Fig. 5 Immunohistochemical staining of (**A**) ASMA, (**B**) desmin, (**C**) CD34, (**D**) ER, and (**E**) PgR.
A, Stromal cells are focally positive for ASMA; **B**, A small population of stromal cells is positive for desmin; **C**, Stromal cells are positive for CD34 as well as endothelial cells; **D**, **E**, Strong and diffuse nuclear immunoreactivity for ER (**D**) and PgR (**E**).

val pedunculated mass with adipose elements and that AMFB should be included in differential diagnosis to avoid misinterpretation.

The diagnosis of AMFB is complicated because of its shared histological features with other soft tissue tumors that can develop in the female genital tract. Clinically, it is important to distinguish between the various entities, because the behavior may vary markedly. One of these, AAM, affects the deep pelvic soft tissue and has a strong propensity for local recurrence when incompletely excised; the widest excision is therefore recommended. In addition, patients require long-term follow-up, as AAM generally appears to be slow-growing and the first evidence of a recurrence may be many years after the initial resection. AMFB is located in superficial soft tissue and is well-circumscribed, with little tendency toward recurrence; local excision with clear margins is therefore adequate treatment. Histologically, AMFB has alternating areas of hypercellularity and hypocellularity with stromal cells characteristically aggregated around small vessels [1–4]. In contrast, AAM does not demonstrate a hypercellular area, and the stromal cells that constitute it are more uniformly distributed and do not exhibit prominent perivascular accentuation. Although immunohistochemical findings do not distinguish between these 2 tumors, the absence or a minimum of stromal mucin in AMFB contrasts with hyaluronic acid-rich stroma of AAM [12].

Diagnostic confusion can also arise between AMFB and cellular angiofibroma (CA), both of which develop in the female genital tract and have prominent vascular components and bland stromal cells, although it is probably not of clinical significance [13, 14]. In addition, both can have adipocytes or a lipomatous component. The presence of round tumor cells clustered around vessels and a lack of numerous thick-walled, hyalinized vessels and wispy collagen bundles help distinguish AMFB from CA. Immunohistochemically, the stromal cells of AMFB include variable expression of desmin, CD34, and AMSA, whereas those in CA tend to be much more frequently immunoreactive for CD 34 than for desmin [13]. The brisk mitotic activity of spindle cells is seen in CA, while the mitotic activity of AMFB has been reported to be low, that is, less than one mitosis per 10 HPF, except for 2 cases of a mitotically active variant of AMFB [15, 16].

The differential diagnostic considerations concern polypoid soft tissue tumors that affect the lower genital tract. Fibroepithelial stromal polyp (FSP) and superficial cervicovaginal myofibroblastoma (SCVM) (myofibroblastoma of the lower female genital tract) clinically tend to form a polypoid mass [11, 17, 18]. Perivascular aggregates of epithelioid or plasmacytoid cells, a common feature in AMFB, are not found in either FSP or SCVM. They are usually small benign lesions with little potential for local recurrence.

The presence of adipocytes in AMFB has already been recognized [1, 2], and Laskin *et al.* have proposed the term "lipomatous variant" for AMFB containing a substantial amount of adipose tissue [5]. In small-sized tumors diagnosed as AMFB, adipose tissue can be an entrapped element. However, it seems reasonable to suppose that the adipose tissue in the present tumor was an integral component, as the cluster of adipocytes existed not only in the peripheral portion but also in the center. There may be a continuous spectrum of differentiation, from AMFB with no adipose tissue, to AMFB with a minor component of adipose tissue, as in our case, to the lipomatous variant of AMFB. It has previously been reported that some stromal cells besides lipocytes are positive for S-100 protein [19]. Some nuclear similarity between stromal cells and adipocytes suggests that they in our case were an integral component of the tumor and fatty differentiation; however, an immunoprofile of stromal cells and intralesional adipocytes could not support this concept.

The cell origin of AMFB remains unclear. Some investigators consider AMFB to be of myofibroblastic origin [8]. The immunohistochemical profiles, which indicate a strong reactivity for vimentin with various expressions of desmin and ASMA, support apparent differentiation for myofibroblasts in most cases. It has been proposed that AMFB might arise from perivascular stem cells, which are capable of differentiating into fatty and myofibroblastic differentiation [9]. Additionally, stromal cells tend to demonstrate a capillary-like pattern, which may lead to possible differentiation into the vessels. It is generally believed that CD34 positive stem cells normally reside around vessels [20]. In some cases, including our case, a substantial population of stromal cells is

obviously positive for CD34. A recent study has shown strong CD34 positivity in many tumors such as solitary fibrous tumor, spindle cell lipoma, inflammatory myofibroblastic tumor, gastrointestinal stromal tumor, and dermatofibrosarcoma protuberans, which can demonstrate myofibroblastic differentiation. Therefore, CD34 immunoreactivity alone may not support the stem cell origin of this tumor. Interestingly, many cases have demonstrated ER and/or PR positivity within AMFB. Though positive staining can be present in a variety of other mesenchymal lesions involving this region [21], this observation raises the possibility that hormonal manipulation might play a role in the management of this lesion. This case represents AMFB that shows unique pedunculated large mass formation, and we believe that AMFB derives from perivascular stem cells with a capacity for myofibroblastic and fatty differentiation.

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