

## Case Report

# Large polypoid angiomyofibroblastoma of the vulva: report of a case

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**Abstract:** We report a case of angiomyofibroblastoma which arose in the vulva of a 46-year-old woman. The tumor formed a large pedunculated polypoid mass, measuring 14 cm in maximal dimension, which hung down from the right labium majus. It consisted of a dense or loose proliferation of fibroblastic and myofibroblastic cells on an edematous background, and the tumor cells occasionally exhibited an increased cellularity around well-developed, medium-sized or small blood vessels. In small areas, conglomerates of capillaries exhibited an appearance resembling that of capillary hemangioma. Tumor cells were immunoreactive for vimentin, desmin, estrogen receptor, and progesterone receptor, but not for  $\alpha$ -smooth muscle actin, CD34, CD10, S-100 protein, calretinin, podoplanin, or cytokeratin. Angiomyofibroblastoma usually appears as a small subcutaneous nodule, and the formation of a large pedunculated polypoid mass is rare. The differential diagnosis from aggressive angiomyxoma and other mesenchymal tumors which preferentially involve the vulvo-vaginal region was briefly discussed.

**Keywords:** Angiomyofibroblastoma, vulva, polypoid lesion

### Introduction

Angiomyofibroblastoma is a relatively rare, benign soft tissue tumor that was first described by Fletcher et al. [1], preferentially arising in the subcutaneous tissue of the vulvo-vaginal region of young to middle-aged women [1-6]. It usually appears as a small nodular lesion measuring less than 5 cm in diameter and is often diagnosed clinically as Bartholin's gland cyst, but rare examples in which the tumor formed a large polypoid mass have also been reported [7-10]. In this article, we report an example of angiomyofibroblastoma of the vulva which formed a large pedunculated polypoid mass, and briefly discuss some pathological diagnostic problems.

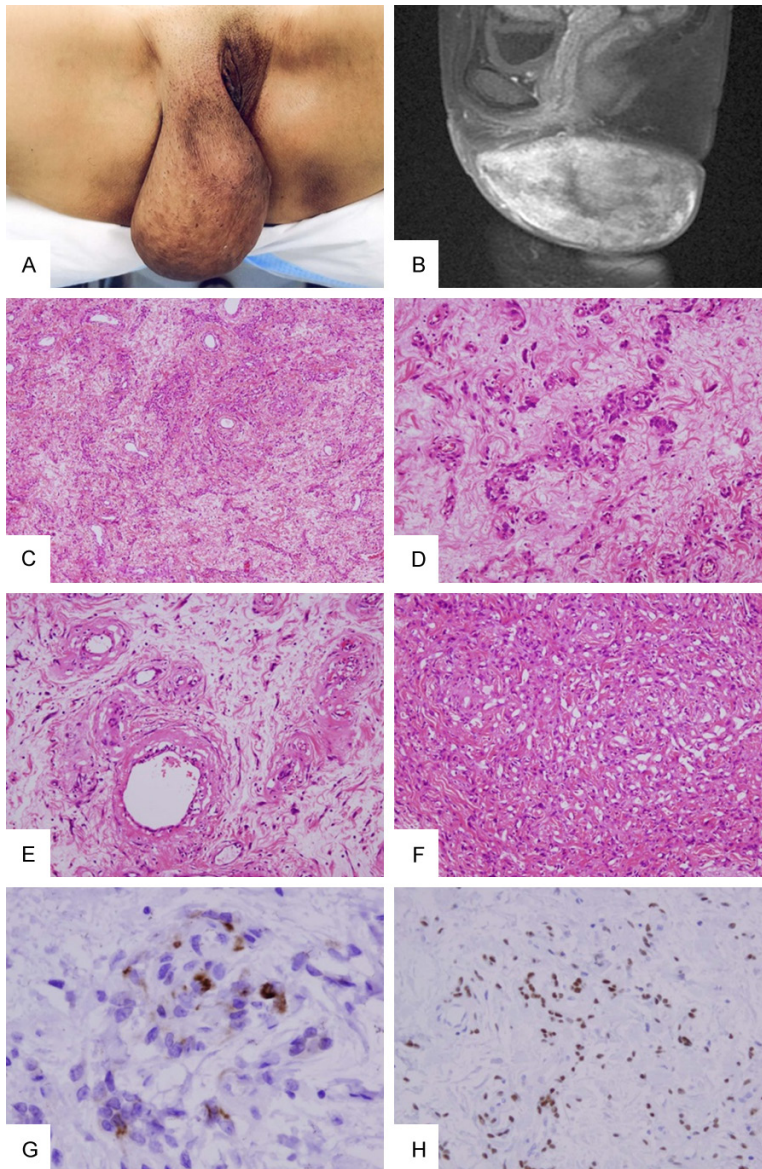
### Clinical history

The patient was a 46-year-old, nulligravid woman, who had noticed a small subcutaneous nodule measuring about 2 cm in diameter in the vulvar region about five years ago. Although no subjective symptoms were present, the nodule gradually enlarged from about one

year before. On gynecological examination, a large pedunculated polypoid mass was found hanging down from the right labium majus (**Figure 1A**). The mass was soft in consistency and covered by skin with a normal color. Neither pain nor tenderness was noted. The uterine cervix was unremarkable, but the uterine corpus was slightly enlarged. Bilateral adnexa showed no remarkable change.

Magnetic resonance imaging (MRI) revealed a well-circumscribed, large polypoid mass with a relatively wide pedicle and measuring about 14 by 8 by 6 cm, in the subcutaneous tissue of the vulva. It showed a homogeneously low intensity on a T1-weighted image and heterogeneously high intensity on a T2-weighted image, suggesting remarkable intralesional edema. The lesion was irregularly enhanced by the administration of a contrast medium (**Figure 1B**). A few small nodules suggestive of leiomyoma were present within the myometrium.

Based on these clinical and MRI findings, a diagnosis of angiomyofibroblastoma of the vulva was made, and total resection of the tumor



**Figure 1.** A: A large polypoid tumor hung down from the right labium majus. B: T1-weighted MRI with contrast enhancement demonstrated a large, well-circumscribed subcutaneous tumor showing an intense and irregular enhancement. C: The tumor was composed of alternating hypercellular and hypocellular areas and consisted of a proliferation of spindle cells on the edematous and highly vascularized stroma. (Hematoxylin-eosin stain,  $\times 10$ ). D: Plump spindle cells surrounded small vessels and occasionally formed small cellular trabeculae or cords. (Hematoxylin-eosin stain,  $\times 25$ ). E: Some blood vessels showed hyalinized thickening of the walls and intramural chronic inflammatory cell infiltration. (Hematoxylin-eosin stain,  $\times 25$ ). F: In small areas, capillary-sized anastomosing blood vessels formed dense aggregates resembling capillary hemangioma. (Hematoxylin-eosin stain,  $\times 25$ ). G: The cytoplasm of some tumor cells was immunoreactive for desmin ( $\times 100$ ). H: The nuclei of most tumor cells were immunoreactive for estrogen receptor ( $\times 25$ ).

was performed. No signs suggestive of recurrence have been noted as of eight years after the operation.

### Pathological findings

The extirpated tumor weighed 495 grams and, although no fibrous capsule was formed, it was well-circumscribed from the surrounding tissue. The tumor was soft, and the cut surface was homogeneous and yellowish-white. No foci of hemorrhage or necrosis were found.

Histopathologically, the tumor was composed of alternating hypercellular and hypocellular areas and consisted of a dense or loose proliferation of plump spindle cells with an edematous background, being accompanied by an accumulation of delicate, curling collagen fibers and a proliferation of abundant medium-sized or small blood vessels (**Figure 1C**). The deposition of acid mucopolysaccharide was not demonstrated in the matrix with colloidal iron or alcian-blue (at pH 2.5) stain. The characteristic perivascular arrangement of plump spindle cells was evident, and some tumor cells also formed small cellular trabeculae or cords reminiscent of epithelial tumors (**Figure 1D**). There was little tendency for tumor cells to form long, sweeping cellular fascicles. No lipomatous component was found within the tumor. Individual tumor cells had elliptical, chromatin-rich nuclei and amphophilic, fibrillary or plump cytoplasm. Nuclear atypism and pleomorphism were absent, and mitotic figures were not detected. The well-developed blood vessels occasionally formed dendritic arborization or showed a “chicken-foot” appearance, and some vessels exhibited mural hyalinization or chronic inflammatory cell infiltration within the walls (**Figure 1E**). Organiz-

ed thrombi were infrequently found within the vascular lumina. In small areas, capillary-sized, anastomosing blood vessels formed dense aggregates and exhibited an appearance resembling capillary hemangioma (**Figure 1F**). Many mast cells were scattered throughout the lesion.

An immunohistochemical study was performed on paraffin sections using the Envision Plus detection system (Dako, Glostrup, Denmark) and employing monoclonal primary antibodies against the following substances: vimentin (clone vim384, Dako, 1:100),  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) (clone 1A4, Dako, 1:100), desmin (clone D33, Dako, prediluted), CD34 (clone QBEnd, Dako, 1:100), CD10 (clone 56C6, Novocastra, Newcastle-upon-Tyne, UK, 1:80), S-100 protein (clone ER-PR8, Dako, 1:500), calretinin (clone DC8, Zymed Labs, San Francisco, CA, USA, prediluted), podoplanin (clone D2-40, Nichirei, Tokyo, Japan, prediluted), cytokeratin (clone AE1/AE3, Dako, 1:500), estrogen receptor (ER) (clone 1D5, Dako, 1:75), progesterone receptor (PgR) (clone PgR636, Dako, 1:500), and Ki67 (clone MIB-1, Dako, 1:100). Heat-induced epitope retrieval using a hot bath was performed prior to the immunostaining. The cytoplasm of tumor cells was uniformly immunoreactive for vimentin, and some of the tumor cells were also immunoreactive for desmin (**Figure 1G**). Nuclei of the vast majority of tumor cells were immunoreactive for both ER (**Figure 1H**) and PgR. Tumor cells were not immunoreactive for  $\alpha$ -SMA, CD34, CD10, S-100 protein, calretinin, podoplanin, or cytokeratin. The Ki67 labeling index of tumor cell nuclei was less than 1%.

### Discussion

Angiomyofibroblastoma was first described by Fletcher et al. as a benign soft tissue tumor of the vulvar region which should be distinguished from aggressive angiofibroma [1]. It consists of a diffuse proliferation of myofibroblasts in association with a proliferation of abundant medium-sized or small blood vessels [1-6]. Mesenchymal tumors which preferentially arise in the vulvar region of young to middle-aged women include, in addition to the above two tumors, various pathologic entities, such as cellular angiofibroma [11], superficial myofibroblastoma [12], and superficial angiofibroma

[13]. In most of these tumors, the nuclei of tumor cells express ER and PgR [3, 5, 6, 11, 12, 14], and they are presumed to be derived from site-specific and hormonally active mesenchymal cells (or perivascular stem cells) which are distributed in the female lower genital tract [1, 5, 6, 12, 14]. Tumors closely resembling angiomyofibroblastoma also arise in the inguinal region or scrotum of male patients [3, 15, 16], and some examples of angiomyofibroblastoma contain mature adipocytes as an integral component of the tumor (lipomatous variant) [4, 5, 7, 15, 16]. Nielsen et al. reported an extremely rare example of the sarcomatous transformation of angiomyofibroblastoma [17]. Although angiomyofibroblastoma shares some morphological characteristics with cellular angiofibroma, mammary type myofibroblastoma, and spindle cell lipoma, a fluorescence in situ hybridization study demonstrated absence of the chromosomal aberration which is commonly seen in these neoplasms, namely, monoallelic loss of 13q14 [6].

Among mesenchymal tumors involving the vulvar region, aggressive angiofibroma forms a large mass lesion which infiltrates the pelvic cavity, and, because of the difficulty in total removal of the lesion, it is prone to recurrence [14, 18, 19]. It is therefore important, especially when the lesion is large, to differentiate angiofibroma from aggressive angiofibroma. However, because both tumors predominantly consist of a proliferation of fibroblasts and myofibroblasts and accompany a marked proliferation of medium-sized or small blood vessels, their distinction is not always straightforward [3]. Some tumors have been known to show a composite morphology with pathological features of these two tumors [19]. However, a recent study showed that aggressive angiofibroma exhibits specific rearrangements of the *HMGA2* gene located on chromosome 12q15, demonstrating that the tumor occupies a biologically distinct position among many kinds of mesenchymal tumors of the female lower genital tract [20]. Aberrant immunohistochemical expression of *HMGA2* protein is observed in the nuclei of tumor cells of most aggressive angiofibromas [21]. In the present case, the MRI findings, that is, a well-circumscribed subcutaneous tumor showing a high intensity on a T2-weighted image and irregular contrast-enhancement, were especially useful

## Polypoid vulvar angiofibromatoma

for clinical differential diagnosis. The usefulness of MRI for the correct preoperative diagnosis of angiofibromatoma has been pointed out by several investigators [8, 22]. In the present case, aggressive angiofibroma was also histopathologically excluded by the relatively high cellularity, absence of the deposition of acid mucopolysaccharide in the stroma, lack of arterial vessels with abnormal morphologies, and the presence of the characteristic perivascular arrangement of tumor cells.

Angiofibromatoma typically represents as a well-circumscribed, relatively small tumor nodule in the subcutaneous tissue of the vulva, and only a few examples which formed a large polypoid mass have been previously reported. These examples, which were reported by Omori et al. [7] (48-year-old, tumor of the labium majus weighing 360 grams), Nagai et al. [8] (48-year-old, tumor of the labium majus weighing 4,534 grams), Ito-Miyazaki et al. [9] (45-year-old, tumor of the labium majus weighing 714 grams), and by Wang et al. [10] (20-year-old, tumor of the labium majus measuring 18 cm in maximal dimension), very closely resembled the tumor in our case on the gross appearance. In these cases including our own, marked stromal edema seems to have significantly contributed to an increase of the tumor volume. The stromal edema and degenerative changes of the vascular wall with thrombus formation in our case probably reflect the long preoperative clinical course.

In small areas of the present tumor, capillary-sized blood vessels formed dense aggregates and exhibited an appearance resembling capillary hemangioma. The proliferation of capillaries reminiscent of capillary hemangioma within the tumor has rarely been described in angiofibromatoma [4, 7]. Whether this finding represents the endothelial differentiation of tumor cells or merely an exaggerated vascular reaction is unknown. Whereas Fukunaga et al. interpreted it as an expression of the diverse differentiation potential of primitive mesenchymal cells [4] and some of the tumor cells in the case of Omori et al. were immunoreactive for CD34 [7], in our case the tumor cells were negative for CD34 and no evidence of the endothelial differentiation of tumor cells was obtained.

In previous reports, the immunohistochemical profiles of tumor cells have been repeatedly

emphasized as useful for the differential diagnosis of angiofibromatoma from aggressive angiofibroma. Tumor cells in the former are characteristically immunoreactive for desmin and negative for  $\alpha$ -SMA [1, 2], whereas tumor cells in the latter are usually immunoreactive for  $\alpha$ -SMA [14, 19]. The immunophenotype of tumor cells in the present case well coincided with these previous findings. However, because the immunohistochemical phenotypes of myofibroblasts are versatile among various pathologic conditions [23, 24] and the immunophenotypes of tumor cells in angiofibromatoma and aggressive angiofibroma are also varying among cases [14, 15, 19], it is not prudent to depend solely upon the immunohistochemical findings of tumor cells in the pathological differential diagnosis of fibroblastic or myofibroblastic tumors of the lower genital tract [3, 19].

In conclusion, we report a rare case of angiofibromatoma which formed a large pedunculated polypoid mass in the vulva. In the case of a large angiofibromatoma, distinction from aggressive angiofibroma is important, and MRI is a useful clinical tool. Various fibroblastic or myofibroblastic tumors of the lower genital tract share clinico-pathological and immunohistochemical characteristics, and their histogenesis is probably similar as well.

### Disclosure of conflict of interest

None.

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### References

- [1] Fletcher CD, Tsang WY, Fisher C, Lee KC, Chan JK. Angiofibromatoma of the vulva. A benign neoplasm distinct from aggressive angiofibroma. *Am J Surg Pathol* 1992; 16: 373-382.
- [2] Hisaoka M, Kouho H, Aoki T, Daimaru Y, Hashimoto H. Angiofibromatoma of the vulva. A clinicopathologic study of seven cases. *Pathol Int* 1995; 45: 487-492.
- [3] Ockner DM, Sayadi H, Swanson PE, Ritter JH, Wick MR. Genital angiofibromatoma. Comparison with aggressive angiofibroma and other myxoid neoplasms of skin and soft tissue. *Am J Clin Pathol* 1997; 107: 36-44.

## Polypoid vulvar angiofibroblastoma

- [4] Fukunaga M, Nomura K, Matsumoto K, Doi K, Endo Y, Ushigome S. Vulvar angiofibroblastoma. Clinicopathologic analysis of six cases. *Am J Clin Pathol* 1997; 107: 45-51.
- [5] Laskin WB, Fetsch JF, Tavassoli FA. Angiofibroblastoma of the female genital tract. Analysis of 17 cases including a lipomatous variant. *Hum Pathol* 1997; 28: 1046-1055.
- [6] Magro G, Righi A, Caltabiano R, Casorzo L, Michal M. Vulvovaginal angiofibroblastomas. Morphologic, immunohistochemical, and fluorescence in situ hybridization analysis for deletion of 13q14 region. *Hum Pathol* 2014; 45: 1647-1655.
- [7] Omori M, Toyoda H, Hirai T, Ogino T, Okada S. Angiofibroblastoma of the vulva. A large pedunculated mass formation. *Acta Med Okayama* 2006; 60: 237-242.
- [8] Nagai K, Aadachi K, Saito H. Huge pedunculated angiofibroblastoma of the vulva. *Int J Clin Oncol* 2010; 15: 201-205.
- [9] Ito-Miyazaki R, Uchi H, Chiba T, Moroi Y, Kiryu H, Furue M. Large pedunculated angiofibroblastoma of the vulva. *Eur J Dermatol* 2013; 23: 520-522.
- [10] Wang Y, Zhang Y, Lv B, Feng Y. Large-sized pedunculated and polypoidal angiofibroblastoma of the vulva. A case report and literature review. *J Obstet Gynecol Res* 2018; 44: 1492-1497.
- [11] Iwasa Y, Fletcher CD. Cellular angiofibroma. Clinicopathologic and immunohistochemical analysis of 51 cases. *Am J Surg Pathol* 2004; 28: 1426-1435.
- [12] Laskin WB, Fetsch JF, Tavassoli FA. Superficial cervicovaginal myofibroblastoma. Fourteen cases of a distinctive mesenchymal tumor arising from the specialized subepithelial stroma of the lower female genital tract. *Hum Pathol* 2001; 32: 715-725.
- [13] Fetsch JF, Laskin WB, Tavassoli FA. Superficial angiofibroma (cutaneous myxoma). A clinicopathologic study of 17 cases arising in the genital region. *Int J Gynecol Pathol* 1997; 16: 325-334.
- [14] Fetsch JF, Laskin WB, Lefkowitz M, Kindblom LG, Meis-Kindblom JM. Aggressive angiofibroma. A clinicopathologic study of 29 female patients. *Cancer* 1996; 78: 79-90.
- [15] Laskin WB, Fetsch JF, Mostofi FK. Angiofibroblastomalike tumor of the male genital tract. Analysis of 11 cases with comparison to female angiofibroblastoma and spindle cell lipoma. *Am J Surg Pathol* 1998; 22: 6-16.
- [16] Shintaku M, Naitou M, Nakashima Y. Angiofibroblastoma-like tumor (lipomatous variant) of the inguinal region of a male patient. *Pathol Int* 2002; 52: 619-622.
- [17] Nielsen GP, Young RH, Dickersin GR, Rosenberg AE. Angiofibroblastoma of the vulva with sarcomatous transformation ("angiofibrosarcoma"). *Am J Surg Pathol* 1997; 21: 1104-1108.
- [18] Steeper TA, Rosai J. Aggressive angiofibroma of the female pelvis and perineum. Report of nine cases of a distinctive type of gynecologic soft-tissue neoplasm. *Am J Surg Pathol* 1983; 7: 463-475.
- [19] Granter SR, Nucci MR, Fletcher CDM. Aggressive angiofibroma. Reappraisal of its relationship to angiofibroblastoma in a series of 16 cases. *Histopathology* 1997; 30: 3-10.
- [20] Medeiros F, Erickson-Johnson MR, Keeney GL, Clayton AC, Nascimento AG, Wang X, Oliveira AM. Frequency and characterization of HMGA2 and HMGA1 rearrangements in mesenchymal tumors of the lower genital tract. *Genes Chromosomes Cancer* 2007; 46: 981-990.
- [21] McCluggage WG, Connolly L, McBride HA. HMGA2 is a sensitive but not specific immunohistochemical marker of vulvovaginal aggressive angiofibroma. *Am J Surg Pathol* 2010; 34: 1037-1042.
- [22] Geng J, Hu S, Wang F. Large paravaginal angiofibroblastoma. Magnetic resonance imaging findings. *Jpn J Radiol* 2011; 29: 152-155.
- [23] Skalli O, Schürch W, Seemayer T, Lagacé R, Montandon D, Pittet B, Gabbiani G. Myofibroblasts from diverse pathologic settings are heterogeneous in their content of actin isoforms and intermediate filament proteins. *Lab Invest* 1989; 60: 275-285.
- [24] Schmitt-Gräff A, Desmoulière A, Gabbiani G. Heterogeneity of myofibroblast phenotypic features. An example of fibroblastic cell plasticity. *Virchows Archiv* 1994; 425: 3-24.