Case Report

Morphological and Immunohistochemical Features of Angiomyofibroblastoma: A Case Report with Review of the Literature

Asangi R Kumarapeli, MD, PhD, Tamera Paczos, MD, Gissou Azabdaftari, MD

Abstract

Angiomyofibroblastoma is a rare tumor seen predominantly in women of childbearing age. Here we report a case of angiomyofibroblastoma with unusual immunohistochemical features in a 62-year-old woman. The patient presented with a 9.5 cm mass in her left labium for one year. Microscopic examination of surgically resected specimen showed a well-circumscribed mass with alternating paucicellular and hypercellular areas in the background of an edematous and collagenous stroma with vascular proliferation. Tumor cells showed high nuclear/cytoplasmic ratio, oval nuclei with finely granular chromatin, inconspicuous nucleoli and a few mitoses (3/per 10 High Power Fields). Immunohistochemically, these cells were positive for vimentin, estrogen receptors and progesterone receptors, and negative for CD34, S-100, HMB45, BerEp4, cytokeratins, synaptophysin and E-cadherin. The above immunohistochemical findings helped us to rule out melanoma, adenocarcinoma, neuroendocrine tumors and metastases from the breast origin. Considering the overall morphological features of the tumor, it was diagnostic of angiomyofibroblastoma. Although a literature review shows that angiomyofibroblastomas are generally diffusely positive for desmin and focally positive for α-smooth muscle actin (SMA) with only very rare exceptions, desmin and SMA immunostains were negative in our case. We like to emphasize that it is important to be aware of the potential variations in the immunophenotypes of angiomyofibroblastomas in order to make a correct diagnosis.

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Introduction

Distinguishing various mesenchymal tumors of the vulvovaginal region can be challenging, owing to their bland histological mimicry and overlapping immunohistochemical presentation. Angiomyofibroblastomas (AMF) are rare, well circumscribed and slow growing tumors seen predominantly in women of reproductive age. The differentiation of these benign tumors from aggressive angiomyxomas has prognostic implications as the latter often tend to recur, likely because of incomplete resection and due to infiltrating margins. Here we present an unusual case of AMF of the labium and discuss its morphological and immunohistochemical features with important differential diagnoses.

Case History

A 62 year old Caucasian woman (P2G2) presented with a one year history of swelling and mass in her left vulva. The patient was obese and also had hyperlipidemia and hypertension. The mass on her left labium majus was slow growing, approximately 6 x 8 cm. at presentation but otherwise asymptomatic. The preoperative clinical suspicion was that of either a very low-hanging inguinal hernia with large bowel content or a Bartholin's cyst. A soft tissue vulval mass was removed during her elective surgery.

Pathology

Gross examination of the surgically resected specimen revealed a 9.5 x 6.4 x 6.0 cm well-circumscribed mass with white whorled tissue and foci of hemorrhage on the cut surface. Microscopically, the tumor cells featured diffuse distribution with alternating paucicellular and hypercellular

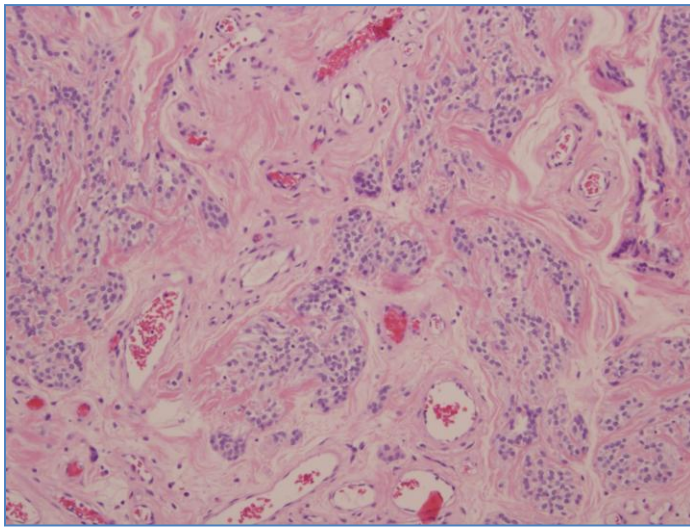

Figure 1. Angiomyofibroblastoma (H&E 10X). A hypercellular region showing tumor cells clustered around multiple thin-walled blood vessels in a loose fibrous stroma.

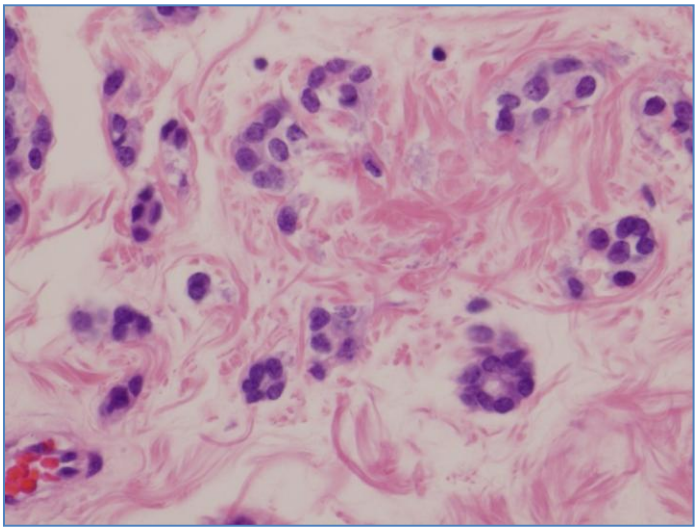

Figure 2. Angiomyofibroblastoma (H&E 40X). The gland-like arrangement of the tumor cells in an edematous stroma. The epithelioid cells show oval nuclei with fine chromatin pattern.

areas in the background of an edematous and collagenous stroma (**Figure 1**). There was extensive thin-walled vascular proliferation with few hyalinized vessels (**Figure 1**). The epithelioid looking tumor cells showed high nuclear/cytoplasmic ratio, oval nuclei with finely granular chromatin, inconspicuous nucleoli (Fig. 2) and a few mitoses (3/10hpf). They showed a tendency to aggregate perivascularly, occasionally clustering to give gland-like arrangements and irregular nests (**Figure 2**). In addition to tumors of mesenchymal origin of the vulva, metastatic adenocarcinoma and breast carcinoma, neuro-endocrine tumors and melanoma were included in the differential diagnosis considering the appearance and unusual arrangement of the tumor cells. Immunohistochemical studies revealed that these cells were positive for vimentin and the hormone receptors of estrogen and progesterone, an almost invariable feature of mesenchymal tumors of this region.[1] The tumor cells did not show staining for desmin, α-smooth muscle actin (SMA) or CD34. Desmin and SMA markers are often positive in AMF but negative in cellular angiofibroma, a variant of AMF.[2] However, cellular angiofibromas present with fusiform cells arrayed near thicker and hyalinized blood vessels which were not seen in this patient. The negative staining for S-100, HMB45, BerEp4, cytokeratins, synaptophysin, and E-cadherin ruled out the other potential diagnoses we considered. Aggressive angiomyxoma, the major contender of the differential diagnoses was ruled out based on the absence of a myxoid stroma and comparatively higher cellularity with plump cells in the lesion. Based on the general histological appearance and limited findings on immunohistochemistry, a diagnosis of AMF was made.

Discussion

Angiomyofibroblastoma (AMF), described nearly two decades ago by Fletcher et al. is an uncommon, yet benign neoplasm of the female lower genital tract, predominantly of the vulvovaginal region.[3] Clinically, these painless, slow growing masses are often misdiagnosed as Bartholin's gland cysts. While majority of the tumors are encountered in the vulva, 10-15% of them occur in the vagina, occasionally in the perineum and the inguinal region while rare reports of fallopian tube lesions are also found.[4, 5] These tumors are commonly seen in women of child-bearing age as well as in middle aged or perimenopausal women. Interestingly however, AMF-like lesions have been reported in the male genital tract involving the scrotum, perineum and the spermatic cord.[6]

Differential diagnosis of mesenchymal neoplasms in the vulvovagina includes an array of lesions that are bland and overlapping in both their morphology and immunohistochemistry. In addition to their rarity, this creates a significant dilemma in making the correct diagnosis. Among these, aggressive angiomyxoma and cellular angiofibroma are the important mimickers of AMF. Aggressive angiomyxoma is a locally aggressive mesenchymal tumor of the perineum with marked tendency to recurrence. It is a soft, gelatinous, poorly circumscribed, deeply situated tumor that could grow into a larger size than the average AMF. Microscopically, aggressive angiomyxoma reveals sparse cellularity composed of bland spindled or stellate cells scattered in a distinct myxoid stroma with numerous vessels ranging from capillary-like to large, thick muscular types. Proper diagnosis of this deep infiltrative tumor is imperative to minimize recurrences due to inadequate resection. In contrast, cellular angiofibroma

which is considered a morphological variant of AMF is a firm, well-circumscribed lesion and similar in size to AMF. This tumor shows moderate cellularity with spindle-shaped cells without atypia around small to medium-sized hyalinized blood vessels set in a fibrous stroma. Sometimes although sparse, mitotic figures can be easily identified in cellular angiofibroma (see **Table 1** for a histological and immunohistochemical comparison of these three tumors). Cellular angiofibroma and AMF are considered benign and non-recurring with the rare exception of sarcomatous transformation and late recurrence of the latter.[7] Local excision with free margins is generally curative for these lesions.

Angiomyofibroblastomas are uncapsulated but well circumscribed tumors that are usually small in size with an average diameter of 4 cm. Their sizes can show wide variation and our patient presented with a fairly large solitary mass in her vulva. These tumors are superficially located in contrast to aggressive angiomyxomas. Pedunculated and very large (over 20 cm) presentations of AMFs with the pedicles extending to deeper tissues have been recently reported.[8, 9] The tumor shows a soft, rubbery consistency with a tan-pink glistening cut surface.

Microscopically, the presence of alternating areas of hypercellularity and hypocellularity in a loose edematous and collagenous stroma is characteristic of AMF. Capillary-like thin walled vascular channels are numerous and tumor cells tend to cluster around them. The myofibroblasts are typically spindle shaped or round but may also appear as epithelioid or plasmacytoid to form nests or cords. They consist of eosinophilic cytoplasm and bland nuclei sometimes with bi- or multinucleation. Mitotic activity is rarely seen. Intra-lesional adipose tissue and mast cell infiltration are also seen in AMF. Morphology often helps differentiate AMF from aggressive angiomyxoma as the latter presents with bland spindle cells in a hypocellular myxoid stroma. Since these tumors are closely related to each other, it is also important to be aware of the possibility that a given vulval tumor could feature both AMF and aggressive angiomyxoma.[10] Such mixed tumors should be regarded aggressive and warrant careful and complete excision to prevent recurrences.

Table 1. Comparison of Major Histological Mimics of Angiomyofibroblastoma.

	Angiomyofibroblastoma	**Cellular Angiofibroma**	**Aggressive Angiomyxoma**
Morphology			
Size	Small, average 4cm (1-10cm), well circumscribed	Small, usually < 5cm, well circumscribed	Large (up to 60cm), less well circumscribed, infiltrative
Cellularity	Hyper- and hypo Bland ovoid, spindled, epithelioid, plasmacytoid	Moderate Bland spindled	Sparse Bland ovoid, spindled, stellate
Stroma	Edematous fibrous Scattered mast cells and lymphocytes +	Fibrous Mast cells and other inflammatory cells +	Abundant myxoid Mast cells and extra-vasated red cells +
Vascularity	Thin walled capillary-like	Small to medium hyalinized	Mixed; capillary to large gaping, hyalinized
Mitotic Figures	Rare	Rare	Rare
Entrapped Fat	+ in 10% cases, around the periphery	+ in 50% cases, in the periphery	+ in the periphery, also with skeletal muscle
Immunohistochemistry			
Vimentin	+	+	+
SMA	+ (focally)	- (often)	+ (variable)
Desmin	+	-	+
CD34	+ (occasional)	+ (variable)	+ (often)
ER/PR	+	+	+
HMGA2	-	-	+

SMA; α-smooth muscle actin, ER; estrogen receptor, PR; progesterone receptor

Ancillary studies of immunostaining tend to give overlapping features that mitigate their utility in the diagnosis of mesenchymal vulval tumors (see **Table 1**). Immunoreactivity for hormone receptors is the norm for AMF and most other tumors as they arise from the subepithelial myxoid stroma of the lower female genital tract

where the stromal cells are hormone responsive.[1] Variable and overlapping immunostaining patterns for SMA, desmin and CD34 are seen in AMF and aggressive angiomyxoma. On the contrary, absence of positivity for desmin helps differentiate cellular angiofibroma from most other mesenchymal vulval tumor varieties that are positive for desmin at least focally. This limited utility of immunohistochemistry has led investigators to explore other approaches such as molecular biological techniques for better differentiation and diagnosis of these tumors. Emerging studies reveal that due to a rearrangement of chromosome 12q15, aggressive angiomyxomas show aberrant expression of HMGA2 protein.[11] Aberrant nuclear HMGA2 expression can serve as a potentially useful marker specific for aggressive angiomyxoma, as similar patterns have not been observed among its histologic mimics. However, genetic studies also show that the HMGA2 gene rearrangement occurs in low frequency (~33%), limiting its usefulness.[12]

Only fewer than 50 reports of vulvar AMF are found in the English literature since its description in the early 1990s. Majority of these tumors are strongly immunoreactive to desmin with occasional exceptions. Our case presents a very rare desmin negative AMF with several notable morphological variations such as gland-like arrangement of predominantly round tumor cells that shows granular nuclear features. While we reiterate the importance of being aware of the potential variations in the immunohistologic phenotypes of AMFs, we also emphasize that it is crucial to consider soft tissue neoplasms which are not specific to the perineum and metastatic tumors, when diagnosing unusual vulvar lesions.

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