



Angiomyofibroblastoma of the Spermatic Cord: A Rare Tumor with Challenging Diagnosis. Report of a Case and a Brief Literature Review

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Abstract

Angiomyofibroblastoma (AMF) is a rare benign neoplasm found in the genital region of both men and women. The origin of tumor growth is uncertain in males; however, reports speculate that it originates from mesenchymal cells in females. Of the reported cases, a handful displayed growth in the spermatic cord. We report a new case of AMF arising in the spermatic cord of a 68-year-old male. The mass was discovered as an incidental finding in this patient when he underwent routine removal of a hernia sac. AMF tumor has striking histomorphologic similarities to other more aggressive soft tissue tumors, such as aggressive angiomyxoma, cellular angiofibroma and myxoid types of sarcoma. Due to this morphologic similarity and generally inconclusive immunohistochemistry pattern, it is occasionally misdiagnosed as a low-grade sarcoma. We report this case to raise the awareness of pathologists and clinicians of this tumor for appropriate diagnosis and optimal management.

ABBREVIATIONS

Aggressive Angiomyxoma (AA), Cellular Angiofibroma (CA), Angiomyofibroblastoma (AMF), Angiofibroma (AF), Estrogen Receptor (ER), Progesterone Receptor (PR), Androgen Receptor (AR), Smooth Muscle Actin (SMA)

INTRODUCTION

Angiomyofibroblastoma (AMF) is an uncommon benign neoplasm most often arising in the pelvic perineal subcutaneous tissue in females of reproductive age. AMF is commonly found in the vulva and occasionally in the vagina of premenopausal women and rarely in postmenopausal women. It is often initially misdiagnosed as a Bartholin's cyst [1]. AMF in males is rare, with a female-to-male ratio of 10:1. When this lesion occurs in men, the most common sites are the scrotum or paratesticular soft tissue such as the perineum and spermatic cord [2]. The etiology of this tumor is generally unknown.

According to previously documented cases, there are similarities shared by AMF tumors in males and females. Male and female AMF tumors both appear as superficial and well-

marginated masses. Histologically, male and female AMFs consist of small- to medium-sized vessels accompanied by myofibroblastic differentiation. Immunohistologically, tumors exhibit marked desmin and varied vimentin, smooth muscle actin and CD34 expression. Recently, it is reported that AMF tumors that occur in male patients demonstrate different clinicopathological features that distinguish them from female tumors such as later onset, composition of spindle- rather than epithelioid-like cells, and increased positivity for muscle specific smooth muscle actin staining [3].

Clinically, AMF has asymptomatic, painless, and slow growing characteristics [3]. The tumor is not encapsulated but is well circumscribed. The nature of this tumor allows it to grow undetected to an average diameter of 5 cm and at times as large as 10 cm. AMF in male patients can be easily mistaken for a sliding or scrotal hernia [4], which accounts for its incidental finding during routine inguinal hernia repairs. Its well-marginated feature allows for simple excision with minimal chance for complication. Surgical excision is the primary treatment for these patients.

AMF can histologically and immunophenotypically mimic other neoplasms such as aggressive angiomyxoma (AA) and cellular angiofibroma (CA), and rarely sarcoma. AMF is a benign lesion with no known reports of local recurrence or metastasis. There is a single reported case of a clinically malignant counterpart of AMF [5]. Less than 40 cases of AMF of the male genital tract are reported in the literature; further data is required in order to improve the definitive diagnostic criteria for optimal management guidelines. To the best of our knowledge, we report the fifth known case of primary angiomyofibroblastoma of the spermatic cord.

CASE PRESENTATION

A 68-year-old male underwent routine removal of a hernia sac. A 2.8 cm soft tissue mass attached to the spermatic cord was found and completely excised. The tumor was described as a well-

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circumscribed neoplasm with a solid soft fibromyxomatous cut surface. The tumor showed variable degree of cellularity with rich vascularity (Figure 1A,B,C). The tumor cells showed mixed spindle and epithelioid appearance, and the cells were often arranged around blood vessels. Cellular atypia was minimal, with rare mitosis < 2 mitosis/10 HPF, and no necrosis. The histomorphology was that of a benign neoplasm with myxoid features, however, a low-grade sarcoma with myxoid features could not be completely ruled out. Differential interpretation of this lesion included deep aggressive angiomyxoma, angiomyofibroblastoma, and cellular angiofibroma, and low-grade myxoid sarcoma. These lesions are known to overlap morphologically; clinical presentation and immunohistochemistry studies are useful for identifying each entity. Immunohistochemistry panel was performed with the following results: focally but strongly positive for Desmin (Figure 1D) and ER (Figure 1E). CD34 outlined the rich vascular component of the tumor (Figure 1F). The tumor cells were negative for smooth muscle actin, PR, and S-100. Proliferative activity was low with 8% nuclear staining with proliferation marker Ki-67. The histomorphology, clinical presentation and immunohistochemistry profile were most consistent with the diagnosis of angiomyofibroblastoma. After surgical excision, there was no need for postoperative treatment. There was no evidence of recurrence during seven years of follow up, after which the patient was lost to follow up.

DISCUSSION

There have been 51 cases of cellular angiofibromas reported by Iwasa and Fletcher in both sexes. The report considered AMF-like tumors and cellular AFs to be similar entities. In that report, the patients' ages ranged from 22 to 78 years; the range of mass sizes was between 0.6 cm and 25 cm; and the primary location was in the subcutaneous tissue but was usually well-margined. The anatomic locations were most frequently the genital area (22

cases) in women and the inguinoscrotal area (19 cases) in men. All tumors featured in the report consisted of spindle-shaped cells, short bundles of wispy collagen, and numerous small- to medium-sized thick-walled vessels. Immunohistochemistry displayed expression of CD34 by 60% of patients, SMA by 21%, desmin by 8%, and no expression of S-100 protein [5].

Prior to our current case, there have been four reported cases of angiomyofibroblastoma of the spermatic cord. Through cross-referencing with the four previous cases, we created a table to summarize and compare the following key features: patient statistics, tumor size, tumor characteristics, immunohistochemistry, and patient follow up results. All cases, including our patient, involved well-circumscribed, vascularized tumors with CD34 + and Desmin + staining. Tumor characteristics varied among all cases and some shared similarities with AA and CA, making the tumor difficult to differentiate. All reported follow ups displayed no recurrence of the tumor. [Table 1]

Due to overlapping immunohistochemical and histomorphologic features of many histiofibrocytic tumors, definitive diagnosis of these tumors can be challenging. The differential diagnosis for AMF often includes aggressive angiomyxoma and cellular angiofibroma, among few others. All three lesions are highly vascularized; blood vessels in AA are always abundant and multifarious, varying from capillary-like to large-caliber vessels with thick muscular walls. AMF differs in that the cells usually show an epithelioid appearance, and the cells are often arranged around blood vessels, which we did identify in our case [10]. AMF tumors are often found in the peripelvic region in females and the inguinal region in males [11]. The cellular origin of AMF among males has not been identified with certainty. Regarding the female patients, it is believed that the tumor is derived from mesenchymal cells in the subepithelial myxoid stromal zone that extends from the endocervix to the

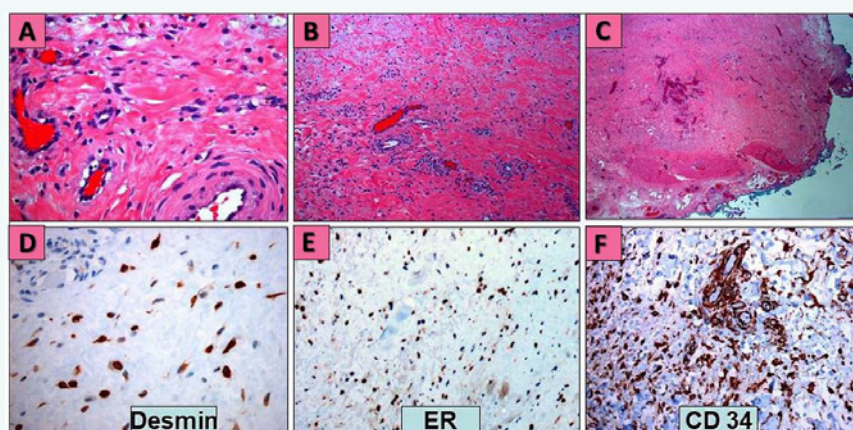


Figure 1 Microscopic examination of the Spermatic cord mass.

A: Rich vascular component of the tumor, and mixed spindle and epithelioid cells, high power (H&E stain X40)

B: Mixed spindle and epithelioid cells, and rich vascular component of the tumor, low power H&E stain X20)

C: Well-circumscribed neoplasm with a solid soft fibromyxoid cut surface ((H&E stain X20)

D: Positive Desmin

E: Positive Estrogen (ER)

F: Positive CD34



Table 1: The findings and comparisons of the five reported cases of angiofibroma of the spermatic cord.

Case	Author	Patient Statistics	Tumor Size (cm)	Tumor characteristics	Immunohistochemistry	Follow Up
1	Siddiqui, et al ⁶ (1997)	51 y/o male	5	Well-circumscribed solid tumor with abundant thick-walled blood vessels arranged haphazardly. Stromal cells were bland looking spindle-shaped or oval with moderate eosinophilic cytoplasm. Nuclei were oval with fine chromatin and inconspicuous nucleoli. No mitotic figures were present. Mast cells were found abundantly. Fibroblastic differentiation of the stromal cells was suggested by a well-developed golgi apparatus and dilated rough endoplasmic reticulum with no basal lamina.	Vimentin + Desmin +	Patient followed up for 14 months and had no recurrence.
2	Tzanakis, et al ¹² (2010)	36 y/o male	4.5	Well-demarcated with spindle-shaped cells proliferating in short fascicles between numerous medium-sized blood vessels with thin and hyalinized walls. Focally, the tumor cells had an epithelioid appearance with eosinophilic cytoplasm and plump nuclei. No mitotic figures. No nuclear atypia.	Vimentin + Desmin + CD34 + Actin + (mildly)	Patient was followed up for five years and had no evidence of recurrence or metastasis.
3	Bouhajja, et al ⁸ (2017)	27 y/o male	3	The tumor was well-circumscribed, myxoid, and composed of spindle cells without atypia and with less than one mitotic figure per 10 high-power fields. Multinucleated cells and mast cells were observed. The stroma was myxoid and edematous with abundant capillary-sized blood vessels.	Desmin + Actin + PR + ER - Low proliferative index of Ki67 (<5%)	Unknown
4	Gongora da Silva, et al ² . (2019)	34 y/o male	6.5 x 5.0 x 4.5	Well-defined tumor with fibroelastic consistency that was cream to brown in color with finely granular appearance.	CD34 + (vascular) Actin + Desmin + S100 + (focal) ER + (stroma) PR + (stroma) AR + (stroma)	Unknown
5	Boyadjian, Chabayta, et al. Current case. (2020)	68 y/o male	2.8	Well-circumscribed neoplasm with a solid soft fibromyxedematous cut surface. The tumor showed variable degree of cellularity with prominent vessels throughout. No cellular atypia.	Desmin + ER + CD34 + (vascular) Actin - PR - S100 - Low proliferative index of Ki67 (8%)	Patient followed up at seven years without evidence of recurrence or metastasis.

vulva. This hypothesis explains to some extent the propensity of this tumor to arise in the lower genital tract [12].

Aggressive angiofibroma, cellular angiofibroma, and angiofibroma may express Estrogen Receptor (ER), Progesterone Receptor (PR), CD34, and Vimentin positivity. Baniyas et al. published a table describing important differences between these three neoplasms using the following five parameters: gross aspects, cellularity, stroma, vascularization and immunoprofile [13]. Angiofibroma and cellular angiofibroma are grossly well-demarcated by a thin fibrous pseudocapsule compared to aggressive angiofibromas which are ill-defined and infiltrate the surrounding tissues. Our patient had a well-demarcated neoplasm. AMF alternates between hypocellular and hypercellular areas where round and spindle

cells (plasmacytoid and epithelioid) are arranged in cords and nests around blood vessels, along with a few mature adipocytes. Mast cells are often seen in AMF. Cellular angiofibromas have a higher cellular density. In our current case, the tumor exhibited variable cellularity in support of the reported AMF characteristics. Cellular angiofibromas have round and spindle-shaped cells distributed haphazardly with few mast cells. AA, however, has hypocellular proliferation of short spindle and stellate cells radiating from the vessel walls with multinucleated cells sometimes seen. The stroma of AMF is edematous with myxoid degeneration and collagen fibers which separate tumor cells, whereas the stroma of CA is collagenous with thicker collagen bundles. Lastly, AA has abundant myxoid stroma that may present with blood extravasate. In our case, the tumor displayed a fibromyxedematous surface.



In terms of vascularization, AMF is abundant with thick-walled, small to medium sized vessels. AA thrives along thin and thick-walled vessels which can be hyalinized or hypertrophic. Cellular angiofibroma grows in prominent large thick-walled vessels mostly with hyalinized walls and no perivascular adipocytes. Our patient's tumor was vascular-rich with prominent vessels. AMF is Desmin positive in all cases and rarely SMA positive whereas CA is almost always Desmin negative and always SMA positive. AA is Desmin positive, but uniquely CD44 positive. The immunohistochemistry panel performed on the tumor cells in this case was focally but strongly positive for Desmin and Estrogen Receptor (ER).

Because AMF and CA involve well-circumscribed lesions with a pseudocapsule, they are often completely excised surgically. AA is a benign tumor that is less clearly circumscribed and does not involve a capsule or pseudocapsule; while it is not malignant, it usually infiltrates surrounding tissue such as skeletal muscle and fat [14]. The risk of local extension makes AA more difficult to completely excise and therefore more likely to recur. Like AMF and CA, surgery is the primary treatment; however, adjuvant treatment with a GnRH agonist may be indicated in select cases. In part, due to its tendency to be well-circumscribed, AMF is typically managed exclusively via surgical excision and reports of recurrence exist. As described in Table 1, three of the five similar cases showed that with follow up over variable times, the patients exhibited no evidence of recurrence. A single case of AMF transitioned to a malignant sarcoma has been reported. Despite the challenges in distinguishing between AMF, CA, and AA, it is important to correctly diagnose these uncommon lesions in order to optimally manage their treatment and follow up [15].

Differentiation of AMF from myxoid sarcomas is based on absence of prominent malignant cellular features, absence of mitosis, and limited mitotic activity. These features were noted in our case and ruled out possible myxoid sarcoma. Yassin Nayel et al reported a very interesting case of a myxoid chondrosarcoma that was closely similar histomorphologically to myxoid liposarcoma and myxoid leiomyosarcoma. In their reported case, molecular testing was the final diagnostic determinant as IHC studies were not conclusive [14].

Angiomyofibroblastoma of the spermatic cord is rare in males. Therefore, there is limited knowledge in the current literature regarding the definitive molecular pathogenesis, pathophysiology, and immunohistochemistry of these patients. It is our hope that this report raises awareness of clinicians and pathologists of this rare tumor in men, and possible diagnostic error, and that continued investigation drives further development of efficacious understanding, diagnosis and safe treatments for improving patient outcomes.

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