Aggressive angiomyxoma of the vagina: a case report and review of the literature

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Summary

Aggressive angiomyxoma (AA) is a rare mesenchymal tumor of the lower pelvis and genital region, characterized by local infiltration and frequent, even multiple recurrences. In the present paper a case of a small-sized AA of the vagina, in a 55-year-old woman is reported. We describe the histological appearance and the immunohistochemical phenotype of this tumor and discuss its differential diagnosis from other mesenchymal lesions occurring in the pelvic and genital region. Furthermore, we attempt to enlighten the possible mechanisms that govern the pathogenesis and the biological behavior of this "mysterious" neoplasm.

Key words: Aggressive angiomyxoma; Immunohistochemistry; Behavior; Treatment; Prognosis.

Introduction

Soft tissue tumors of the vulvovaginal region represent a heterogeneous group of lesions which demonstrate significant variability in their biological profile and clinical behavior [1]. Norris and Taylor published the first description of stromal lesions occurring in the distal female genital tract in 1966 [2]. Since then, a large variety of vulvovaginal stromal neoplasms has been recognized, including aggressive angiomyxomas, angiomyfibroblastomas, superficial angiomyxomas, myxoid liposarcomas, low-grade myxofibrosarcoma and sarcoma botryoides.

Aggressive angiomyxoma (AA) is a rare mesenchymal tumor that preferentially involves the pelvic and perineal regions. It was first described as a separate histopathologic entity by Steeper and Rosai in 1983 [3]. To date, approximately 132 cases have been reported in the world literature [4]. AA exhibits a locally infiltrative behavior, as well as, a pronounced tendency for local, often multiple recurrences. Although it is believed to be a non-metastazing neoplasm, a case of AA with widespread metastasis has been reported recently [5]. AA was originally thought to develop only in women. However, it is now known to affect the inguinal and scrotal region of men [6, 7]. Interestingly, there is a difference in the age of presentation between the two sexes. More specifically, in women AA tends to occur during the reproductive years, with a median incidence in the fourth decade. In contrast, in men the median age of presentation is the sixth to seventh decades.

AA is a highly vascularized, large myxoid lesion, with a grossly gelatinous appearance. Histologically, it is characterized by the presence of a mixture of spindle or stellate cells within a copious myxoid stroma. The stroma is composed of collagen fibers and medium to large, thick-walled, often hyalinized vessels, which do not demonstrate an arborizing pattern. The tumor cells display bland, round to ovoid nuclei with dispersed chromatin and moderate amounts of palely eosinophilic cytoplasm. Nuclear atypia and mitotic activity are exceedingly low. Complete surgical excision of the tumor remains the cornerstone of treatment [8].

Case Report

The patient was a 55-year-old Caucasian woman who enrolled in a screening program at the Obstetrics and Gynecology Department of the University Hospital of Ioannina, Greece. She was a moderately built and nourished woman. She had no special complaints and was asymptomatic. Systemic examination was unremarkable. During the gynecological examination the cervix and uterus appeared normal. However, a protruding mass located at the posterior vaginal wall was palpated. The mass was painless, superficial and had a soft consistency. Its macroscopic appearance gave the clinical impression of a vaginal cyst. Complete surgical excision was performed and pathologic evaluation followed. The patient recovered uneventfully, and remains without evidence of recurrent disease three months after the resection.

Gross and Histologic Findings

On gross examination the tumor measured 2.5 x 2 x 1 cm, was well circumscribed but not encapsulated. It was almost utterly covered by epithelium. The cut surface had a homogeneous tan color, glistening appearance, soft-myxoid consistency and areas of congestion and hemorrhage.

Microscopically, the tumor was predominantly hypocellular. Nonetheless, areas of sporadic foci with increased cellularity were encountered. The neoplastic cells were stellate and spindle-shaped, embedded in a loose myxoid stroma. They had uniform nuclei with a fine chromatin network and inconspicuous nucleoli. Their cytoplasm was eosinophilic, while the

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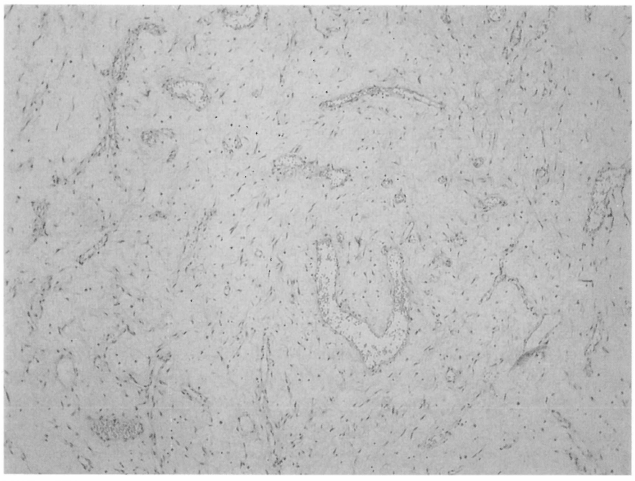
Fig. 1A



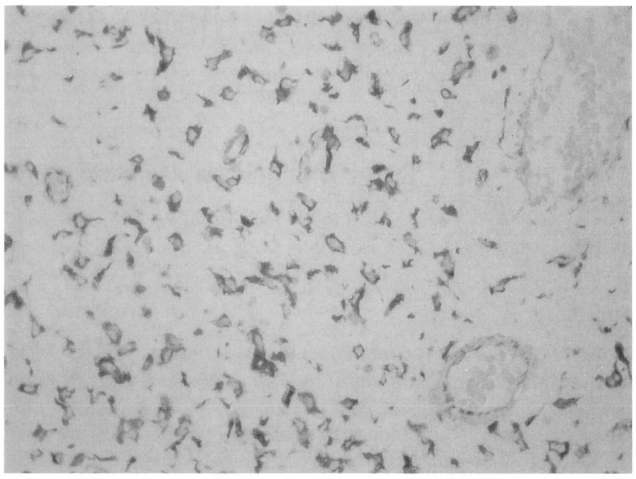


Fig. 1C

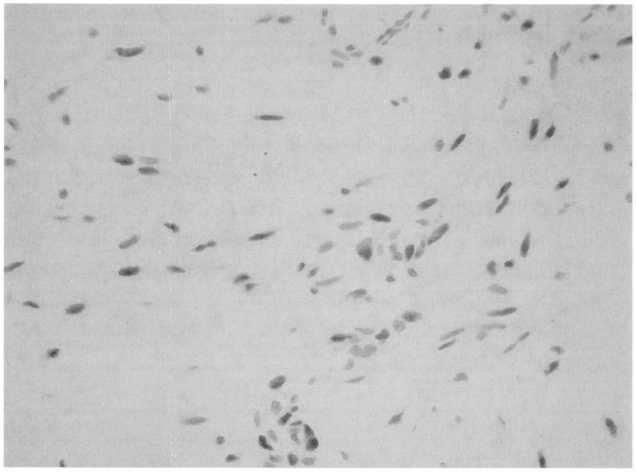


Figure 1. — **A:** At low magnification the aggressive angiomyxoma is hypocellular with spindle-shaped cells embedded in a loose myxoid stroma. The vascular component is conspicuous (H&E x 100). **B:** The neoplastic cells are immunopositive for vimentin (DAB x 400). **C:** The majority of tumor cells exhibit nuclear immunopositivity for estrogen receptors (DAB x 400).

nucleus to cytoplasm ratio was quite low. Mitotic figures were not observed. Wavy, delicate bundles of collagen were frequently noted in the supporting tissue surrounding the bland-appearing tumor cells. A striking microscopic feature was a prominent vascular pattern, with arborizing capillaries and medium-sized arteries that were distributed haphazardly throughout the myxoid stroma (Figure 1A). Most of the vessels were dilated, while their walls exhibited mild to moderate hypertrophy. Several mast cells were present in the background.

Special staining for mucosubstances (Alcian Blue) revealed only weak staining of the tumor matrix, suggesting that edema was prominent in the stroma.

On immunohistochemical examination, the neoplastic cells were strongly positive for vimentin (Figure 1B), which is a cytoplasmic intermediate filament characteristic of cells of mesenchymal origin (namely fibroblasts, osteoblasts, myoblasts, chondroblasts). In addition, they expressed weak immunopositivity for desmin, a muscle-type intermediate filament that is found in muscle cells and in a lesser amount in myofibroblasts. Tumor cells were also reactive to estrogen (Figure 1C) and progesterone receptors. On the other hand, they were negative for cytokeratins, carcinoembryonic antigen (CEA), smooth muscle actin (SMA), muscle-specific actin (MSA), myosin, S-100 and CD-31, CD-34, α-1-antitrypsin and α-1-antichymotripsin.

Excision margins were assessed histologically and found free of neoplastic infiltration (tumor was located further than 1mm from the inked margin).

Discussion

Aggressive angiomyxoma (AA) is a rare neoplasm that derives chiefly from the mesenchyme of the pelvi-perineal region. It exhibits infiltrative behavior and has a tendency for local recurrence. AA was first reported in 1983 as a distinct variant of myxoid neoplasms of the female vagina and pelvis. The vast majority of AA occurs in females during the reproductive years. This observation indicates that estrogen might stimulate the growth of the neoplasm. The size of the tumor varies, measuring between 3 and 60 cm in the greatest dimension. However, in the majority of cases the greatest dimension is over 10 cm. In the present case report, the patient was a 55-year-old woman in menopause. Although reported in the world literature, AA occurs infrequently in postmenopausal women. The neoplasm was a 2.5 x 2 x 1 cm, well-circumscribed, soft tissue nodule, displaying a glistering, bulky, myxoid appearance. It is interesting to note that the size of the tumor was smaller than average. This finding could be explained by the fact that the patient was in menopause, a state characterized by very low estrogen production, and is consistent with the concept that female sex hormones stimulate tumor growth. This perception is further supported by a previous report of rapid growth of AA during pregnancy, a condition of estrogen and progesterone overproduction [9, 10].

On immunohistochemical examination, the neoplasm exhibited strong positive immunoreactivity for vimentin and weak positivity for desmin. In contrast, the tumor cells were negative for cytokeratins, CEA, SMA, MSA, S-100 and CD-31, CD-34, α-1-antitrypsin and α-1-antichymotrypsin. These findings suggest a fibroblastic origin and myofibroblastic features of neoplastic cells. Moreover, tumor cell nuclei were immunoreactive to estrogen and progesterone receptors. This result offers an additional confirmation of the hormone-dependent nature of the neoplasm. In a recent publication it has been denoted that a recurrent aggressive angiomyxoma (AA) of the vulva responded to GnRH agonist medication and showed complete resolution, at least radiographically [11]. Therefore, it is possible that conservative medication may offer a therapeutic alternative to AA, especially when surgical intervention is prohibited. Identification of novel factors that trigger the growth of this tumor may expand the horizon of AA therapy. Until then, surgical excision remains the basis of AA management.

Our patient had a focal neoplasm that did not metastasize. In a recent study, Kaur *et al.* reported on a woman who developed two distinct tumors located at the right perivesical space and the left labium [12]. The tumors exhibited histological and immunohistochemical phenotype of AA. This report highlights the likelihood of a multifocal presentation of this neoplasm, and emphasizes the requirement for complete investigation for additional masses in all cases examined. AA has an infiltrative growth pattern and potential for local, destructive recurrence. Despite histological and biological indicators of aggressiveness, it is classically considered as a non-metastazing tumor. However, there is a description of AA of the pelvis, which spread diffusely throughout the abdominal cavity and caused multiple metastases to the mediastinum and both lungs [5]. This impressive clinical course addresses the possibility that AA should be reconsidered as an aggressive, potentially systematic disease rather than a purely localized lesion. The aforementioned data strengthen the notion that AA is a neoplasm with a puzzling nature and unpredictable clinical behavior. They also stress the necessity for further investigation towards the understanding of the molecular events that govern the pathogenesis of this tumor.

The differential diagnosis of AA comprises the whole gamut of mesenchymal neoplasms that are located in the vulvovaginal region, including angiomyofibroblastoma, fibroepithelial stomal polyps, and a variety of myxoid tumors such as superficial angiomyoma, myxoid neurofibroma, low grade fibrosarcoma and myxoid malignant peripheral nerve sheath tumor (MPNST). Among them angiomyofibroblastoma, and fibroepithelial stomal polyps cause the most pronounced differential diagnostic problems. Given the fundamental that AA has the potential for local infiltration (if not metastasis) and multiple recurrences, compared to the indolent course of most of the other lesions, distinction between these pathologic entities is of major clinical importance. To this end, investigations are directed towards the clarification of the genetic profile of this disease. Recently, a clonal chromosomal translocation [t(8;12)(p12;q15)] has been discovered in a case of recurrent AA [1]. This translocation induces aberrant expression of the transcription factor HMGI-C. Immunohistochemical analysis revealed expression of HMGI-C protein in the bland neoplastic cells of AA [1]. Rearrangements and overexpression of HMGI-C have been reported in a variety of benign mesenchymal neoplasms, namely endometrial polyps, cutaneous lipomas, endometrial polyps and uterine leiomyomata. Nevertheless, overexpression of HMGI-C detected by immunohistochemistry may potentially be used as a marker of residual disease, as well as an indicator of recurrence or even metastasis.

In conclusion, AA is a slow growing, locally infiltrating neoplasm of the genital and pelvic area, mostly occurring in females during the reproductive years. It is believed to be a focal, non-metastatic tumor. However, a case of a multifocal as well as a case of metastatic AA have been described. These reports highlight the need for a careful search for additional masses and metastatic foci in all cases of AA. The mainstay of therapy is radical surgical excision of the tumor. Identification of the molecular mechanisms that govern the pathogenesis of this neoplasm may facilitate an improved prediction of the tumor's clinical behavior and potentially be exploited in designing novel conservative treatment regimens.

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