Case Reports

Pedunculated aggressive angiomyxoma arising from the vaginal suburethral area: Case report and review of literature

B. Piura[1], *M.D., F.R.C.O.G.*; **R. Shaco-Levy**[2], *M.D.*

[1]*Unit of Gynecologic Oncology, Department of Obstetrics and Gynecology, and* [2]*Institute of Pathology, Soroka Medical Center and Faculty of Health Sciences, Cancer Research Center, Ben-Gurion University of the Negev, Beer-Sheva (Israel)*

Summary

Background: Aggressive angiomyxoma (AA) is an uncommon, slow growing, locally infiltrative but non-metastasizing, distinctive mesenchymal tumor that predominantly affects the pelvis and perineum of premenopausal women. The mainstay of treatment is local excision with tumor-free margins; however, recurrences are common and related to inadequate primary excision.

Case: A pedunculated 3-cm mass arising from the vaginal suburethral area in a 49-year-old premenopausal woman was resected around the base of its pedicle. Microscopic examination revealed numerous blood vessels of various sizes set in myxoid stroma with spindle shaped fibroblasts. Immunohistochemical staining was strongly diffusely positive for vimentin, desmin, estrogen receptor (ER) and progesterone receptor (PR), weakly focally positive for CD34, and negative for S-100 protein, actin and Ki-67. These findings are compatible with the diagnosis of AA. To date, six months after surgery, the patient is alive and without evidence of recurrence.

Conclusions: AA is often clinically misdiagnosed and it is only the microscopic examination strengthened with immunohistochemical staining that definitely and undeniably contributes to the final diagnosis of AA. Based on this case report and on the previously reported five cases of pedunculated AA arising from the vulvovaginal region, including one tumor arising from the vaginal suburethral area, it seems that pedunculated AAs arising from the vulvovaginal region are at negligible risk of recurrence after local excision.

Key words: Mesenchymal tumor; Stroma; Fibroblast; Blood vessels; Pedicle; Vagina.

Introduction

Aggressive angiomyxoma (AA) is an uncommon, slow growing, locally infiltrative but non-metastasizing, distinctive mesenchymal tumor that predominantly affects the pelvis and perineum of premenopausal women. Since Steeper and Rasai [1] first recognized it as a separate entity in 1983, fewer than 150 cases of this disorder have been reported in the literature. Histologically, AA is characterized by the presence of numerous blood vessels of various sizes set in myxoid stroma with spindle shaped fibroblasts [2-13]. The optimal treatment for AA is complete local excision with tumor-free margins; however, recurrences are common and related to inadequate primary excision [2-13]. Because of its rarity, most reports include singular cases or series of patients in which patient accrual occurred over a prolonged period of time, during which diagnostic methods and treatment modalities changed. Thus, very few individuals and even referral centers can build up an adequate experience related to this entity. We report a case of pedunculated AA arising from the vaginal suburethral area and review the pertinent literature.

Case Report

A 49-year-old, gravida 8, para 6, married premenopausal Arab Bedouin woman was referred in December 2004 because of a 3-cm cystic mass protruding from her vaginal orifice and causing spraying of urine during voiding and difficulty with normal sexual intercourse for the previous six months. She had experienced menarche at age 16. Her menses were irregular with cycles ranging from 40 to 60 days and flow lasting five days. She had never practiced any contraceptive method. Her past medical history included schizophrenia, appendectomy and one cesarean section. Her family history was unremarkable.

Physical examination disclosed an essentially healthy appearance and normal vital signs. On inspection of the external genitalia, a pedunculated globular mass measuring 3 cm in its largest dimension was seen protruding through the vaginal introitus. The pedicle of the mass originated from the vaginal wall beneath the urethra at a distance of approximately 1 cm from the external urethral meatus. The mass was non-tender, smooth and of uniform cystic consistency. The vulva grossly appeared normal. On speculum examination, the rest of the vagina and the uterine cervix appeared normal. Bimanual vaginal pelvic examination disclosed a normal uterus with no adnexal masses and no involvement of the paravaginal tissues. Rectal examination revealed no involvement of the rectum and/or the pararectal tissues. The initial diagnosis was a pedunculated vaginal simple cyst. Under general anesthesia, an incision was made around the base of the pedicle and the mass with its pedicle were completely excised. Subsequent meticulous pelvic examination confirmed the absence of any residual or additional mass in the pelvis and perineum.

On gross examination, the cut surface of the mass was gray with a yellowish hue and had a soft myxoid consistency. On microscopic examination, the tumor exhibited numerous blood vessels of various sizes with thick muscular walls embedded in a loose myxoid stroma with spindle-shaped fibroblasts and myofibroblasts without mitotic figures (Figure 1). Immunohis-

Revised manuscript accepted for publication July 2, 2005

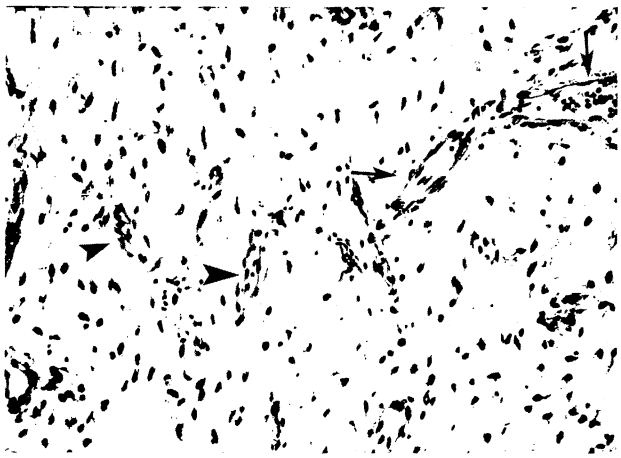

Figure 1. — Aggressive angiomyxoma. The tumor is composed of blood vessels of various sizes, including small blood vessels (arrowheads) and large blood vessels (arrows), embedded in hypocellular myxoid stroma with spindle-shaped fibroblasts devoid of atypiality or mitotic activity (hematoxylin-eosin x 400).

tochemical staining was strongly and diffusely positive for vimentin, desmin, estrogen receptor (ER) and progesterone receptor (PR), weakly positive for CD34 mainly in the blood vessels, and negative for S-100 protein, actin and Ki-67. The final diagnosis was AA.

The immediate postoperative course was unremarkable. The patient had a thorough work-up with imaging studies including X-ray of the chest, ultrasound examination of the abdomen and pelvis, computerized tomography [CT] scanning of the chest, abdomen and pelvis, and magnetic resonance imaging [MRI] of the abdomen and pelvis that did not disclose abnormal findings and in particular no residual mass in the pelvis or perineum. To date, six months after surgical excision, the patient is alive and without evidence of recurrence.

Discussion

Steeper and Rasai [1] first coined the term "aggressive angiomyxoma" (AA) in 1983. They described nine cases of a distinctive mesenchymal tumor of the female genitalia and pelvic soft tissues histologically characterized by the presence of numerous blood vessels of various sizes set in hypocellular myxoid stroma ("angiomyxoma") and added the prefix "aggressive" to indicate the locally infiltrative nature and strong propensity for local recurrence of this tumor [1]. Since then, fewer than 150 cases of AA have been reported in the world literature. It is believed that this tumor arises from the fibroblasts and myobibroblasts of the subepithelial mesenchymal myxoid stroma of the lower female genital tract that extends from the cervix to the vulva. Consequently, the stromal cells of many of these tumors exhibit positive immunohistochemical staining for ER and PR [13]. The final diagnosis of AA is based on the following characteristic pathological features [2-13]: 1) *Gross appearance.* The tumor is typically poorly circumscribed with a rubbery, fibrous, gelatinous, or myxoid consistency. The cut surface is gray with a yellowish hue and soft myxoid consistency. 2) *Microscopic findings.* The tumor exhibits numerous large, medium and small sized blood vessels with thick hyalinized muscular walls embedded in loose myxoid stroma with spindle-shaped fibroblasts and myofibroblasts devoid of atypicality and mitotic activity. 3) *Immunohistochemical findings.* Tumor cells are typically immunoreactive with vimentin and frequently with desmin, CD34 and smooth muscle actin. Tumor cell nuclei are usually positive for ER and PR [13-15]. These features differentiate AA from other mesenchymal tumors and tumor-like lesions of the female genital tract such as angiomyofibroblastoma (less myxoid and more fibrous stroma, blood vessels are usually thin-walled), cellular agniofibroma (higher cellularity, more fibrous and less myxoid stroma, greater hyalinization of vessel walls, no staining with smooth muscle markers), fibroepithelial stromal polyp (higher cellularity, presence of bizarre multinucleated stromal cells that may extend up to the dermal-epidermal junction), leiomyoma/leiomyosarcoma (typical spindle shaped cells positive for smooth muscle markers), superficial cervicovaginal myofibroblastoma (well circumscribed but unencapsulated lesions with surface epithelium and moderately cellular stroma), and superficial angiomyxoma (less variable appearance of blood vessels, less thick-walled blood vessels, presence of stromal neutrophils, absence of ER and PR immunostaining) [10-13]. A translocation between chromosome 8 and 12, t(8;12)(p12;q15), inducing expression of aberrant HMGA2 gene, has been demonstrated in AA [16-18].

AAs usually involve the soft tissues of the vulvovaginal region, pelvis, and perineum of females. The age of the patients with AA ranges from six to 77 years, with a peak incidence at 35-40 years of age [2-13]. Similar lesions have been described in the inguinoscrotal region of males; however, the female to male ratio is six to one [13]. AAs are usually locally invasive and extend into neighboring tissues. Sometimes, they grow and occupy the whole pelvis, invading paravaginal and prerectal spaces and displacing pelvic structures [19]. Invasion into the bladder, gastrointestinal tract, retroperitoneal space and bone has been described [20]. The size of AAs has been reported to be extremely variable, ranging from 1 to 60 cm, but most often > 10 cm [2-13, 19, 20]. Imaging studies, including MRI, CT scan, ultrasound, intravenous pyelography (IVP), bone scan, barium enema, and pelvic angiography are important diagnostic tools to the preoperative evaluation, since the extent of the tumor is often underestimated by physical examination [10, 21, 22]. Because of its locally infiltrative nature, AA has a strong propensity for local recurrence. Studies have shown that 33%-72% of AAs tend to recur locally at an interval ranging from ten months to 15 years after excision [2-13, 19-22]. The ischiorectal fossa, perineum, pelvis and retroperitoneum are the common sites of recurrence. Distant metastasis of AA is an extremely rare phenomenon [13]. Since most gynecologists are not aware of AA, this entity is clinically frequently misdiagnosed and is often

mistaken for a vulvar mass, vulvar abscess, Bartholin's duct cyst, Gartner duct cyst, vaginal cyst, vaginal prolapse, pelvic floor hernia and other benign and malignant soft tissue tumors of the pelvis and perineum [10-13]. It is only the microscopic examination, strengthened with immunohistochemical staining, which definitely and undeniably contributes to the final diagnosis of AA.

The optimal treatment for AA is complete local excision with tumor-free margins. Most recurrences are likely to be related to inadequate initial excision and if a resected margin of the mass shows the presence of a tumor, a second excision is required. Many of these tumors are positive for ER and PR and there are case reports describing the potential responsiveness of this tumor to gonadotropin-releasing hormone (GnRH) agonist [14, 15]. Nevertheless, the role of hormone therapy in the management of AA has yet not been established. Due to the low mitotic activity, it is unlikely that radiation therapy or chemotherapy will be a useful adjunct to primary surgical treatment of AA.

We are aware of only five previously reported cases of pedunculated AA arising from the vulvovaginal region. Mittal *et al.* [5] described in 1998 a 40-year-old woman with a 10 cm sized AA arising from the right labium major with a 10 cm long pedicle. The tumor was locally excised around the base of the pedicle under local anesthesia and the patient was free of recurrence at follow-up after two years. Yalinkaya *et al.* [9] described in 2003 a 38-year-old woman with a right labial peduculated AA measuring 45 x 15 x 7 cm and weighing 850 grams. The tumor was resected around the base of the pedicle under local anesthesia and the patient was free of recurrence two years after resection. In a series of 12 female patients with AA reported by Amezcua *et al.* [11] in 2005, three had a pedunculated tumor. Of the three peduculated AAs, two originated from the vulva (measuring 2.8 x 2.7 cm in a 20-year-old woman and measuring 4 x 3 x 2 cm in a 32-year-old woman) and one originated from the vaginal suburethral area (measuring 5 x 3 x 3 cm in a 45-year-old woman). All three pedunculated AAs were locally excised and the patients were alive with no evidence of recurrent disease at follow-up after 36, three and two months, respectively. Thus, the patient described herein represents the sixth case of pedunculated AA arising from the vulvovaginal region and the second case of pedunculated AA arising from the vaginal suburethral area reported in the literature. In this patient, the tumor was locally excised around the base of the pedicle and until to date, six months after excision, there is no evidence of recurrent disease. Thus, based on the five previously reported cases of pedunculated AA arising from the vulvovaginal region (including one case arising from the suburethral area) and this case of pedunculated AA arising from the suburethral area, it seems that resection at the base of the pedicle provides a wide enough margin to adequately remove the tumor and cure the patient.

In conclusion, AA is an uncommon distinctive mesenchymal tumor that predominantly affects the pelvis and perineum of premenopausal women. It is often clinically misdiagnosed and it is only the microscopic examination strengthened with immunohistochemical staining that definitely and undeniably contributes to the final diagnosis of AA. Because of its locally infiltrative nature, its complete excision with tumor-free margins is occasionally a serious surgical challenge. It seems, however, that when AAs of the vulvovaginal region are pedunculated and without evidence of infiltration of the pedicle, the risk of recurrence after local excision is negligible.

References

[1] Steeper T.A., Rosai J.: "Aggressive angiomyxoma of the female pelvis and perineum. Report of nine cases of a distinctive type of gynecological soft tissue neoplasm". *Am. J. Surg. Pathol.,* 1983, *7,* 463.

[2] Begin L.R., Clement P.B., Kirk M.E., Jothy S., McCaughey W.T., Ferenczy A.: "Aggressive angiomyxoma of pelvic soft parts: a clinicopathologic study of nine cases". *Hum. Pathol.,* 1985, *16,* 621.

[3] Elchalal U., Lifshitz-Mercer B., Dgani R., Zalel Y.: "Aggressive angiomyxoma of the vulva". *Gynecol. Oncol.,* 1992, *47,* 260.

[4] Fetsch J.F., Laskin W.B., Lefkowitz M., Kindblom L.G., Meis-Kindblom J.M.: "Aggressive angiomyxoma: a clinicopathologic study of 29 female patients". *Cancer,* 1996, *78,* 79.

[5] Mittal S., Kumar S., Baurasi P., Sharma M.C.: "Aggressive aniomyxoma of the vulva - a case report". *Eur. J. Obstet. Gynecol. Reprod. Biol.,* 1998, *81,* 111.

[6] Hanoch J., Prus D., Milwidsky A.: "Aggressive vulvar angiomyxoma". *Acta Obstet. Gynecol. Scand.,* 2000, *79,* 712.

[7] Kaur A., Makhija P.S., Vallikad E., Padmashree V., Indira H.S.: "Multifocal aggressive angiomyxoma: a case report". *J. Clin. Pathol.,* 2000, *53,* 798.

[8] Cinel L., Taner D., Nabaei S.M., Dogan M.: "Aggressive angiomyxoma of the vagina". *Acta Obstet. Gynecol. Scand.,* 2000, *79,* 232.

[9] Yalinkaya A., Askar I., Bayhan G., Kilinc N., Yayla M.: "Aggressive angiomyxoma of the female pelvis and labium". *Acta Obstet. Gynecol. Scand.,* 2003, *82,* 298.

[10] Gungor T., Zengeroglu S., Kaleli A., Kuzey G.M.: "Aggressive angiomyxoma of the vulva and vagina. A common problem: misdiagnosis". *Eur. J. Obstet. Gyncol. Reprod. Biol.,* 2004, *112,* 114.

[11] Amezcua C.A., Begley S.J., Mata N., Felix J.C., Ballard C.A.: "Aggressive angiomyxoma of the female genital tract: a clinicopathologic and immunohistochemical study of 12 cases". *Int. J. Gynecol. Cancer,* 2005, *15,* 140.

[12] Nielson G.P., Young R.H.: "Mesenchymal tumors and tumor-like lesions of the female genital tract: a selective review with emphasis on recently described entities". *Int. J. Gynecol. Pathol.,* 2001, *20,* 105.

[13] McCluggage W.G.: "A review and update of morphologically bland vulvovaginal mesenchymal lesions". *Int. J. Gynecol. Pathol.,* 2004, *24,* 26.

[14] Fine B.A., Munoz A.K., Litz C.E., Gershenson D.M.: "Primary medical management of recurrent aggressive angiomyxoma of the vulva with a gonadotropin-releasing hormone agonist". *Gynecol. Oncol.*, 2001, *81,* 120.

[15] Poirier M., Fraser R., Meterissian S.: "Aggressive angiomyxoma of the pelvis: Response to luteinizing hormone-releasing hormone agonist". *J. Clin. Oncol.*, 2003, *21*, 3535.

[16] Betz J.L., Meloni A.M., Uren L.A., Moore G.E., Sandberg A.A.: "Cytogenetic findings in a case of angiomyxoma of the vaginal wall". *Cancer Genet. Cytogenet.*, 1995, *84,* 157.

[17] Kazmierczak B., Rohen C., Wanschura S., Schoenmakers E., Van de Ven W., Bullerdick J.: "Involvement of the MAR region in two rare benign mesenchymal tumors: a hamartoma of the breast and an aggressive angiomyxoma". *Cancer Genet. Cytogenet.,* 1995, *84,* 148.

[18] Nucci M.R., Weremowicz S., Neskey D.M., Sornberger K., Tallini G., Morton C.C., Quade B.J.: "Chromosomal translocation t(8;12) induces aberrant HMGIC expression in aggressive angiomyxoma of the vulva". *Genes, Chromosomes & Cancer,* 2001, *32*, 172.

[19] Chen L-M., Schink J.C., Panaras B.N., Barbuto D., Lagasse L.D.: "Resection of a giant aggressive angiomyxoma in the Philippines". *Gyncol. Oncol.,* 1998, *70,* 435.

[20] May F., Luther A., Mohr W., Bachor R., Hautmann R.E.: "Recurrent aggressive angiomyxoma of the urinary bladder". *Urol. Int.,* 2000, *65,* 57.

[21] Steiner E., Schadmand-Fischer S., Schunk K., Bezzi I., Weikel W., Pilch H., Knapstein P.G.: "Perineal excision of a large angiomyxoma in a young woman following magnetic resonance and angiographic imaging". *Gynecol. Oncol.*, 2001, *82,* 568.

[22] Jeyadevan N.N., Sohaib S.A.A., Thomas J.M., Jeyarajah A., Shepherd J.H., Fisher C.: "Imaging features of aggressive angiomyxoma". *Clin. Radiol.*, 2002, *58,* 157.

Address reprint requests to:
B. PIURA, M.D., F.R.C.O.G.
Unit of Gynecologic Oncology
Department of Obstetrics and Gynecology
Soroka Medical Center
and Faculty of Health Sciences
Ben-Gurion University of the Negev
P.O. Box 151
84101 Beer-Sheva (Israel)