Aggressive angiomyxoma of the vulva: our experience of a rare case with review of the literature

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Summary

Aggressive angiomyxoma is a rare, benign but locally aggressive mesenchymal neoplasm, which occurs almost exclusively during the reproductive years of women. A 28-year-old woman developed an aggressive angiomyxoma within the left labium minus of the vulva. The tumor was excised, but the lesion was expanded to the surgical margins. Microscopically, sections showed many walled vessels of various sizes, a loose myxoid and collagenous stroma and stellate and spindle-shaped neoplasmatic cells. Immunohistochemically, the neoplasmatic cells showed strong positivity for vimentin and desmin and moderate positivity for CD34 and estrogen receptors. In conclusion, aggressive angiomyxoma of the vulva should be distinguished from the benign and malignant myxoid tumors or tumor-like conditions of vulva. The pathologic and immunohistochemic characteristics, the difficulties in determining the surgical margins and the treatment of this tumor are discussed. Also, the international literature is reviewed.

Key words: Aggressive angiomyxoma; Surgical excision; Pathology; Immunohistochemistry; Vulva.

Introduction

Aggressive angiomyxoma of the vulva was described originally by Steeper and Rosai in 1983 as a distinct type of vulvar mesenchymal tumour [1]. It is an extremely rare, locally infiltrative neoplasm that affects almost exclusively women of childbearing age and occurs mostly in the vulva, perineum and other pelvic soft parts [2-5]. Also, few cases of this tumor have been reported in males originating from the perineum, scrotum, groin, spermatic cord and pelvis. In males with aggressive angiomyxoma the ages ranged from 19 to 80 years and the most common clinical presentation was a slowly growing scrotal, perianal, inguinal or perineal mass [4-6].

Histologically, aggressive angiomyxomas are composed of stellate, spindle-shaped cells loosely distributed in a myxoid and/or loose collagenous background, with prominent vasculature of small to medium caliber with thin and thick walls, cytologically bland nuclei, few mitoses and variable fibrosis. Also, aggressive angiomyxomas are histologically characterized by ill-defined margins because their dominant bland myxoid histologic pattern causes them to blend into the surrounding tissues without encapsulation. Therefore, adequate surgical clearance is difficult to be achieved, and local recurrence is frequently observed [2, 4, 6, 7].

We herein present a new case of aggressive angiomyxoma of the vulva; its gross, histopathologic and immunohistochemic diagnostic features are highlighted and the English-language literature is reviewed.

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Case Report

Clinical Findings

A 28-year-old para 2, gravida 2 woman presented to the Gynecologic Outpatient Clinic of the Department of Obstetrics and Gynecology "George Chantzikosta" State General Hospital, Ioannina, Greece with the complaint of a painless mass of the left vulva for the previous four months. The mass had increased rapidly to the size of 8 cm. There were no other significant symptoms. Physical examination disclosed a soft, non-tender pedunculated mass within the left labium minus (Figure 1). The tumor was treated by clamping (Figure 2) and simple excision under local anesthesia and the gap in the labia was closed with simple interrupted stitches. The patient had no postoperative problems. The follow-up period was 36 months and the patient remains well with no evidence of recurrence.

Pathological Findings

Macroscopic findings

The maximum diameter of the vulvar mass was 8 cm. The tumor was well circumscribed (Figure 3), had gelatinous consistency and on the cut surface the tumor was non-encapsulated and had a grayish-white appearance with hemorrhagic infiltrations and fibroelastic constitution.

Microscopic findings

Histologically, the lesion was composed of stellate and spindle-shaped neoplasmatic cells embedded in a myxoid and collagenous stroma. Nuclear atypia and mitoses were abscent. The lesion had an important vascular component; the blood vessels were of various sizes and had thick or thin walls (Figures 4 and 5). Infiltration into the pedicle of the neoplasm was observed and the lesion was expanded to the surgical margins.

Fig. 1

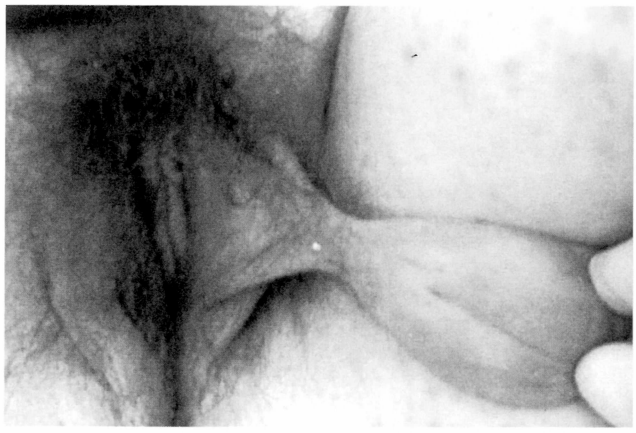
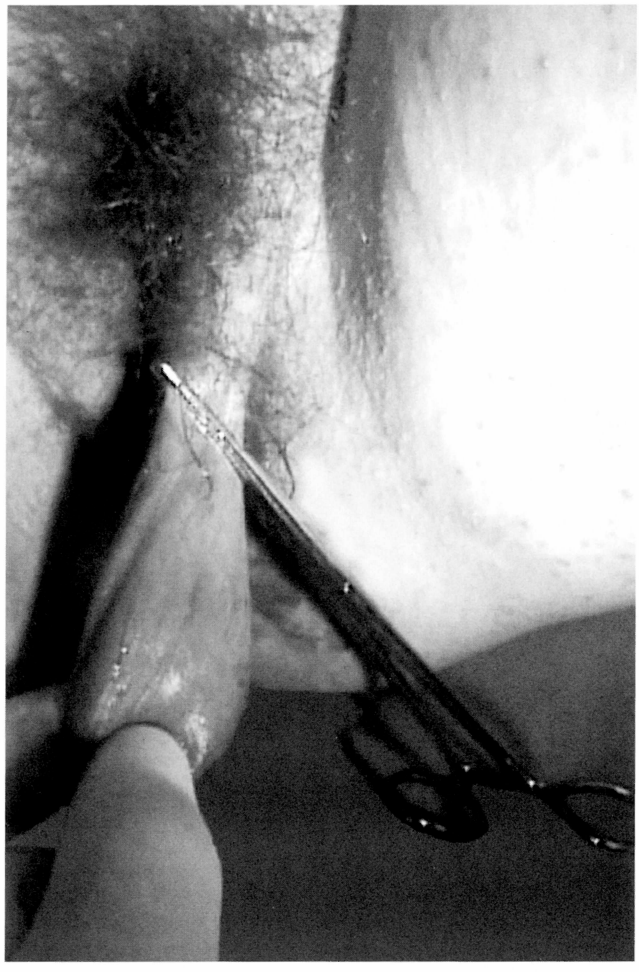


Fig. 2



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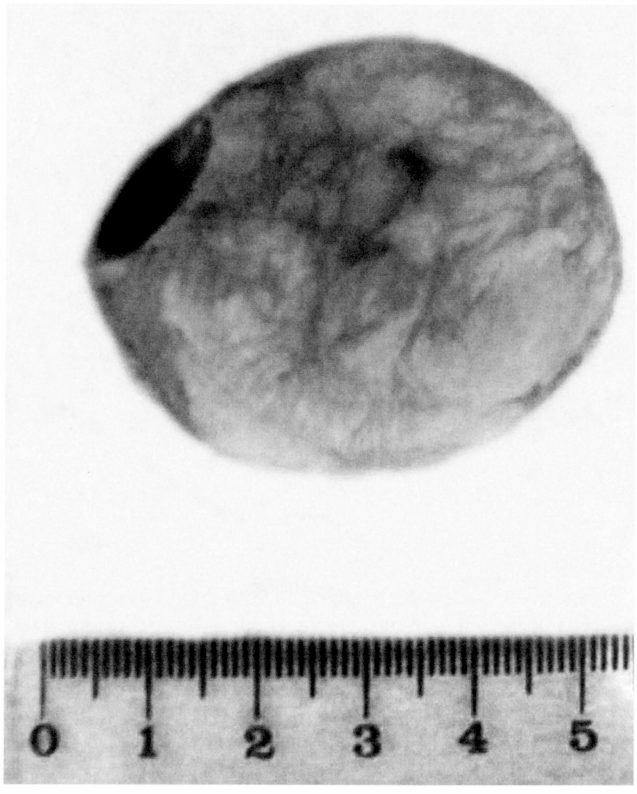


Figure 1. — A 28-year-old woman with a soft, non-tender mass.

Figure 2. — Clamping and resection of the vulval mass.

Figure 3. — Gross appearance of surgically excised aggressive angiomyxoma of the vulva.

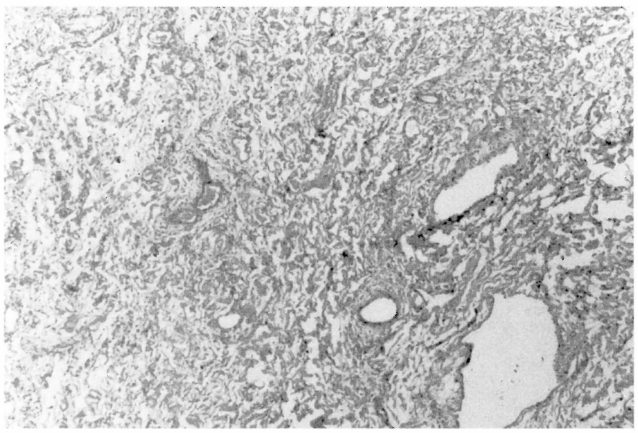
Immunohistochemical findings

Immunohistochemically, the tumor cells stained strongly for vimentin (Figure 6) and desmin (Figure 7). The tumor cells were moderately positive for CD34 and estrogen receptors (Figure 8). The results for cytokeratin AE1/AE3, smooth muscle actin, actin HHF-35, S-100 protein, factor 8, factor XIIIa and progesterone receptors were negative. The histologic and immunohistochemic findings were compatible with the diagnosis of an aggressive angiomyxoma of the vulva.

Discussion

Aggressive angiomyxoma is a very rare neoplasm, which occurs almost exclusively during the reproductive years of women; the youngest age reported is 15 years, but the tumor has occurred in women as old as 63 years [8]. Aggressive angiomyxoma grows slowly and insidiously and invasively extends into the neighboring tissues. Sometimes, it may occupy the whole pelvic region invading the paravaginal and prerectal spaces, displacing pelvic structures and extending into the retroperitoneal space [9]. Because aggressive angiomyxoma is not locally encapsulated and has the same consistency as normal connective tissue, complete tumorectomy is difficult to perform [10]. Incomplete surgical resection accounts for the high recurrence rate of this neoplasm and hence the described term "aggressive". Most recurrences of aggressive angiomyxomas occur within the first three years [11]. However, recurrence 14 years postoperatively has been reported [10, 12]. The high recurrence rate was initially estimated to be 67% to 80% [1, 12]. Later studies reported lower recurrence rates of 33% to 56%, but these studies had very limited follow-up periods of six to 198

Fig. 4



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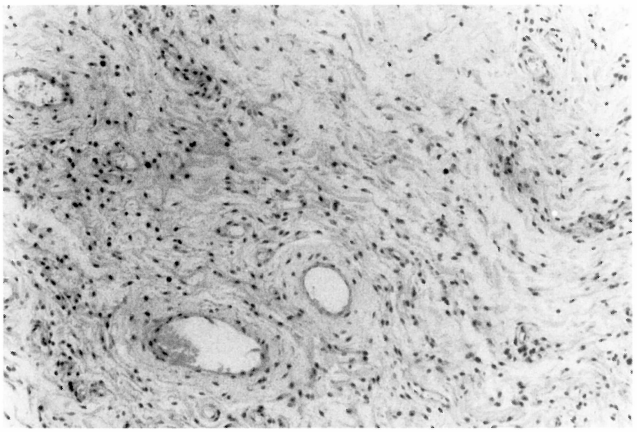
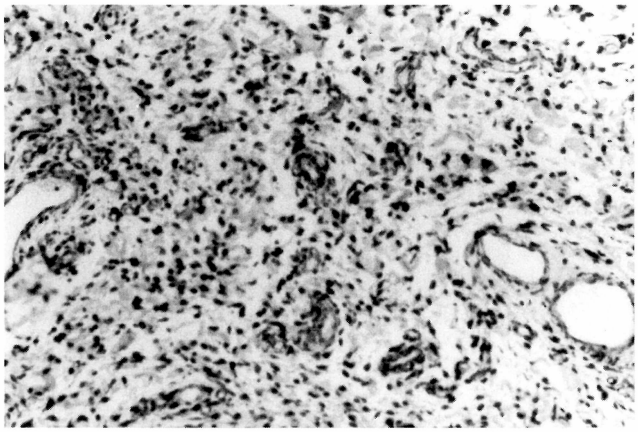


Fig. 6



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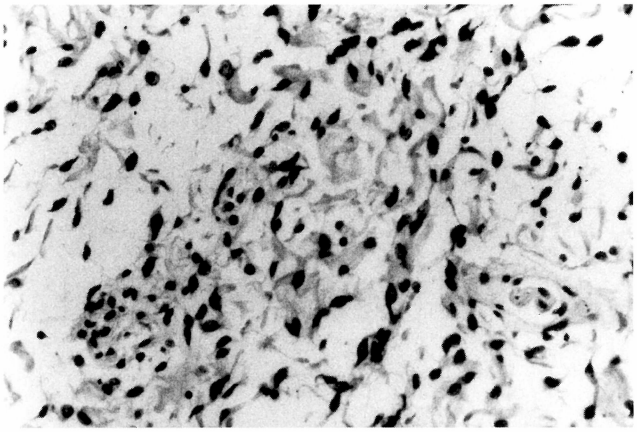

Fig. 8

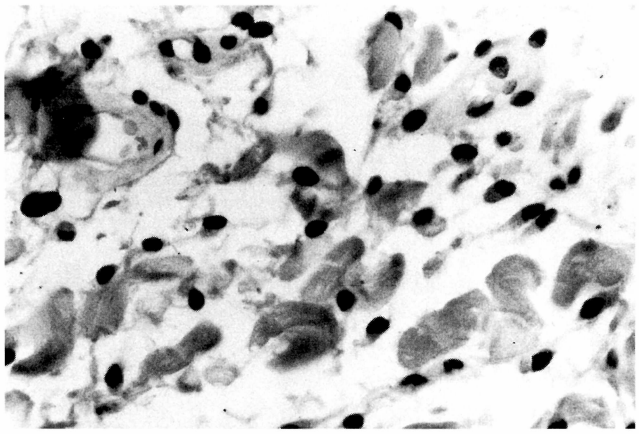

Figure 4. — Histologic appearance of aggressive angiomyxoma of the vulva shows many walled vessels of various sizes, and spindle-shaped cells embedded in a myxoid and collagenous stroma (hematoxylin-eosin, x 40).

Figure 5. — The same as Figure 4 (hematoxylin-eosin, x 100).

Figure 6. — Expression of vimentin in tumor cells (x 100).

Figure 7. — Expression of desmin in tumor cells (x 200).

Figure 8. — Focal positivity of estrogen receptors (x 400).

months [13-15]. Despite frequent recurrences, the prognosis of aggressive angiomyxomas is generally good, although two cases of metastasizing aggressive angiomyxomas have been reported [16, 17]. The first case was reported in 1999 in a letter to the editor and the investigators described an aggressive angiomyxoma of the pelvis with massive bilateral pulmonary, mediastinal, iliac and aortic lymph node and peritoneal metastases, ending in death [16]. In the second case, the authors described an aggressive angiomyxoma of the vulva with multpiple local recurrences, the first occurring six years after the original vulvar resection. The second vulvar relapse occurred one year later, and pulmonary metastases were found two years later. The patient died the following year, and an autopsy confirmed the metastatic nature of the pulmonary metastases [17].

In our case, the neoplasm was pedunculated. Histopathologic examination demonstrated the presence of stellate and spindle-shaped neoplastic cells embedded in a collagenous and myxoid stroma. It was highly vascular with blood vessels of various sizes within this myxoid stroma. This was harmonious to those reported in the English-language literature. Also, in our case infiltration was observed into the pedicle of the neoplasm. On gross examination, aggressive angiomyxoma is a grayish-colored, solid, nonencapsulated tumor with an edematous

or gelatinous consistency. The size of the tumor is usually large and its external surface is smooth, as was seen in our case; the mass is lobulated and non-nodular. The cut surface reveals a glittering gray tumor of homogeneous consistency with focal areas of congestion and hemorrhage [4-7, 9, 10, 18].

Differential diagnosis of aggressive angiomyxoma includes a series of benign and malignant soft tissue tumors including: myxoma, myxoid liposarcoma, myxoid-type malignant fibrous histiocystoma, sarcoma botryoides, myxoid neurofibroma, myxoid leiomyoma, myxoid liposarcoma, spindle cell lipoma, vaginal polyp, malignant mesenchymoma, mixed mesodermal tumor, sclerosing hemangioma, cellular fibroangioma, embryonal rhabdomyosarcoma, angiofibromyoblastoma and nerve sheath myxoma (neurothekeoma) [5, 10, 19, 20]. Among these tumors, angiofibromyoblastoma clinically and histologically overlaps with aggressive angiomyxoma [10]. Also, clinically it is mistaken for vulvar lipoma, abscess, Bartholin's cyst, Gartner's duct, vaginal cyst, vaginal prolapse or levator hernia [9]. The final diagnosis of aggressive angiomyxoma is confirmed on histopathology and lies in the identification of its rich vascularity and the blandness of its spindly cellular component [5]. The light microscopic features of angiomyofibroblastoma that distinguish it from aggressive angiomyxoma are the following: 1) marginal circumscription; 2) much higher cellularity; 3) large number of blood vessels lacking hyalinization or hypertrophy; 4) minimal stroma; 5) often plump stromal cells with perivascular accentuation; 6) paucity of stromal mucin; and 7) rarity of erythrocyte extravasation [9, 10, 21]. In addition, in angiomyofibroblastoma there is no recurrence.

Aggressive angiomyxoma is probably derived from myofibroblasts. In our case, immunohistochemistry showed strong positivity for vimentin and desmin and moderate positivity for CD34 and estrogen receptors. The staining for progesterone receptors was negative. Immunohistochemically, the spindle stromal cells in aggressive angiomyxoma are positive for vimentin and variably positive for muscle-specific actin [6]. In regard to immunoreactivity for S100, this marker is generally positive in tumors of mesodermal origin, including peripheral nerve-sheath tumors, adipose-tissue tumors, and cartilage tumors, while it is usually negative in aggressive angiomyxoma [10] as in our case. Estrogen and progesterone receptor expression is not specific for soft-tissue tumors, with angiomyofibroblastoma, myxoid leiomyoma and desmoid tumor all showing such positivity [10]. The growth of aggressive angiomyxoma during pregnancy and its positivity for estrogen and progesterone receptors suggest that in some instances aggressive angiomyxoma might possibly be hormone-dependent.

Surgical excision of aggressive angiomyxoma is the treatment of choice; long-term follow-up is necessary in these patients because of the possibility for recurrence. In regard to postoperative adjuvant therapy for aggressive angiomyxoma some authors have suggested a possible role for antihormonal therapy (such as tamoxifen) because aggressive angiomyxoma occurs predominantly in women of reproductive age and rapid growth has been observed during pregnancy [10, 13]. Nyam *et al.* suggested another adjuvant experimental therapy [20]. The authors published a case of large aggressive angiomyxoma located in the perirectal area. Preoperative angiographic embolization was performed causing ischemia of the tumor and improving the visualization of the lesion. In addition, preoperative external beam irradiation and intraoperative electron beam radiotherapy have been used to minimize the chances of local recurrence [22]. Alternative treatment to surgical excision of recurrent aggressive angiomyxoma in premenopausal women is the use of a gonadotropin-releasing hormone (GnRH) agonist in the cases where estrogen and progesterone receptors are expressed strongly positive. Fine *et al.* reported a case of vulvar aggressive angiomyxoma in a 34-year-old woman who presented with her second recurrence of the neoplasm following two prior surgical excisions [23]. Analysis of the recurrent tumor for estrogen and progesterone was strongly positive. The patient was unwilling to accept radical surgery to treat another recurrence and was treated with three months of a gonadotropin-releasing hormone (GnRH) agonist (leuprolide acetate, 3.75 mg IM). Comparison of pre- and post-treatment magnetic resonance imaging (MRI) scans showed complete radiographic resolution of the tumor. Also, the physical examination confirmed these findings. An additional three months of treatment with leuprolide acetate was given and the patient was placed on periodic surveillance without further medical or surgical intervention. The authors concluded that medical management of aggressive angiomyxoma with a GnRH agonist in the primary or adjuvant setting might be a promising alternative for patients in whom the estrogen and progesterone receptor status of the neoplasm is strongly positive [23]. In our case, the neoplasm was expanded to the surgical margins, but we did not try to re-operate on the patient because of the infiltrative behavior of the tumor; no adjuvant experimental therapy was given. We explained to the patient the possibility of local tumor recurrences and recommended long-term follow-up.

In conclusion, we have reported the gross features and the pathologic and immunohistochemic characteristics of a new very rare case of aggressive angiomyxoma of the vulva and discussed its histogenesis, differential diagnosis and treatment.

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