

Aggressive angiomyxoma of the vulva: expression of estroprogestinic receptors and follow-up

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Summary

Purpose of investigation: To analyze aggressive angiomyxoma hormone-dependency.

Method: Estroprogestinic receptor expression was studied by immunohistochemistry in 5 patients with aggressive angiomyxoma of the vulva.

Results: The immunohistochemical results confirm the positivity of angiomyxoma for estrogen and progesterone receptors.

Conclusions: We hypothesized that the concomitant factor favoring neoplastic growth is a different genetic substrate specific in the female sex. Analysis of the data regarding the distribution of angiomyxomas in different age groups has strengthened this hypothesis suggesting that this tumor is correlated with complete maturity, in all probability hormonal. However it cannot be excluded that the tumor begins to develop at an early age, but since it has a slow growth rate, the phenomenon is delayed and is related to hormonal stimulation.

Key words: Aggressive angiomyxoma; Vulva; Myxoid tumors; Estro-progestinic receptors.

Introduction

As is well known aggressive angiomyxoma is a rare neoplasia which involves almost exclusively the soft tissue of the vulva and perineal region [1] prevailing in women of fertile age. It is a slow growing tumor; in some cases the karyotype stands out for both the loss of sexual chromosome X and the translocation of chromosome 12 in the multiple aberration region (MAR) involved in the genesis of other neoplasms such as uterine leiomyoma, adipomas and salivary gland tumors [2].

Macroscopically aggressive angiomyxoma appears as a well circumscribed nodule, apparently encapsulated, elastic in consistency, whitish-gray in color and small in dimension which increases in volume during the luteal phase and during pregnancy [3].

Usually asymptomatic, it can lead to an incorrect diagnosis of cysts of the Bartholin's gland or duct.

Microscopically angiomyxoma is characterized mainly by the presence of small or medium size blood vessels and starshaped myofibroblasts immersed in a myxoid matrix surrounded by a fine network of connective tissue [4], the absence of a capsule [5] and by few cells with minimum nuclear atypia and rare mitosis. In the more aggressive forms of angiomyxoma epithelioid elements forming gland-like structures with mucous secreting activity have been described. Electron microscopic studies have shown an abundant rough-surfaced endoplasmic reticulum rich in ribosomes and intermediate filaments. Despite the rare mitosis and apparent benign cytology angiomyxoma has the tendency to local aggressive growth and it is often

associated with multiple relapses and, in rare cases, metastases have been found [6, 7].

The pathological differential diagnosis could be intramuscular myxoma, liposarcoma, neurofibroma and angiofibroma [8].

Therapy is exclusively based on surgical exeresis of the lesion with a wide margin of surrounding healthy tissue to prevent local recurrences.

The immunohistochemical reactions show a positivity for Desmin, Actin and Factor VIII, whereas the reactions to S 100, cytokeratins and CEA are negative; a variable responsiveness to the antibodies anti-ES and anti-PR by the myoepithelial cells has recently been shown [3, 5, 9].

In our clinical experience we have observed some very interesting cases of vulvar angiomyxoma. In view of the rarity of the diagnosis we have examined our cases, particularly in regard to immunohistochemical reactions, recurrence incidence and survival rate.

Materials and methods

Case 1: A. D., age 48, para 2002, menstrual cycle regular, was hospitalized in 1994 for a vulvar neof ormation, 2 cm in diameter, pedunculated and localized in the vulvar vestibule. The neof ormation was removed and the pathological examination showed an aggressive angiomyxoma.

Case 2: A. I., age 41, para 2012, menstrual cycle regular, was hospitalized in 1996 for a neof ormation of the right labia majora, pedunculated and 3.5 cm in diameter. The neof ormation was removed and the pathological examination revealed aggressive angiomyxoma.

Case 3: V. F., age 49, para 1001, menstrual cycle regular, was hospitalized for a Bartholin's cyst in 1996. The cyst was 5.5x4x2.5 cm in size and was surgically removed. The pathological exam showed an aggressive angiomyxoma.

Received May 14, 1998

revised manuscript accepted for publication August 20, 1998

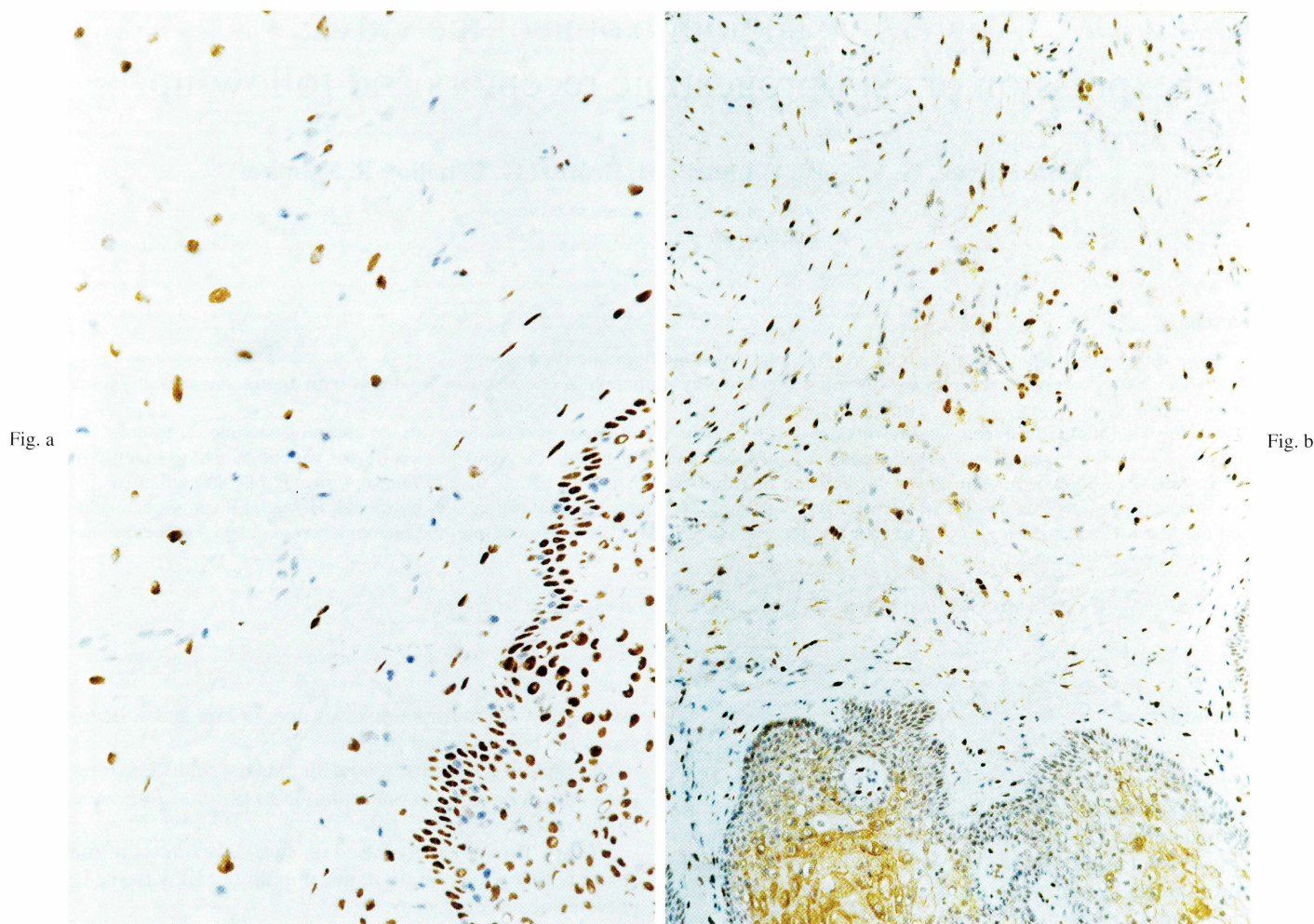


Figure 1. — Sensitivity for hormonal receptors in angiomixoma is clear. Fig. a: for ER receptors; Fig. b: for PR receptors.

Case 4: M.M., age 47, para 2002, menstrual cycle regular, was hospitalized in 1997 for a III grade uterine prolapse, cystocele and rectocele. The patient underwent vaginal hysterectomy with anterior and posterior colpoplasty. During surgery a solid whitish-gray neof ormation 0.5x0.3 cm in size, located in the posterior vulvar commissure was removed. Pathological examination showed an aggressive angiomixoma. At follow-up, six months later, a second lesion, a few millimeters in size, was found at the same site. Pathological examination showed a recurrence of the same aggressive angiomixoma.

For each case numerous histological preparations were obtained from tissue fixed in buffered formalin and embedded in paraffin.

In all cases, besides the normal routine stainings, immunohistochemical reactions using the following mono and polyclonal antibodies were performed.

• Monoclonal antibody ER was able to react with the N-terminal dominion of the 67kd polypeptide chain of the estrogen receptor (Biosenecs).

• Monoclonal antibody PR was able to react with proteinic receptor for human progesterone; it strongly reacted with the epithelial cells of the progesterone dependent tissue (Bios-pnecs).

• Monoclonal antibody AE1 was able to show the high molecular weight base type cytokeratins 19, 16, 15, 14, 10, High P. M. arial type (DAKO).

• Monoclonal antibody AE3 was able to show the high molecular weight base type cytokeratins 8, 7, 6, 5, 4, 3, 2, 1, High PM basic type (DAKO).

• Polyclonal antibody against the perineural fibroblast derivative.

Table 1.

Case	Year	Age	Vulvar Localisation	Symptomatology	Immunohistochemic.		Relapses	Survival
					ER	PR		
A.D.	1994	48	Vestibule	Small neof ormation	++	+	no	alive
A.I.	1996	41	Labia majora	Small neof ormation	+	+	no	alive
V.F.	1996	49	Bartholin's gland	Small neof ormation	++	++	no	alive
M.M.	1997	47	Posterior commissure	Absent	+	+	Yes (1998)	alive

vatives (S 100) was able to differentiate the glial and ependymal cells as well as the Schwann cells of the peripheral nervous system.

- Monoclonal antibody Desmin was able to show the 53 KD intermediate proteic filaments in the smooth muscles (DAKO).

- Monoclonal antibody Vimentin was able to show the 53 KD proteinic filaments in mesenchymal cells (DAKO).

For each patient the following clinical parameters were considered: age, site of tumor, symptomatology, survival and recurrence (Table 1).

Morphologic aspects were based on the WHO classification proposed by R. E. Scully in 1994 [11].

In addition, mitotic figures and nuclear polymorphism were considered as to size, colour and morphologic variability of the nucleus.

Results

From January 1994 to January 1998 four cases, one with recurrence, of aggressive angiomyxomas were found in women hospitalized in our Institute. The average age of the patients at diagnosis was 45 years (ranging from 41 to 49 years). In three cases the tumor was localized in the vulvar-perineal region while in one the tumor simulated a Bartholin's cyst.

Pathological examination of the cases and of recurrence showed: 1) no evidence of nuclear polymorphism and mitosis; 2) a rather homogenous cellular pattern which was characterized by cellular elements, stellate and fusiform in shape with cytoplasm with well-defined borders of different sizes; 3) a vascular structure with hyalinosis walls sometimes appearing thin or thick. Everything appeared immersed in a myxoid matrix rich in collagen fibres with small haemorrhagic foci. Sometimes the myxoid matrix was replaced by an intense collagen proliferation.

The immunohistochemical reactions showed vimentin and desmin positivity while instead, cytokeratine, AE1, AE3, CAM 5, 2 and polyclonal antibody S100 negativity. The estrogen and progesterone receptors were positive in the angiomyxoma.

Follow-up revealed a relapse in the same site in only one case six months after surgery. This could be due to the persistence of aggressive cellular nests which escaped the surgical radicality rather than a revival of the disease itself.

Conclusions

Angiomyxomas are a small, barely quantifiable percentage of the soft tissue neoplasia of the vulva and perineal region. Among the low female genital tract tumours they are a very rare neoplasia frequently with recurrence [3, 6, 7, 11].

In general, angiomyxomas, globally considered, are more prevalent in females than in males [1, 2, 3, 9] which may be because they are rich in estrogen and progesterone receptors.

We believe that hormonal or genetic factors, correlated with the female sex, are responsible for neoplastic growth. The high incidence of this tumour in middle-aged women (40-50 years old) confirms, in our opinion, the role of hormonal activity. It could be possible that the tumour begins at an early age (a single pediatric case has been reported [12]) and develops slowly with delayed clinical manifestations.

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