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РЕКУРЕНТЕН АГРЕСИВЕН АНГИОМИКСОМ НА ВУЛВА. ПРИКАЗ НА СЛУЧАЈ

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Извадок

Вовед: Агресивниот ангиомиксом е редок, бениген, споро-растечки, локално агресивен тумор, кој најчесто се јавува кај жените во репродуктивната возраст.

Приказ на случај: Прикажан е случај на агресивен ангиомиксом на вулвата, иницијално клинички интерпретиран како циста, кој се појавил кај пациентката на возраст од 32 години. По некомплетното отстранување, туморот рецидивирал уште десет пати во следните 28 години. При првичната хистопатолошка анализа, туморот бил интерпретиран од патолог како дерматофибром/дерматофибросарком. Направен е осврт на диференцијално-дијагностичките и тераписките можности.

Заклучок: Со навремено препознавање и адекватна терапија на агресивниот ангиомиксом, може да се намали ризикот од појава на рекурентен тумор кај овие пациенти.

Клучни зборови: агресивен ангиомиксом, вулва, диференцијална дијагноза, естрогенски рецептор, прогестеронски рецептор, имунохистохемија

RECURRENT AGGRESSIVE ANGIOMYXOMA OF THE VULVA. A CASE REPORT

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Abstract

Introduction: Aggressive angiomyxoma is a rare, benign, slow-growing, locally aggressive tumor, occurring in women in their reproductive years.

Case report: A case of aggressive angiomyxoma of the vulva, clinically interpreted as a cyst, occurring in a 32 year-old female patient is presented. After incomplete removal, the tumor recurred more than ten times in the next 28 years. During the initial histopathological examination of the recurrent tumors, they were misinterpreted as dermatofibroma/dermatofibrosarcoma. Differential diagnostic and therapeutical possibilities are discussed as well.

Conclusion: The risk of recurrence in patients with aggressive angiomyxoma can be signifficantly reduced with appropriate recognition and adequate therapy.

Key words: aggressive angiomyxoma, vulva, diferential diagnosis, estrogen receptors, progesterone receptors, immunohistochemistry

Introduction

The soft tissue tumors occurring in the distal part of the female genital tract were initially classified in 1966 as "benign stromal polyps". Today, several distinct entities are recognized in this group, such as aggressive angiomyxoma, angiomyofibroblastoma and cellular angiofibroma. Given their common origin from the vulvo-vaginal mesenchyme, these histologically similar tumors are diagnostically challenging [1,2,3].

The aggressive angiomyxoma as a distinct entity was first described by Steeper and Rosai in 1983. This is a rare, benign, slow-growing, but locally aggressive mesenchymal tumor, commonly found in women in their reproductive years [4,5]. The aggressive angiomyxoma is generally localized deep in the soft tissues of the pelvis, vulva, or the perineum. This tumor has initially been detected in women, but it can also be found in the inguino-scrotal region and retroperitoneum in men [6]. Even though this tumor has a benign histological appearance and no metastatic potential, it has infiltrative growth pattern and increased tendency for local, often multiple recurrences [7,8].

Several studies have been published in the last few years, suggesting that the aggressive angiomyxoma is a hormone-dependent tumor, often positive for estrogen and progesterone receptors. Rapid growth of these tumors was also observed in pregnant women [6].

The aim of this study is to present a case of aggressive angiomyxoma of the vulva, initially clinically diagnosed as a cyst, while histopathologically misinterpreted as dermatofibroma/dermatofibrosarcoma. A comment is given on the clinical and histopathological differential diagnosis with other pathological conditions and mesenchymal tumors occurring in the external female genital organs. Therapeutic possibilities are also discussed.

Case report

Clinical data

A sixty-year old female patient (menarche at the age of 15, two deliveries at the age of 22 and 23 years, and menopause at the age of 50) presented with a recurrent vulvar tumor. According to the anamnestic data, the primary tumor of the vulva occurred when the patient was 32 years old (1979). At that time, she was investigated for pelvic inflammatory disease. The tumor was clinically

misinterpreted by the gynecologist as a cyst, and an attempt for marsupialisation was made. The tumor was excised, but only few months later, the first recurrent tumor appeared. In the next 28 years, more than ten excisions of the recurrent tumors of the vulvar, inguino-femoral or pubic region were made. The primary and the majority of the recurrent tumors (except one) before 1995 have been excised in a local hospital and therefore the histopathological reports of these tumors are not available. A total of eight recurrent tumors, the first submitted for analysis in 1984 and the last 7 recurrent tumors in the period between 1995 and 2007, were subjected for histopathological evaluation at the Department of Histopathology and Clinical Cytology at the Institute of Radiotherapy and Oncology in Skopje.

Material and methods

The operative materials submitted for histopathological analysis at our Department were fixed in 10% formalin for 24 hours. Subsequently, several 2.5 mm thick tissue sections were taken from the tumors and from the surgical margins. They were routinely processed, according to the standard procedure for formalin-fixed, paraffin-embedded tissue. Slides were initially stained with hematoxyllin and eosin stain.

To confirm the diagnosis of aggressive angiomyxoma, additional histochemical (Jones' silver, PAS and Alcian blue) and immunohistochemical stains (vimentine, alpha-smooth muscle actin, desmin, caldesmon, CD34, CD68, collagen IV, Ki-67, estrogen and progesterone receptor) were also performed on selected sections from the last recurrent tumor.

For the immunohistochemistry, 4 μm-thick sections were cut from one of the paraffin blocks and were placed on pretreated slides (poly-L-lysine). Slides were then baked overnight in the oven at 58°C. After deparaffinization and rehydration, the slides were treated with 0.3% hydrogen peroxide in methanol, in order to block the endogenous peroxidase activity. Subsequently, the slides were soaked in a 0.01 M citrate buffer with pH 6.0 and were cooked in a microwave oven at 400W for 15-30 minutes. After pretreatment, 100 μl from each of the primary antibodies were applied on the sections. Antibodies were incubated for one hour at room temperature. The characteristics of the primary antibodies are given in Table 1.

The conjugated primary antibody was visualized using standard streptavidin-biotin-avidin peroxidase complex (Vectastain universal elite ABC kit, Vector Laboratories, Inc. USA). 3.3'-diaminobenzidine (DAB) was used as chromogen, whereas for better visualization of the cellular morphology, counterstain with hematoxyllin was used.

The evaluation for the most of the antibodies was semiquantitative and the results were reported as negative (-), focally positive (±) and diffusely positive (+). For the Ki-67 proliferative index, the percentage of positive cells was assessed by counting 1,000 consecutive cells in the tissue. The positivity for the estrogen and the progesterone receptors was evaluated semiquantitatively, as negative (-), weakly positive (+), moderately positive (++) and intensely positive (+++), depending on the percentage of stained cells.

Results

Initially, in 1984, when one of the recurrent tumors was submitted to the Department for analysis, it was interpreted by the pathologist as dermatofibroma. Eleven years later, one of the eight recurrent tumors was also submitted for analysis. Having in mind that the tumor recurred and was localy aggressive, the pathologist revised the slides from the previously analyzed tumor and changed the diagnosis to protuberant dermatofibrosarcoma. In this operative material, as well as in all other recurrent tumors in which the pathologist assessed the surgical margins, they were involved by the tumor (Table 2).

All operative materials consisted of protuberant lobulated tumors, covered with thinned, focally ulcerated skin. The tumor diameter measured between 3.5 and 11cm

Table 1. Characteristics of the primary antibodies

Antibody	Clone	Dilution	Incubation	Manufacturer	Results
Ki-67	MIB-1	1:50	60 min	Dako, Glostrup Denmark	<5%
CD68	EBM11	1:50	60 min	Dako, Glostrup Denmark	±
Collagen IV	CIV 22	1:50	60 min	Dako, Glostrup Denmark	-
CD34	QBEnd 10	1:50	60 min	Dako, Glostrup Denmark	-
Alpha SMA	HHF35	1:50	60 min	Dako, Glostrup Denmark	±
Caldesmon	h-CD	1:50	60 min	Dako, Glostrup Denmark	±
Desmin	D33	1:50	60 min	Dako, Glostrup Denmark	±
Vimentin	V9	1:50	60 min	Dako, Glostrup Denmark	+
ER	1D5	1:50	60 min	Dako, Glostrup Denmark	++
PgR	PgR 636	1:50	60 min	Dako, Glostrup Denmark	++

Legend: ER, estrogen receptor; PGR, progesterone receptor; SMA, smooth nuscle actin; ±, focal positivity; +, diffuse positivity; ++, moderate positivity for the estrogen and progesterone and receptors

Table 2. Description of the available clinical and histopathological data from the recurrent tumors analyzed at our Department

Number of the recurrent tumor	Age	Localization	Tumor diameter (cm)	Surgical margins
1	37	Inguino-femoral	11	Free
2	47	Pubic/inguinal	5,5	No data
3	49	Inguinal	4,6	No data
4	49	Vulva	6	Involved
5	50	Vulva	3,7	No data
6	52	Vulva	3,5	Involved
7	56	Inguino-femoral	11	No data
8	60	Vulva	10	Involved

Table 3. Morphological and immunohistochemical characteristics of the mesenchymal neoplasms of the external genital organs [1,18,20,21,23].

Tumor	CC	CA	CK	VIM	DES	ACT	S100	CD34	CD57	ER	GA
Aggressive angiomyxoma	0	0	0	+	±	±	0	0/±	0	±	ra12q13-15
Angiomyofibroblastoma	±	0	0	+	±	±	0	0	0	±	/
Fibroepithelial stromal polyp	+	±	0	+	±	0/±	0	±	0	±	/
Peripheral nerve sheath tumor	0	+	0	+	0	0	±	±	±	0	/
Intramuscular myxoma	+	0	0	±	0	0	0	±	0	0	/
Superficial angiomyxoma	+	0	0	+	0	0/+	0/±	+	0	0	/
Myxoid neurofibroma	+	0	0	+	0	0	±	0	0	0	/
Myxoid liposarcoma	±	+	0	+	0	0	±	0	0	0	t(12;16)(q13;p11) (12;22)(q13;p11)
Myxofibrosarcoma	0	+	0	+	0	0/±*	0	0	0	0	Ring chromosome
Dermatofibrosarcoma protuberans	0	±	0	+	0	0	0	+	0	0	/

Legend: ACT, actin; CA cytologic atypia; CC, circumscribed; CK,cytokeratin; DES, desmin; ER, estrogen receptor; GA, genetic alterations; ra, rearangement; S100, S100 protein; VIM, vimentine;, in high grade tumors.*

(Table 2). On cut surface, the tumors were gray-white, semi-elastic and poorly demarcated from the surrounding connective tissue and adipose tissue (Figure 1).

Histologically, the tumor was composed of stellate and spindle cells, without clear cytoplasmatic margins, set within a myxoid matrix, containing variably sized, thick walled, hyalinized vessels. Most of the tumor was paucicellular, but more cellular areas were also evident. The cells did not show any atypia and mitotic figures were rare. Delicate fibrils of collagen were dispersed throughout the myxoid stroma and were characteristically condensed around the blood vessels. Focal perivascular lymphocytic inflammatory infiltrate was also evident. Small areas of the tumor, containing epithelioid cells in perivascular arrangement, had the appearance of angiomyofibroblastoma. These areas were not circumscribed and seem to blend in with the surrounding tumor tissue. In the last operative material, at the invasive front the tumor infiltrated the subcutaneous adipose tissue and striated muscle. Surgical margins were also involved.

Immunohistochemically, the tumor cells were positive for vimentine (Fig. 4), while focal positivity was observed for desmin (Fig. 5), alpha-smooth muscle actin (Fig. 6) and caldesmon. All other markers were negative. Ki-67 proliferative index was less than 5% (Fig. 7). Tumor cells also showed moderate positivity for estrogen (Fig. 8) and progesterone receptors.

Fig. 1. Macroscopic appearance of the last recurrent tumor

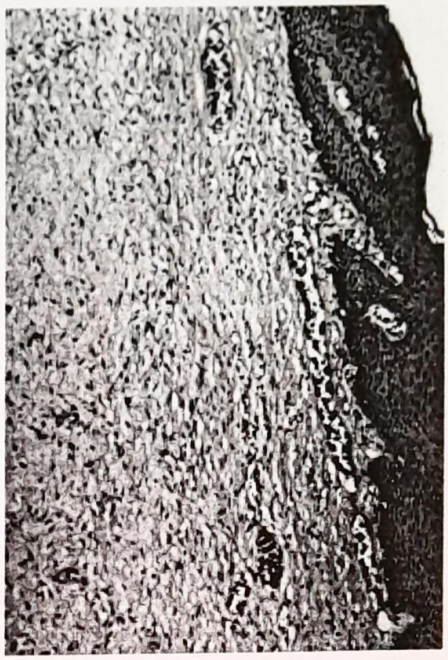

Fig. 2. Low power microscopic appearance of the tumor (hematoxyllin and eosin, x100)

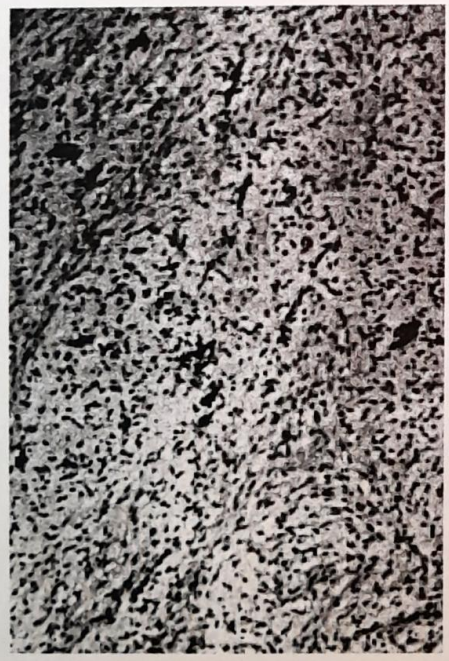

Fig. 3. Low power microscopic appearance of the tumor with prominent blood vessels and myxoid stroma (hematoxyllin and eosin, x100)

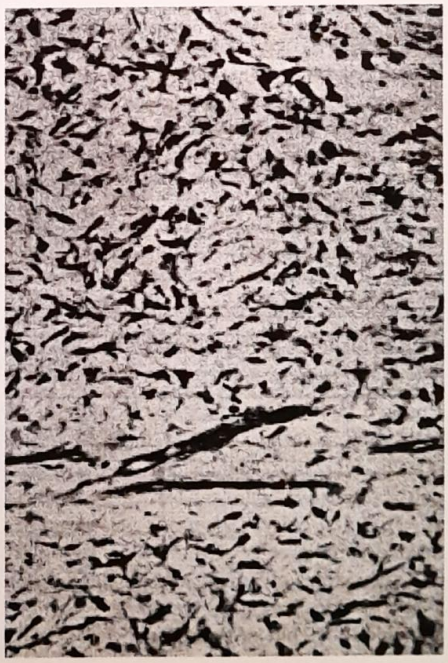

Fig. 4. The tumor cells show diffuse positivity for vimentine (x200)

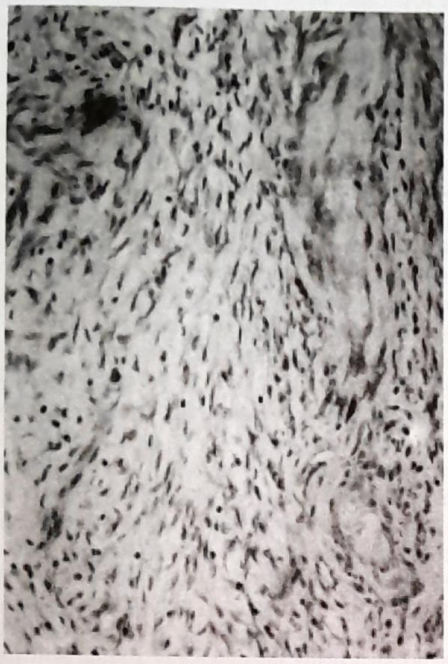

Fig.5. The tumor cells show focal positivity for desmin (x200)

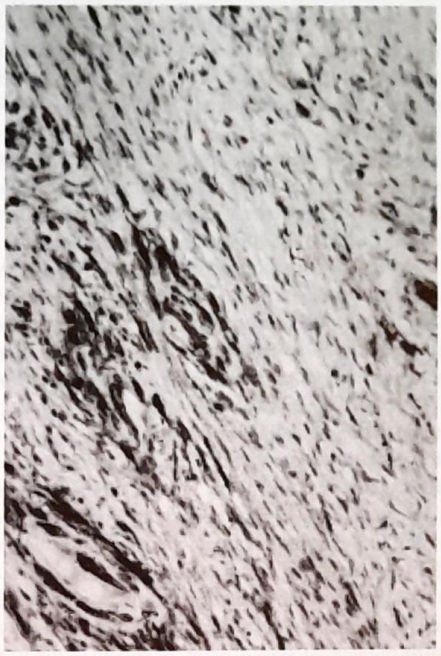

Fig.6. The tumor cells show focal positivity for alpha-smooth muscle actin (x200)

Fig. 7. Ki-67 proliferative index is <5% (x200, arrow)

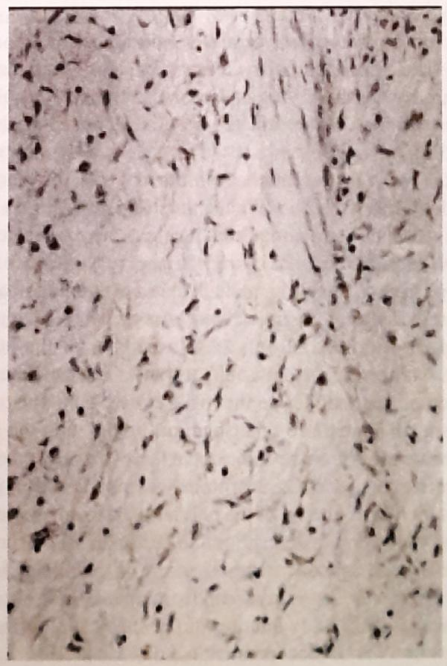

Fig. 8. The cells show moderate positivity for estrogen receptor (x200, arrow)

Discussion

Aggressive angiomyxoma is a rare benign mesenchymal tumor of the pelvis and perineum in women, and less frequently of the inguino-scrotal region in men. Ninety percent of the cases are found in women in the second to fourth decade of life [8,9]. On the contrary, in men, this tumor usually occurs in the sixth or seventh decade [3].

According to the available literature, the average size of these tumors is between 5 and 23 cm [10]. The dimensions of all recurrent tumors analyzed in our case are within these limits.

Etiopathogenesis of the aggressive angiomyxoma is still controversial. The current opinion is that the tumor cells have fibroblastic/myofibroblastic origin [11]. The theory of myofibroblastic origin of the tumor cells is supported by many authors, such as Steeper and Rosai (1983), who demonstrated ultrastructural characteristics of myofibroblasts in the cells of these tumors. In the recent years, a few authors reported positivity for desmin in the tumor cells. For example, Skalova et al. (1993), reported that three of the seven cases included in their study showed positivity for this marker [12]. In the study of Granter et al. (1997), in which sixteen cases of aggressive angiomyxoma were evaluated, the spindle cells around the blood vessels showed myofibroblastic differentiation. In eleven of the fourteen cases tested, these spindle cells were positive for desmin, whereas in ten of the eleven tested cases they were positive for alpha-smooth muscle actin [11]. These findings are in concordance with our case, in which focal, mainly perivascular positivity for desmin and alpha-smooth muscle actin was found.

In the recent years, several studies have reported on the genetic alterations of the aggressive angiomyxomas. Cytogenetic analyses revealed clonal aberrations of the twelfth chromosome. For example, Nucci et al. (1999), published a case of aggressive angiomyxoma of the vulva with clonal chromosomal translocation that included the twelfth chromosome t(8;12)(p12;q15) [13]. This translocation resulted in aberrant expression of HMGA2 protein, involved in the regulation of the transcription. Rearrangement or aberrant expression of this protein is found in other benign mesenchymal tumors, such as endometrial polyps, leiomyomas of the uterus, lipomas, or hamartomas of the lung. The pathogenetic mechanisms that define the infiltrative phenotype of this tumor, in contrast to other benign tumors with the same translocation, are still unclear. On the other hand, aberrant expression of HMGÀ2 protein was not found in other mesenchymal tumors of the pelvis, apart from one case of angiomyofibroblastoma. For that reason, HMGÀ2 protein can be used as a diagnostic marker for the distinction of the aggressive angiomyxoma from other similar tumors, as well as for the evaluation of the surgical margins and detection of microscopic residual disease [1,13].

The aggressive angiomyxoma is commonly misinterpreted by the clinicians as a cyst of the Bartholin's gland, vaginal cyst, or vulvar hernia [3,11,14]. Htwe et al. (1995) and Fine et al. (2001) each published a case of recurrent aggressive angiomyxoma, clinically misinterpreted as a cyst of the Bartholin's gland [15,16]. In the first case, the tumor was excised, whereas in the second the tumor was treated with incision and drainage with marsupialisation of the cyst. Ribaldone et al. (2004), published a case where aggressive angiomyxoma was misinterpreted by the clinician as lipoma [10]. Furthermore, Dragoumis et al. (2005), published two cases of aggressive angiomyxoma of the vulva, one of which was diagnosed as lipoma, and the other as a cyst of the Bartholin's gland [17]. A similar study was also published by Gungor et al. (2004), in which one of the two cases was interpreted as a vaginal cyst and the other as vulvar hernia [14]. A more extensive study was done by Granter et al., in which sixteen cases of aggressive angiomyxoma were included. The initial clinical diagnosis in three of the cases was cyst of the Bartholin's gland, vaginal cyst in two cases, inguinal hernia in other two, and the rest were diagnosed as lipoma, periurethral cyst, or abscess [11]. According to some authors, the aggressive angiomyxoma is clinically misinterpreted in 82% of the cases [14]. Similarly, in our case the tumor was initially misinterpreted by the gynecologist as a cyst, with an attempt for marsupialisation, while one of the recurrent tumors was misinterpreted by the surgeon as fibro-myxo-lipoma.

In the differential diagnosis of aggressive angiomyxoma, many histologically similar soft tissue tumors are included, such as angiomyofibroblastoma, fibroepithelial stromal polyp, as well as many other myxoid tumors: superficial angiomyxoma, myxoid neurofibroma, myxofibrosarcoma of low grade, myxoid malignant peripheral nerve sheath tumor, and intramuscular myxoma [4,11,18,19].

Contrary to aggressive angiomyxoma, the *angiomyofibroblastoma* is a well circumscribed, more cellular tumor, which consists of large epithelioid cells arranged around the blood vessels. The immunohistochemical profiles of angiomyofibroblastoma and aggressive angiomyxoma are similar; however, angiomyofibroblastoma is more often positive for desmin and negative for alpha-smooth muscle actin. The distinction between these two entities is important because angiomyofibroblastoma has lower risk of recurrence, contrary to aggressive angiomyxoma [18,19,20].

Fibroepithelial stromal polyps are superficial tumors with less myxoid stroma. In the subepithelial stroma, bizarre, angulated and often multinucleated cells are seen [18,19].

Schwannomas, or the so called *peripheral nerve sheath tumors* (benign or malignant), have different immunohistochemical characteristics than the myofibroblastic tumors. In fact, these tumors are always positive for either S100 or CD57 markers [21].

Intramuscular myxoma is rarely included in the differential diagnosis of aggressive angiomyxoma, because of its typical intramuscular localization. The vascular network of this tumor is mainly composed of capillary blood vessels, in contrast to the thick walled vessels of the aggressive angiomyxoma [11].

Superficial angiomyxoma can occur in the vulva, but does not show infiltrative growth pattern and contains less conspicuous vascular network. The presence of polymorphonuclear leucocytes in the stroma is a characteristic feature of this tumor. In addition, the cells of the superficial type do not show smooth muscle phenotype and are negative for desmin. The absence of positivity for the estrogen and progesterone receptors also favors the diagnosis of superficial angiomyxoma [1,11,19].

The cells of the *myxoid neurofibroma* contain slender wavy nuclei, and are positive for the S100 protein. The vascular network is also less prominent than in aggressive angiomyxoma [11].

Because of its infiltrative growth pattern and tendency for local recurrences, the aggressive angiomyxoma can simulate sarcoma. However, the *myxoid liposarcoma*, which is extremely rare at this localization, differs from the aggressive angiomyxoma by the presence of a characteristic arborizing vascular network that has a chicken wire pattern. Lipoblasts can also be observed [11]. Sometimes the deep adipose tissue is infiltrated by the tumor which can simulate well differentiated liposarcoma. This diagnosis can be excluded by the absence of atypia of the nuclei of the adipocytes, absence of lipoblasts and absence of bizarre, hyperchromatic stromal cells.

Myxofibrosarcoma (myxoid malignant fibrous histiocytoma) differs from aggressive angiomyxoma by the presence of curvilinear blood vessels and the presence of atypical hyperchromatic cells and bizarre lipoblast-like cells that contain mucin [11].

Protuberant dermatofibrosarcoma appears in the cutis and subcutaneous tissue. Its histology and biologic behavior are reminiscent of aggressive angiomyxoma. Prominent myxoid stroma can be observed in around 2% of these tumors. In such cases the stroma is usually paucicellular, containing small stellate or spindle cells, while the vascular network is more prominent. However, the nuclei show moderate pleomorphism. Mitoses are frequent. 95% of these tumors are positive for CD 34, which is not a characteristic of aggressive angiomyxoma [18,21].

This group of histologically similar mesenchymal tumors sometimes causes diagnostic difficulties. For example, in the study of Laskin et al., fourteen cases of superficial cervico-vaginal myofibroblastomas were evaluated, thirteen of which were initially histologically misinterpreted. Four of the cases were interpreted as fibroepithelial polyps, two as angiomyofibroblastomas, and the other seven as angiofibroma, sclerosing hemangioma, vascularised fibrous proliferation, protuberant dermatofibrosarcoma, benign polypoid neoplasm, spindle cell neoplasm and low grade neoplasm with characteristics of hemangiopericytoma [22].

The morphological and inmmunohistochemical characteristics of the different mesenchymal tumors of the vulva that are included in the differential diagnosis of aggressive angiomyxoma are summarized in Table 3 [1,18,20,21,23].

Extremely rare cases of metastatic aggressive angiomyxoma are published in the literature, one of which was metastatic to the lungs [1]. On the other hand, this tumor has an increased tendency for local recurrences which, according to some authors, appear in nearly 70% of the cases in the period of two years [8,9]. In our case, the first recurrent tumor occurred just few months after the initial excision.

The recurrent aggressive angiomyxoma has a more fibrous stroma, sometimes mimicking protuberant dermatofibrosarcoma. Correspondingly, in our case the first recurrent tumor evaluated in 1984 was misinterpreted as dermatofibroma, while the second tumor which recurred in 1995 was interpreted as protuberant dermatofibrosarcoma. The initial diagnosis of dermatofibroma was given just one year after the establishment of the aggressive angiomyxoma as a distinct entity. Moreover, because of the morphology and the local aggressiveness of one of the subsequent recurrent tumors, the diagnosis was changed to protuberant dermatofibrosarcoma. Back then, the immunohistochemical stainings were not yet available at our department.

Fetsch et al. (1996) published a study in which 22 cases of aggressive angiomyxoma were followed in a period from 8 to 198 months. In the period from ten months to seven years the tumor recurred in eight of the patients [23]. In the study of Granter et al. (1997), recurrent tumor occured after one to eight years in four of the eleven cases with clinical follow up [11]. Also, Fine et al. (2001) published a case of a 27-year old patient in which a recurrent tumor appeared twice, one and seven years after the initial excision [16].

The only reliable unfavorable prognostic risk factor regarding the tumor reccurence are positive surgical margins [3]. In our case, the tumor recurred more than ten times, probably because it was never removed with clear surgical margins. However, the size of the tumor is not correlated to the risk of tumor recurrence. Hence, multiple recurrences were observed even in tumors less than 3 cm in diameter, occuring in a period of many years [3].

The therapy of choice is wide excision with free margins. Unfortunately, due to erroneous preoperative clinical diagnosis, the primary surgical excision is often incomplete. In such cases, the patients are not sent to magnetic resonance of the pelvis; hence, the surgeon is not aware of the extent of the tumor spread in the pelvis and perineum [17].

Radiotherapy is not an option, because due to the low proliferative index, these tumors are usually resistant to radiotherapy [4].

In many studies, the aggressive angiomyxomas are described as hormone dependent tumors, which showed positivity for estrogen and/or progesterone receptors [1,10,15,24]. In the study of McCluggage et al. (2000), positivity for the estrogen receptor was found in all five cases of aggressive angiomyxoma, whereas four of the five cases also showed positivity for the progesterone receptor [6]. Htwe et al. in 1995, published a case of aggressive angiomyxoma that occurred and was

intensively growing during the pregnancy of the patient. This neoplasm was positive for the progesterone, but not for the estrogen receptor [15]. Ribaldone et al. (2004) published a case of aggressive angiomyxoma that also occurred during pregnancy [10]. In men, positivity for the androgen receptor has also been observed [6].

Considering their hormone dependence, therapeutic attempts were made using agonists of gonadotropin-releasing hormone, such as leuprolide acetate. For example, Fine et al. (2001) published a case of second recurrent tumor in a patient who had been subsequently treated for three months with leuprolide acetate, followed by complete regression of the tumor [16]. McCluggage et al. in 2006, published a case of a 35-year old patient with aggressive angiomyxoma which infiltrated deeply into the pelvis, and was not amenable to complete surgical excision. Postoperatively the patient received adjuvant therapy with an agonist of gonadotropin releasing hormone (zoladex). Eight months later, the tumor completely regressed [25].

Even though aggressive angiomyxoma is a rare tumor, its early recognition by the clinician and the pathologist is necessary. When aggressive angiomyxoma is suspected, the patient should undergo computerized tomography or magnetic resonance scan of the pelvis, in order to determine the depth of the tumor infiltration and to adequately plan the operation. Sometimes, rectal examination can be informative for deeply infiltrating tumors.

Considering the diagnostic difficulties in our case, we can conclude that careful evaluation of the patient by the clinician and the operative material by the pathologist is needed in order to obtain an accurate diagnosis of aggressive angiomyxoma. With appropriate therapy, consisting primarily of a wide surgical excision with clear margins, it is possible to some extent to influence the occurrence of recurrent tumors and to improve the quality of the life in these patients. In fact, the multiple recurrent tumors which occurred in our patient are probably due to incomplete excision. The possibility of adjuvant or neoadjuvant therapy with agonists of gonadotropin-releasing hormone should also be considered, especially in residual primary or recurrent tumors with proven positivity for the estrogen and progesterone receptors.

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