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Aggressive angiomyxoma of the vagina: a case report

Angiomixoma agressivo de vagina: um relato de caso

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ABSTRACT

Aggressive angiomyxoma (AAM) is a rare infiltrative tumor of mesenchymal origin that has high rates of local recurrence. We present the case of a 42-year-old patient with a lump in the vaginal canal, treated with excisional biopsy. Histopathologic evaluation revealed myxoid spindle-cell proliferation in the subepithelial region, and immunohistochemical analysis was positive for CDK4, CD34, desmin, estrogen and progesterone receptors. The markers S100 and smooth muscle actin were negative, what corroborated the diagnosis of AAM. Because of its high recurrence rates, we opted for outpatient follow-up during the two subsequent years.

Key words: neoplasms; immunohistochemistry; genitalia female; myxoma.

INTRODUCTION

Aggressive angiomyxoma (AAM) is a locally aggressive neoplasm of mesenchymal origin and myxoid appearance[1-3]. It was first described in 1983 by Steeper and Rosai, who reported nine cases in young female patients[4]. A few more than 130 cases of AAM have been described in the international literature[5].

The lesions originate from mesenchymal cells of pelvic or perineal soft tissues, present slow growth and are locally infiltrative[6]. They are termed aggressive due to their alarming recurrence rate and their invasive local growth[1, 2, 4], however the occurrence of metastasis is infrequent[7, 8].

AAM is a rare entity, frequently erroneously diagnosed, with 95% of the cases affecting women of childbearing age, especially between the third and fourth decade of life[1, 2, 6]. Its female-to-male ratio is 6-7:1[1, 9, 10].

The objective of this article is to report the case of a patient with AAM of the vagina, to analyze the histological and immunohistochemical findings, as well as to discuss the therapeutic possibilities.

CASE REPORT

A 42-year-old patient visited the gynecological clinic in May 2010 for a routine examination, complaining of menstrual migraine. She had a history of a cesarean section and denied comorbidities. Local examination revealed a lump in the left vaginal wall, apparently benign, and the decision was made to monitor it. Complementary exams were performed, such as Pap test, blood count, mammography, and breast and transvaginal ultrasonography, which did not reveal any pathologic findings. In July 2010, the patient returned for evaluation of the vaginal lesion, whose change in aspect justified a biopsy.

Although the biopsy was intended to be just incisional, it accidently turned out to be excisional, with the removal of a specimen of 0.7 × 0.6 × 0.4 cm, of whitish color and soft consistency.

Histopathological examination revealed locally infiltrative myxoid spindle-cell proliferation in the subepithelial region (**Figure 1**), with narrow surgical margin, and no muscular layer. Immunohistochemical analysis revealed the following results: CDK4 (polyclonal, Santa Cruz Biotechnology) positive +/3 diffuse, S100 (polyclonal, Dako) negative, CD34 (monoclonal, Dako) positive + to ++/3 diffuse, smooth muscle actin (monoclonal, Dako) 1 to 4 negative, desmin (monoclonal, Dako) positive ++ to +++/3 diffuse (**Figure 2**), estrogen receptor (monoclonal, Bio SB) 80%-90% moderate positive nuclear staining, progesterone receptor (monoclonal, Dako) 90% strong positive nuclear staining (**Figure 3**), and Ki67 (monoclonal, Dako) lower than 1%. Immunohistopathological findings confirmed the diagnosis of AAM.

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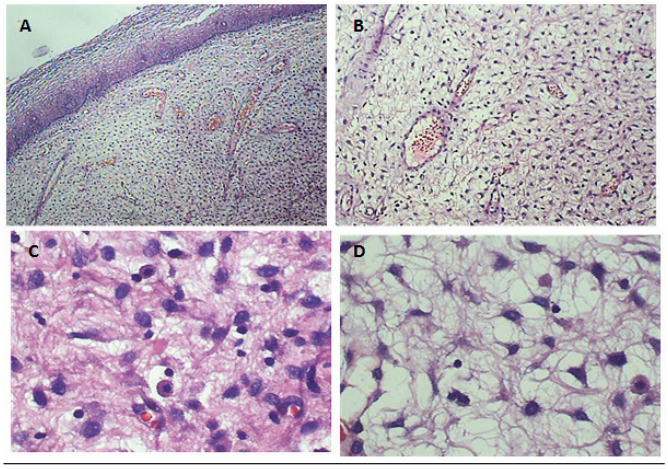

FIGURE 1 – *AAM in HE staining revealing a fragment of squamous mucosa with spindle-cell neoplastic proliferation in loose collagenous stroma with a myxoid matrix embedding irregular vessels and inflammatory cells. A) 40×; B) 100×; C) 400×; D) 400×*

AAM: aggressive angiomyxoma; HE: hematoxylin and eosin.

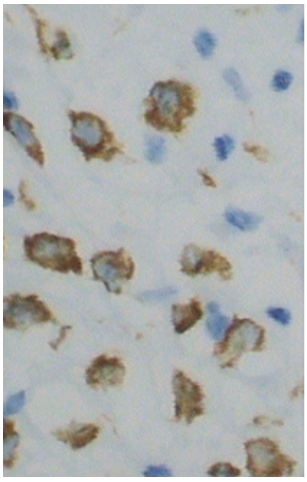

FIGURE 2 – *Desmin immunostaining (400×)*

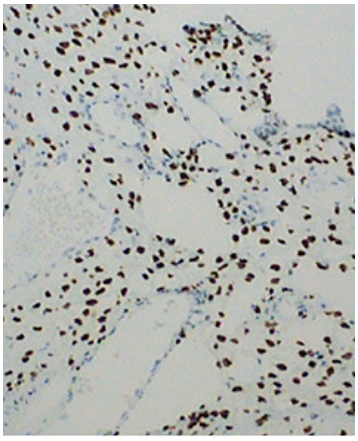

FIGURE 3 – *Strongly positive immunostaining for progesterone receptor (100×)*

The patient was advised to undergo pelvic magnetic resonance imaging (MRI) every six months, and to keep follow-up appointments to check the operation site every three months during two years. After that period, she did not present local recurrence.

DISCUSSION

AAM has a variable clinical presentation, still unclear pathogenesis, and symptoms that are generally associated with growth[4, 7]. Patients usually complain of a palpable mass, because most AAMs are larger than 10 cm[1]. In our case, as the tumor was discovered at an early stage during a routine gynecological visit, it did not present the customary dimensions found in the literature.

Pain is uncommon in AAM, but may arise in perineal lesions, due to trauma[7]. Another characteristic of this tumor is its slow and insidious growth: it may take the patient from two months to 17 years to notice a painless lesion and seek medical help[11].

Genetic aberrations involving principally the long arm of chromosome 12 have been described as the main responsible for the pathogenesis of mesenchymal tumors, including AAM[12]. This chromosomal region contains several genes, such as the high-mobility group AT-hook 2 (*HMGA2*), cyclin-dependent kinase 4 (*CDK4*), murine double minute 2 (*MDM2*), tetraspanin 31 (*SAS*), GLI family zinc finger 1 (*GLI1*) and DNA damage inducible transcript 3 (DDIT3), with the first two carrying broader implications in the occurrence of AAM. *HMGA2* encodes a deoxyribonucleic acid (DNA)-binding protein, belongs to the high-mobility group protein family, and is important for transcription regulation[12, 13]. *CDK4* is a cyclin-dependent kinase whose mutation is associated with the promotion of the cell cycle. Some authors have observed strong immunoreactivity for *CDK4* in AAM cases, suggesting that the encoding of this gene implies, directly or indirectly, the disease[12]. In spite of that, Bigby *et al*. (2011)[13], in an analysis of eight AAM cases, obtained five (62.5%) reagents for *CDK4*, of weak intensity, and stated that their significance and diagnostic value were uncertain. An angiomyofibroblastoma in that same work also obtained positivity for *CDK4*, confirming the authors' hypothesis as a finding that does not help in the diagnosis of AAM. In our case, weakly positive *CDK4* has no diagnostic or prognostic correlation with AAM, but, as shown in the literature[12, 13], this finding is not atypical.

The term "aggressive" was chosen to indicate its high risk of recurrence and local infiltration, with only two cases of metastasis reported in the literature, both in pulmonary tissues[11]. Differential

diagnosis needs to exclude diseases that also present perineal masses, such as lipoma, vulvar abscess, Bartholin's cyst, edema caused by chronic venous stasis, vaginal prolapse, anorectal tumors, Gartner's duct cyst, and lymphadenomegaly, among others[7, 14]. Diagnostic errors range from 70% to 100%, even with the use of imaging techniques. Thus, in most cases, diagnosis is reached by histological examination of the first surgical excision, or by biopsy[11, 14].

Grossly, up to one-fourth of AAMs present as pedunculated swellings in the vulvovaginal region[3]. However, they are also characterized as non-encapsulated masses in the pelvic cavity, with finger-like projections infiltrating the surrounding tissues[3, 6]. At the section, they present as a mass of gelatinous consistency and grayish color due to the abundant presence of collagen[2, 9].

It is important that histological differentiation be made between AAM and other perineal soft-tissue tumors, such as leiomyoma, myxolipoma, myxoid neurofibroma, angiomyofibroblastoma, myxoid leiomyoma, malignant fibrous histiocytoma, myxofibrosarcoma, leiomyosarcoma, lymphangioma, botryoid rhabdomyosarcoma, sclerosing hemangioma, and others[11]. Microscopically, the tissue from an AAM exhibits a large amount of thick-walled vessels immersed in a matrix of edematous appearance, which presents spindle-shaped or stellate neoplastic cells[10, 11]. Mitotic activity is low and there are no abnormally shaped nuclei[2, 6]. Immunohistochemistry demonstrates that almost all of these tumors express estrogen and progesterone receptors. Positivity for desmin, vimentin, and smooth muscle actin is also common[1, 10, 14]. Besides, they are negative for S100 protein and myosin[4, 5]. These characteristics allow AAM to be differentiated from the other aforementioned soft-tissue tumors[10, 11].

The presence of estrogen and progesterone receptors explains why this tumor grows rapidly in pregnant women[15]. Once in a while, a relapse can occur during pregnancy[11, 14], therefore careful follow-up is important for patients with a history of AAM resection.

Surgical excision is the treatment of choice, but controversy exists as to success against recurrence, described in up to 32%-71% of the cases, even in margin-free resections[1, 7, 8, 16]. Neoadjuvant or adjuvant therapy consisting of chemotherapy or radiotherapy appears not to be effective, as this type of tumor has low proliferative activity[1, 17, 18]. Embolization and chemoembolization are not effective treatments too, because most AAMs are nourished by a network of blood vessels. The employment of gonadotropin-releasing hormone (GnRH) agonists proved effective to decrease the size of AAMs, or even to extinguish them when surgery is not an option[16, 19]. However its long-term usage can cause side effects, such as bone loss and menopausal symptoms[11, 17]. Nowadays the ideal treatment duration is not known to achieve maximum effectiveness against the neoplasm.

Many doubts exist as to the best post-operative follow-up strategies for this rare disease[10]. As there are reports of relapse from 10 months to 14 years after the initial surgical treatment, a long-term follow-up of 1-2 yearly intervals is recommended[8, 9]. During that time, it is necessary to conduct careful clinical examinations, besides periodical MRI to detect possible recurrences[3, 5]. In case the tumor relapses, surgery, chemotherapy or hormone therapy may be used again[11, 14, 16]. And while the literature has not established which of these therapeutic modalities is more beneficial in recurrence, whether or not associated, there is a tendency to opt for surgical resection and/or GnRH agonists[11, 14].

RESUMO

O angiomixoma agressivo (AA) é uma neoplasia rara de origem mesenquimal, caráter infiltrativo e altas taxas de recidiva local. Apresentamos o caso de uma paciente de 42 anos com nódulo no canal vaginal, submetida à biópsia excisional. A avaliação histopatológica demonstrou proliferação fusocelular mixoide na região subepitelial, e a análise imuno-histoquímica revelou positividade para CDK4, CD34, desmina e receptores de estrogênio e progesterona. Os marcadores S100 e actina de músculo liso foram negativos, o que corroborou o diagnóstico de AA. Devido às altas taxas de recidiva, optou-se por acompanhamento ambulatorial pelos dois anos subsequentes.

Unitermos: *neoplasias; imuno-histoquímica; genitália feminina; mixoma.*

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