Vulvovaginal aggressive angiomyxoma mimicking lymphedema complicated with Behcet's disease: a case report and review of the literature

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Abstract This report describes a case of aggressive angiomyxoma (AAM), arising in the vulvovaginal region, which was initially misdiagnosed as lymphedema due to a vaginal ulcer caused by Behcet's disease. AAM is a very rare disease, usually found only in women of reproductive age, occurring predominantly in the pelviperineal region. AAM is basically a benign tumor usually treated by surgical resection. However, even after apparently complete resection, local recurrence of the tumor often occurs, thus its characterization as “aggressive” angiomyxoma. In contrast, vulvar edema is a condition with a very similar appearance that is observed relatively commonly, and which has many causes, e.g., obesity, inflammation, and benign or malignant tumors. Here we report a case of AAM which was initially mistaken for vulvovaginal edema, and initially believed to arise as a result of an ulcerative vaginal lesion associated with the patient's underlying Behcet's disease. We have reviewed the literature concerning vulvovaginal edema. We present herein this work to others as a precautionary tale, to prevent similar misdiagnosis and delay of treatment.

Keywords Aggressive angiomyxoma · Behcet's disease · Vulvovaginal edema

Introduction

Aggressive angiomyxoma (AAM) is a very rare disease usually found in women of reproductive age. It occurs predominantly in the pelviperineal region. AAM is basically a benign disease usually treated by surgical resection. Even after complete resection of the tumor, recurrence often occurs, hence its characterization as an “aggressive” angiomyxoma. The site of recurrence is mainly local, with distant metastasis uncommon. In contrast, the similar appearing condition vulvar edema is observed relatively commonly, and arises from many causes, e.g., obesity, inflammation, or benign and malignant tumors. Here we report a case of a vulvovaginal AAM which was initially mistaken as edema due to a Behcet's disease vaginal ulcer. We have also reviewed the literature on vulvovaginal edema and present this work to others to prevent similar misdiagnosis and delay of treatment.

Case

A 41-year old female with complete Behcet's disease presented to our clinic complaining of vulvular discomfort. She had a very soft and edematous mass in the right vulvovaginal region (Fig. 1). At the same time, an ulcer 2 cm in diameter was observed in the right vaginal surface in contact with the edematous mass. From the patient's information, this ulcer had appeared repeatedly for several years. Therefore, the edematous mass was initially diagnosed as lymphedema due to an ulcerative vaginal lesion of Behcet's disease. We performed an aspiration biopsy on the mass and found no malignancy. To treat the vaginal ulcer, a steroid unguentum was prescribed. One year later,

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Fig. 1 Macroscopic appearance of the enlarged right vulva

the tumor persisted in the same condition, although the ulcer had disappeared. Pelvic magnetic resonance imaging (MRI) showed a mass in the vulvovaginal region (Fig. 2). The tumor was 8 cm × 3.5 cm in diameter and was iso-intense with muscle on T1-weighted images. On T2-weighted images, the mass had a well-circumscribed high signal intensity interspersed with “swirled” or “layered” intensity of lower signal intensity. Aggressive angiomyxoma or angiomylblastoma was the most probable diagnosis at that time. We offered surgical resection and the patient agreed.

During the operation, from the lithotomy position, we made a vertical straight incision on the right vulva. The soft gelatinous tumor was easily separated from adjacent normal tissue (Fig. 3). After the entire surface of the tumor had been exposed, we found a vessel from the pelvic floor which fed the tumor (Fig. 4). We cut the vessel and completely removed the tumor, without further complication.

Fig. 2 Sagittal (a) and coronal (b) sections of MRI images of the AAM. Arrows show the “swirled or layered strand patterns” of the AAM

On gross inspection, the tumor was very soft and gelatinous; the weight was 100 g (Fig. 5). The cut-surface of the tumor was white and uniform. On histopathological examination, H&E staining revealed small, uniform, spindle to stellate cells, without atypia. Abundant myxoid stromas with areas of numerous vessels were also observed (Fig. 6a). On immunohistochemical analysis, the tumor cells were positive for both estrogen and progesterone receptors (Fig. 6b, c). The Ki-67 labeling index was <1 %, indicating this was a benign tumor (Fig. 6d). S-100 protein and α -smooth muscle actin (SMA) staining were both negative. Consequently, the tumor was diagnosed as AAM.

The patient had an uncomplicated postoperative course and was discharged 7 days after the surgery without any adjuvant therapy. There was no evidence of recurrence of the disease 2 years after surgery.

Discussion

AAM is rare benign mesenchymal tumor, first described in 1983 by Steeper and Rosai [1]. It occurs primarily in the female pelvic soft tissue, urinary bladder, vagina, vulva, and perineum. AAM is observed mainly in women of reproductive age, with a 6:1 ratio of cases in females and men. The size of these masses frequently exceeds 10 cm [2].

Although the pathogenesis of the AAM has not been elucidated completely, some researchers have reported possible routes to tumorigenesis. Nucci et al. [3] reported that rearrangements of the DNA architectural factor gene HMGIC on chromosome 12 may be an important event for tumorigenesis of AAM. They investigated tissue from a recurrent AAM and found a clonal translocation between chromosomes 8 and 12 [46,XX,t(8;12)(p12;q15)]. This translocation caused abnormal expression of HMGIC in the

Fig. 3 At surgery, the tumor was easily separated from adjacent normal tissue

Fig. 4 The tumor was fed by vessels arising from the pelvic floor

tumor. They concluded that inappropriate expression of this DNA-binding protein may be important in the pathobiology of AAM.

Although AAM is a benign tumor, recurrence often occurs. Smith [4] reported the incidence of recurrence to be approximately 70 %. The pattern of recurrence is mainly repeated local recurrence. The characteristic of this neoplasm is slow growth, as Smith et al. [4] experienced one case of recurrence 23 years after the original resection. However, some cases of mortality have also been reported. Blandamura et al. [5] reported a death due to pulmonary metastasis, and Smith [4] reported a death from a urinary bladder invasion. Clinical symptoms depend on the lesion

Fig. 5 The tumor was soft and gelatinous and its cut surface was white and uniform

where AAM grows. Patients are sometimes asymptomatic, even if they have a visible peripheral mass. Patients often report experiencing pelvic fullness and pressure, perineal swelling, vulvovaginal pain, dysmenorrhea, and dyspareunia. When AAM infiltrates the intestine or bladder, patients have bowel or bladder dysfunction. Because of its rarity, it is misdiagnosed in more than 80 % cases, and most are misdiagnosed as a bacterial abscess.

Behcet's disease causes chronic inflammation of blood vessels throughout the body. Although the exact cause of Behcet's disease is unknown, both genetic and environmental factors are thought to be responsible for the disease. Behcet's disease leads to numerous symptoms, e.g., oral and genital ulcers, dermal rashes and lesions, and ocular inflammation. Vaginal ulcer is the most often observed gynecological lesion in patients with Behcet's disease, and this ulceration can often cause vulvar lymphedema. Because our patient had Behcet's disease, we initially misdiagnosed her mass as this commonly associated lymphedema. Conversely, because of their similar clinical features, some researchers have misdiagnosed lymphedematous pseudotumors as AAM and have even reported them as thus [6, 7]. Therefore, it follows that the differential diagnosis of vulvovaginal enlargement is important. Diseases included in the category of similar diseases are AAM, myxoma, lymphedema, neurofibroma, angiomyofibroblastoma, myxoid liposarcoma, dermatofibrosarcoma protuberans, malignant fibrous histiocytoma, and malignant peripheral nerve sheath tumor, as summarized in Table 1.

Diagnostic imaging CT, particularly MRI, are useful tools for determining the extent of the tumor, better enabling us to plan our surgical approach. On CT imaging, AAM has low attenuation relative to muscle. When we used enhanced CT, it revealed a swirling pattern within the tumor. On MRI, the tumor was isointense relative to muscle on the T1-weighted image, and hyperintense on a T2-weighted image. Also, avid and heterogeneous enhancement was observed after

Fig. 6 H&E staining revealed spindle and stellate cells without atypia (a, $\times 400$). Immunohistochemistry was positive for both estrogen receptor (b, $\times 400$) and progesterone receptor (c, $\times 400$). The Ki-67 labeling index was $<1\%$ (d, $\times 200$)

administration of intravenous contraction, with a characteristic “swirling” or “layering internal” pattern [8]. It is thought that the hypodensity on CT and the hyperintensity on T2-weighted MRI are because of the high water content and loose myxoid matrix of the tumor; enhancement is believed to be because of its high vascularity. The “swirling” or “layering strand” pattern is a characteristic feature from imaging studies and is found in approximately 83 % of patients [8].

AAM has bland histological features on H&E staining: spindled and stellate cells without atypia, and abundant myxoid stroma with areas of numerous vessels. Immunohistochemistry staining for desmin, SMA, vimentin, CD34, S100 protein, and particularly for estrogen and progesterone receptors, is useful [9, 10]. In our case, the estrogen and progesterone receptor statuses were positive, and S100 protein was negative, indicative of the typical features of AAM.

Resection is regarded as the initial treatment of choice for AAM. The objective of resection is to remove the tumor completely to prevent recurrence, although it is very

difficult to achieve the necessary negative margins because of the infiltrative nature of AAM and the absence of a defined capsule. Chan et al. reported that patients who received radical surgery with clear resection margins have similar chances of remaining disease-free as those with tumor-involved resection margins. They concluded that incomplete or partial resection is acceptable, especially when high operative morbidity is expected and preservation of fertility is desired [11].

AAM occurs mainly in females of reproductive age who often desire preservation of their fertility. Incomplete surgery is acceptable when operative morbidity is expected with a radical approach and preservation of fertility is an issue [11]. Chemotherapy and radiation therapy are not preferable because of the low mitotic activity of the tumor [2], but use of radiotherapy for local control or alleviation of symptoms has been described [12]. Angiographic embolization was also attempted by Nyam et al. [13], who performed angiographic embolization 2 days before the

Table 1 Differential diagnosis of vulvar edematous diseases

Tumor type	Refs.	Clinical or imaging features	Pathologic features
Aggressive angiomyxoma	[8]	Usually larger than 10 cm, high recurrence. Swirled pattern (MRI)	Low mitotic activity. Positive IHC for ER and PR
Myxoma	[16]	High signal intensity, similar to that of fluid (MRI)	Circumscribed, typically hypocellular and hypovascular
Lymphedema	[7]	Related to obesity, trauma, infection, or associated inflammatory skin disease	Dilated and tortuous, lymphatic
Neurofibroma	[17]	Usually do not exceed 3 cm, vulvar neurofibroma can be seen in as many as 18 % of patients with von Recklinghausen's disease	Wavy spindle, wire-like, collagen bundles, Wagner–Meissner body
Angiomyofibroblastoma	[18, 19]	Usually <6 cm, has not been associated with increased body mass index or immobilization. Heterogeneous signal intensity observed on T2-weighted MRI and fast and persistent inhomogeneous enhancement on dynamic gadolinium-enhanced MRI	Circumscribed lesion with plump, plasmacytoid to spindled cell arranged predominantly around capillary-sized vessels
Myoid liposarcoma	[20]	Commonly occurs in lower extremities within the intramuscular fat planes in middle-aged people who present with a painless slow growing mass. Homogenous enhancement after administration of contrast material (MRI)	Plexiform vasculature, lipoblasts which are bland rounded to fusiform cells
Dermato fibrosarcoma protuberans (DFSP)	[21]	Fibrous tumor of intermediate grade malignancy, with a tendency to local recurrence; rarely metastasizes. Survival is 91–100 %, and local recurrence is 20–49 %	Composed of fascicles of fibroblast like cells arranged in a herringbone pattern and associated with a degree of nuclear pleomorphism and mitotic activity
Malignant fibrous histiocytoma (MFH)	[22]	Usually present as a large solitary mass, occurs mainly in elderly postmenopausal women	At least 50 % of tumor has highly vascularized myxoid stroma
Malignant peripheral nerve sheath tumor (MPNST)	[23]	Extremely rare, especially in the vulva	Resembles fibrosarcoma or MFH that arise from nerve or neurofibroma or that express S-100 protein or other neural markers

MRI magnetic resonance imaging, *IHC* immunohistochemistry, *ER* estrogen receptor, *PR* progesterone receptor

resection operation. During the operation they confirmed the discolored embolized area, which enabled them to visualize the border between normal tissue and tumor.

Because AAM has both estrogen and progesterone receptors, hormonal therapy, for example administration of a GnRh agonist or tamoxifen, has been conducted successfully [14, 15]. Also, for patients with a completed family, oophorectomy may be potential useful, although the efficacy of conducting a prophylactic oophorectomy is still under investigation. Adjuvant hormonal therapy including GnRh agonist and tamoxifen may be an option.

Conclusion

AAM is very rare disease and is often misdiagnosed as an infection or edema. When a vulvovaginal enlargement is found in patients still of reproductive age, the physician should consider the possibility of AAM. Complete surgical resection does not guarantee cure of the tumor. Because of its positive estrogen receptor and progesterone receptor

status, hormonal therapy may be a crucial treatment for control of the disease.

Conflict of interest There are no conflicts of interest to declare in relation to this article.

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