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Case Report

## Aggressive angiomyxoma of the vulva - a rare entity: case report and review of literature

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### ABSTRACT

Aggressive angiomyxoma (AA) is an extremely rare locally invasive mesenchymal tumor with a high risk of recurrence. Till date, only about 350 cases reported worldwide. Because of the rarity it should be considered as differential diagnosis whenever patient present with vulvovaginal growth. The diagnosis is clinched on histopathology. These are hormone-dependent and have estrogen and progesterone receptors. Hence sometimes GnRH agonists are used for ovarian estrogen secretion suppression but long-term use is not advocated due to side effects. A 45-year-old P4 L4 perimenopausal female presented to the GOPD with a 4×4×3 cms pedunculated painless globular mass on right labia majora. On palpation, the globular mass was firm, non-tender and with a smooth surface. Mass was excised and on gross histopathology, cut sections showed white myxoid areas. On microscopy epidermal lined tissue with stellate and spindle-shaped mesenchymal cells was found, embedded in a loose myxoid stroma with few collagen fibers. The cells were small and bland and lacked nuclear atypia. Small to medium-sized blood vessels were present with the thickened wall. Entrapped nerves and adipocytes were also present. No necrosis or mitosis was identified. All these features were suggestive of an aggressive angiomyxoma. Immunohistochemistry markers ER, PR, CD34, desmin, SMA were all positive. Imaging was done to rule out metastatic lesions and wide local excision was done around the stump with laparoscopic bilateral oophorectomy. Aggressive angiomyxoma is a rare disease. In women with asymptomatic growth in the vulvovaginal region, perineum or pelvis, aggressive angiomyxoma should be considered as a differential diagnosis. Ideal treatment is a wide local excision to prevent local recurrences, which are common and a hypoestrogenic milieu is created by either GnRH Agonists or by bilateral oophorectomy due to their hormone-sensitive nature.

**Keywords:** Angiomyxoma, Hormone dependent, Locally invasive, Recurrent

### INTRODUCTION

Aggressive angiomyxoma (AA) is a rare mesenchymal neoplasm that most commonly arises in the vulvovaginal region, perineum, and pelvis of women. (only about 350 cases described in the literature). AA occurs predominantly in women of reproductive age, with a peak incidence in the fourth decade of life and an age range of 11 to 77 years. It is termed as aggressive owing to the infiltrative nature of the tumor and its frequent association with local recurrence. Because of the rarity, it

is important to have knowledge of how to treat patients with this soft tissue mesenchymal neoplasm. This tumor usually presents as other non-specific entities such as lipomas or Bartholin gland cysts and are diagnosed histopathologically only after excision. It grows slowly as a painless solid mass with unclear borders and often infiltrates the deep tissues. It rarely produces clinically recognisable symptoms even if the tumor infiltrates the bladder, the rectum, the retroperitoneum, the pelvic bone or the levator ani muscle. Distant metastases are rare but have been reported in the mediastinum or lungs. Wide

local excision of the tumor is the primary management. Resected margins frequently come out positive for tumor because the AA tumor is poorly circumscribed and infiltrates adjacent soft tissues. With all such characteristics, AA is considered as an indolent neoplasm with locally aggressive nature.<sup>1-3</sup>

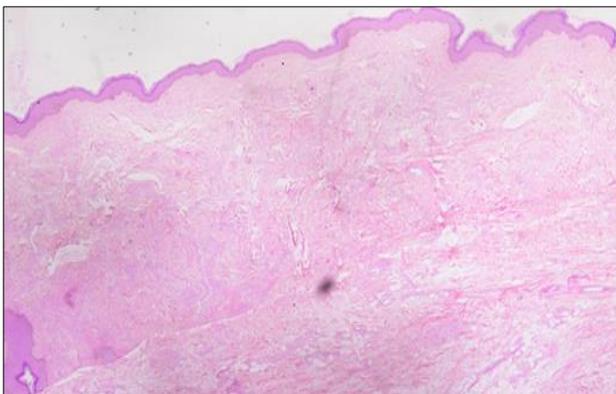
### CASE REPORT

A 45-year-old P4L4 perimenopausal woman came to the gynaecology outpatient clinic in AIIMS Rishikesh in September 2019 with complaints of an abnormal mass appearing in the perineum for last 1 year which was insidious in onset and gradually increasing in size. The mass was painless and non-tender. It was associated with difficulty in walking. She had no menstrual complaints. Bladder and bowel habits were normal (Figure 1).



**Figure 1: Gross appearance of the lump.**

On local examination, a 5×5×5 cms pedunculated globular mass was seen originating from the right labia majora lateral to introitus at 7 o'clock position. The lump was, smooth, well defined and no ulcer or dilated vein was present over the surface. On palpation, the globular mass was firm, non-tender with a smooth surface. Per speculum and per vaginum examination was unremarkable. With an informed consent lump was excised and sent for histopathological examination.

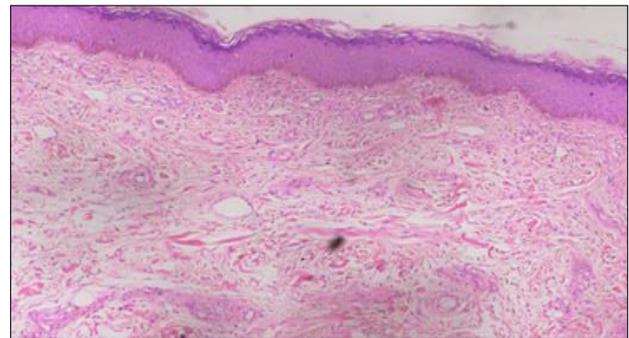


**Figure 2: Mesenchymal cells embedded in loose myxoid stroma (microscopic view).**

### Pathological examination

On microscopy epidermal lined tissue with stellate and spindle-shaped mesenchymal cells was found, embedded in a loose myxoid stroma with few collagen fibers (Figure 2). The cells were small and bland and lacked nuclear atypia.

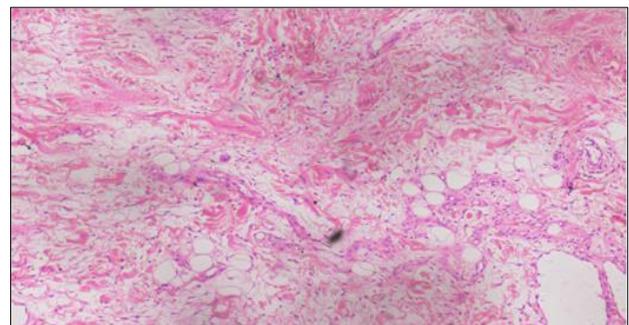
Small to medium-sized blood vessels were present with the thickened walls (Figure 3). Entrapped nerves and adipocytes were also present (Figure 4). No necrosis or mitosis was identified. All these features were suggestive of an aggressive angiomyxoma.



**Figure 3: Dilated blood vessels with thickened wall (microscopic view).**

### Immunohistochemical examination

Estrogen receptor ER, progesterone receptor PR, CD34, desmin, smooth muscle antigen SMA were all positive in the tumor cell. The histopathological features further confirmed by immunohistochemical markers were suggestive of aggressive angiomyxoma. Further Imaging was done to ascertain the depth of tumor invasion and to look for distant metastasis.



**Figure 4: Invasion into skeleton muscle and fat (microscopic view).**

CEMRI- whole abdomen with pelvis was done, which showed ill-defined area of altered signal intensity which was hyperintense on T2W/STIR lesion measuring 3.14×1.87×1.37 mm seen in the vulval region just posterior to perineal body.

The uterus was retroverted and measured 7×4 cm. Both ovaries were well visualized. There was no solid or cystic mass in the pelvis. These findings led to the impression of postoperative changes in the vulval region with no obvious residual disease.

In view of positive ER, PR status laparoscopic bilateral oophorectomy along with wide local excision around the stump was done as patient had completed her family and was perimenopausal.

## DISCUSSION

Aggressive angiomyxoma is a rare mesenchymal tumor. Due to its rarity, it is frequently misdiagnosed as condyloma acuminata, bartholin duct cysts, lipoma, vulvar abscess, gartner duct cyst, vaginal wall cyst, or sarcoma. It is difficult to estimate its exact incidence among other intraabdominal mesenchymal tumors as it is rarely encountered. Although it is almost exclusively seen among females in reproductive age but rare cases have been diagnosed in the perimenopausal female, children, and male patients.<sup>4-5</sup> It is a hormone-dependent tumor hence estrogen may stimulate its growth, which is supported by a case report showing its rapid growth during pregnancy.<sup>6</sup>

The median age of presentation is 33 years with a wide range from 1 to 82 years. It is more common among females as compared to male (6.6:1).<sup>4</sup> It is mostly located in the perineum and/or pelvic region.<sup>5</sup> However, cases of lung, liver, larynx, and orbital aggressive angiomyxoma also have been reported.<sup>7,8</sup>

The pathogenesis of AA is not well understood. Studies demonstrate a translocation at chromosome 12, with a consequent aberrant expression of the high-mobility group protein isoform I-C (HMGIC) protein involved in DNA transcription. Detection of this inappropriate expression may also be used as a marker for microscopic residual disease.<sup>9</sup>

Patients are often asymptomatic, with a visible perineal or vulvar mass that is discovered during initial pelvic examination. It can also present with dysuria, dysmenorrhea, constipation and chronic abdominal/pelvic pain due to pressure effect on adjacent organs. The true extent of AAM is often underestimated on initial pelvic examination because the visible portion of the tumor usually represents only a fraction of the more-extensive involvement of the deep soft tissues of the pelvis and retroperitoneum.<sup>10</sup>

On sonographic imaging, aggressive angiomyxomas typically appear as a hypoechoic or cystic mass. CT imaging typically demonstrates a mass with well-defined margins, slightly hypodense to muscle.<sup>11,12</sup> On MRI, these tumors are usually hyperintense on T2-weighted images, likely related to high water content and loose myxoid matrix. On T1-weighted images, the tumors are

isointense to muscle. Characteristically, the mass will have internal areas of “swirled” linear low-intensity signal on both T1-weighted and T2-weighted images, thought to be related to the fibrovascular stroma. The “swirled” appearance is less frequently appreciated on contrast-enhanced CT. Aggressive angiomyxomas demonstrate significant contrast enhancement, likely due to the high internal vascularity.<sup>13-15</sup>

On gross evaluation, the tumors are tan-gray to pink and have a rubbery consistency with a gelatinous and glistening cut surface. Histologic examination shows a sparsely cellular tumor composed of pale to eosinophilic stroma studded with numerous haphazardly arranged blood vessels that stand out against the myxoid background and range in size from thin-walled capillaries and venules to larger muscular arteries.<sup>16</sup>

There is no specific immunohistochemical marker for AAM. The tumor generally shows diffuse immunopositivity for vimentin and desmin. Smooth muscle actin highlights myoid bundles and may be positive in individual tumor cells. S100 reactivity is not a feature of AA but may be observed in entrapped nerves. The most characteristic feature is estrogen receptor and progesterone receptor positivity. One or both of these hormone receptors displays strong nuclear positivity in most of the tumor cells and thereby play a pivotal role in deciding the definite treatment of the tumor.<sup>17</sup>

The term “aggressive” denotes its propensity for local aggression and recurrence after excision but it is not always aggressive, and the recurrence rate is about 30%. The first line of therapy for AA is surgery, although achieving negative resection margins is difficult because of the infiltrative nature of the tumor and the absence of a defined capsule. Complete excision with negative margins may be achieved in cases of more-superficial tumors of the vulva or vagina but larger, deep-seated tumors of the pelvis may require more extensive surgery with partial or complete resection of some pelvic organs, conferring a higher risk of morbidity.

Chan YM et al, followed 73 patients with aggressive angiomyxoma, out of total 73 patients, 34 patients (47%) had recurrent disease. The data showed that there was no statistical difference in remaining disease-free between groups of patients with positive and negative resection margin results (40% and 50% in 10 years, respectively). Even though complete surgical resection is the desired goal, incomplete removal is acceptable when significant operative morbidity is anticipated or when fertility preservation is a concern.<sup>18</sup> Hence, long-term follow-up is recommended even after complete surgical excision. Nevertheless, prognosis is generally quite good. Steeper TA et al, and Skalova A et al, study reported a recurrence rate from 33% to 83%. Recurrence has been reported mostly within the first 3 years.<sup>19</sup>

In 1992, Simo et al, concluded, “a wide surgical excision based on a correct histopathological diagnosis is the basis of curative treatment”. The success of adjuvant therapy with a GnRH agonist following complete surgical excision of an aggressive angiomyxoma led to study use of leuprolide acetate as a primary method of treatment.<sup>20</sup>

Han-Geurts et al, reviewed 7 female patients treated over a period of 20 years, 3 out of which were pregnant at the time of diagnosis. All patients underwent primary surgical treatment. In five patients the surgical margins were involved. One patient received adjuvant radiotherapy treatment. Three patients experienced a total of four recurrences after 2-10 years. These patients were treated with selective embolization or surgery. With follow-up ranging from 2 to 20 years after last treatment, they found all patients to be disease free. In their opinion, there was no place for extensive, mutilating surgery as a first option.

If arterial embolization and/or hormonal treatment is ineffective with persisting complaints, resection can be offered, where narrow margins are accepted (R1 resection). Radical surgery does not seem to lead to a significantly lower recurrence rate of aggressive angiomyxoma when compared to incomplete resection. The role of radiotherapy remains unclear but can be considered in cases without response to embolization or hormonal treatment with persisting complaints and in whom major surgery is warranted to respect the tumour.

They concluded that Radical surgery does not seem to lead to a significant lower recurrence rate of aggressive angiomyxoma when compared to incomplete resection (R1), with or without radiotherapy or arterial embolization. This casts doubt on the necessity of extensive surgery, especially in cases where an extensive surgical procedure will lead to great morbidity.<sup>21</sup>

Srinivasan S et al, proposed that hormonal therapy (raloxifene, tamoxifen, GnRH agonist) can also be used to both shrink the tumor before excision and treat recurrences. Fine et al, achieved a complete resolution of recurrent cases who refused redo surgery using gonadotropin-releasing hormone agonist. However, long term use of these drugs is associated with side effects such as menopausal symptoms and bone loss. Moreover, the optimal duration of therapy is unknown.<sup>22,23</sup>

Rhomberg et al, and Suleiman et al, have achieved local control by radiotherapy in cases with local recurrence. But chemotherapy and radiation are generally considered to be poor treatment options due to the tumor's low mitotic activity. In addition, embolization is usually not used, as the tumors frequently have numerous feeding vessels.<sup>24,25</sup>

There are no specific guidelines for postoperative management of aggressive vulvar angiomyxoma. However, due to high recurrence rate and potential

morbidity associated with undiagnosed recurrences, several authors recommend a periodic evaluation with physical examination and MRI up to 15 years after excision.

## CONCLUSION

Aggressive angiomyxoma is a rare disease. In women with asymptomatic growth in the vulvovaginal region, perineum or pelvis, aggressive angiomyxoma should be considered as a differential diagnosis. Ideal treatment is a wide local excision to prevent local recurrences, which are common and a hypoestrogenic milieu is created by either GnRH Agonists or by bilateral oophorectomy due to their hormone-sensitive nature. Long-term follow-up is necessary because of repeated local recurrence.

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