Original Article

Deep Aggressive Angiomyxoma of Vulva: A Rare Entity

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Abstract

Background: Deep aggressive angiomyxoma (DAA) is a rare soft tissue neoplasm occurring mainly in young females. Due to its rarity and presentation mainly as a labial cyst, it is often misdiagnosed. It is a low-grade neoplasm with high local recurrence following incomplete excision because of its aggressive infiltrative nature. We report nine cases of vulval DAA, describing the clinical, radiological, histopathological, and immunohistochemical features to raise awareness of this rare entity so as to avoid its misdiagnosis.

Materials and Methods: A retrospective observational study was conducted from 2012 to 2023. Patient details were obtained from the hospital database. All the slides and blocks were reviewed.

Results: The mean age of presentation was 36 years. All the cases presented as a vulval mass ranging in size from 5 to 26 cm and showed a classic type of morphology. Myoid differentiation was identified in six out of nine cases. Estrogen receptors were positive in all cases, while the progesterone receptor was negative in one case. All the patients were alive on follow-up, with one case showing recurrence after 70 months.

Conclusion: DAA should always be kept in mind while dealing with vulval masses. MRI is an important tool for its preoperative diagnosis. Due to the tendency of DAAs for recurrence, complete surgical excision is the treatment of choice. Both estrogen and progesterone receptor status of excised specimens are required, as the administration of a gonadotropin-releasing hormone agonist is helpful. Moreover, further molecular studies on DAA should be conducted for a better understanding of this entity and to develop targeted therapy.

Keywords:

Angiomyxoma, MRI, Recurrence, Vulval mass

Introduction

Deep aggressive angiomyxoma (DAA) is a rare lower genital tract mesenchymal tumor of uncertain differentiation. It occurs mostly in the vulvovaginal region, perineum, and pelvis of reproductive-aged women. It was first described by Steeper and Rosai in 1983 as a locally infiltrative tumor that tends to recur, resulting in significant morbidity; hence the term aggressive [1]. It is a relatively rare tumor, with fewer than 350 cases reported to date [2]. Due to its rarity and presentation, it is often misdiagnosed as a Bartholin's gland cyst, vaginal cyst, abscess, leiomyoma, lipoma, or hernia [3]. Recognition of this entity is crucial because of its high recurrence rate (35–76%) [4][5] and rare incidences of metastasis [6][7].

We report our experience of seven primary and two recurrent cases of DAA, with emphasis on the clinical, radiological, histopathological, and immunohistochemical features to raise awareness of this rare entity and avoid misdiagnosis. Accurate and early diagnosis of DAA can prevent incomplete excision and recurrence, spare additional surgery, and offer hormonal therapy options. We also emphasized the diagnostic challenges associated with other mesenchymal genital tumors and discussed management strategies for these tumors.

Materials and Methods

A retrospective observational study was conducted in the Department of Oncopathology at The Gujarat Cancer and Research Institute from 2012 to 2023. Patient details (demographic data, previous history of any disease/treatment, and follow-up data) were obtained from the hospital database. All the slides and blocks were reviewed. The histopathological and immunohistochemical features were also analyzed.

Results

Only nine cases of DAA were retrieved after reviewing the hospital database over the past eleven years. The mean age at presentation was 36 years. Two cases presented as recurrent masses following 14 months and 22 months after previous surgeries performed at outside hospitals.

All cases presented as vulval masses ranging in size from 5 to 26 cm and were detected by MRI and/or CT scan. Grossly, the tumors were unencapsulated solid masses with a tan-pink to tan-grey gelatinous appearance (Figure 1). Microscopically, the tumors showed paucicellular areas composed of bland-looking oval to spindle cells arranged haphazardly in a myxedematous and collagenous stroma. Many prominent vessels were also noted. Myoid differentiation, typically arranged around vascular components, was identified in six out of the nine cases (Figure 2).

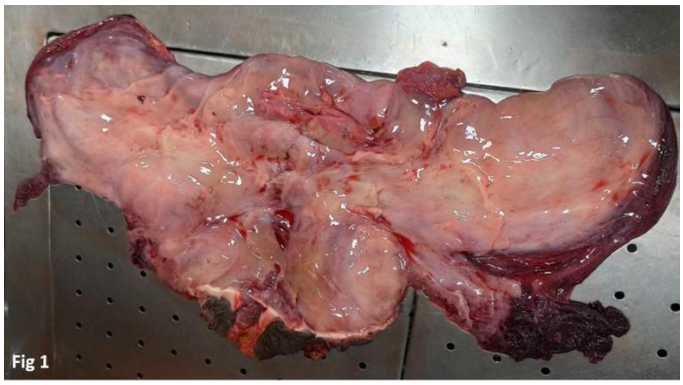

Figure 1: Cut surface is tan pink with gelatinous appearance

Immunohistochemically, estrogen receptors (ER) were positive in all cases, while the progesterone receptor (PR) was negative in one case. At least one of the smooth muscle markers—smooth muscle actin (SMA), desmin, or calponin—was positive in all cases (Figure 3).

The surgical resection margins were free of tumors in eight out of nine cases. However, neither revision surgery nor adjuvant therapy was administered to the patient with a positive margin, as she was lost to follow-up one month post-surgery and returned only with recurrence after 70 months.

All patients were alive on follow-up (mean: 46 months). The clinicopathological features are summarized in Table 1.

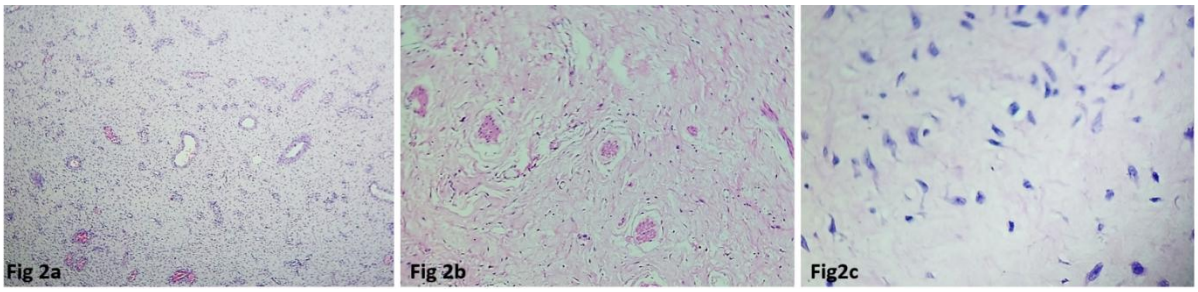

Figure 2: (2a) Small tumor cells embedded in myxoid to loose collagenous stroma, with varying-sized blood vessels [H&E 40X] (2b). Loosely organized collections of eosinophilic myoid cells [H&E 100X] (2c). Small oval to spindle-shaped cells with relatively bland nuclei [H&E 400X].

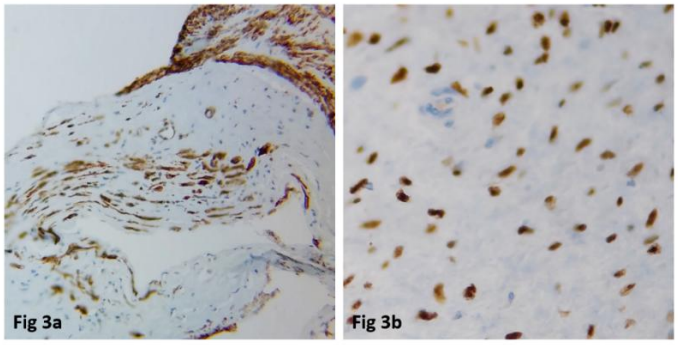

Figure 3: (3a) Smooth muscle actin is expressed by the perivascular myoid cells and the smooth muscle cells of the vessel wall [IHC 100X]. (3b) Strong and diffuse nuclear positivity for ER [IHC 400X].

Discussion

DAAs typically occur in the pelvis and perineum of reproductive-aged women. Occasionally, men can also present with DAAs, which exclusively occur in the genital area (scrotum, spermatic cord, inguinal region, perianal region, and pelvic soft tissue) [8,9]. The female-to-male ratio is 6.6:1. It is considered a soft tissue tumor of uncertain differentiation [10]. It has a high recurrence rate (35–76%) following incomplete excision. Most patients present with a slow-growing, deep-seated, painless mass. Due to its clinical presentation as a vulval or vaginal soft tissue mass, it is often misdiagnosed as a Bartholin's gland cyst, vaginal cyst, abscess, leiomyoma, lipoma, or hernia.

Ultrasound can be a valuable imaging method for the preoperative diagnosis, evaluation of the scope, and follow-up of DAAs. However, MRI is the preferred method for delineating the exact extent of the tumor [11]. MRI features of DAA include iso- or hypo-intensity on T1-weighted images, hyperintensity, and characteristic swirling/laminated layering on T2-weighted images (due to the myxoid matrix), and intense progressive enhancement on post-contrast T1-weighted images reflecting inherent vascularity [12].

Table 1: showing the clinic-pathological features of the cases

	Age (years)	H/O recurrence	Imaging	Size (cm)	Morphology	IHC (positive markers)	Follow up (duration in months)
Case 1	23	Absent	CT	26x11x11	Classical + myoid differentiation	ER, PR, SMA	Alive (65)
Case 2	36	Present	MRI	5x2.6x2.3	Classical + myoid differentiation	ER, PR, SMA	Alive (12)
Case 3	37	Absent	MRI	11x10x9.8	Classical + myoid differentiation	ER, PR, SMA	Alive (26)
Case 4	38	Present	MRI	6.1X4X3.5	Classical	ER, PR, Desmin	Alive (66)
Case 5	30	Absent	MRI	7.5X4.3X4	Classical	ER, PR, SMA	Recurred but alive (**)
Case 6	53	Absent	CT	5.3x4.6x4.3	Classical + myoid differentiation	ER, Calponin	Alive (32)
Case 7	36	Absent	MRI	17x10x6	Classical + myoid differentiation	ER, PR, Calponin	Alive (120)
Case 8	38	Absent	MRI	7x5x4	Classical	ER, PR SMA	Alive (60)
Case 9	38	Absent	MRI	17x10x6	Classical + myoid differentiation	ER, PR, Calponin	Alive (32)
****Case 5 was lost to follow up after 1 month post surgery and came back after 70 months with recurrence.**							

In our study, the mean age of presentation was 36 years. Tumor size varied from 5 to 26 cm, as in most other studies [13]. Grossly, most cases presented as a poorly circumscribed, lobulated mass with irregular extension into surrounding tissues and a glistening or myxedematous, pink or reddish-tan-colored cut surface.

All our nine cases showed the classical histomorphology of low to moderate cellularity, uniform and relatively small stellate-shaped and spindled cells set in a loosely collagenous, myxedematous matrix. The tumor cells have scant eosinophilic cytoplasm with ill-defined borders and bland nuclei with small central nucleoli. Scattered vessels of varying caliber are also noted. Mitotic figures were infrequent. A loosely arranged collection of myoid cells situated around the vessels, a characteristic finding, was noted in six of the cases. Magro G et al. also noticed myoid cells in a few cases of their study [14].

Besides the classical histomorphology seen in our cases, uncommon features such as hypercellularity, a neurofibroma-like appearance, perivascular hyalinization, and prominent fibrosclerotic stroma can be encountered [13]. None of these features were observed in our cases. Hypercellularity is often regarded as an atypical finding in recurrent tumors [4,9]. However, the two recurrent cases also displayed the same histopathological features as the primary ones.

Jingping and Chunfu illustrated the immunohistochemistry results of 71 patients, in which vimentin, SMA, and CD34 were positive. The positive rate of PR was 70%, and that of ER was 65%; S-100 and CD68 were negative [15]. All our nine cases were positive for ER, while PR was negative in one case. At least one of the smooth muscle markers (SMA, desmin, or calponin) was positive in all cases. Recently, HMGA2 has been used as a nuclear marker for DAAs [16]. It is not a specific marker of DAAs, as it can be found in other genital mesenchymal lesions such as leiomyomatous neoplasms, but it could help in assessing the margins and detecting small foci of residual or recurrent tumors in re-excision specimens [17].

Diagnosing genital mesenchymal tumors is usually challenging given their rarity and many similar clinicopathological features. The differential diagnosis includes superficial angiomyxoma, angiomyofibroblastoma (AMFB), cellular angiofibroma, myxoid

and edematous smooth muscle tumors, pelvic fibromatosis, and low-grade myxofibrosarcoma.

Superficial angiomyxoma occurs in superficial cutaneous and subcutaneous locations and shows a lobulated growth pattern with well-defined borders. It contains more delicate thin-walled vessels and is negative for desmin, in contrast to DAAs. Simple excision is the treatment of choice [12].

AMFB is also a benign mesenchymal tumor of the distal female genital tract that occurs in reproductive-aged women. In contrast to DAAs, it is a nonrecurring, well-circumscribed, typically subcutaneous mass. Alternating hypocellular and hypercellular areas are noted, with more numerous blood vessels, mostly capillary-sized, as opposed to the uniformly hypocellular areas and large thick-walled vessels of DAAs. The epithelioid lesional cells of AMFB tend to cluster around vessels, which is another characteristic finding. AMFB shows indolent behavior and rarely recurs after complete surgical excision. Positive margins do not necessitate re-excision [18].

Cellular angiofibroma presents as a relatively small, superficial, and well-circumscribed mass with high vascularity and a moderately cellular spindle cell population. It often shows perivascular hyalinization, may occasionally have more pronounced mitotic activity, and is much less likely to express desmin. Considering that, even with positive surgical margins, no reported recurrences or metastasis occur, and given the relatively high risk of surgery-associated complications from reoperation, these tumors are treated by simple residue-free excision if possible [19].

Myxoid and edematous smooth muscle tumors usually show larger tumor cells with spindled morphology, abundant eosinophilic cytoplasm, and sometimes juxtanuclear vacuoles. Our cases lacked these features. Treatment for benign tumors is simple excision, for smooth muscle tumors of uncertain malignant potential is complete excision with negative margins, and for malignant tumors, wide local excision is required. (Neo)adjuvant chemotherapy or radiation is used as per clinical indication.

Pelvic fibromatosis is poorly circumscribed, with firm masses often intimately associated with fascia and muscle. They are moderately cellular, infiltrative spindle cell lesions with only mild nuclear atypia and loose fascicular and broad storiform growth patterns. Evenly spaced thin-walled vessels are noted. Like DAAs, they also show positivity for smooth muscle markers, but the vast majority of them show at least focal nuclear staining for beta-catenin. The mainstay of treatment is surgical resection, which can result in significant morbidity. An increasing tendency to follow with observation only has also been noted. Radiotherapy or systemic therapy (tamoxifen) is sometimes used.

Myxofibrosarcomas predominantly occur in older adults and have more pronounced cytologic atypia and mitotic activity, even in lower-grade tumors. The presence of prominent elongated, curvilinear, thin-walled vessels with a perivascular condensation of tumor cells and/or inflammatory cells is a characteristic feature of myxofibrosarcomas. It frequently shows pseudolipoblasts. DAAs lack all these features. Repeated local recurrences unrelated to histological grade and metastasis closely related to histological grade occur in myxofibrosarcoma [20]. Aggressive surgery combined with radiotherapy is advised to achieve improved local control.

Preoperative diagnosis of DAA is beneficial for optimizing surgical management. However, biopsy results usually lead to a differential instead of a definitive diagnosis given limited tissue, tumor heterogeneity, lack of sensitive diagnostic features, and infiltration [12]. Even frozen sections pose a lot of diagnostic difficulty, and the final diagnosis is deferred to permanent sections.

Most reports conclude that surgical excision is the treatment of choice [21]. Because of its high rate of recurrence and unique potential for local invasion, infiltrating the paravaginal and pararectal tissue, and rare incidence of metastasis, wide local excision

with negative margins of at least 1 cm is necessary for its treatment. Surgical margins were free of tumor in all our cases except one, which later recurred. Administration of gonadotropin-releasing hormone agonists, aromatase inhibitors, and ER and PR blocker therapy can be considered since these tumors are immunopositive for ER and PR. Some studies have shown that with the use of radiation therapy on recurrent patients, recurrence was not observed for two to three years [22]. A multimodality treatment, including excision of the tumor without mutilation, adjuvant therapy like arterial embolization or hormonal therapy, and radiotherapy in symptomatic patients resistant to embolization/hormonal therapy, is suggested by Han-Guerts et al. [23].

DAA metastasizes extremely rarely to the lung, peritoneum, and lymph nodes [6,7]. Though there are no definite recommendations for post-surgery management of DAA, due to the high rate of local recurrences and possible metastasis, patients should be advised to undergo long-term follow-up until 15 years after the primary excision [24].

HMGA2-YAP fusion was noted in a woman diagnosed with DAA who was responsive to ER antagonism. This fusion creates an imputed t(11;12)(q22.1;q14.3) translocation involving exons 1-3 of HMGA2 on chromosome 12 to exons 2-7 of YAP1 on chromosome 11. This will allow the development of new targeted therapies [25].

Conclusion

DAA is a rare, locally infiltrative, and non-metastasizing mesenchymal tumor primarily occurring in the pelvic-perineal regions of reproductive-aged women. We reported nine cases of DAA and described their clinico-pathological features, which can help in the effective workup, diagnosis, and management of these tumors by gynecologists. MRI is an important tool for achieving a correct diagnosis in both primary and recurrent cases. DAA cases with positive margins or recurrence may respond to adjuvant hormonal treatments, although evidence is still lacking due to the rarity of the condition. A multicenter retrospective analysis of DAA should be promoted to conduct more molecular studies on these tumors to better understand their clinical characteristics and molecular features.

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