Gynecologic Oncology Reports 55 (2024) 101464

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case series

Vulvo-vaginal stromal tumours – Case series of a rare entity from an oncology centre in India

Biswajit Dash [a,*], Sushmita Rath [b], Bharat Rekhi [c,**], Neha Mittal [c], Rohini Kulkarni [a], T.S. Shylasree [d,a], Amita Maheshwari [a]

[a] Department of Surgical Oncology, Gynecologic Oncology Division, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, India
[b] Department of Medical Oncology, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, India
[c] Department of Pathology, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, India
[d] Department of Gynaecological Oncology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB252ZN, UK

ARTICLE INFO

Keywords:
Vulvo-vaginal
Stromal
Tumours
Angiomyxoma
Myofibroblastoma
Angiomyofibroblastoma

ABSTRACT

Vulvo-vaginal stromal tumours are a rare and diverse group of mesenchymal neoplasms unique to hormone-responsive stroma of the vulva and vagina. These tumours are mostly benign, except for the locally aggressive deep angiomyxomas. Often these tumours pose diagnostic challenges, resembling certain malignant vulvo vaginal tumours.

This case series highlights clinicopathological features of four angiomyxomas; a single angiomyofibroblastoma, and another superficial myofibroblastoma, including their clinical outcomes. All patients were in their 4th or 5th decade of life. Only 1/4 angiomyxomas was correctly diagnosed at the referring hospitals. Three out of four patients harbouring angiomyxomas achieved clinical remission post-surgery, while one patient was lost to follow-up. By immunohistochemistry, tumor cells showed variable positivity for desmin, SMA, ER, and PR, and negativity for S100P and CD34. The angiomyofibroblastoma was initially misdiagnosed as a liposarcoma, and the patient was lost to follow-up after diagnosis. Immunohistochemically, the tumor cells were diffusely positive for SMA and ER; weakly and focally positive for desmin, and negative for AE1/AE3, CD34, and S100P. The patient with superficial myofibroblastoma is in clinical remission post-excision with an 18-month follow-up. Immunohistochemically, the tumor cells showed CD34 positivity. Therapeutically, none of the patient received adjuvant treatment, except for a single patient with angiomyxoma, who underwent chemoradiation for a synchronous cancer cervix post-surgery.

This case series provides valuable insights into the clinical heterogeneity, diagnostic intricacies, and outcomes of vulvo-vaginal stromal tumours from an oncology centre in India, further contributing to a better understanding of these rare tumours.

1. Introduction

Vulvo-vaginal stromal tumours are a rare group of soft tissue tumours that occur commonly in the hormone-responsive stroma of the vulva and vagina. The various subtypes of the vulvo-vaginal stromal tumours include fibro-epithelial polyp, myofibroblastoma (superficial/mammary-type), cellular angiofibroma, angiomyofibroblastoma, angiomyxoma (superficial/deep-aggressive), prepubertal vulval fibroma, and lipoblastoma-like tumours of the vulva (Fisher, 2013; Schoolmeester and Fritchie, 2015). These tumours are thought to originate from a distinct zone of the sub-epithelial stromal cells or sub-epithelial mesenchyme of the lower female genital tract. The rarity; overlap in morphology and immunohistochemistry of these tumours poses diagnostic and management challenges (Schoolmeester and Fritchie, 2015; Angelico et al., 2022). Given most of these are benign; it is essential to differentiate such tumours from other benign tumours and sarcomas of the vulva and vagina. A subset of these tumours are histogenetically related and share chromosomal aberrations (Tajiri et al., 2021). Around 8 cases of superficial myofibroblastoma of the vulva are reported in published literature (Fucà et al., 2019).We hereby present a

* Corresponding author at: Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Dr E. Borges Road, Parel, Mumbai 400012, India.
** Corresponding author at: Department of Pathology, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, India.
E-mail addresses: drbiswajitdash123@gmail.com (B. Dash), rekhi.bharat@gmail.com (B. Rekhi).

https://doi.org/10.1016/j.gore.2024.101464
Received 22 April 2024; Received in revised form 17 June 2024; Accepted 14 July 2024
Available online 28 July 2024

case series consisting of 4 angiomyxomas; angiomyofibroblastoma and a superficial myofibroblastoma; of the vulva and vagina from a tertiary cancer centre over 9 years duration (Jan 2015- Dec 2023).Appropriate written informed consents were obtained where body parts were photographed.

2. Case presentation

2.1. Case 1

A 45-year-old lady presented at a local hospital with perineal pain and vulval swelling. Biopsy confirmed a diagnosis of vulval angiomyxoma for which she was prescribed leuprolide. Earlier, she underwent a total abdominal hysterectomy and left-sided adnexectomy for uterine fibroids and a benign adnexal lesion. Three and a half years later, she presented with a mass and continued perineal discomfort at our institute. After a pelvic magnetic resonance imaging (MRI) evaluation (see Table 1) and a histopathological diagnosis of an angiomyxoma, she was planned for surgical excision. Intraoperatively, a lipomatous tumour was observed towards the left side of the perineum. The tumour stalk extended upward in close approximation with the external anal sphincter and rectum. She underwent complete excision of the tumour via an abdominoperineal approach.

Histopathological examination showed features of an aggressive angiomyxoma. (Fig. 1). The skin and soft tissue margins were free of tumor; however, the base was involved by the tumor. She was kept on a close follow-up. Two years later, she developed a parathyroid adenoma, which was excised. She is in clinical remission 66 months, till date.

2.2. Case 2

A 36-year-old lady presented with a gradually progressive lump in her perineal region over two- and half-year duration. After MRI pelvis evaluation (see Table 1) she underwent a wide local excision of the left paravaginal mass in January 2019.Histopathological examination revealed a benign spindle cell lesion of myofibroblastic origin with alternate myxoid hypocellular areas and areas with collagen condensation and free surgical margins. A diagnosis of an angiomyxoma was made. The patient was kept on observation and is in remission for the last 58 months.

2.3. Case 3

A 33-year-old lady presented with heaviness in her lower abdomen and perineal discomfort of 5 years duration. A radiological impression of lipoma vs. an inflammatory myofibroblastic tumour vs. a soft tissue sarcoma, including a leiomyosarcoma was considered on pelvic MRI (Table 1). The histopathological examination of the resected specimen confirmed a diagnosis of an aggressive angiomyxoma with free surgical margins (Fig. 2). Post-surgery, the patient is free of disease 87 months.

2.4. Case 4

A 39-year-old lady, para 4, presented in October 2021 with menorrhagia of one-year duration and progressively increasing vulvar swelling for 5 months. On evaluation, she had FIGO Stage III B squamous carcinoma of cervix along with a 2 cm x 2 cm pedunculated left labia majus growth. After pelvic MRI evaluation (Table 1), she underwent wide local excision of the vulvar lesion with adequate margins and further planned for concurrent chemoradiotherapy for cervical cancer. Histopathological examination confirmed a diagnosis of an angiomyxoma. Unfortunately, she was lost to follow-up after 3 months post-radiation treatment.

2.5. Case 5

A 45-year-old premenopausal lady with human immunodeficiency (HIV) seropositivity presented with vaginal swelling for the last 3 months. She underwent a pelvic MRI examination (see Table 1) followed by a biopsy of the lesion at a local hospital, which demonstrated myxoid liposarcoma. Two weeks later, she presented with a 3.5 cm x 2 cm sized left-sided vulval swelling, involving the inner aspect of the labia minora, sparing the urethra and clitoris, with surrounding skin induration. A histopathological review confirmed a diagnosis of an angiomyofibroblastoma. She was initiated on antiretroviral therapy, but was lost to follow-up before a final management plan was established.

2.6. Case 6

A 49-year-old postmenopausal woman presented in March 2022 with a gradually increasing vulval swelling of 12 months duration. Fine needle aspiration cytology (FNAC) examination at a local hospital suggested chronic inflammation. Clinically, there was a 3 cm x 3 cm sized lesion over the clitoris and mons pubis, 1.5 cm away from the external urethra meatus (Fig. 3A). After a pelvic MRI evaluation (Table 1 and Fig. 3B), she underwent wide local excision of the vulvar lesion with primary closure (Fig. 3C,3D,3E). Histopathological examination revealed features of a superficial myofibroblastoma (Fig. 3F,3G). The tumour involved the dermis, but the overlying epidermis was free of tumour. She was kept on observation under regular follow-up and clinically disease-free for 18 months.

The detailed clinicopathological and radiological features of all cases are summarized in Table 1.

3. Discussion

Vulvovaginal stromal tumours constitute a rare and heterogeneous group of generally benign, or locally aggressive tumours, originating from the genital stromal mesenchymal cells (Fisher, 2013; Schoolmeester and Fritchie, 2015). Morphologically and immunohistochemically; these tumours exhibit overlapping features. Only one of out of four angiomyxomas was correctly diagnosed at the referring hospital in the present study. Histopathologically, angiomyxomas comprise spindle cells, stellate cells with relatively hypocellular myxoid areas, collagenous areas, along with interspersed blood vessels, as seen in all four angiomyxomas of the present series. A superficial myofibroblastoma exhibits relatively bland spindle cells in a collagenous stroma as noted in the third case. Angiomyofibroblastoma is composed of polygonal cells with myoid appearance in a myxoid matrix, as noted in case 5. This leads to consideration of certain differential diagnoses, especially in angiomyofibroblastoma that was initially considered as “malignant” at our institute and finally diagnosed with a critical review of microscopic features and the support of immunohistochemical stains. Immunohistochemically, these tumours display variable expression of desmin, SMA, and CD34, coupled with diffuse nuclear immunoreactivity for ER and PR, the latter 2 in most tumours, as noted in all four tumours in the present series, where these immunostains were tested (Angelico et al., 2022).

Angiomyxoma, a locally aggressive mesenchymal tumor arising from the perineum or lower pelvis, often presents as a polypoidal mass with a gelatinous appearance on the cut section. Immunohistochemically, the tumour cells display strong ER and PR positivity. Emerging data suggest potential therapeutic roles for tamoxifen, Gonadotrophin releasing hormone (GnRH) agonists, and aromatase inhibitors, although further research through clinical trials is warranted (Choi et al., 2015). Although female sex hormone dependence is postulated, rarely this tumor has been reported in prepubertal children and postmenopausal women. A complete surgical resection is desired. Notably, deep angiomyxoma is locally aggressive with a high likelihood of local recurrence (Fucà et al., 2019). However; whether a surgical margin positivity leads

Table 1
Summary of clinic-pathological features and outcomes of 6 female genital stromal tumours.

Feature	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age(years)at diagnosis	45	36	33	39	45	49
Site of presentation	Perineum	Vulva	Perineum	Vulva	Vulva	Vulva
Pathological tumour size (cm)	7.4 x 4.5	9 x 6	10.3 x 7.2	2 x 2	3.5 x 2	3 x 3
Diagnosis at local hospital	Aggressive Angiomyxoma* (diagnosed 3.5 years ago)	Fibro collagenous tissue ? neoplastic	Imaging: Lipoma. Well differentiated leiomyosarcoma	Not applicable	Myxoid liposarcoma	Chronic inflammation
Review diagnosis at our Institute	Aggressive Angiomyxoma	Angiomyxoma	Initially, leiomyomatous tumor and inflammatory myofibrobalstic tumor. Finally,Aggressive Angiomyxoma	Angiomyxoma	Initially, malignant tumor. Finally, Angiomyofibroblastoma	Superficial myofibroblastoma
IHC features	Desmin+/ SMA +/H caldesmon +, vimentin + ER (80 %) +/PR+ (30 %)	Desmin+/SMA/ER+/PR + S100P-, CD 34 −	SMA+, Desmin+, ER+, PR+	Not available	SMA+, ER+ AE1/AE3-, CD34-, S100-	CD 34+, Desmin-, S100P-, STAT 6 −, ALK 1 −
Radiological features (MRI Pelvis)	A 7.4 cm x 4.5 cm irregular soft tissue mass in the left perineal region extending along the anal canal and lower rectum, indenting the wall with unclear fat planes. It appeared iso to hypointense on T1-weighted images and hyperintense on T2-weighted and STIR sequences. Post-contrast scans showed homogeneous enhancement.	A 9 cm x 6 cm peripherally enhancing thick-walled cystic lesion observed on the left labia majora. On T1-weighted images, it tends to be iso to low signal, while on T2-weighted images, it predominantly showed high signal.	A well-encapsulated lesion measuring 10.3 cm x 7.2 cm in the lower abdomen, T2-hyperintense with multiple fibrotic strands, extending into the right ischiorectal fossa. It displaces the uterus and upper 2/3rd of the vagina towards the left.	Subtle asymmetric T2 intermediate signal intensity with wall thickening noted on the left labium majus, without any involvement of underlying fat or suspicious inguinal lymph nodes. Additionally, a 6 cm x 5 cm-sized cervical lesion with parametrial extension and suspicious pelvic lymphadenopathy.	A 3.5 cm x 2 cm-sized vulvar lesion is noted, exhibiting heterogenous mixed to high signal intensity on T2-weighted imaging.	Heterogeneous altered signal density lesion with T1 hyperintense areas exhibiting signal drops on fat-saturated images, suggesting the presence of a macroscopic fat component (Fig. 3B).
Treatment received	Wide local excision	Wide local excision	Excision.	Wide local excision	Lost to follow up** (Enucleation at local centre)	Wide local excision
Margins in HPR	Base positive	Negative	Negative	Negative	NA	Negative
Adjuvant Treatment	None	None	None	None	Unknown	None
Follow up period	66 months	58 months	87 months	3 months	1 month	18 months
Recurrence	Nil	Nil	Nil	Unknown	Unknown	Nil
Status at last follow up	Alive with clinical remission	Alive with clinical remission	Alive with clinical remission	Lost to follow up	Lost to follow up	Alive with clinical remission

Abbreviations: "+" Implies positive staining result, "- "implies negative staining result.
NA – not applicable HPR – Histopathology report, IHC – immunohistochemistry.
MRI – Magnetic resonance imaging.
* Presented with recurrent tumour at our centre.
** Lost to follow up for definitive treatment (Underwent cyst enucleation at local place).

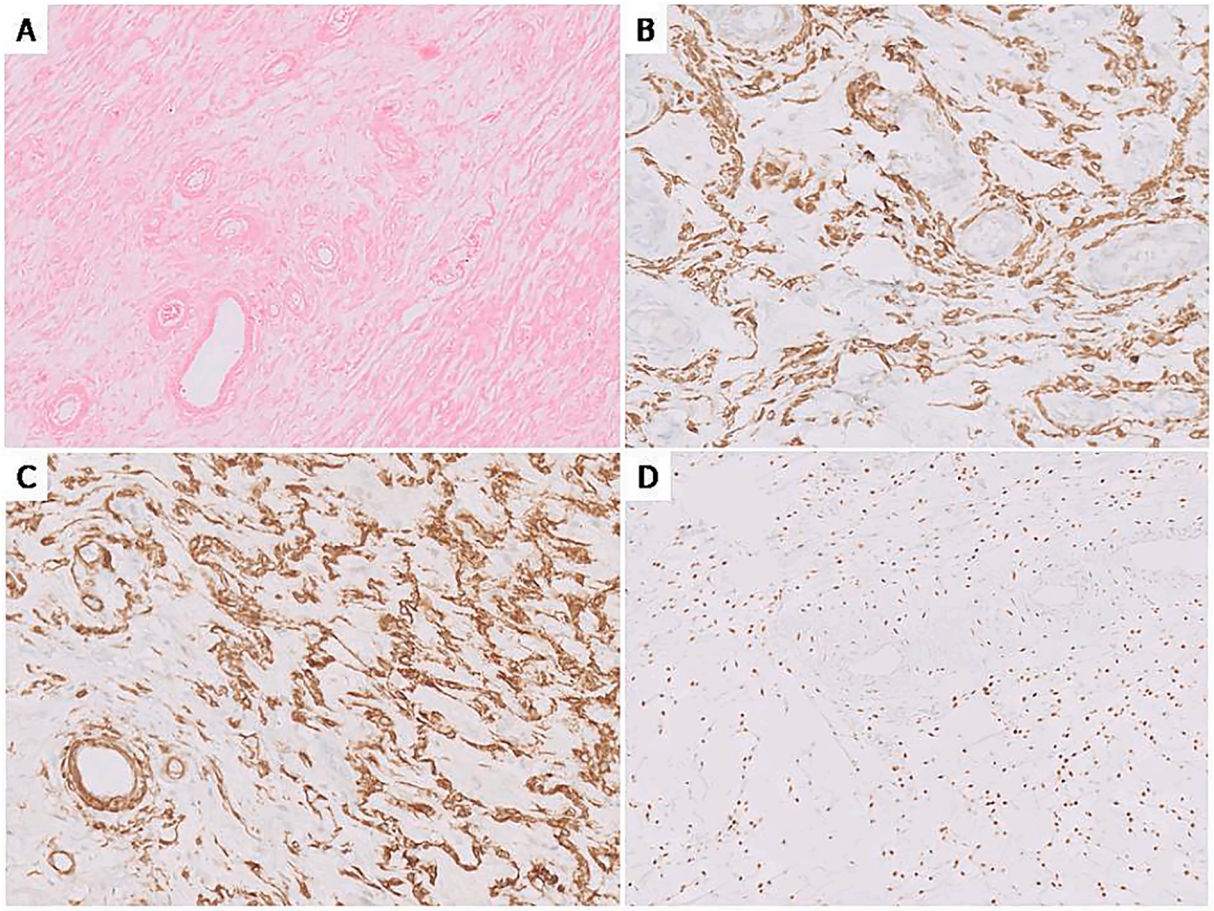

Fig. 1. Case 1. Deep aggressive angiomyxoma: Microscopic features. A. Variably sized hyalinized blood vessels with perivascular collagen and intervening myxoid areas with relatively bland appearing spindle and stellate cells. H and E, x200. B. Tumor cells displaying desmin positivity. DAB, x 200. C. H-caldesmon positivity. DAB, x 400. D. Diffuse estrogen receptor (ER) positivity, DAB x 400.

to a recurrence, is unknown. A retrospective analysis of 106 such cases revealed that patients with clear resection margins have similar chances of remaining disease-free as those with tumor-involved resection margins (Chan et al., 2000). Additionally; there was no correlation to tumour size and recurrence, The authors suggested that while complete resection is the goal, incomplete or partial resection is acceptable, particularly when high operative morbidity is expected. In the present case, re-excision of involved margins might have resulted in a permanent bowel stoma as tumour was in close proximity to external anal sphincter and rectum. After thorough counselling, the patient opted for close follow-up in our case.

Although recurrences are reported in the perineum or pelvis, recurrences in the peritoneal cavity and even at distant sites including lung, at intervals from 1 month to 20 years, have been reported in some patients. Deaths are associated with distant metastasis. Adjuvant radiotherapy and chemotherapy have been attempted; however, evidence is limited given tumours have low proliferation potential. Whether maintenance hormonal therapy prevents recurrence in hormone-positive tumours is unknown. Our patient (Case 1) is disease-free for more than 66 months without any adjuvant therapy, even though surgical margins were microscopically positive. The 3rd patient with an aggressive angiomyxoma who underwent surgical resection without adjuvant therapy is also disease-free over a duration of 87 months.

Angiomyofibroblastoma represents an unusual benign mesenchymal neoplasm of the vulva and vagina. Typically presenting as a well-circumscribed tumor measuring less than 5 cm, angiomyofibroblastoma is managed primarily via local excision (Nielsen et al., 1996). These tumours can be misdiagnosed as Bartholin's cyst or other mesenchymal tumours such as lipoma or liposarcoma; as noted in case 5. Negative expression of epithelial immunostains, such as keratin ruled out a possibility of a carcinoma in that tumour, which was another differential diagnosis.

Clinical differentiation from an aggressive angiomyxoma is facilitated by its circumscribed borders and stromal cells condensing the perivascular area.

Superficial myofibroblastoma, a rare benign tumour arising from the hormone-sensitive lower genital tract, displays a low proliferation index. Typically presenting as polypoid masses ranging from 0.4 to 6.5 cm, these tumours commonly occur in the vulva, cervix, and vagina (Zhang et al., 2022). Immunohistochemically; tumour cells show strong reactivity to CD34, desmin, vimentin, ER, and PR. A combination of clinical features, imaging characteristics, and pathological features help in differentiating superficial myofibroblastoma from aggressive tumours. Given certain overlapping histopathological features and CD34 positivity, a differential diagnosis of solitary fibrous tumour in the case of the present series (case 6) was ruled out based on STAT6 negativity (Rekhi et al., 2019). Differentiating a superficial myofibroblastoma from aggressive tumours is crucial; and imaging, clinical, and pathological features play a pivotal role. Our patient (Case 6) is in clinical remission for more than 18 months following surgery.

Notably, certain studies have shown a genetic link among various vulvo-vaginal stromal tumors. In a study, Zhang et al (Angelico et al., 2022) showed that cellular angiofibroma; mammary-type myofibroblastoma, and extramammary myofibroblastoma share a deletion of the 13q14 region. Moreover, a genetic fusion, MTG1::CYP2E1 has been

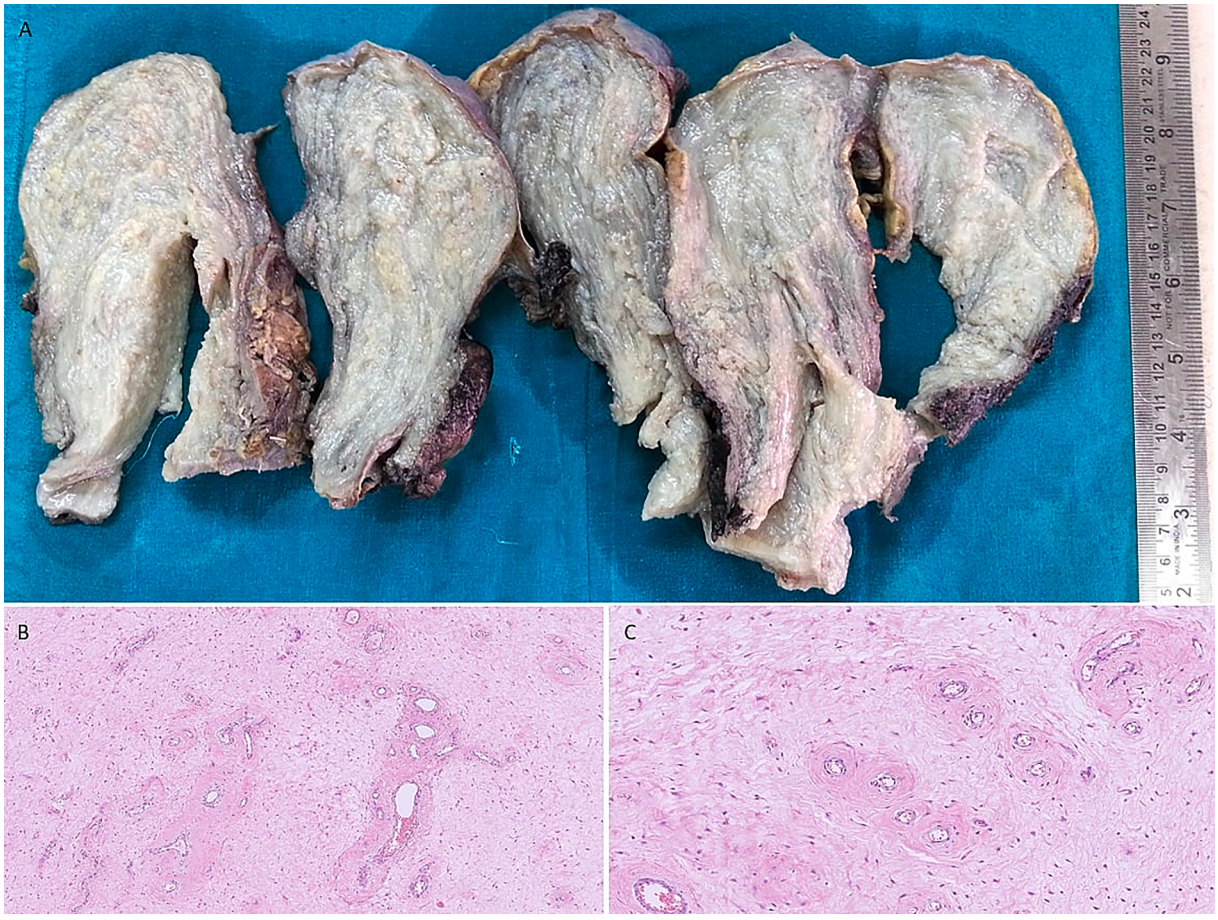

Fig. 2. Case 3. Aggressive angiomyoxoma. A. Gross appearance: Cut surface showing an infiltrative, poorly circumscribed tumour exhibiting a glistening, gelatinous appearance with areas of fibrosis. B &C Microscopic features: B. Relatively hypocellular tumour composed of oval to spindle-shaped and stellate cells in a myxoid stroma with interspersed medium-sized blood vessels exhibiting characteristic perivascular cuffing of delicate fibrillary collagen. H and E, x 200. C. Higher magnification showing the characteristic perivascular hyalinization and delicate fibrillary collagen amidst a hypercellular tumour, comprising oval to spindle-shaped and stellate cells lacking significant atypia and mitosis. H and E, x 400.

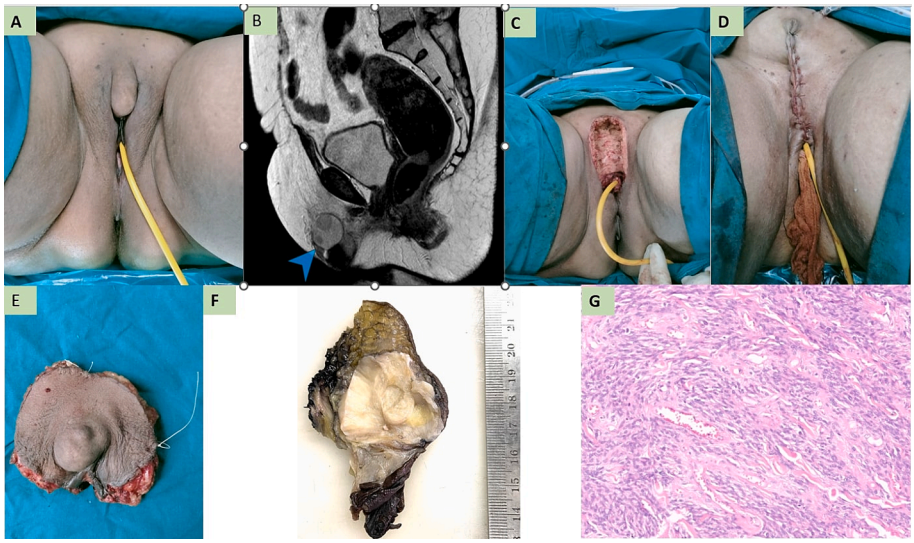

Fig. 3. Case 6. Superficial myofibroblastoma: A. Vulvar lesion of 3 x 3 cm over the clitoris and mons with smooth skin surface B. Pelvic MRI (sagittal sections) showing a heterogenous altered signal intensity lesion (pointed arrow) with T1 hyperintense areas suggestive of fat component. C & D. Vulvar defect post excision was repaired by primary closure. E. Lesion immediately after excision oriented with short thread at 12′O clock position and long thread at 3′O clock position. F. Gross appearance: A well circumscribed tumour below the epidermis with a fleshy, grey-white cut surface. G. Microscopic features: Relatively bland appearing spindle cells arranged in a pattern less manner in a variably collagenous stroma. H and E, x 200.

identified in both angiomyofibroblastoma and mammary-type myofibroblastoma, implying a potential genetic proximity between these two tumours (Boyraz et al., 2022).

4. Conclusion

Vulvo-vaginal stromal tumours of the vulva are rare, but distinct mesenchymal tumours primarily affecting middle-aged women. The current series constitutes one of the first comprehensive studies on these tumours from our country. All the tumour entities/subtypes exhibit distinct pathological features. Immunohistochemistry reveals variable positivity for desmin, vimentin, as well as ER and PR, the latter two in most tumours. Surgical excision with clear margins is the mainstay of treatment, while the efficacy of adjuvant chemotherapy and radiotherapy remains uncertain. Emerging data indicate a potential role for hormonal therapy, although further validation is needed. A potential pathogenetic link has been identified between angiomyofibroblastoma and superficial myofibroblastoma in the female lower genital tract, based on a novel *MTG1::CYP2E1* fusion, seen in both the tumors (Tajiri et al., 2021). Collaborative research efforts are essential to improve understanding and management strategies for these rare tumours.

CRediT authorship contribution statement

Biswajit Dash: Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Sushmita Rath:** Writing – original draft, Methodology, Investigation, Data curation. **Bharat Rekhi:** Pathology review writing – critical review & editing, Supervision, Project administration, Methodology, Investigation, Data curation. **Neha Mittal:** Writing – review & editing, Data curation. **Rohini Kulkarni:** Writing – review & editing. **T. S. Shylasree:** Writing – review & editing. **Amita Maheshwari:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We would like to thank the members of Gynecologic oncology disease management group, Tata Memorial Centre, Mumbai, India

References

Angelico, G., Marletta, S., Broggi, G., Vigneri, P., Vecchio, G.M., Salvatorelli, L., et al., 2022. Practical approach to the diagnosis of the vulvo-vaginal stromal tumors: An overview. Diagnostics. 12 (2).

Boyraz, B., Tajiri, R., Alwaqfi, R.R., Paula, A.D.C., Ye, Q., Nielsen, G.P., et al., 2022. Vulvar angiomyofibroblastoma is molecularly defined by recurrent MTG1-CYP2E1 fusions. Histopathology. 81 (6), 841–846.

Chan, I.M., Hon, E., Ngai, S.W., Ng, T.Y., Wong, L.C., 2000. Aggressive angiomyxoma in females: Is radical resection the only option? Acta Obstet Gynecol Scand. 79 (3), 216–220.

Choi, H., Park, C., Ji, Y.-I., 2015. Alternative surgical approaches for aggressive angiomyxoma at different sites in the pelvic cavity. Obstet & Gynecol Sci. 58 (6), 525–529.

Fisher, C., 2013. Atlas of soft tissue tumor pathology. Atlas Soft Tissue Tumor Pathol.

Fucà, G., Hindi, N., Ray-Coquard, I., Colia, V., Dei Tos, A.P., Martin-Broto, J., et al., 2019. Treatment outcomes and sensitivity to hormone therapy of aggressive angiomyxoma: A multicenter, international. Retrospective Study. Oncologist. 24 (7), e536–e541.

Nielsen, G.P., Rosenberg, A.E., Young, R.H., Dickersin, G.R., Clement, P.B., Scully, R.E., 1996. Angiomyofibroblastoma of the vulva and vagina. Mod Pathol. 9 (3), 284–291.

Rekhi, B., Bapat, P., Shetty, O., 2019. A rare case of a vaginal solitary fibrous tumor, presenting as a cystic mass, showing NAB2ex4-STAT6ex2 fusion and STAT6 immunostaining. Int J Gynecol Pathol. 38 (1), 21–26.

Schoolmeester, J.K., Fritchie, K.J., 2015. Genital soft tissue tumors. J Cutan Pathol. 42 (7), 441–451.

Tajiri, R., Shiba, E., Iwamura, R., Kubo, C., Nawata, A., Harada, H., et al., 2021. Potential pathogenetic link between angiomyofibroblastoma and superficial myofibroblastoma in the female lower genital tract based on a novel MTG1-CYP2E1 fusion. Mod Pathol. 34 (12), 2222–2228.

Zhang, M., Shi, P., Zhou, B., Liu, J., Li, L., 2022. Superficial myofibroblastoma of the lower female genital tract: A clinicopathological analysis of 15 cases. Ann Diagn Pathol. 1, 60.