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Mesenchymal lesions of the vulva

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ABSTRACT

Mesenchymal lesions of the vulva include site-specific entities limited to the lower genital tract, as well as a range of non-site-specific tumors that are more common at extragenital sites. Site-specific lesions include fibroepithelial stromal polyp, cellular angiofibroma, angiomyofibroblastoma, and aggressive angiomyxoma. Non-site-specific tumors that may occur in the vulva include those of smooth muscle, skeletal muscle, vascular, neural, adipocytic, and uncertain differentiation. This review discusses both site-specific and non-site-specific vulvar mesenchymal lesions including non-neoplastic proliferations, benign neoplasms, locally aggressive neoplasms with a predilection for local recurrence, neoplasms of indeterminate biologic potential, and frankly malignant neoplasms with a high risk of distant metastasis and death. Accurate diagnosis is essential for proper management, and is facilitated by correlation with clinical findings and targeted application of immunohistochemical and molecular studies.

Introduction

A wide variety of site-specific and non-site-specific mesenchymal lesions may arise in the vulva. Site-specific entities include non-neoplastic proliferations, benign neoplasms with negligible risk of recurrence, and locally aggressive neoplasms that infiltrate surrounding soft tissues and recur in a significant number of patients. Non-site-specific tumors arising in the vulva span the full spectrum of neoplasms that are more common at extragenital sites, including those of smooth muscle, skeletal muscle, vascular, neural, adipocytic, and uncertain differentiation. We begin with a detailed review of the site-specific lesions (summarized in Table 1), then continue with select non-site-specific tumors that occur with some frequency in the vulva or may cause diagnostic confusion with certain site-specific entities.

Site-specific tumors

Fibroepithelial stromal polyp

Fibroepithelial stromal polyp (FESP) of the female genital tract was first described by Norris and Taylor in 1966.[1] FESPs present across a broad age spectrum (range, 15 to 86 years; rarely in infants),[1–5] with two-thirds in reproductive-aged women.[1,2,5] Approximately 15% occur in pregnant patients, in whom lesions are more likely to be multiple, recurrent, or morphologically atypical, and a small subset arise in women taking tamoxifen.[5] Although the vagina is the most frequently affected site in the female genital tract, FESPs also develop in the vulva and rarely the cervix.[4–8] Shared topographical, morphological, and ultrastructural features suggest they arise from a subepithelial stromal band extending from the endocervix to the vulva, thought to play a role in postpartum contraction of cervical and vulvovaginal tissues.[4,9]

Vulvar FESPs typically present as a slow growing painless mass, present for weeks to years before diagnosis.[6] They typically range from 0.5 to 4.0 cm,[1,2,4] but may be larger in pregnancy,[1,5] and occasional lesions in non-pregnant patients may exceed 20 cm ("giant fibroepithelial polyp").[10,11] On gross examination, FESPs are poorly circumscribed, nodular or frond-like, soft or rubbery masses with a grey-white cut surface.[1] At low magnification, FESPs are comprised of a proliferation of loose, hypocellular stroma, which directly abuts the overlying squamous epithelium (i.e. Grenz zone is absent), have an ill-defined border with non-lesional tissue, and contain a central vascular core composed of capillaries and larger, sometimes hyalinized vessels (Fig. 1A, C). At high magnification, fine wispy to thick hyalinized collagen and scattered spindle to stellate cells are present in a fibrous, edematous, or myxoid stroma. Approximately half of FESPs have bland cytomorphology, whereas half contain scattered large cells with atypical nuclei, showing either smudgy chromatin or coarse chromatin with prominent nucleoli (Fig. 1B, D).[1,2,5] Scattered lymphocytes,

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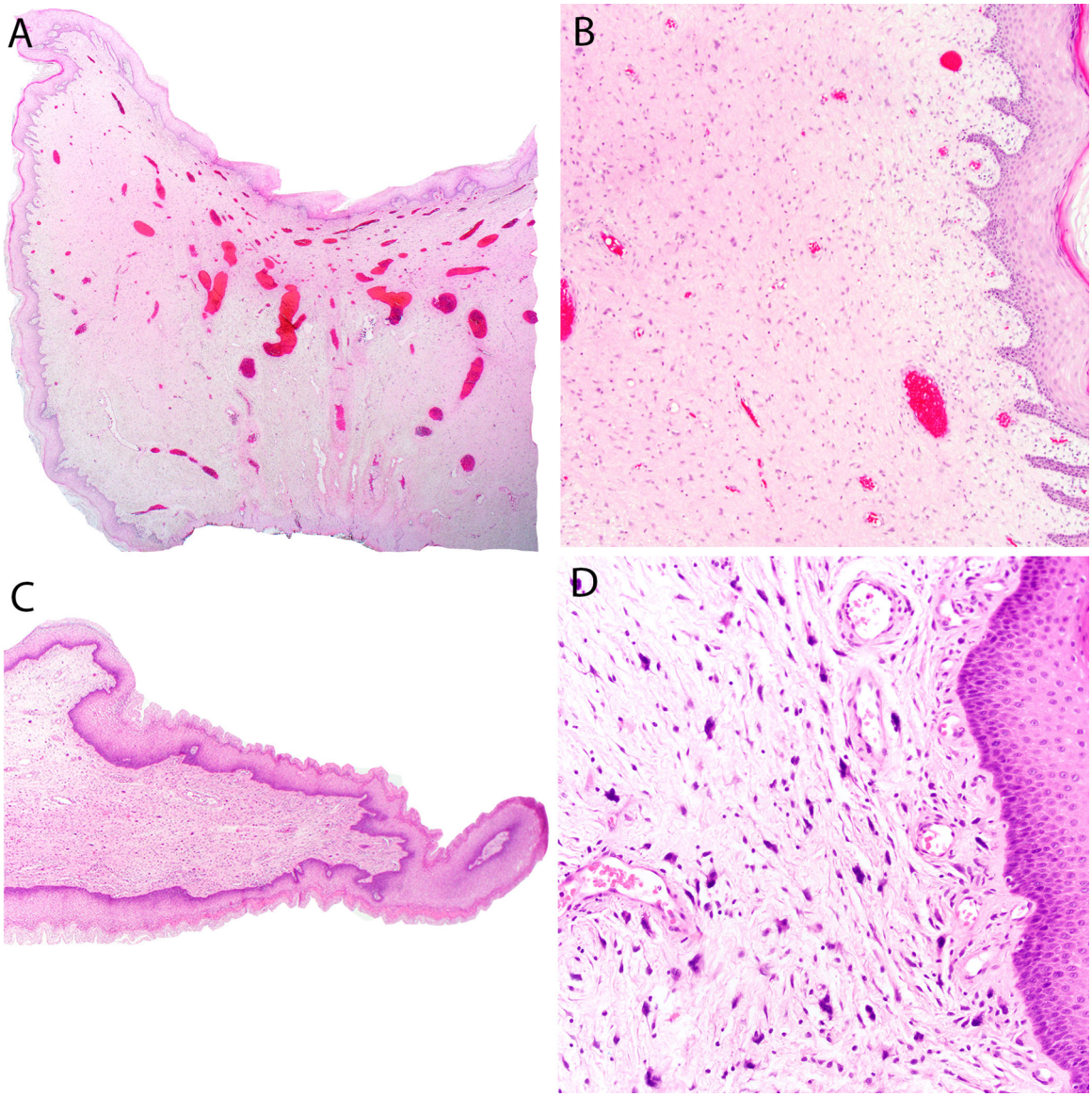

Fig. 1. Fibroepithelial stromal polyp with a prominent central fibrovascular core (A, 20x) and bland spindle to stellate cells (B, 100x). Fibroepithelial stromal polyp with scattered atypical stromal cells visible at low (C, 20x) and high (D, 200x) magnification. Note the absence of a Grenz zone in both polyps.

plasma cells, and mast cells may be seen. Necrosis is absent, and mitoses are generally infrequent.[1,2,12] Occasional FESPs show multiple atypical features including nuclear atypia, hypercellularity (usually most pronounced centrally), increased mitoses (> 10 per 10 high-power fields (hpf)), and/or atypical mitoses.[3,5] Such atypical lesions are often larger and occur more frequently in pregnancy.

The stromal cells in FESPs are usually positive for desmin (58 to 92% in recent studies), [5,7] ER, and PR. SMA is positive in approximately 10%.[5] Cytokeratin, EMA, and S100 are negative. Rare lesions are myoD1[7] or myogenin[13] positive, though expression is generally weak and focal. Ki67 index may be up to 60%, particularly in pregnancy, but imparts no increased clinical risk.[8] Molecular features are not well characterized.

FESPs (including those with atypical features) are benign reactive proliferations with no potential for distant spread or true sarcomatous transformation. However, indolent local recurrence occurs in approximately 10%,[8] and may be more frequent in pregnancy.[5] Conservative local excision is considered adequate treatment of both primary and recurrent lesions.[1–3,6]

Cellular angiofibroma

Cellular angiofibroma (CA) was first described by Nucci et al. in 1997.[14] They are diagnosed at a median age of 47 (range, 22 to 75) years and most commonly involve the vulva, with occasional cases in the vagina or perineum.[14–16] Most present as a painless, slowly enlarging mass, present for weeks to years before diagnosis, often resembling a Bartholin cyst.[14,16] They range from 0.6 to 12 (mean 3.4) cm,[14–17] and are generally centered in the subcutaneous tissue. On gross examination, CAs are generally well-circumscribed, firm to rubbery, with a white-tan to grey cut surface. Occasional lesions are multilobulated.[16]

Microscopically, CAs are usually well-demarcated but may extend into the dermis or rarely, adjacent skeletal muscle. A subset is invested by a fibrous pseudocapsule.[14,16,18] The tumor stroma is fibrous, edematous, or myxoid, and contains short wispy collagen bundles admixed with small to medium, thick-walled hyalinized vessels (Fig. 2A). They are generally quite cellular and composed of intersecting fascicles or palisades of spindle cells with bland ovoid to fusiform nuclei (Fig. 2B). Scattered multinucleated cells, often with a degenerative appearance, are not uncommon (Fig. 2C).[14,16,18] Mitoses are usually infrequent (< 1

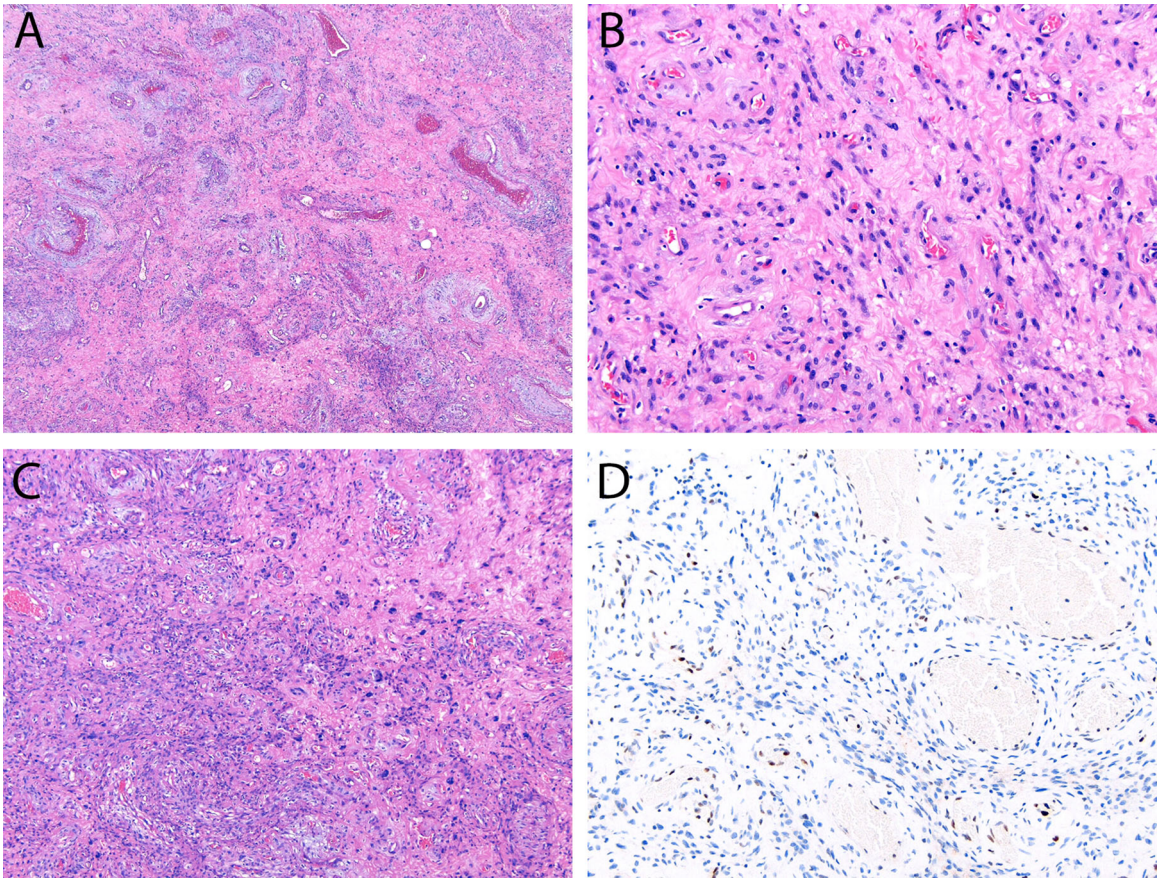

Fig. 2. Cellular angiofibroma with thick-walled vessels (A, 40x) and bland spindle cells (B, 200x). Scattered foci of atypical cells may be seen (C, 100x). Rb is negative. (D, 200x).

per 10 hpf), but occasionally brisk (> 10 per 10 hpf), whereas necrosis and hemorrhage are absent.[14,16] Mast cells and lymphocytic aggregates are common.[14,16,18] Nearly half of CAs show focal adipocytic differentiation, and rare cases have quite prominent adipocytic differentiation, composing 30 to 50% of the lesion.[16] Other features that may be observed include hemangiopericytoma-like vessels, pseudovascular spaces filled with proteinaceous fluid, cytoplasmic inclusions, and nuclear grooves.[14–19] Discrete nodules of so-called sarcomatous transformation, resembling pleomorphic liposarcoma, atypical lipomatous tumor, or undifferentiated pleomorphic sarcoma are rarely present.[15,19,20]

Approximately half of CAs are CD34 positive, and most express ER and/or PR.[16–18] Occasional cases express SMA, but desmin and caldesmon are generally negative.[14–17] EMA is very rarely positive, whereas S100 and cytokeratin are uniformly negative.[14,15,17,18] All CAs tested by fluorescence in-situ hybridization (FISH) have shown monoallelic loss of the chromosome 13q region containing *RB1* and *FOXO1* genes.[15,20] This often correlates with loss of Rb by immunohistochemistry (Fig. 2D), although interpretation of the Rb immunostain can be challenging.[21] As this same chromosomal region is lost in spindle cell lipoma and mammary-type myofibroblastoma, these three entities are considered to be a family of tumors with shared pathogenesis, despite certain clinical and morphologic differences.[22] In CAs with sarcomatous transformation, the sarcomatous areas often show multifocal or diffuse p16 positivity, but are negative for MDM2 and CDK4.[19,23] In a minority, the sarcomatous areas also show strong and diffuse p53 expression, which appears to correlate with underlying *TP53* mutation.[19,23]

Simple excision is considered curative.[14–16] Recurrences are exceptionally rare and may sometimes follow incomplete excision,[18] although no recurrences were reported in one study of seven tumors with positive margins.[15] Increased risk of recurrence has not been associated with nuclear atypia and/or sarcomatous transformation,[19] and no cases of distant metastasis are reported.

Angiomyofibroblastoma

Angiomyofibroblastoma (AMFB) is a morphologically distinctive myofibroblastic tumor of the lower genital tract, originally described by Fletcher et al. in 1992.[24] AMFB predominantly affects the labia majora of women in the fourth to fifth decades (reported range, 21 to 71 years).[24–27] Some authors suggest that AMFB arises from the vulvovaginal subepithelial stroma, akin to FESP,[24] whereas others have suggested a perivascular origin.[26]

AMFB typically presents as a slow growing, painless mass, present for weeks to years prior to diagnosis, and clinically resembles a Bartholin cyst or lipoma.[24,25] On gross examination, AMFBs are well-circumscribed and range from 0.5 to 12 (mean, 4) cm.[24–28] The cut surface is generally tan-white and firm, although the lipomatous variant may be yellow and fatty. Microscopically, AMFBs are located in the dermis or subcutis, and may have a fibrous pseudocapsule. At low magnification, AMFB shows alternating hypo- and hypercellular zones (Fig. 3A). Plump myofibroblastic cells tend to cluster around abundant small to medium, thin-walled vessels (Fig. 3B, C), although in hypocellular areas they may be more haphazardly distributed in an edematous to collagenous stroma. The myofibroblastic cells range from spindle to epithelioid to plasmacytoid, and bland multinucleated forms are frequently noted. Mitoses are uniformly low (0 to 7 per 50 hpf in one study[26]), and necrosis is absent. Mast cells and scant perivascular lymphocytic inflammation are common.[24] Adipocytic differentiation

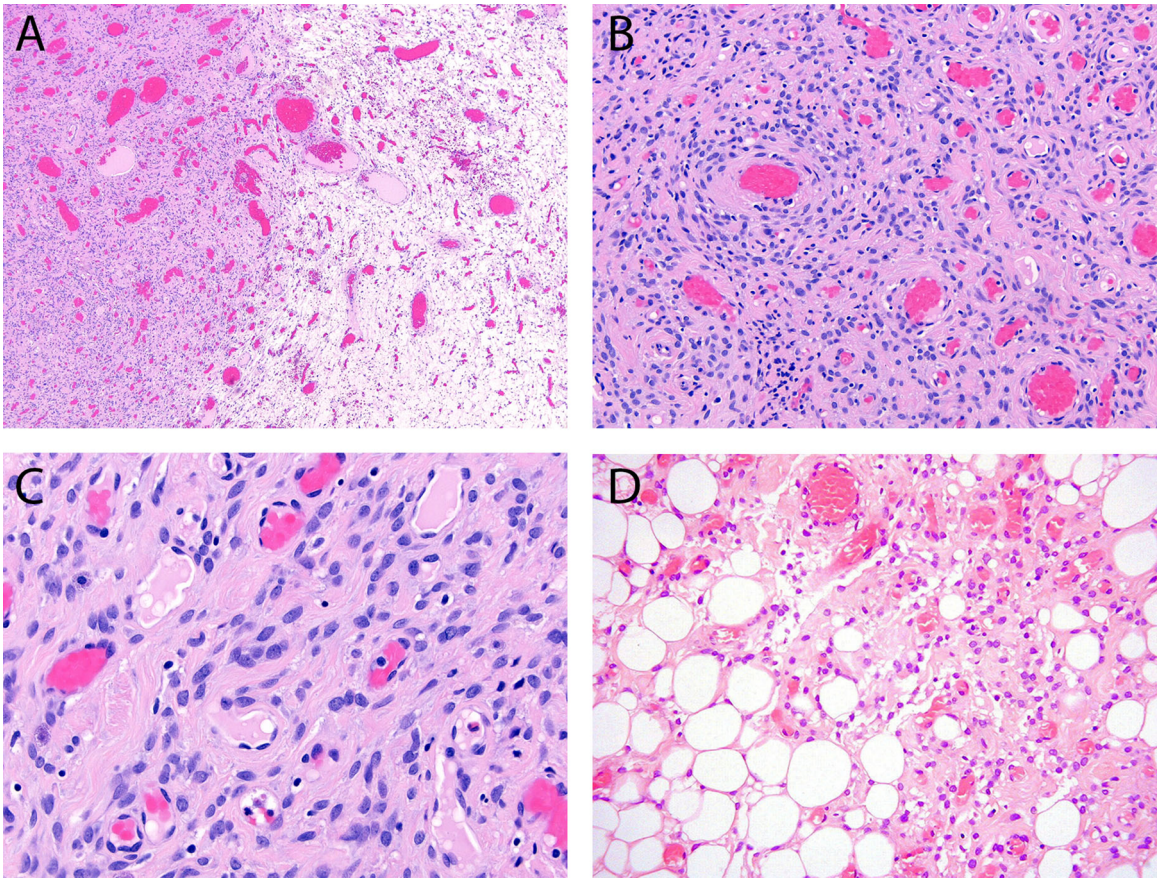

Fig. 3. Angiomyofibroblastoma characteristically shows alternating hypercellular (left) and hypocellular (right) zones (A, 40x). Plump spindle to epithelioid cells cluster around small to medium vessels (B, 100x; C, 200x). A subset shows adipocytic differentiation (D, 100x; Contributed by Dr. W. Glenn McCluggage, Belfast Health and Social Care Trust).

may be present (Fig. 3D), and when it composes > 50% of the tumor, a diagnosis of "angiomyofibroblastoma, lipomatous variant" may be rendered.[26,27,29]. One AMFB with sarcomatous transformation ("angiomyofibrosarcoma") has been reported,[30] characterized by large size (13 cm), gross hemorrhage, necrosis, and a morphologic transition from classical AMFB to a hypercellular component with nuclear atypia and increased mitoses (up to 7 per 10 hpf).

Most AMFBs are positive for desmin, ER, and PR.[24–28] CD34 and SMA are expressed in a minority,[25,26] while S100, cytokeratin, and EMA are negative.[24,25,27]. Their molecular pathogenesis remains unclear. They lack the 13q14 deletion characteristic of CA,[27] and while one tumor reportedly harbored increased *HMGA2* transcripts,[31] a larger FISH-based study did not identify *HMGA1* or *HMGA2* rearrangements.[32]

As nearly all AMFBs are benign, simple local excision is adequate management.[24–27] Local recurrence is exceptionally rare, even among cases with positive margins.[27] In the sole report of angiomyofibrosarcoma, local recurrence was treated with hemivulvectomy and radiation therapy, with no evidence of disease five months later.[30]

Aggressive angiomyxoma

Although reports of infiltrative myxomatous tumors of the lower female genital tract date back more than a century, aggressive angiomyxoma (AA) as such was first designated by Steeper and Rosai in 1982,[33] and has since been detailed in multiple case series.[34–41] AA is a tumor of the lower genital tract and deep pelvic soft tissues. It may occur at nearly any age, but most patients are in their fourth and fifth decades.[33–35,38,40–42] Like most site-specific tumors, its histogenesis is unclear. Fetsch et al. and Skalova et al. proposed an origin from site-specific hormone-responsive stromal cells,[36,37] whereas Martinez et al. suggested an origin from a perivascular stem cell.[43] Although morphologic and immunophenotypic overlap initially suggested that AA and AMFB might occupy two ends of a biologic spectrum,[34,37] lack of shared molecular features indicates that they are biologically distinct.[32]

AA most often presents as an ill-defined, slow-growing vulvar mass, which may clinically resemble a Bartholin cyst, lipoma, or hernia.[34,37] However, clinical examination may substantially underestimate the size of these infiltrative lesions, which can extend to perineal, paravaginal, perirectal, retroperitoneal, and gluteal tissues.[33,35,36] Depending on tumor extent, patients may present with abdominopelvic fullness, urinary frequency, dyspareunia, or dyschezia,[37] and rapid growth in pregnancy has been reported.[44,45] Grossly, AAs range from 3 to 60 cm, with most greater than 10 cm.[33–36,38,40] Lesions are poorly delineated and lobulated with finger-like projections infiltrating adjacent tissue. The cut surface is generally grey-white and gelatinous (Fig. 4A), although recurrent lesions may be more fibrous.[33,35] Necrosis is absent, but punctate hemorrhage or cystic degeneration may be seen.

Histologically, AA is unencapsulated and poorly circumscribed, with extensive infiltration and entrapment of adjacent fat, skeletal muscle, and nerves (Fig. 4B).[36] The tumor is composed of loose myxoid stroma with variable amounts of delicate collagen fibrils and a sparse population of bland spindle to stellate cells (Fig. 4C). Scattered foci with mildly increased cellularity may be seen,[33,34] but mitoses are rare (< 1 per 10 hpf). Tumor vasculature is prominent but heterogeneous, consisting of smaller capillary-sized vessels admixed with medium to large vessels, often with medial hypertrophy (Fig. 4D) or hyalinization (Fig. 4E). Thin fascicles of smooth muscle cells are commonly seen near or around vessels (Fig. 4F).[34,36] Extravasated red blood cells are typically present.[33,37] Recurrences may be histologically similar to the

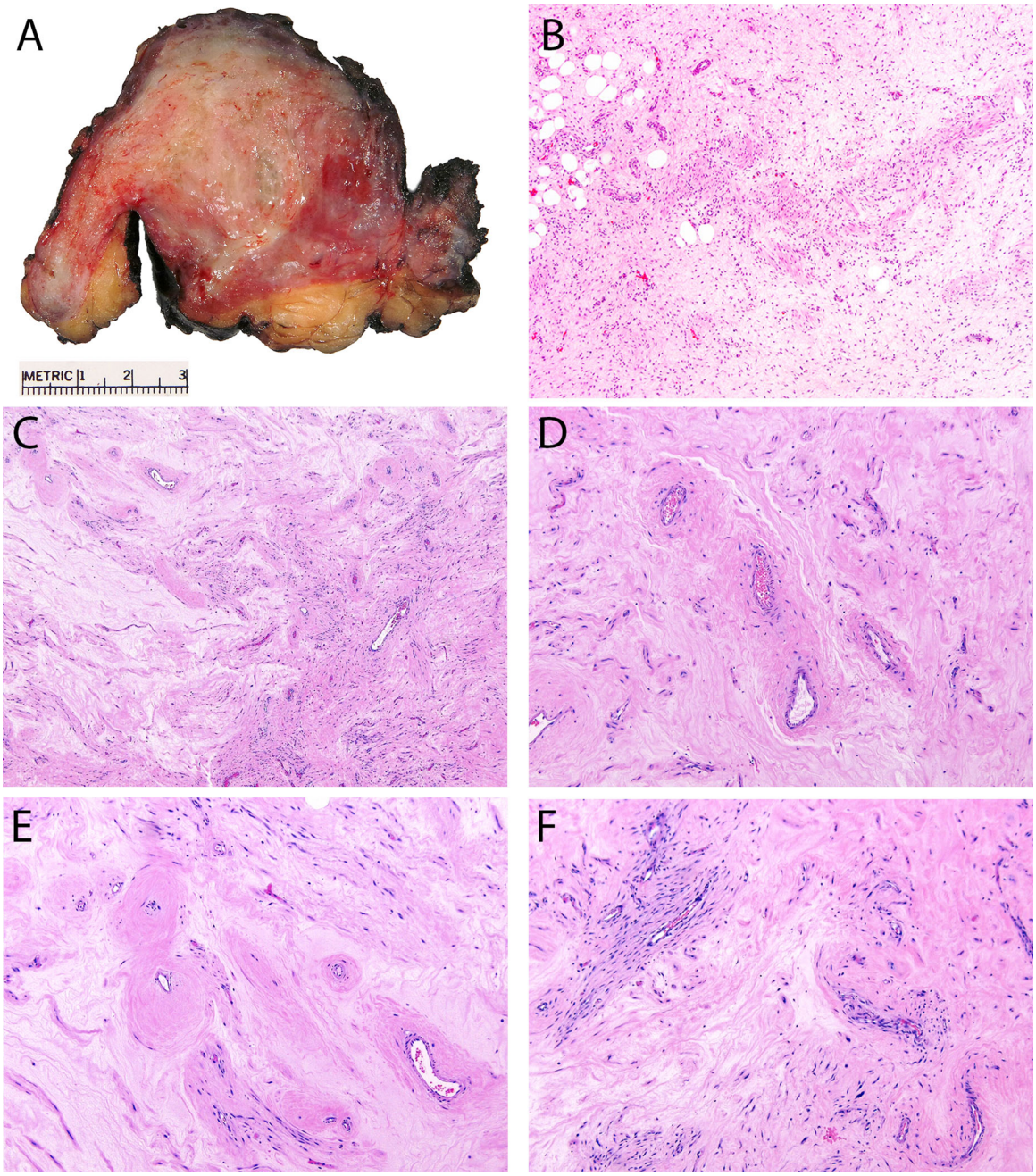

Fig. 4. Aggressive angiomyxoma is ill-defined with a gelatinous cut surface (A). Extensive infiltration of surrounding soft tissue is typical (B,100x). The lesion is hypocellular with myxoid stroma (C, 40x). Vessels are variable in size and may show medial hypertrophy (D, 200x) or hyalinization (E, 200x). Perivascular myoid bundles are common (F, 200x).

primary lesions, or show increased cellularity, vascularity, and stromal collagen.[33]

Desmin and SMA highlight lesional stromal cells and perivascular myoid bundles in most tumors, although staining may be focal.[34,36,38,43] ER and PR are consistently positive,[36,38,41,43,46,47] CD34 is expressed in approximately half of cases,[36,43] and S100 is negative. In one study, all AAs were CDK4 positive, but MDM2 co-expression was not identified.[39] HMGA2 immunohistochemistry is positive in the spindle cell population in approximately 90%.[48–50] One large study found rearrangements of the *HMGA2* locus on chromosome 12 in only one-third of AAs,[32] suggesting that other mechanisms may drive *HMGA2* overexpression. Among AAs with *HMGA2* rearrangement, translocation breakpoints and fusion partners show considerable variation.[32,47,49,51–55]

AA carries an approximately 30 to 40% risk of local recurrence,[33,34,36,37,41,42] particularly in tumors with positive surgical margins.[35,40,41] There are no reports of sarcomatous transformation, and only rare cases of distant metastasis or disease-related death.[169,170] Optimal management is by wide local excision with negative margins, although this may be complicated by extensive tumor infiltration and cosmetic or functional considerations. Adjuvant radiation or hormonal therapy may be considered in some patients.[56] Rare AAs show minor foci with histologic features of AMFB.[34] These hybrid tumors may be better circumscribed, but have the potential to recur locally and thus warrant close follow-up.

Although it rarely involves the vulva, superficial angiomyxoma (SA) is often considered in the differential diagnosis of AA and warrants brief mention. Vulvar SA affects young women (median age, 21 years) as a slowly growing, painless nodular or multinodular mass on the labia majora and mons pubis.[55,57,58] Grossly, lesions are usually less than 3 (range, 1 to 13) cm, with a mucoid cut surface.[55,57,58] Microscopically, they are composed of one or more dermal-based nodules with hypocellular myxoid stroma, small to medium curvilinear thin-walled vessels, bland spindle to stellate cells, and only rare mitoses (< 1 per 50 hpf) (Fig. 5A, B).[57,59,60] Stromal neutrophils are consistently present (Fig. 5C).[59] Occasional lesions contain bi- or multinucleated tumor cells, acellular stromal mucin pools (Fig. 5D), or entrapped epithelial elements.[57,59,60] Vulvar SA is CD34 positive, while a subset focally expresses muscle-specific actin, SMA, S100, and Factor XIIIa. In contrast to AA, desmin, ER, and PR are negative.[57,58] Approximately 30 to 40% of vulvar SAs show non-destructive local recurrence, usually within one year, often secondary to positive margins.[57,59,60] Sarcomatous transformation and distant metastasis are not reported. SA is associated with Carney complex,[61] which should be excluded clinically; however, no vulvar SAs have been described with this association.[57,58]

Other site-specific tumors

In addition to those entities reviewed above, prepubertal vulvar fibroma,[62–64] superficial cervicovaginal myofibroblastoma,[65–67] and lipoblastoma-like tumor of the vulva[68–70] are also considered site-specific tumors. As these tumors are exceptionally rare, the reader is referred to the above references for further information.

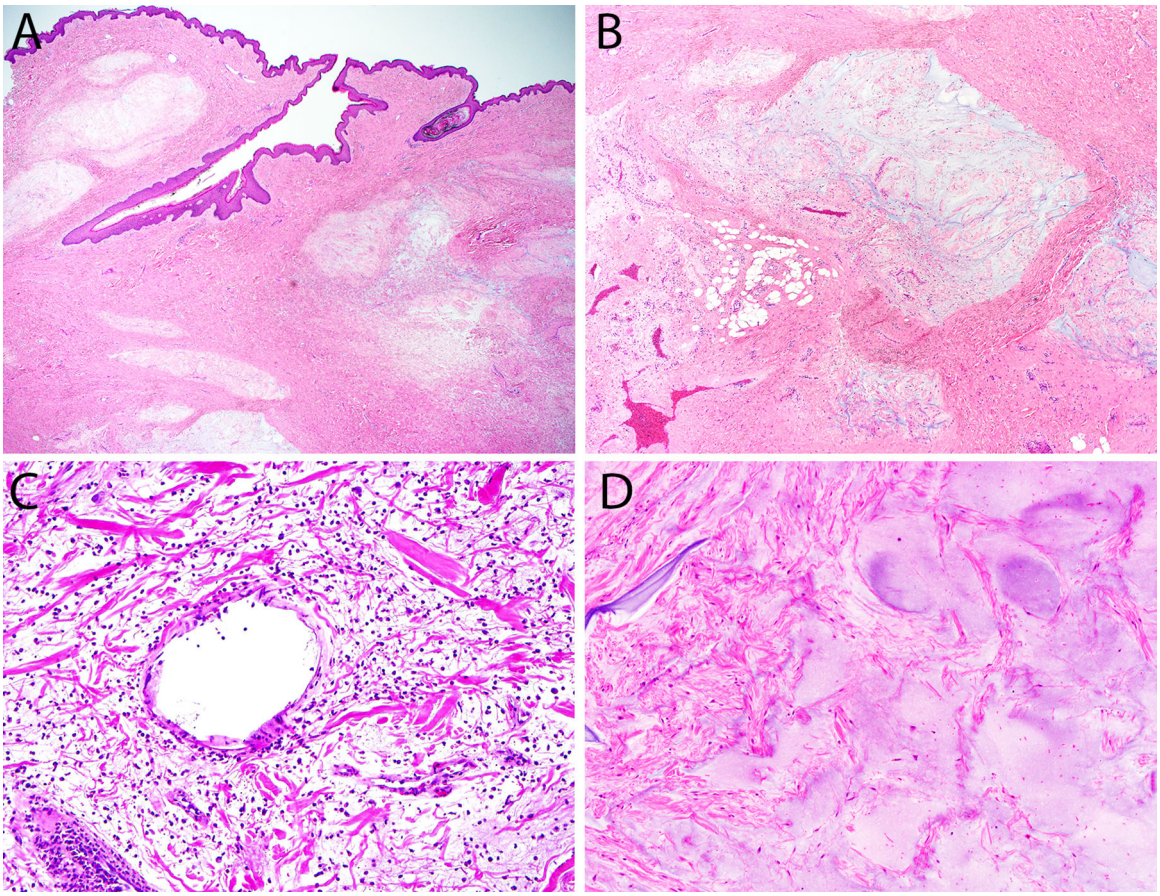

Fig. 5. Superficial angiomyxoma with multiple myxoid lobules in the dermis (A, 20x; B, 40x). The nodules are hypocellular with bland spindle cells, stromal neutrophils (C, 100x), and acellular myxoid pools (D, 100x).

Table 1
Site-specific soft tissue lesions of the vulva.

Diagnosis	Age	Location	Clinical presentation	Gross features	Morphologic features	Immunophenotype	Molecular features	Clinical behavior
Fibroepithelial stromal polyp	• 15-86 years • Most in reproductive-age women	Vagina > vulva and cervix	Slow growing painless mass	• Poorly circumscribed • Most 0.5-4 cm • Occasional lesions up to 20 cm	• Spindle to stellate cells in loose stroma • No Grenz zone • Fibrovascular core • Nuclear atypia in half	• Positive: ER, PR, desmin (58-92%), SMA (10%) • Negative: CK, EMA, S100	Unknown	• Benign • Local excision is adequate • Local recurrence in 10%
Cellular angiofibroma	• 22-75 years • Median, 47 years	Vulva > vagina and perineum	Slow growing painless mass	• Well circumscribed • 0.6-12 cm	• Short fascicles of spindle cells with bland ovoid nuclei • Edematous, myxoid, or fibrous stroma with wispy collagen • Small to medium thick-walled hyalinized vessels • Adipocytic differentiation in a subset	• Positive: ER, PR, CD34 (50%), SMA (rare), EMA (rare) • Negative: Desmin, caldesmon, S100, CK, Rb (lost)	Monoallelic loss of the chr 13 region containing *RB1* and *FOXO1*	• Benign • Local excision is adequate • Rarely recur locally after incomplete excision
Angiomyofibroblastoma	• 21-71 years • Most often in fourth and fifth decades	Labium majus	Slow growing painless mass	• Well circumscribed • 0.5-12 cm	• Plump myofibroblastic cells, characteristically clustering around thin-walled vessels • Alternating hypo- and hypercellular zones • Adipocytic differentiation in a subset	• Positive: Desmin, ER, PR, SMA (rare), CD34 (rare) • Negative: CK, EMA, S100	Unknown	• Benign • Local excision is adequate • Local recurrence exceptionally rare
Aggressive angiomyxoma	• 12-77 years • Most often in fourth and fifth decades	Vulvar, perineal, deep pelvic, retroperitoneal, or gluteal mass	• Often present as a painless pelvic mass • May manifest with mass effect	• Poorly circumscribed • 3-60 cm (most > 10 cm) • Gelatinous cut surface	• Loose myxoid stroma with delicate collagen fibers • Hypocellular; bland spindle to stellate cells • Prominent variably sized vessels • Perivascular cuffs of smooth muscle cells	• Positive: Desmin, SMA, ER, PR, HMGA2, CD34 (50%) • Negative: S100	*HMGA2* rearrangements in approximately one third	• Locally aggressive • Wide local excision with negative margins is optimal • Local recurrence in 30-40%

Non-site specific tumors

Smooth muscle tumors

Leiomyoma and leiomyosarcoma are, respectively, the most common benign and malignant soft tissue tumors of the vulva and vagina (with vaginal smooth muscle tumors approximately three times more frequent).[71–74] Vulvovaginal smooth muscle tumors affect women of all ages (range, 15 to 87 years), but are most often diagnosed in the fourth and fifth decades.[71,72,74–77] They most commonly affect the labia majora and mons pubis, but the labia minora may also be involved.[72,77] Lesions may present incidentally or as a painless, tender, or prolapsing mass, present for weeks to years before diagnosis.[71,72,74,75,77]

Grossly, vulvovaginal smooth muscle tumors range from 0.5 to 16 cm, with most < 5 cm.[71,72,74,76,77] Leiomyomas are well-circumscribed, with a rubbery, white-tan, whorled surface,[71,72,75] whereas leiomyosarcomas are often poorly circumscribed, with a fleshy surface, hemorrhage, and/or necrosis.[74] On microscopic examination, vulvovaginal smooth muscle tumors are identical to their more common uterine counterparts, composed of intersecting fascicles of spindle cells with cigar-shaped nuclei and eosinophilic cytoplasm (Fig. 6A).[76,77] They span the morphologic spectrum from banal leiomyomas to markedly atypical leiomyosarcomas, and include the same morphologic (most notably, epithelioid and myxoid) variants seen in the uterus (Fig. 6B, 6C).[71,72,74–79]

Criteria for vulvar leiomyosarcoma have evolved. Site-specific criteria for vulvar leiomyosarcomas were first proposed by Tavassoli and Norris in 1979: vulvar tumors ≥ 5 cm with an infiltrative border and ≥ 5 mitoses per 10 hpfwere diagnosed as leiomyosarcoma.[72] (Note, the same authors simultaneously proposed slightly different criteria for vaginal leiomyosarcoma[71]). In 1996, Nielsen et al. added moderate to severe nuclear atypia to the three original vulvar criteria, diagnosing leiomyosarcoma if 3 or 4 criteria were fulfilled, atypical leiomyoma if 2 were fulfilled, and leiomyoma for the others.[76] However, a recent study demonstrated that uterine leiomyosarcoma criteria (i.e., at least two of the following: moderate or severe atypia, ≥ 10 mitoses per 10 hpf, coagulative necrosis) are more sensitive and specific for vulvovaginal leiomyosarcoma than the site-specific criteria of Tavassoli or Nielsen.[74] Some data suggest that uterine criteria for smooth muscle tumor of uncertain malignant potential (STUMP) also apply to vulvovaginal tumors, but case numbers are limited.[74, 75, 80] Optimal criteria for classifying epithelioid and myxoid smooth muscle tumors of the vulva remain unclear.

Treatment and prognosis of vulvovaginal smooth muscle tumors depend on pathologic classification. Leiomyomas are clinically benign, and conservative simple excision is adequate, with a negligible risk of recurrence even with positive resection margins.[74] In contrast, vulvovaginal leiomyosarcoma carries a guarded prognosis. In one study with median follow-up of 64 months, 80% of vulvovaginal leiomyosarcomas recurred, two-thirds developed distant metastasis, and disease-specific mortality exceeded 50%.[74] Wide local excision is advocated, and neoadjuvant or adjuvant chemotherapy or radiotherapy may be applied at clinical discretion. Recurrences are reported up to 10 years after primary diagnosis,[76] and hence, long-term follow-up is crucial .

Solitary fibrous tumor

Solitary fibrous tumor (SFT) is a fibroblastic neoplasm of indeterminate biologic potential, which can occur at virtually any site. SFT of the female genital tract most commonly affects the vulva,[81–85] and occurs across a wide age range (22 to 81 (mean, 52) years in one large study[81]). Vulvar SFTs range from 1 to 15 cm,[82–88] and typically present as a painless, slow growing mass, which may be present for years prior to diagnosis.[81,82,87,88] Grossly, vulvar SFTs are well-circumscribed and firm, with a tan-white to yellow cut surface.[81,85,89]

Microscopically, SFT characteristically shows monotonous spindle cells with alternating hypo- and hypercellular foci and prominent thin-walled, dilated, branching “staghorn” or “hemangiopericytoma-like” vessels (Fig. 7A, B). The hypercellular zones consist of bland spindle cells with even chromatin and inconspicuous nucleoli (Fig. 7C)

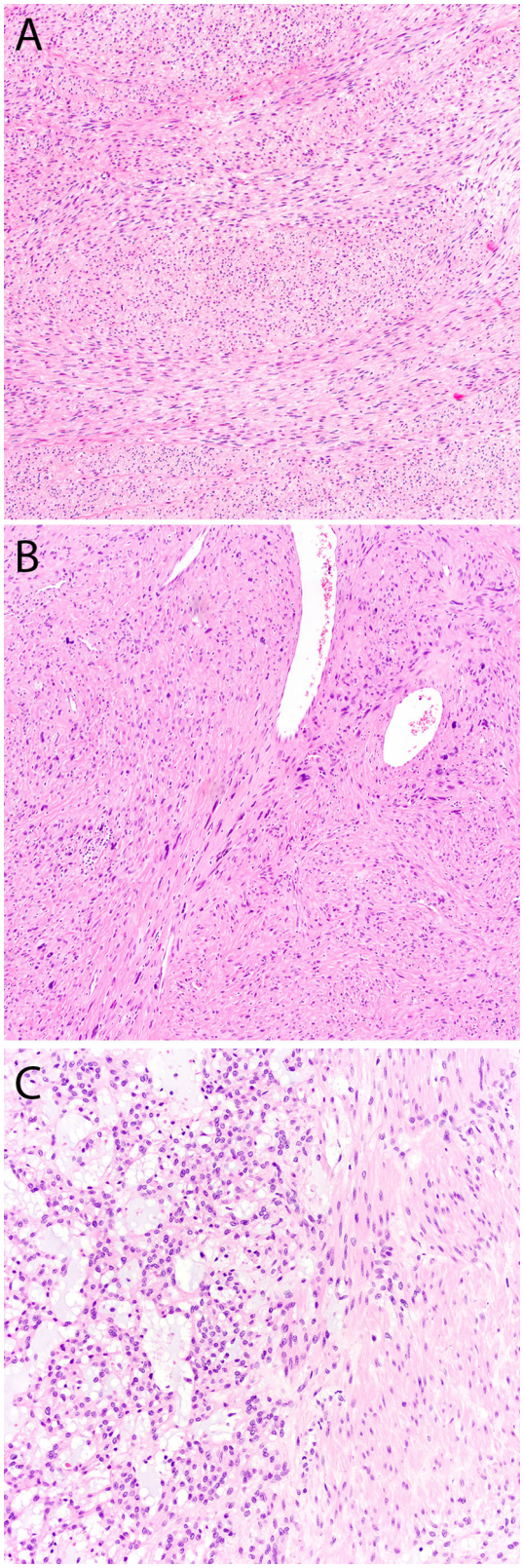

Fig. 6. Banal vulvar leiomyoma (A, 200x). Vulvar leiomyoma with bizarre nuclei (B, 200x). Vulvar smooth muscle tumor (C, 200x) with myxoid change (left) and banal spindle cells (right).

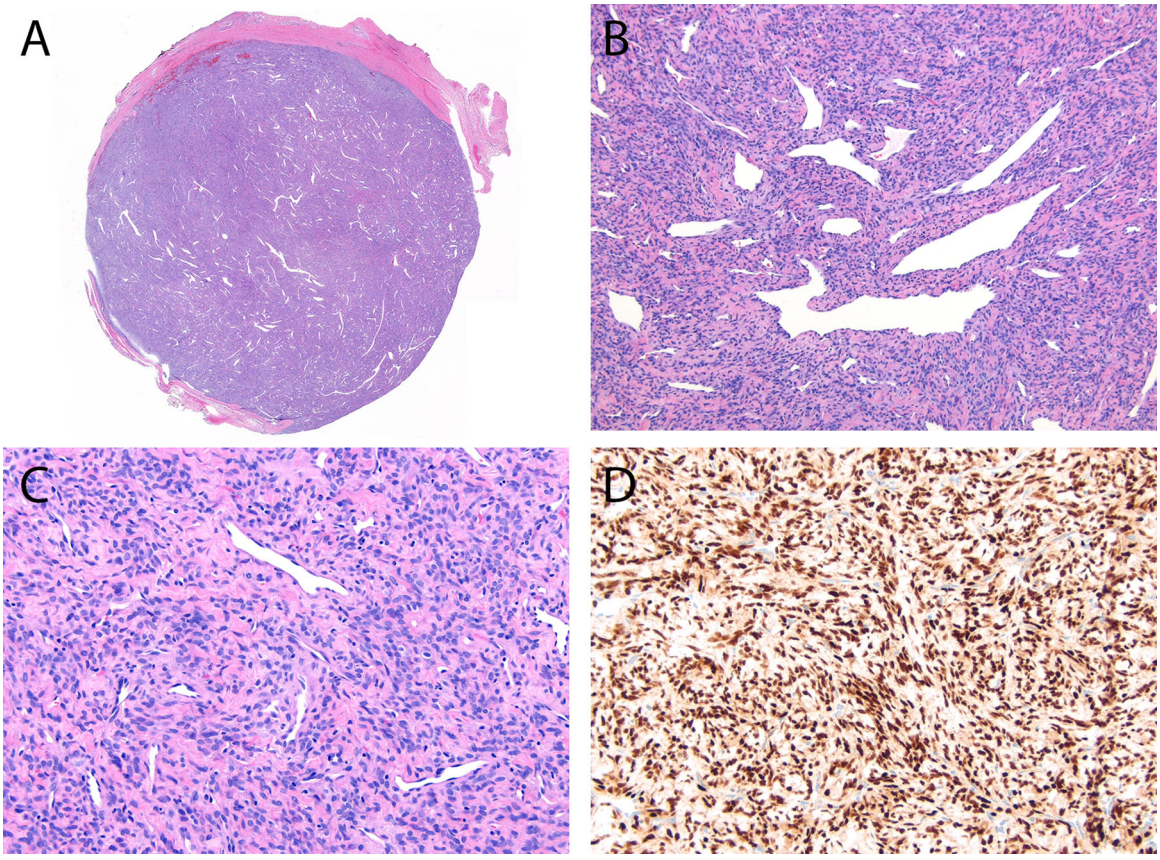

Fig. 7. Solitary fibrous tumor is typically well-circumscribed (A, 10x) and composed of bland spindle cells, thick bands of stromal collagen, and prominent staghorn vessels (B, 100x; C, 200x). STAT6 is positive (D, 200x).

arranged haphazardly or in fascicles, while the hypocellular areas are dominated by bands of dense keloid-like collagen. Mitotic activity ranges from 1 to 56 (mean, 6) per 10 hpf, and necrosis is rare.[81,85] Among all extrathoracic SFTs, approximately 10% show atypical morphologic features (i.e., diffuse hypercellularity, nuclear pleomorphism, necrosis, or mitoses > 4 per 10 hpf), but in the largest series of gynecologic SFTs, 11/25 (44%) showed increased mitoses and were considered histologically malignant.[81]

Gynecologic SFTs are positive for CD34 and CD99,[82,83,85,87,89,90] and at least 90% are positive for STAT6 (Fig. 7D).[81] SMA, desmin, caldesmon, EMA, and S100 are negative. Hormone receptors are not well characterized. To our knowledge, the intrachromosomal *NAB2-STAT6* fusion on chromosome 12 (pathognomonic for SFT) has only been evaluated in three gynecological tumors (2 vulvar and 1 vaginal), each of which harbored this rearrangement.[90,91] Detection of this fusion may be technically challenging due to highly variable breakpoints.[92] Rare complex fusion events may eliminate the epitope recognized by STAT6 immunohistochemistry, which may explain sporadic STAT6-negative SFTs.[81]

SFTs are considered tumors of indeterminate biologic potential, as a small subset shows local recurrence or distant metastasis. Complete excision is recommended, and radiation is applied in some cases at clinical discretion.[84, 90] Increased potential for local recurrence or metastasis may be associated with atypical morphologic features or positive margins,[81, 93, 94] but histologically banal tumors may rarely recur or metastasize, sometimes years after initial diagnosis.[93, 95] Accordingly, long-term follow-up is advised. Death from metastatic SFT of the gynecologic tract is exceptional, but has been reported.[84]

Dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberans (DFSP) is a low-grade dermal sarcoma, which predominantly affects the trunk and proximal limbs of young to middle-aged adults. However, DFSP can arise at virtually any cutaneous site, including the vulva.[96–104] Vulvar DFSP occurs across a wide age range, but most commonly affects women in the fourth and fifth decades.[98,101,104] Tumors involve the labia majora and mons pubis, sparing the mucosa.[98,101,105] Most present as a painless, slow-growing mass, which may be present for years prior to diagnosis.[98] Occasional cases (including some in pregnant patients) present with rapid growth, pain, and ulceration of the overlying skin.[98,106] Vulvar DFSP may clinically resemble an abscess, Bartholin cyst, sebaceous cyst, or nonspecific soft tissue tumor.[98,104]

Vulvar DFSP is morphologically, immunophenotypically, and molecularly indistinguishable from DFSP at other sites. On gross examination, it is generally a multinodular, firm mass ranging from 1 to 6 cm, although tumors up to 15 cm are reported.[96-98,101,104,105] The cut surface is fibrous, and lesions may appear deceptively well-circumscribed grossly. Microscopically, DFSP is a moderately cellular neoplasm composed of bland spindle cells with storiform or pinwheel architecture and extensively infiltrative borders that entrap subcutaneous fat in an interdigitating “honeycomb” pattern (Fig. 8A, B). Vasculature is delicate and inconspicuous. Mitoses are rare, ranging from 0 to 7 (median, 2) per 10 hpf,[97,98,101,104] and necrosis is absent. Rare morphologic variants of DFSP also occur in the vulva, including those with myxoid stroma[101,103] and myoid differentiation.[102] Fibrosarcomatous

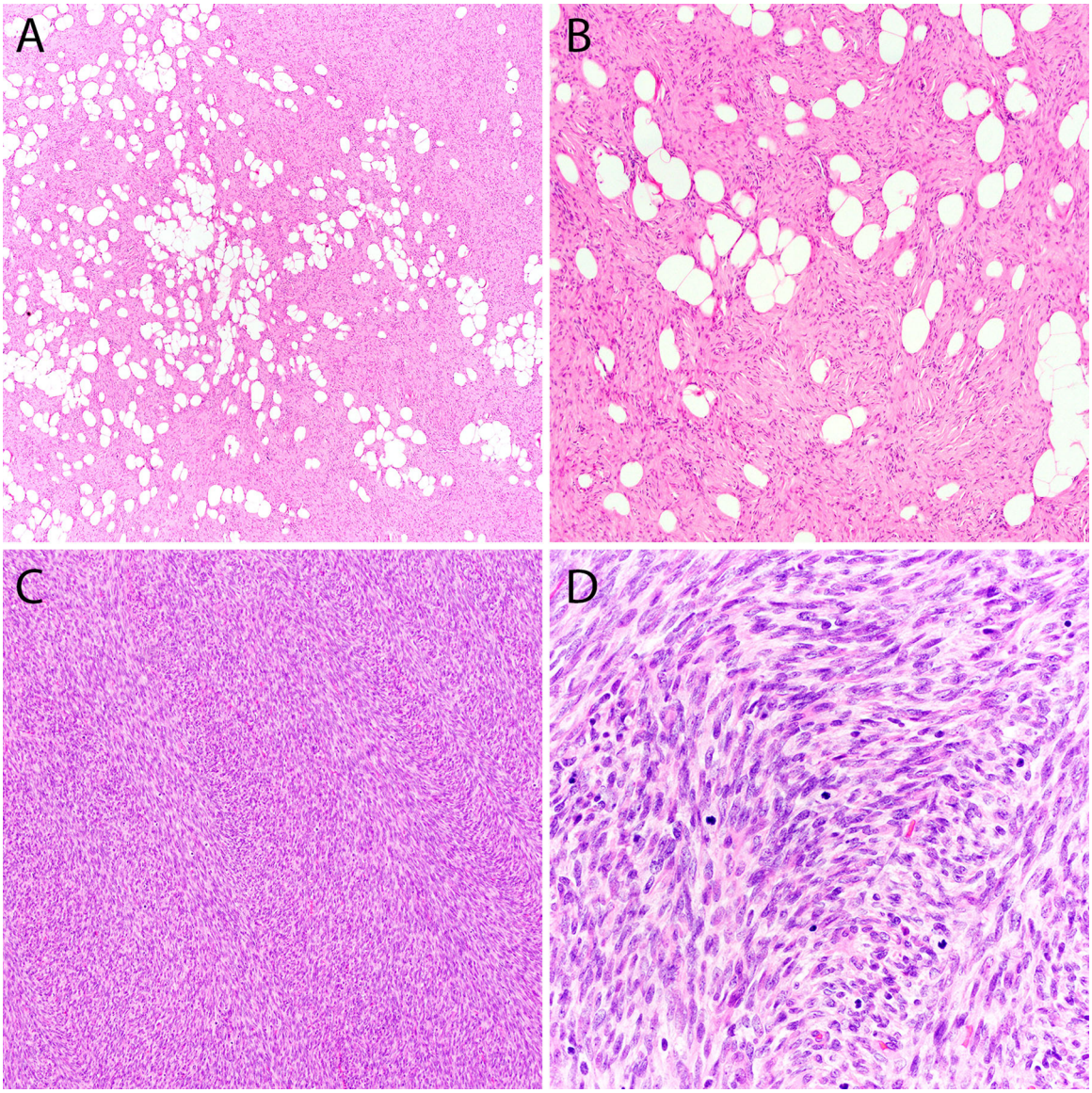

Fig. 8. Dermatofibrosarcoma protuberans with bland spindle cells in a storiform pattern, entrapping subcutaneous fat ("honeycomb" appearance) (A, 40x; B, 100x). Fibrosarcomatous transformation with increased cellularity, sweeping fascicles in a herringbone pattern, and brisk mitoses (C, 100x; D, 400x).

transformation is characterized by long, sweeping, relatively hypercellular "herringbone" fascicles and increased mitotic activity (Fig. 8C, D).[97,98,101,104]

Vulvar DFSP is invariably positive for CD34,[98,100,101,104] although CD34 may be weak or focal in areas of fibrosarcomatous transformation.[104,107] Immunostains for PDGFR-beta, PDGFR-alpha, and c-abl are positive,[101] in keeping with the underlying gene fusion and supporting treatment with imatinib in some cases. ER, PR, SMA, desmin, S100, cytokeratin, CD68, and Factor XIIIa are negative.[97,98,100,101,103] As elsewhere, vulvar DFSP harbors a t(17;22) *COL1A1-PDGFR* fusion, most often as a supernumerary ring chromosome, which can be detected in approximately 90% of tumors by RT-PCR or FISH.[100,104] Unusual breakpoints in *COL1A1* may account for rare tumors with no detectable fusion.[100]

DFSP is a locally aggressive sarcoma with a propensity for local recurrence but low risk of distant metastasis or disease-related death. Wide local excision with 3 cm of negative margins is considered optimal treatment,[97,108] but positive surgical margins are common, and up to 50% of patients experience local recurrence.[101,104,105] Recurrence typically occurs within three years of surgery, but occasionally may be a late event.[109] Patients with persistent positive margins on repeat excisions may undergo hemivulvectomy[96] or radiation.[104] Distant metastases (most often to the lung) occur in < 5% of morphologically classic DFSPs, usually following multiple local recurrences.[109,110] Risk of distant metastasis and death from disease is thought to be higher in DFSP with fibrosarcomatous transformation.[107,110,111] The tyrosine kinase inhibitor imatinib has produced long-term progression-free survival in patients with metastatic disease,[101,112] and detection of *COL1A1-PDGFR* fusion appears to be predictive of imatinib response.[112]

Epithelioid sarcoma

Two distinct types of epithelioid sarcoma (ES) are recognized. Distal-type (classical) ES predominantly affects the distal extremities of men in the second and third decades, and was first described by Enzinger in 1970.[113] In contrast, proximal-type ES—described by Guillou and colleagues in 1997[114]—predominantly affects the soft tissues of the pelvis and limb girdles, shows distinct histomorphology, and exhibits more aggressive clinical behavior.

Vulvar ES has been reported in women between the ages of 17 and

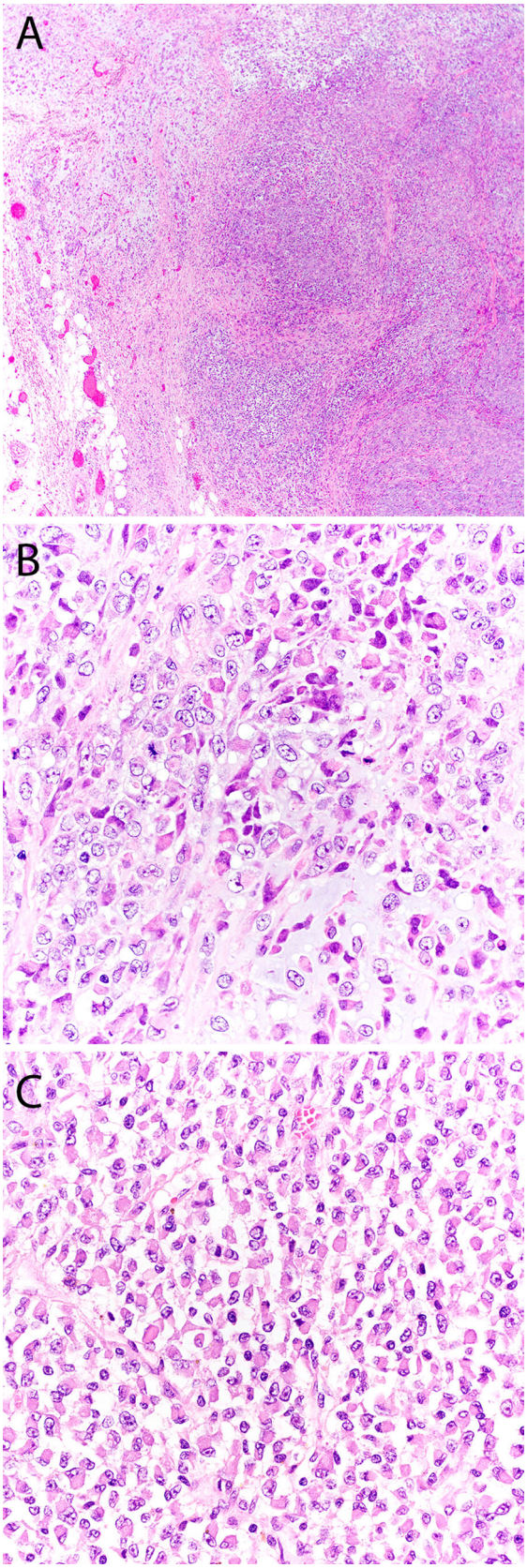

Fig. 9. Proximal-type epithelioid sarcoma infiltrating surrounding fat (A, 40x). Admixture of rhabdoid and non-rhabdoid cells in a variably myxoid stroma (B, 400X). Proximal-type epithelioid sarcoma with exclusively rhabdoid morphology (C, 400x).

80, with most cases presenting in the fourth or fifth decade.[114–121] The superficial labia majora and mons pubis are the most common locations, but the superficial inguinal region or deep soft tissues in the pelvis, buttock, and sacrum may also be affected.[114,115] Vulvar ES most often presents as a painless, slow-growing mass, present for weeks to years before diagnosis (median interval, 4 months).[114,115] Occasional tumors are painful or pruritic.[116,120] On gross examination, vulvar ES is poorly circumscribed, consisting of one or multiple nodules, ranging from 1 to 8 (average, 3 to 5) cm (although tumors in the deep pelvic soft tissues may be larger).[114,115,118–120,122,123] The cut surface is white to tan-grey, with fleshy to firm consistency.

Histologically, the vast majority of vulvar ESs are, unsurprisingly, of proximal type,[114,115,118] with only exceptional cases showing distal-type morphology.[116,119] Proximal-type ES is composed of atypical polygonal cells, growing as nodules, sheets, or cords in a collagenous to myxoid stroma, with infiltration of the dermis and subcutis (Fig. 9A, B). A spindle cell component may be seen peripherally or admixed with epithelioid cells. Some proximal-type ESs are predominantly or entirely composed of rhabdoid-type cells, with a conspicuous eosinophilic cytoplasmic inclusion displacing the nucleus (Fig. 9C). Tumor nuclei have vesicular to clumped chromatin with one or two prominent nucleoli. Mitotic index varies substantially in reported series, with median values from 8 to greater than 20 per 10 hpf,[114,115] and may be higher in tumors with exclusively rhabdoid morphology.[114] Atypical mitoses may be observed.[119] Lymphovascular invasion, tumor necrosis, hemorrhage, cystic degeneration, and peritumoral inflammation are common findings in proximal-type vulvar ES, but a well-developed pseudogranulomatous pattern is distinctly absent.[114,115] Rare instances of distal-type ES of the vulva are morphologically identical to the more common extragenital tumors, reviewed in detail elsewhere.[113,124,125]

Both ES subtypes have the same immunophenotype. Tumors are universally positive for cytokeratin, EMA is positive in approximately 90%, and CD34 in about 50%.[114–116,119] Focal SMA or desmin expression may be seen, while S100 and CD31 are negative. Loss of INI1/SMARCB1 is observed in greater than 90%,[126,127] reflecting the underlying *SMARCB1* gene deletion present in 80 to 90% of both types of ES.[119,126,128,129] Given morphologic and molecular overlap, the distinction between extrarenal malignant rhabdoid tumor and proximal-type ES with exclusively rhabdoid morphology remains an area of debate.[114,116,120,121]

Women with proximal-type ES of the vulva have a high rate of local recurrence, lymph node metastasis, and distant metastasis (particularly to the lung), and approximately 50% die from disease, usually within two years of diagnosis.[114–119,121] Optimal management of vulvar ES includes early recognition and complete excision with wide margins.[118] However, desire for acceptable cosmetic and functional outcome may complicate complete excision, and some ESs recur despite wide excision and clear margins. Robust studies of adjuvant therapy are lacking, although review of published reports suggests that adjuvant radiation may reduce local recurrence and mortality.[119,121] Recurrence or metastasis may follow diagnosis by several years, and long-term follow-up is critical.

Other non-site-specific tumors

The vulva may be affected by a wide spectrum of benign and malignant soft tissue tumors seen more often at extragenital sites. Vascular tumors in the vulva include hemangioma,[130–132] epithelioid and pseudomyogenic hemangioendothelioma,[133–135] and angiosarcoma.[136–139] Vulvar angiosarcomas may arise secondary to radiation therapy for vulvar squamous cell carcinoma[136,138] and prognosis is poor.[137] The vulva may also be involved by neural tumors including schwannoma,[140–143] neurofibroma,[144,145] perineurioma, and malignant peripheral nerve sheath tumor.[146–148] A subset occurs in the context of neurofibromatosis.[144,145] Well-differentiated liposarcoma[149,150] and more rarely, myxoid liposarcoma may occur.[150,151] Skeletal muscle

tumors are infrequent with alveolar rhabdomyosarcoma being more common than embryonal rhabdomyosarcoma.[152–156] Additional tumors that can arise in the vulva include alveolar soft part sarcoma,[157–159] synovial sarcoma,[160,161] low-grade fibromyxoid sarcoma,[162] extraskeletal myxoid chondrosarcoma,[163,164] Ewing sarcoma,[165–167] and *CIC*-rearranged sarcomas.[168] Awareness of these tumors' occurrence in the vulva is critical for accurate diagnosis, together with judicious application of immunohistochemical and molecular studies.

Conclusion

Vulvar soft tissue tumors include a variety of site-specific and non-site-specific entities, each of which is encountered only rarely in routine diagnostic practice. Furthermore, given the potential for some of these lesions to behave in an aggressive fashion, accurate diagnosis is essential for proper clinical management. As a result, vulvar mesenchymal lesions can pose a considerable diagnostic challenge. However, careful morphologic evaluation and integration of clinical, immunophenotypic, and molecular features should enable accurate diagnosis in most cases. Some tumors may defy straightforward classification, and expert consultation should be sought when necessary.

Declaration of Competing Interest

The authors have no conflicts of interest to declare. All authors have participated in the preparation of this manuscript and approved the submitted copy.

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