Soft Tissue Lesions of the Vulva and the Vagina

8

Carlos Parra-Herran

Abstract

With the exception of fibroepithelial stromal polyps, the entities covered in this section are uncommon. For this reason, a broad differential diagnosis must be considered when evaluating a soft tissue lesion in the vulvovaginal region. This differential can be narrowed by patient age (for instance, prepubertal vulvar fibroma and embryonal rhabdomyosarcoma in young women), clinical presentation (slow vs. rapidly growing mass, superficial vs. deep), and morphology (myxoid vs. fibromatous appearance; spindle vs. round tumor cells; obvious smooth muscle, adipocytic, fibroblastic/myofibroblastic, vascular, or Schwannian cell differentiation). Some lesions harbor characteristic genetic abnormalities (loss of the 13q14 locus in cellular angiofibroma and mammary-type myofibroblastoma or amplification of the 12q13-15 locus in atypical lipomatous tumor); in others, the diagnosis fully relies on histopathologic features. In any spindle cell proliferation of the vulva or vagina, *spindled invasive squamous cell carcinoma* and *desmoplastic malignant melanoma* should be considered and excluded through detailed examination and ancillary studies (immunohistochemistry, HPV testing). Entities included in this chapter are organized into benign, locally aggressive, and malignant categories (with the exception of smooth muscle tumors, which are covered together). The chapter emphasizes on lesions with anatomic predilection for the lower genital tract and likely derivation from specialized vulvovaginal stromal cells; while morphologic overlap exists among these lesions, their behavior and clinical management are indolent, with the exception of aggressive angiomyxoma. The latter, thus, should be always considered and excluded through careful assessment, radiologic correlation, and thorough margin assessment on excision material.

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8.1 Benign Lesions

8.1.1 Vulvovaginal Stromal Lesions

The lesions described in this section present preferentially in the vulvovaginal region. Tumors in this category are believed to originate in the specialized stroma of the vaginal and vulvar mucosa, since most express estrogen and progesterone receptors. There is significant morphologic and immunophenotypic overlap among these tumors. The following paragraphs aim to describe the most salient features of each entity and clues in their differential diagnosis. These are also presented schematically in Fig. 8.1.

8.1.1.1 Fibroepithelial Stromal Polyp

Clinical Features

Formerly known as "vulvovaginal polyp" [1], this lesion is common in the vagina [2, 3] and vulva [4] of women predominantly in their fourth decade; however, age rage is wide [1, 5, 6]. Associations with pregnancy and hormone therapy have been observed [2, 5, 7]. The lesion is typically asymptomatic and discovered incidentally on examination in most of cases, while in others it can present with bleeding or pain.

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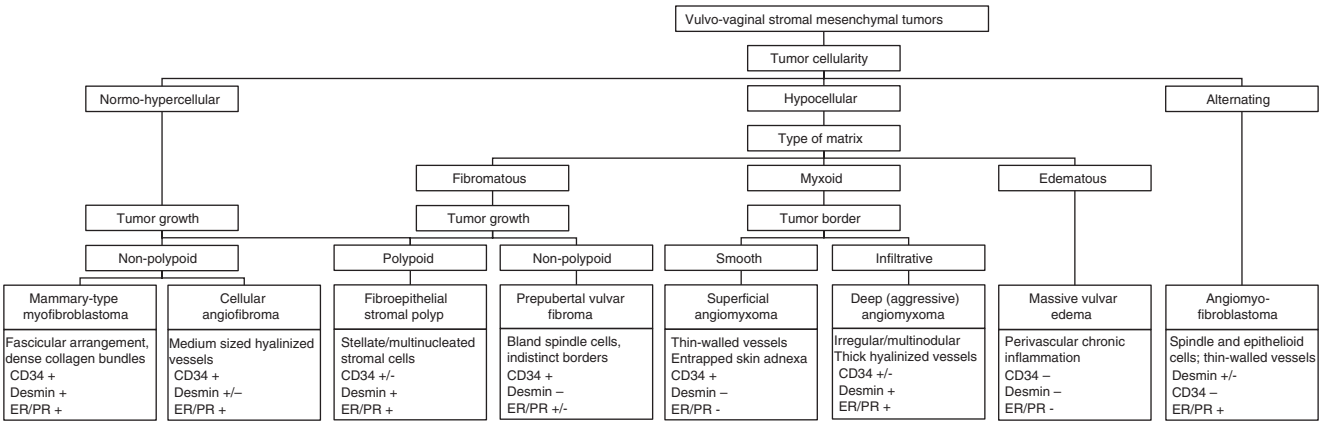

Fig. 8.1 Algorithmic approach to the diagnosis of vulvovaginal stromal tumors. Despite the significant morphologic and immunophenotypic overlap, the proposed features are relatively distinct for each entity and in combination can aid in the differential diagnosis

Pathologic Features

Macroscopically, the lesion is polypoid and pedunculated; when multiple and large, it may acquire a frond-like appearance. Size is variable, ranging from less than 1 to 18 cm [8]. On sectioning, the tissue is uniform white and soft to rubbery.

Microscopically, fibroepithelial stromal polyp is characterized by a uniformly collagenous stromal component containing bland myofibroblastic spindle cells. The lesion has variably sized blood vessels, which often are thick and large at the base of the polyp. Toward the superficial (subepithelial) aspect of the lesion, the stromal cells appear stellate and multinucleated with larger and more hyperchromatic nuclei (akin to the subepithelial stromal cells sometimes found in the normal vaginal mucosa, Fig. 8.2). Lesions are frequently bland, hypocellular, and may present significant atypia. Indeed, initial descriptions in the literature termed fibroepithelial polyps as "pseudosarcoma botryoides" and "cellular pseudosarcomatous fibroepithelial stromal polyp," alluding to the frequent presence of large bizarre cells which could be mistaken for a malignant process [6, 9]. This scenario appears to be more common in cases presenting during pregnancy [4, 6].

Ancillary Studies

The stromal cells in fibroepithelial polyps are reported to express desmin, vimentin, estrogen, and progesterone receptors [1, 6, 10]. No recurrent molecular alterations have been reported to date.

Differential Diagnosis

Acrochordon (skin tag) is a term used for polyps outside of the genital area. While morphologically similar to skin tags, fibroepithelial polyp is the preferred term in the vulvovaginal region as it may have a different pathogenesis, given its association with sex hormone expression and the distinct presence of stellate stromal cells, native to the lower genital tract mucosa.

Fibroepithelial polyps exhibiting hypercellularity and stromal pleomorphism should be distinguished from malignant proliferations, importantly rhabdomyosarcoma. Unlike the latter, fibroepithelial stromal polyp lacks a cambium layer and has scattered bizarre stromal cells extending to the epithelial base. Embryonal rhabdomyosarcoma and genital rhabdomyoma both have cells with identifiable striations, which will be absent in cellular fibroepithelial polyp. Furthermore, embryonal rhabdomyosarcoma usually presents in prepubertal girls.

Fibroepithelial polyps may undergo torsion, which gives them an edematous, hypocellular, and congested appearance, potentially mimicking an angiomyxoma. Unlike fibroepithelial polyp, deep (aggressive) angiomyxoma involves deep connective tissue in an infiltrative fashion and is less likely polypoid. Superficial angiomyxoma is frequently lobulated, multinodular, and well demarcated from the underlying tissue. Lastly, vulvar hypertrophy is usually unilateral, and its stroma highly resembles fibroepithelial polyp microscopically; however, vulvar hypertrophy presents as non-polypoid enlargement of the labium minus. Some consider both entities part of a spectrum of stromal response to sex hormones [11].

Prognosis and Management

Fibroepithelial stromal polyps are benign, although they may recur if incompletely excised or during pregnancy [4, 6].

8.1.1.2 Angiomyofibroblastoma

Clinical Features

With few exceptions reported in the scrotum and upper female genital tract, angiomyofibroblastoma predominantly occurs in the vulva and vagina of reproductive-aged women,

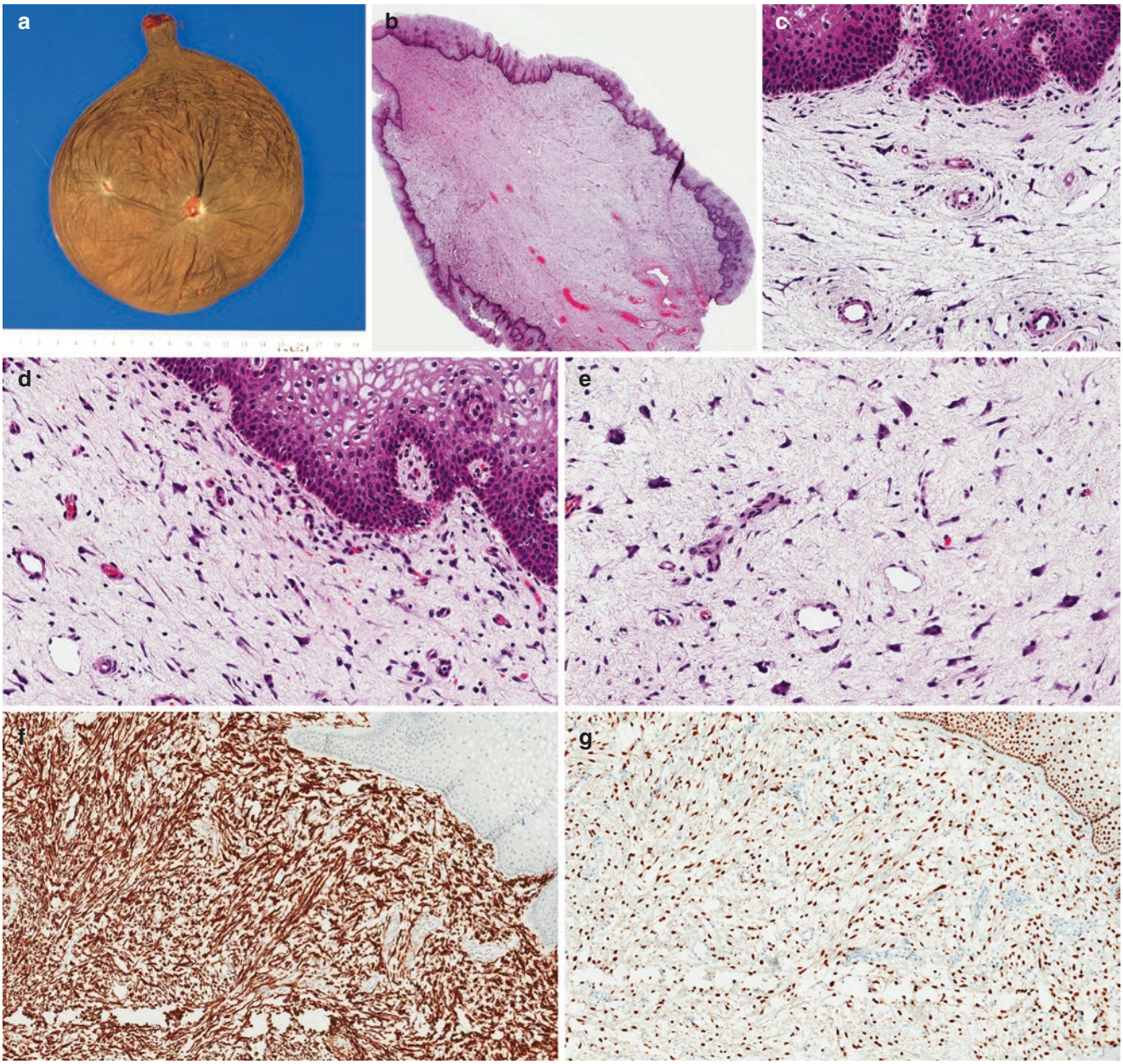

Fig. 8.2 Fibroepithelial stromal polyp. This lesion is usually exophytic and can be quite large (**a**, courtesy of Dr. C Matthew Quick); it contains uniform stromal cellularity and prominent vasculature toward the polyp base (**b**); stromal cells are characteristic with mildly enlarged multinucleated and stellate nuclei in a subepithelial location (**c**–**e**). They are usually positive for desmin (**f**) and ER (**g**)

presenting as a slow-growing painless mass [12–15]. The lesion is commonly excised under a clinical impression of lipoma or Bartholin gland cyst.

Pathologic Features

The tumor is soft and uniform under macroscopic examination. Size is ~5 cm on average but can be as large as 30 cm [15]. Histologically, the tumor is composed of mildly enlarged spindle and epithelioid stromal cells clustered around vessels, which are thin walled (capillary sized) and evenly distributed. Plasmacytoid and multinucleated forms can be observed. The lesion is well demarcated from the surrounding tissue. The lesion has heterogeneous cellularity under low-power magnification, given the presence of edema and perivascular stromal cell condensation (Fig. 8.3). In addition, adipose tissue is commonly present; indeed, a lipomatous variant has been proposed [16].

Ancillary Studies

Expression of smooth muscle markers is variable: 30–60% are positive for desmin, whereas 15–20% are positive for

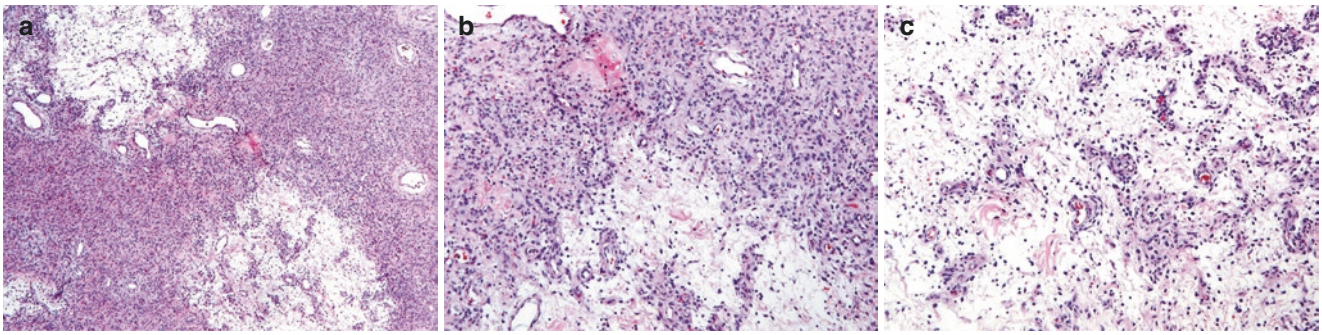

Fig. 8.3 Angiomyofibroblastoma. A biphasic pattern is noted in low power view (**a**), comprised of alternating hypercellular fascicular (**b**) and hypocellular edematous areas (**c**). Courtesy of Dr. C. Matthew Quick (University of Arkansas)

smooth muscle actin. CD34 tends to be negative (although expression is seen in up to 15% of cases) [17]. *HMGA2* rearrangements and monoallelic loss of *FOXO1* loci (13q14), characteristic of aggressive angiomyxoma, and cellular angiofibroma, respectively, are absent in angiomyofibroblastoma [17, 18].

Differential Diagnosis

The characteristic pattern of alternating hypocellular and hypercellular areas in angiomyofibroblastoma is an important clue in excluding other vulvovaginal mesenchymal lesions, importantly aggressive angiomyxoma which displays uniform hypocellularity. In addition, aggressive angiomyxoma contains thick-walled vessels, which are typically absent in angiomyofibroblastoma. Cellular angiofibroma tends to have larger (medium-sized) vessels with hyalinized walls, contrasting with the capillary-sized vasculature of angiomyofibroblastoma. In addition to having a more uniform cellular distribution, cellular angiofibroma, prepubertal vulvar fibroma, and mammary-type myofibroblastoma are all positive for CD34.

Prognosis and Management

Angiomyofibroblastoma is benign, and conservative local excision is curative. Sarcomatous transformation within angiomyofibroblastoma has been reported [19].

8.1.1.3 Cellular Angiofibroma

Clinical Features

Unlike other vulvovaginal mesenchymal proliferations, cellular angiofibroma presents at similar rates in the male inguinoscrotal region. Similar to angiomyofibroblastoma, vulvovaginal cellular angiofibroma preferentially occurs in adult women as a superficial, painless, slow-growing nodule [20, 21].

Pathologic Features

The lesion is usually less than 5 cm in size and grossly appears as non-polypoid and well circumscribed, although polypoid exceptions occur [22]. Histologically, cellular angiofibroma is composed of bland spindle-shaped cells arranged in a cellular distribution, intersected by short bundles of wispy collagen and small- to medium-sized hyalinized vessels (Fig. 8.4). Atypical features can be rarely seen, ranging from occasional atypical nuclei to focal frank sarcomatous transformation [23, 24]. The latter is identified as an abrupt transition to highly pleomorphic sarcoma with either liposarcoma or high-grade pleomorphic sarcoma appearance.

Ancillary Studies

By immunohistochemistry, the stromal cells have a "fibroblastic" phenotype with relatively high rates of CD34 (up to 60%) in addition to low rates of desmin and smooth muscle actin positivity (20%), as well as absence of H-Caldesmon expression [22]. As with other vulvovaginal stromal lesions, estrogen and progesterone receptor staining is positive in most cases. Cellular angiofibroma harbors monoallelic deletions of *RB1* and *FOXO1* at the 13q14 locus. These abnormalities are shared with spindle cell lipoma and mammary-type myofibroblastoma, which has led to an understanding of these three entities as a spectrum of the same biologic entity [25, 26].

Differential Diagnosis

The relative hypercellularity, overall absence of thick vessels, and positivity for CD34/desmin in cellular angiofibroma are helpful features in its distinction from aggressive angiomyxoma (thick vessels, hypocellular, CD34/desmin often negative) and angiomyofibroblastoma (thin vessels, alternating cellularity, CD34 negative). Of note, cellular angiofibroma shares significant morphologic, immunophenotypic, and molecular overlap with mammary-type myofibroblastoma, described below.

Prognosis and Management

Conservative local excision with negative margins is sufficient as these lesions behave in a benign fashion with no

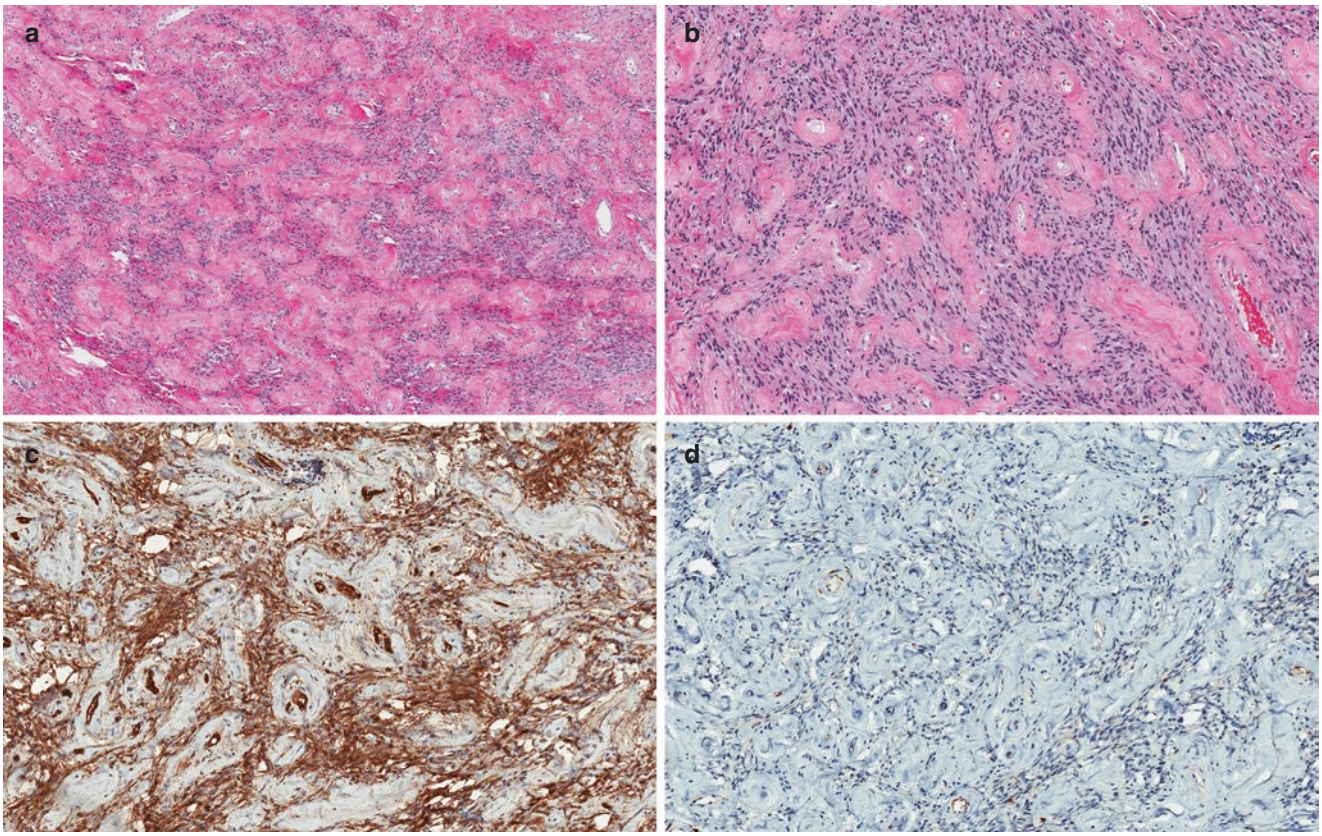

Fig. 8.4 Cellular angiofibroma. Stromal cells are densely packed imparting a hypercellular appearance (**a**); medium-sized vessels with hyalinized walls are uniformly dispersed (**b**). Stromal cells are positive for CD34 (**c**) and negative for desmin (**d**)

recurrences or metastatic potential. This seems to apply even to cases with atypia or sarcomatous transformation, although clinical follow-up is limited [23].

8.1.1.4 Mammary-Type Myofibroblastoma

Clinical Features

This tumor is not exclusive to the lower genital tract. As the name implies, mammary-type myofibroblastoma was first described in the breast, but its anatomic distribution is wide. It is, however, described in this section given its similarity with the other vulvovaginal lesions discussed [27]. Myofibroblastoma of the lower genital tract, also known as "superficial cervicovaginal myofibroblastoma," has a wide age of presentation (23–80 years); most cases arise in the vagina [28].

Pathologic Features

Myofibroblastoma grossly appears as a polypoid or superficial, soft to rubbery nodular mass, usually less than 10 cm in size [28]. Microscopically, the tumor features a sharp demarcation from the superficial dermis [29]. The neoplastic cells are bland and spindle in shape, arranged in fascicles, and separated by dense collagen (Fig. 8.5). Intratumoral adipose tissue and myxoid change have been described.

Ancillary Studies

Neoplastic cells in myofibroblastoma usually express estrogen and progesterone receptors (>95%), desmin (~90%), and CD34 (68%) [28, 29]. Monoallelic loss of *FOXO1* on 13q14 has been documented in lower genital myofibroblastoma [30], similar to its extragenital counterparts and related tumors (spindle cell lipoma and cellular angiofibroma).

Differential Diagnosis

Compared to mammary-type myofibroblastoma, aggressive angiomyxoma is less cellular and has an infiltrative interface. Cellular angiofibroma and mammary-type myofibroblastoma are related lesions, distinguishable only based on the more prominent vascular component and the absence of interspersed collagen bundles in the former. Angiomyofibroblastoma is different from myofibroblastoma in its alternating cellularity and delicate vasculature. Prepubertal vulvar fibroma presents in younger women, has an ill-demarcated interface, and lacks the fascicular architecture of myofibroblastoma.

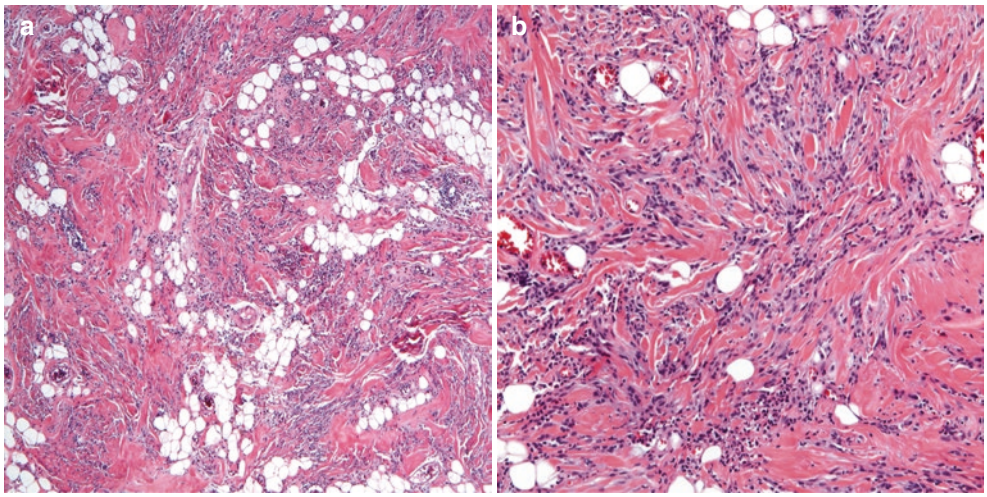

Fig. 8.5 Mammary-type myofibroblastoma. The lesion is composed of bland fusiform cells arranged in fascicles surrounding dense collagen bundles and with variable amounts of adipose tissue (**a**, **b**). Courtesy of Dr. C. Matthew Quick (University of Arkansas)

Prognosis and Management

Mammary type myofibroblastoma is a benign process with no recurrences or metastases documented to date.

8.1.1.5 Prepubertal Vulvar Fibroma

Clinical Features

With occasional exceptions seen in postmenopause [31], prepubertal vulvar fibroma affects premenarchal girls [32, 33]. The nature of prepubertal vulvar fibroma is uncertain; it may represent a response of the vulvar mesenchyme to the surge in sex hormones during puberty [33]. However, its unilaterality and potential for recurrence are features suggestive of a neoplastic process [32]. Patients present with slow-progressing, unilateral, painless vulvar enlargement, usually in the labium majus.

Pathologic Features

Prepubertal vulvar fibroma is characteristically superficial and small in size (median 4 cm). The microscopic borders tend to be indistinct, and extension to the resection margins is usually observed [32]. The lesion is comprised of bland fusiform cells individually dispersed in a fibrotic stroma, encasing adipose tissue and skin adnexa. The stroma can contain variable amounts of myxoid matrix, edema, and/or collagen.

Ancillary Studies

The spindle cell population is positive for estrogen receptor and CD34 but negative for desmin, smooth muscle actin, and S-100. Progesterone receptor expression is variable [33]. It is unknown if this lesion is associated with any recurrent genomic abnormality.

Differential Diagnosis

Prepubertal vulvar fibroma can simulate morphologically aggressive angiomyxoma, as both entities are hypocellular and have ill-defined margins. Aggressive angiomyxoma presents in reproductive-age and postmenopausal women and has a diffuse myxoid component. In challenging cases, CD34 can be of value (positive in vulvar fibroma, more often negative in aggressive angiomyxoma).

Prognosis and Management

Conservative surgical treatment is usually recommended. Prepubertal vulvar fibroma appears to be benign, although it may recur if margins are positive.

8.1.1.6 Superficial Angiomyxoma

Clinical Features

This lesion is not exclusive to the genital area. In fact, it is most frequent in the trunk and neck [34]. It is, nonetheless, closely related to the other tumors presented in this section. As its name implies, the tumor is typically superficial and frequently polypoid. An association between genital superficial angiomyxoma and Carney's complex has not been observed [35]. However, the occurrence of multiple angiomyxomas in other anatomic locations is highly associated with this condition.

Pathologic Features

Superficial angiomyxoma is usually small (less than 5 cm), multilobulated, and gelatinous. On microscopic examination, demarcation from the overlying superficial dermis can be appreciated. The neoplastic population is composed of bland spindle and stellate-shaped cells in a prominent myxoid background with a thin-walled vasculature (Fig. 8.6). Nests of benign epithelium (presumably entrapped adnexal structures) can be seen.

Ancillary Studies

Stromal cells are positive for CD34 and negative for desmin. Unlike most other vulvovaginal stromal tumors, superficial

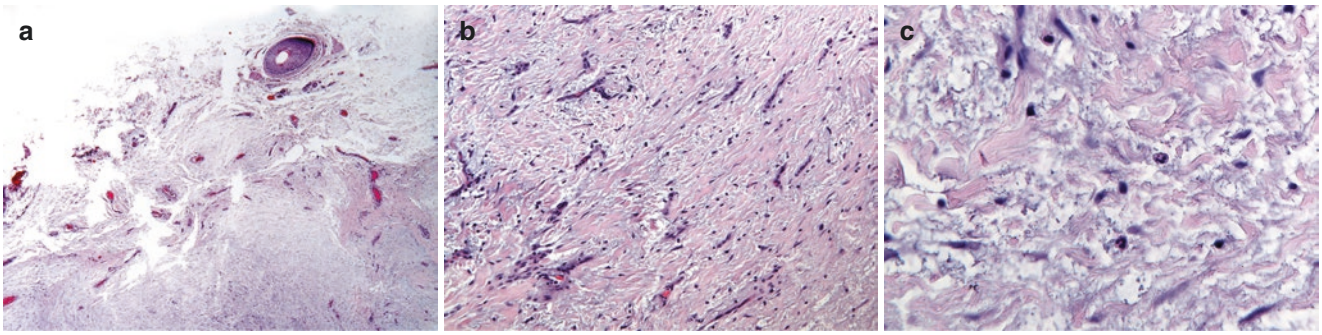

Fig. 8.6 Superficial angiomyxoma. Uniformly hypocellular lesion, commonly with intratumoral entrapped skin adnexal structures (**a**); stromal cells and thin-walled vessels are uniformly distributed (**b**); stromal cells are bland (**c**). Courtesy of Dr. Matt Quick (University of Arkansas)

angiomyxoma is negative for estrogen and progesterone receptors [36].

Differential Diagnosis

Outside of the vulvovaginal region, common mimickers of superficial angiomyxoma include sheath myxoma, trichodiscoma, trichofolliculoma, and low-grade myxofibrosarcoma [34]. In the female lower genital tract, the most important differential diagnosis is deep (aggressive) angiomyxoma. The latter tends to be large (>10 cm) and involves deep subcutaneous tissue, whereas superficial angiomyxoma is small and confined to the skin. Superficial angiomyxoma is multinodular, but the borders are smooth unlike deep angiomyxoma which is infiltrative. Positivity for desmin, estrogen receptor, and/or progesterone receptor argues against superficial angiomyxoma and should raise the possibility of aggressive angiomyxoma. Fibroepithelial stromal polyp is an important differential with superficial angiomyxoma, since both lesions are polypoid and when torsion and subsequent edema are present in the former. Superficial angiomyxoma is favored in the presence of a definitive myxoid stroma and when the lesion is well demarcated from the surrounding dermis.

Prognosis and Management

While regarded as a benign tumor, nondestructive recurrence has been reported, usually in the context of a positive margin [35]. Thus, excisional management should aim for a wide negative margin.

8.1.2 Other Benign Lesions

8.1.2.1 Genital Rhabdomyoma

Clinical Features

Extracardiac rhabdomyomas are rare and unrelated to tuberous sclerosis (unlike the more common cardiac rhabdomyoma). Rhabdomyoma of the genital type is very rare, accounting for 10% of all extracardial rhabdomyomas [37, 38]. They usually appear in the vagina of middle-aged women as a painless and slow-growing exophytic mass. The clinical impression is usually of a fibroepithelial polyp [39].

Pathologic Features

On gross examination, genital rhabdomyoma is polypoid and small, usually less than 3 cm. The lesion is comprised of fascicles of spindle and polygonal cells with abundant cytoplasm and striations identifiable under light microscopy. The nuclei are bland, round, and uniform with pale chromatin and conspicuous nucleoli. Mitotic activity, if present, is low. The striated cells are distributed throughout the lesion, predominantly in the subepithelial stroma.

Ancillary Studies

By immunohistochemistry, striated cells are positive for desmin, MyoD1, and myogenin (MYF4). No significant copy number alterations were identified in two cases recently tested [39]. Importantly, there was absence of heterozygosity in chromosomes 9q22.32 (*PTCH* gene) and 10q24.32 (*SUFU* gene), which has been reported in rhabdomyoma of cardiac, adult, and fetal types.

Differential Diagnosis

Genital rhabdomyoma is usually clinically mistaken for a fibroepithelial polyp. Microscopic identification of bland rhabdomyoblastic cells will point toward the right diagnosis. Immunohistochemistry is not generally needed, and it is key to bear in mind that fibroepithelial polyps can be positive for myogenin [40]. Another important differential diagnosis is embryonal rhabdomyosarcoma, which occurs in younger patients and displays conspicuous atypia, proliferation, and a characteristic cambium layer in the submucosa.

Prognosis and Management

Genital rhabdomyoma is benign with no recurrences or malignant transformation reported following local excision [39].

8.1.2.2 Lipoma

Clinical Features

Adipocytic neoplasms are exceedingly rare in the vulvovaginal region, presumably because of the scant amount of fat tissue in this anatomic location. Lipomas are typically described as single or multiple slow-growing, painless, mobile masses found in areas of swelling [41]. The diagnosis of lipoma is usually suspected clinically due to the characteristic soft consistency and mobility of the lesion. Interestingly, cases reported in children have a strong predilection for the right vulva [42, 43].

Pathologic Features

Vulvar lipoma appears grossly as a well circumscribed, soft, yellow, and tan mass. Microscopically, the lesion is composed of mature adipose tissue with variable amounts of collagenous septa (Fig. 8.7). A spindle cell/pleomorphic lipoma variant containing floret-like multinucleated cells has also been described in the vulva [44].

Differential Diagnosis

The principal differential diagnosis is with adipocytic malignancies, discussed later in this chapter. Lower genital angiomyofibroblastoma and mammary-type myofibroblastoma may contain significant amounts of adipose tissue, similar to lipoma. However, thorough examination and sampling will identify stromal areas diagnostic of these entities.

Prognosis and Management

Lipomas are benign. Observation is advisable unless symptoms persist, in which case excision is curative.

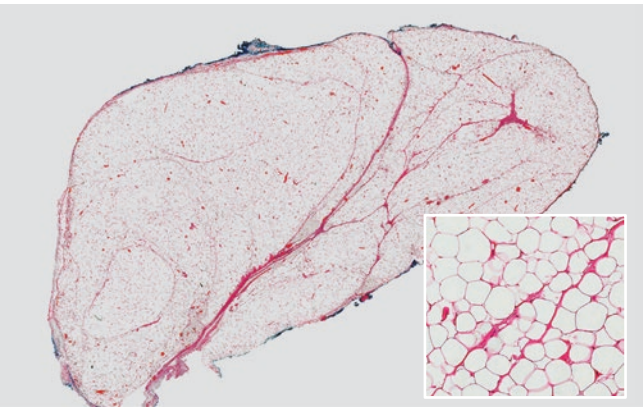

Fig. 8.7 Lipoma. Well-circumscribed lesion composed of mature adipose tissue and bands of collagen of variable thickness (insert)

8.1.2.3 Schwannoma and Neurofibroma

These benign lesions derived from peripheral nerve are occasionally seen in the vulvovaginal region and are described together given their benign nature and morphologic overlap.

Clinical Features

Vulvar schwannoma has been rarely described in this anatomic region [45–51]. Remarkably, of the few cases reported, the vast majority are located in the clitoris. It presents as a non-tender, soft mass, or as de novo clitoral enlargement [45, 46]. Age range widely varies, with predilection for middle-aged women.

Neurofibroma of the lower genital tract is similarly infrequent, occurring sporadically or in the context of neurofibromatosis type 1. The tumor frequently involves the clitoris causing clitoromegaly or a distinct mass [52–55]. Indeed, clitoromegaly can be a presenting sign of vulvar neurofibromatosis [56]. A case of a vaginal benign triton tumor (neurofibroma with rhabdomyomatous differentiation) has been reported [57].

Pathologic Features

Schwannomas are encapsulated lesions. Classic tumors display the characteristic alternating Antoni type A and Antoni type B areas. The former is composed of tightly packed sheaths of spindle cells with palisading and swirling patterns, while the latter is comprised of loosely packed spindle cells (Fig. 8.8). Cystic degeneration and Verocay body-like structures can be observed. A cellular variant, composed exclusively of Antoni A areas, has been described. Plexiform schwannoma, also reported in the vulva [46–48], is characterized by intraneural multinodular anastomosing growths (hence the term plexiform) with either conventional or cellular morphology. Ancient schwannoma is characterized by degenerative myxoid and hyalinized areas and bizarre hyperchromatic nuclei within Antoni B regions [50].

Neurofibroma arises within peripheral nerves and can be localized (single lesion within an otherwise preserved nerve), diffuse (large, obliterating the nerve, and involving surrounding fibroadipose tissue), or plexiform (mass of expanded nerves). Microscopically, neurofibroma is well circumscribed but not encapsulated. It is comprised of a mixture of spindle cells, small nerves, and mast cells embedded in a myxoid to collagenous stroma. Spindle cells have pointed ends, similar to schwannoma.

Ancillary Studies

Similar to extragenital sites, schwannomas are positive for S100 (stronger in Antoni A areas), GFAP, and CD57. Neurofibromas are also consistently positive for S100 but in a less diffuse fashion. Collagen type IV is positive in a pericellular fashion in both lesions. At the ultrastructural level,

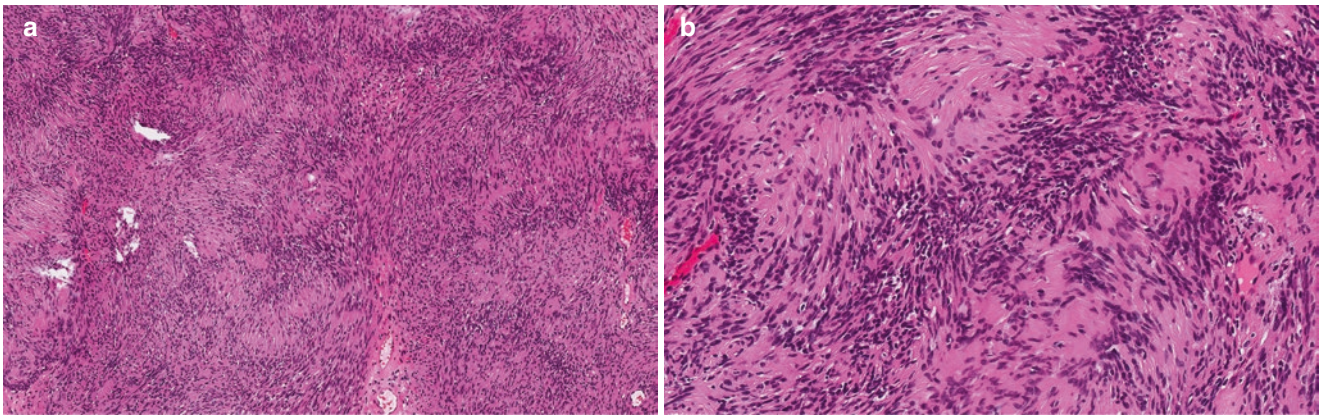

Fig. 8.8 Schwannoma. Lesion with alternating zones of hypercellularity (Antoni A) and hypocellularity (Antoni B) (**a**) and nuclear palisading on high-power magnification (**b**)

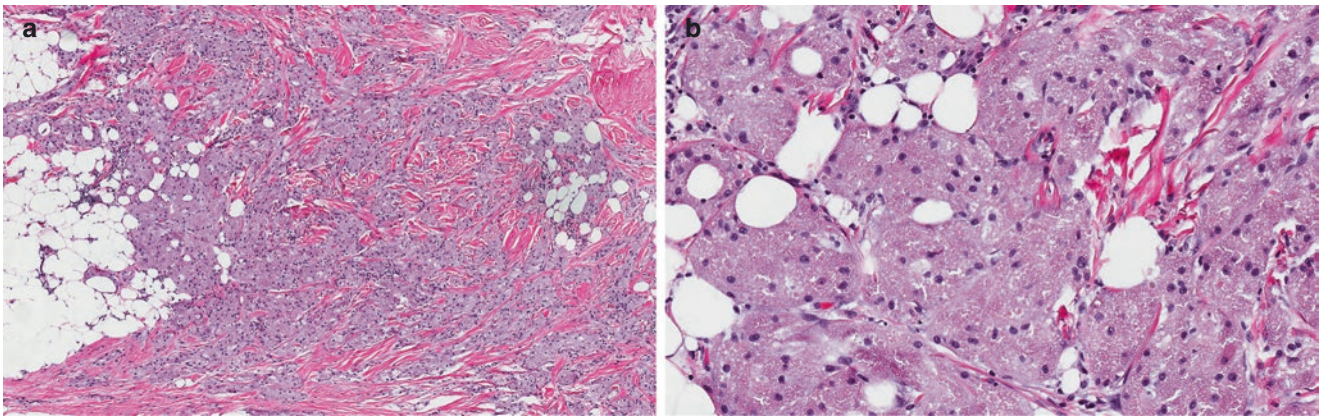

Fig. 8.9 Granular cell tumor. The tumor usually has an infiltrative interface with the surrounding tissue (**a**); it is composed of bland polygonal cells with abundant granular cytoplasm (**b**)

neurofibromas are composed of Schwann cells, perineurial cells, and fibroblasts.

Differential Diagnosis

Schwannoma and neurofibroma are clinically and morphologically similar. Distinguishing features of schwannoma include the presence of a true capsule, a biphasic cellular pattern, and diffuse positivity for S100. An important, and often difficult, distinction is between these two benign lesions and malignant peripheral nerve sheath tumor. The presence of the following features should suggest malignancy: prominent cellular atypia, hyperchromasia, necrosis, and proliferation (>1 mitosis in 10 HPFs).

Prognosis and Management

The treatment of choice for both schwannoma and neurofibroma is complete excision. Prognosis is favorable with no recurrences reported in the vulvar region [48].

8.1.2.4 Granular Cell Tumor

Clinical Features

Granular cell tumor is an uncommon neoplasm of neural sheath origin; 4–10% of cases arise in the vulva, usually the labium majus [58, 59]. It occurs more commonly in black and perimenopausal women (mean age 50 years) [60, 61]. The tumor is superficial and slow growing, often found incidentally.

Pathologic Features

Tumor size rarely exceeds 10 cm. Histologically, it consists of polygonal cells with abundant eosinophilic granular cytoplasm and round to ovoid central nuclei (Fig. 8.9). The interface with the surrounding tissue can be smooth or, less frequently, infiltrative. Perineural involvement is a common finding. The overlying epithelium usually displays reactive changes including pseudoepitheliomatous hyperplasia, which can be quite prominent [62].

Ancillary Studies

Tumor cells display ultrastructural evidence of neural (Schwannian) derivation and are positive for S100. The cells may also stain for NKI-C3, a nonspecific antibody against lysosomes. Intracytoplasmic granules (lysosomes) are periodic acid-Schiff (PAS)-positive, diastase-resistant.

Differential Diagnosis

The most relevant differential diagnosis, particularly in superficial biopsy specimens, is with squamous cell carcinoma, since the overlying epidermis of granular cell tumor is frequently hyperplastic. Upon close examination, a syncytial-like proliferation in the superficial dermis is characteristic of granular cell tumor.

Prognosis and Management

Conservative complete excision is the preferred treatment, since most lesions are indolent. Recurrence is uncommon, more likely seen in tumors with infiltrative edges and perineural invasion [58]. One case with malignant behavior has been reported [63].

8.1.2.5 Hemangioma

Clinical Features

Capillary hemangiomas are common in the vulvar region, seen as dome-shaped purple papules predominantly in elderly women [64]. Cavernous hemangiomas (also termed venous malformations) have a wider age of presentation including infants and adolescents (median age 44 years in a small series) [65]. Lesions tend to grow after puberty, at which point become symptomatic causing bleeding or mass effect. An association with pregnancy and postpartum complications has been reported [66, 67]. Cases mimicking clitoromegaly have also been described [68, 69].

Pathologic Features

Capillary hemangiomas are typically small (<2 cm). Cavernous hemangiomas, on the other hand, can be large and even efface the vaginal or vulvar surface macroscopically [65]. Like those in other anatomic locations, vulvovaginal hemangiomas contain irregularly dilated thin-walled venous channels lined by a monolayer of flat endothelial cells and surrounded by a thin muscular layer (Fig. 8.10). Intraluminal thrombosis can be observed.

Prognosis and Management

Capillary hemangiomas rarely require treatment; when symptomatic, electrocautery is a safe approach. Cavernous hemangiomas can be managed with simple excision or embolization. Prognosis is excellent after conservative treatment [65].

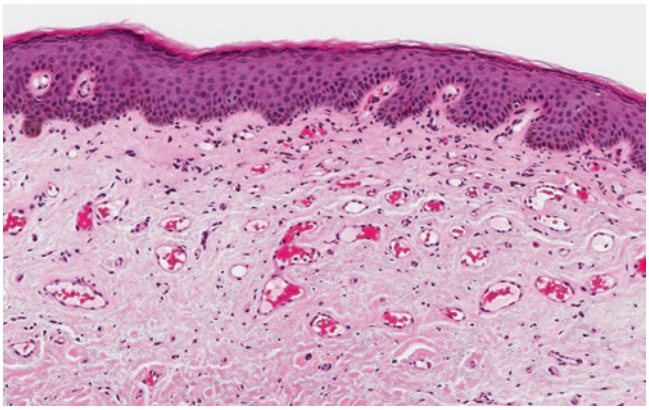

Fig. 8.10 Capillary hemangioma. Superficial proliferation of thin and small blood vessels lined by bland endothelium

8.1.2.6 Acquired Lymphangiectasia

Clinical Features

Acquired lymphangiectasia (lymphangioma circumscriptum) of the vulva is a reactive condition, most commonly secondary to lymphatic obstruction and distortion of the pelvic lymphatic vascular network. A recent case series, documenting cumulative evidence in the literature, grouped cases according to the cause of lymphatic obstruction as malignancy-associated (61%), Crohn's disease-associated (12%), and tuberculosis-associated (9%) [70]. Malignancy-related lymphangiectasia is due to lymphatic obstruction by a tumor and/or treatment (lymphadenectomy, radiation). In these patients, acquired lymphangiectasia can appear years after the initial cancer diagnosis. Patients usually complain of vulvar swelling, pain, discharge, and skin irritation, frequently leading to superimposed infection [71]. Median age at presentation is ~50 years [70].

Pathologic Features

Lesion size varies and can exceed 10 cm [72]. On gross examination, the overlying skin frequently appears irritated, and hyperplastic verrucoid changes can be exuberant. Histologically, the lesion is composed of markedly dilated intradermal lymphatics. Channels are lined by a single layer of flat endothelium and devoid of a muscular layer (Fig. 8.11).

Ancillary Studies

Endothelium lining the dilated channels is positive for CD31 and D2–40 by immunohistochemistry; CD34 is usually negative [72].

Prognosis and Management

Management depends on the clinical presentation and the condition of the locoregional lymphatic network. It includes laser therapy, cryotherapy, electrocautery, and surgical excision.

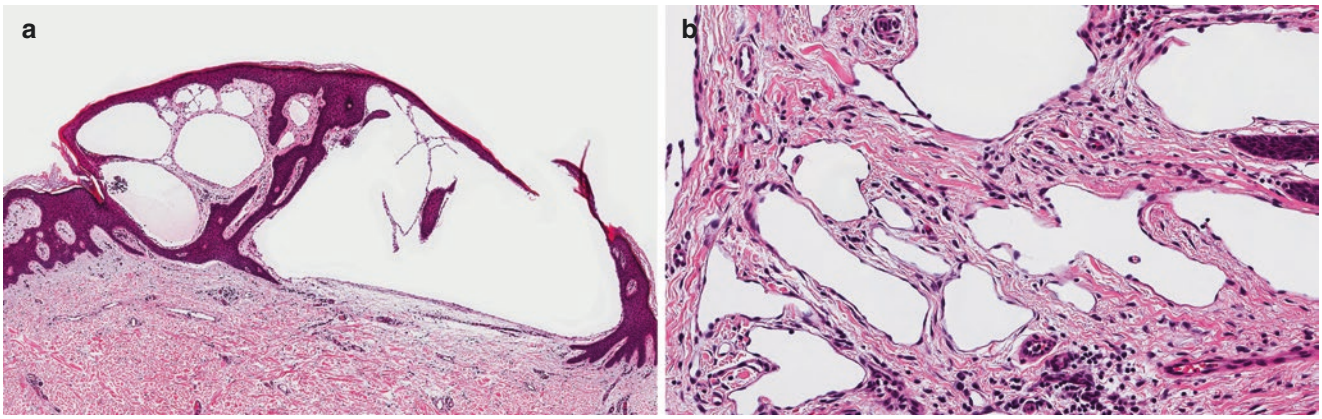

Fig. 8.11 Acquired lymphangiectasia. Markedly dilated lymphatic channels in the papillary dermis (**a**); vessels are lined by unremarkable endothelium and lack a muscular layer (**b**)

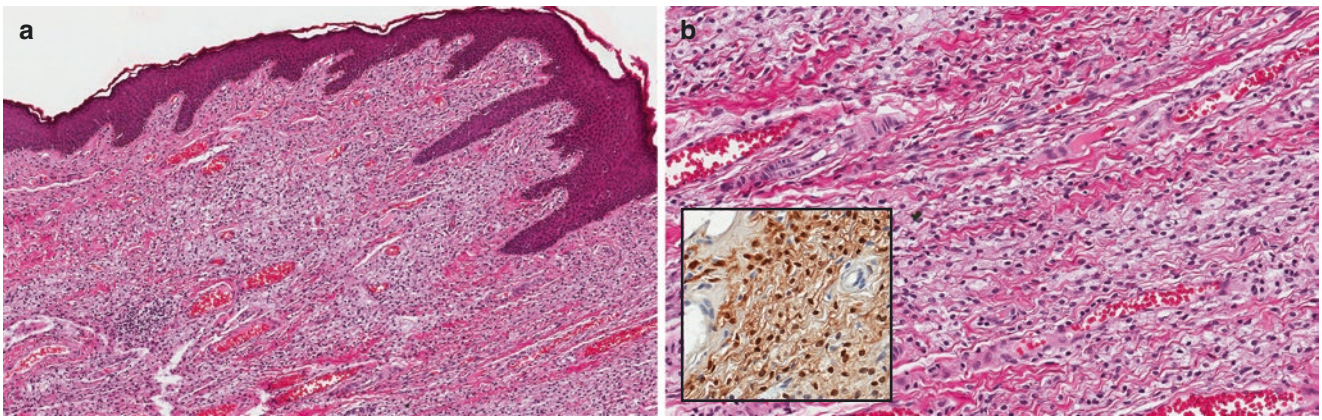

Fig. 8.12 Dermatofibroma. Subepithelial spindle cell proliferation with a storiform pattern (**a**). Cells dissect collagen bundles (**b**); they are positive for factor XIIIa (insert)

8.1.2.7 Angiokeratoma

Clinical Features

Angiokeratoma is a lesion that has a predilection for the vulvar region. Like other benign vascular proliferations discussed in this chapter, angiokeratoma is thought to represent a reactive ectatic process rather than true neoplasia. Vulvar angiokeratoma is also termed angiokeratoma of Fordyce (genital type), one of four types described in the literature [73]. Vulvar lesions are typical of perimenopausal women, although pediatric cases have been reported [73–75].

Pathologic Features

Vulvar angiokeratoma usually appears as a small (<1 cm) papule or warty nodule [76]. The lesion is comprised of dilated blood vessels in the papillary dermis, immediately surrounded by acanthotic and hyperkeratotic epidermis.

Prognosis and Management

In most cases, the lesion can be observed. If symptomatic, local excision is curative. In patients with multiple lesions, the possibility of Fabry's disease should be considered, especially if extending outside the genital area.

8.1.2.8 Dermatofibroma

Clinical Features

Dermatofibroma arises in the superficial dermal stroma. The vulva is an uncommon location, compared to more frequent locations like the extremities and trunk [77].

Pathologic Features

On gross examination, dermatofibroma appears as a flesh-colored or pigmented nodule or papule. On histologic examination, most vulvar dermatofibromas display a classic morphology: a relatively well-circumscribed spindle cell proliferation with a storiform pattern (Fig. 8.12). The spindle cells surround collagen bundles, more prominently at the lesion edges (polarized light can help visualized entrapped collagen within the lesion).

Ancillary Studies

Dermatofibroma is positive for factor XIIIa (diffusely) and usually negative for CD34 [78].

Differential Diagnosis

The principal diagnostic differential is dermatofibrosarcoma protuberans. Unlike dermatofibroma, this lesion infiltrates subcutaneous tissue and lacks the entrapped birefringent collagen and overlying epithelial hyperplastic changes seen in dermatofibroma. In addition, it tends to be diffusely positive for CD34 and negative for factor XIIIa.

Prognosis and Management

Classic dermatofibroma is considered benign; hence, observation or localized excision is appropriate. Other types (cellular, aneurysmal, atypical) have the potential for local recurrence; thus, initial sampling should be followed by re-excision if margins are positive [79, 80].

8.2 Locally Aggressive and Malignant Lesions

8.2.1 Vulvovaginal Stromal Lesions

8.2.1.1 Deep (Aggressive) Angiomyxoma

Clinical Features

Deep (aggressive) angiomyxoma is a locally infiltrative tumor predominantly described in the pelvis of women (vulva, vagina, and perineum) and men [81–84]. Sometimes the tumor is clinically mistaken for a Bartholin gland cyst; however, the lesion commonly reaches a large size (>10 cm), involves deep soft tissue structures, and distorts the pelvic anatomy at presentation, raising clinical suspicion for a more aggressive condition. In these instances, diagnostic imaging is warranted in order to determine the extent of the tumor. Rapid growth during pregnancy has been reported.

Pathologic Features

Upon macroscopic examination, aggressive angiomyxoma has a multinodular to frankly irregular outer aspect as well as soft and gelatinous cut surface. Microscopically, the tumor is composed of bland fusiform cells, individually dispersed in an abundant myxoid matrix. Although the vasculature pattern varies, large, thick, and hyalinized vessels tend to predominate. These large vessels are surrounded by stromal cells in a more dense fascicular distribution. The neoplasm dissects surrounding stroma in a frankly infiltrative fashion. Because of its low cellularity, the infiltrative nature of the tumor may not be apparent in routine preparations (Fig. 8.13).

Ancillary Studies

Aggressive angiomyxoma is positive for the estrogen receptor, desmin, and smooth muscle actin, particularly in the perivascular fascicles [85, 86]. Expression of CD34 is variable (up to 45%). Alterations of the *HMGA2* gene in the 12q15 locus have been documented in ~30% of aggressive angiomyxomas [18, 87]. Immunohistochemical expression of HMGA2 occurs in 37–83% of tumors, but does not correlate entirely with *HMGA2* gene rearrangement status [85, 88]. It is important to note that HMGA2 immunohistochemical expression has also been shown in leiomyomas, myxoid leiomyosarcoma, fibroepithelial polyps, and angiomyofibroblastomas [86, 88], limiting the specificity of this marker in the diagnosis of aggressive angiomyxoma. Nonetheless, when positive, HMGA2 can aid in determining the extent of

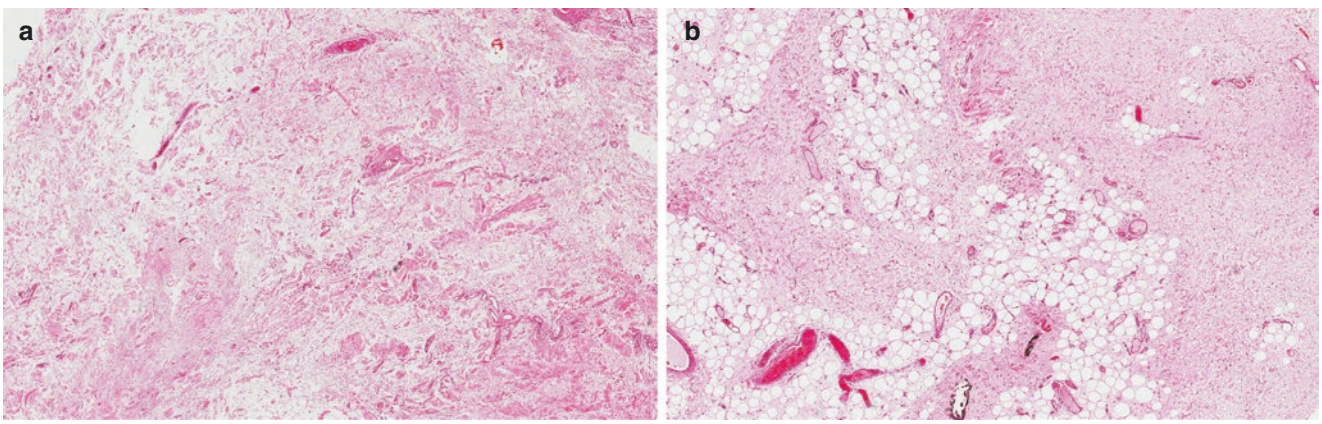

Fig. 8.13 Aggressive angiomyxoma. The lesion is uniformly hypocellular (**a**); given this deceptively bland appearance, the infiltrative tumor interface is difficult to distinguish from normal tissue (**b**); resection margins are frequently positive (**c**). Vasculature varies in size and distribution; however thick-walled vessels are consistently present (**d**). Neoplastic spindle cells are bland (**e**) and individually dispersed in a myxoid stroma (**f**, alcian blue stain pH 2.5). Tumor cells are positive for desmin (**g**), ER (**h**), and CD34 (**i**) and negative for smooth muscle actin (**j**)

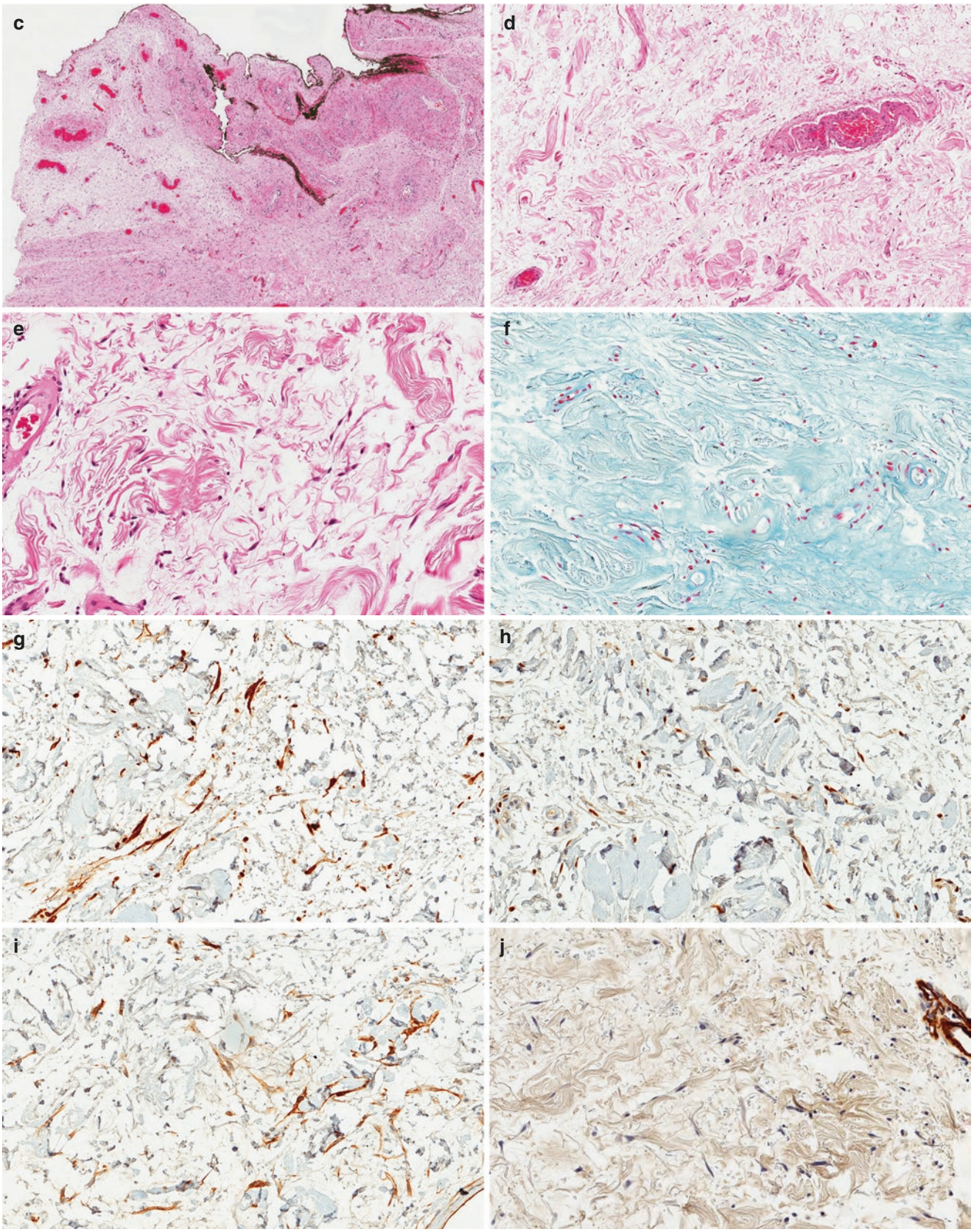

Fig. 8.13 (continued)

the tumor into adjacent tissues (which can be subtle) and assessing resection margins.

Differential Diagnosis

Virtually any of the other vulvovaginal stromal lesions discussed previously can overlap with aggressive angiomyxoma. Key distinguishing features of aggressive angiomyxoma are its large size, infiltrative nature, and involvement of deep soft tissues. Not discussed previously, *massive vulvar edema* can mimic aggressive angiomyxoma. Vulvar edema can be secondary to obesity, prolonged immobilization or previous pelvic lymphadenectomy. Unlike aggressive angiomyxoma, massive vulvar edema is characteristically bilateral and superficial. Microscopically, the presence of edematous fluid (instead of myxoid stroma) and the presence of perivascular chronic inflammation is in keeping with vulvar edema [89]. In two cases of vulvar edema reported, desmin, CD34, and hormone receptors were all negative [90].

Prognosis and Management

Local destructive recurrence occurs in 30–40% of aggressive angiomyxomas, sometimes years after the initial diagnosis. For this reason, long-term follow-up is necessary. A positive margin is a risk factor for recurrence [81, 82]; thus, a wide excision margin (at least 1 cm) is recommended after careful mapping of the lesion with preoperative imaging. Distant metastases and fatal cases are exceedingly rare [91]. There is sporadic evidence of response to gonadotrophin-releasing hormone (GnRH) agonists, which can be considered in recurrent and unresectable lesions [92].

8.2.2 Other Aggressive Lesions

8.2.2.1 Vulvovaginal Smooth Muscle Tumors

The English literature on primary vulvovaginal smooth muscle neoplasms has addressed benign, malignant, and unknown malignant potential (STUMP) categories together, given the rarity of these tumor types and the evolution of the diagnostic criteria used for their classification. These criteria differ from cutaneous and extragenital locations, since vulvovaginal smooth muscle neoplasms express hormone receptors and have clinical differences with their non-genital counterparts [93]. While traditionally the criteria have also differed from those used in the uterus, recent data supports a unified approach for both uterine and vulvovaginal neoplasms.

Clinical Features

Smooth muscle tumors involving the vagina and vulva occur more frequently in perimenopausal patients, although age range is wide. The lesions are usually superficial, non-tender, and commonly detected by the patient on self-examination.

Pathologic Features

Macroscopically, tumors tend to have a rubbery to soft consistency and whorled appearance. Tumor size varies and tends to be associated with behavior: benign tumors tend to be small (<3 cm), whereas malignant tumors are frequently larger than 5 cm.

Similar to uterine tumors, vulvovaginal smooth muscle neoplasms can be divided morphologically in conventional (spindle cell), epithelioid, and myxoid types. Spindle cell tumors are composed of intersecting fascicles of fusiform cells with tapered-end nuclei. Epithelioid tumors have varying proportions of round cells with eosinophilic to clear cytoplasm. Myxoid tumors are characterized by a prominent myxo-hyaline matrix dissecting fascicles and giving a lacy or plexiform appearance.

The criteria for the diagnosis of malignancy (leiomyosarcoma) were initially described by *Tavassoli and Norris* in 1979 [94, 95] and subsequently updated by *Nielsen* et al. in 1993 [96]. Recently, *Sayeed* et al. compared these criteria to those used in the classification of uterine smooth muscle tumors as per the World Health Organization [97]. While the 1979 criteria have high sensitivity, validation data and have been in use for decades, this recent study showed that the uterine smooth muscle criteria had superior specificity. This is by virtue of better classification of benign versus unknown malignant potential tumors. Importantly, coagulative necrosis is a criterion not included in the 1979 and 1996 criteria. Table 8.1 lists the criteria for the diagnosis of vulvovaginal leiomyosarcoma in these classification systems. In view of the current evidence, it is advisable to apply uterine smooth muscle criteria first and to include tumor size and border in the evaluation of equivocal cases (those that would be classified as STUMP or leiomyoma variant by uterine smooth muscle tumor criteria).

Table 8.1 Criteria for diagnosis of vulvovaginal leiomyosarcoma [97]

Vulvar [94, 95]	**Vulvar** [13, 96]	**Uterine smooth muscle** [97]
At least two of the following:	*At least three of the following:*	*At least two of the following:*
Tumor size ≥5 cm	Tumor size ≥5 cm	Moderate to severe nuclear atypia
≥5 mitoses/10 HPFs	Moderate to severe nuclear atypia	≥10 mitoses/10 HPFs
Infiltrative margins	≥5 mitoses/10 HPFs	Tumor cell necrosis
	Infiltrative margins	
Vaginal [94, 95]		
One of the following:		
Moderate to severe nuclear atypia AND ≥5 mitoses/10 HPFs		
Infiltrative margins		

In principle, the diagnosis of leiomyoma can be made when none of the listed features are identified after thorough sampling (Figs. 8.14 and 8.15). If features are present, but insufficient for leiomyosarcoma (either by uterine smooth muscle or by site specific criteria), the possibility of STUMP (also known as atypical smooth muscle tumor) should be considered [98].

Ancillary Studies

Vulvovaginal smooth muscle tumors express at least one smooth muscle marker [93], desmin and smooth muscle actin being the most sensitive and H-caldesmon the most specific. Cytogenetic abnormalities have been reported in sporadic cases of vulvar leiomyoma, including translocation (7;8)(p13:q11.2) [99] and inv.(12)(p12q13-q14) which is associated with *HMGA2* activation [100].

Prognosis and Management

Diagnostic criteria described above were based on patient outcomes, particularly local recurrence and distant metastases. Conservative complete excision usually suffices in tumors classified as leiomyoma. Conversely, leiomyosarcoma and tumors of unknown malignant potential should ideally have a wide (>1 cm) margin of excision, as well as close and long-term follow-up. Chemotherapy and radiation are usually considered for patients with tumor recurrence and/or metastases.

8.2.2.2 Rhabdomyosarcoma

Clinical Features

This tumor type is better characterized in the pediatric population, also known as "sarcoma botryoides," a subset of embryonal rhabdomyosarcoma involving the submucosa of the vagina and cervix. Mean age at presentation is ~6 years [101]. While most are sporadic, cases related to Li-Fraumeni syndrome and neurofibromatosis type 1 have been reported [102–104]. Genital rhabdomyosarcoma in adult women is very infrequent. The mass commonly manifests clinically with abnormal bleeding and/or pain.

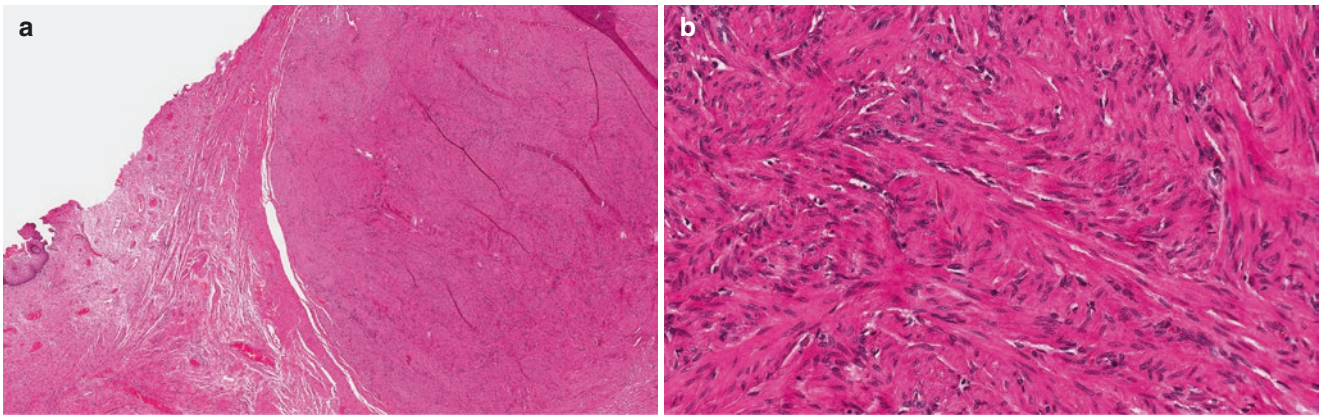

Fig. 8.14 Leiomyoma. Well-demarcated mass (**a**) composed of uniformly distributed fascicles of spindle cells; nuclei have tapered borders and uniform euchromatic nuclei (**b**)

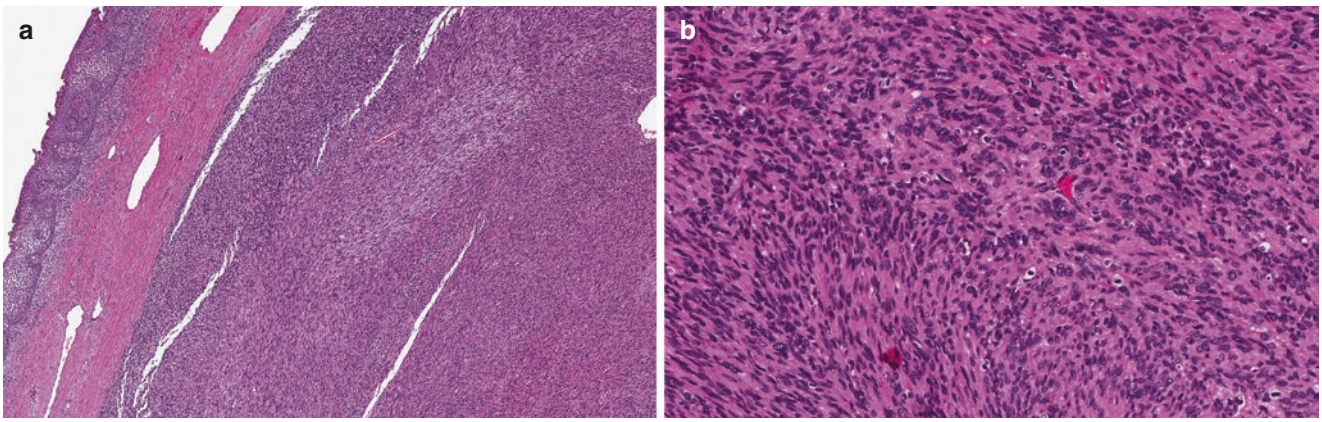

Fig. 8.15 Leiomyosarcoma. In contrast with the previous example, this lesion is hypercellular (**a**) and composed of markedly atypical and hyperchromatic nuclei with evident mitoses (**b**). Courtesy of Dr. Andre Pinto (University of Miami)

Pathologic Features

Median tumor size is 6 cm. In pediatric cases, tumors tend to grow as polypoid, frond-like masses (hence the name "*botryoides*"). The cut surface is typically homogeneous and soft; overlying mucosa can be ulcerated [102].

Most cases are of embryonal type (75% in one series) [105, 106]. Embryonal rhabdomyosarcoma is characterized by immature, round to spindle rhabdomyoblasts interspersed in a myxoid stroma. Cells contain oval nuclei and eccentric protrusions of eosinophilic cytoplasm resembling a tennis racket; striations can be seen. Chondroid differentiation can be observed. In the botryoid type, a layer of cells densely organized immediately beneath the vaginal epithelium is characteristic (cambium layer). The typical areas of hypercellularity can be subtle, since they are typically limited to the superficial stroma and absent in deeper portions of the tumor.

Non-embryonal types are mostly seen in postmenopausal women [105, 106]. Alveolar rhabdomyosarcoma is characterized by round blue cells forming sac (alveolar)-type spaces, interspersed with pleomorphic and giant cells. Pleomorphic rhabdomyosarcoma resembles other adult-type pleomorphic sarcomas with a storiform and fascicular appearance; definitive rhabdomyoblastic differentiation (cross-striations) is rare, and when present is only focal.

Ancillary Studies

The tumor cells are positive for desmin and specific skeletal muscle markers (myoglobin, MyoD1, and myogenin).

Differential Diagnosis

Cellular fibroepithelial stromal polyps can harbor atypical and pleomorphic cells mimicking botryoid rhabdomyosarcoma. However, they occur more frequently in adults, and the cellularity is concentrated toward the center of the lesion as opposed to the subepithelial cambium layer typical of botryoid embryonal rhabdomyosarcoma. Genital rhabdomyoma can also be polypoid; however, its population is bland, lacking the atypia and proliferation expected in genital rhabdomyosarcoma.

Prognosis and Management

The 5-year overall survival for lower genital rhabdomyosarcoma was 68% in one recent large series. Distant metastases are rare (~7% of cases) [105]. Younger age, early stage, and embryonal histology were associated with better prognosis. Indeed, outcome is favorable in most pediatric patients treated with surgery (local excision or radical resection), chemotherapy, and radiotherapy [101, 107]. In contrast, adult cases tend to be aggressive with high rates of advanced stage and nodal metastases, as well as low 5-year disease-specific survival (~30%) [105, 106]. The botryoid (exophytic) variant of embryonal rhabdomyosarcoma has an excellent prognosis (92% 10-year survival) in comparison with the usual (nonexophytic) type of embryonal rhabdomyosarcoma (68% 10-year survival) and other subtypes, particularly the alveolar subtype, which carries a much worse prognosis [108].

8.2.2.3 Atypical Lipomatous Tumor and Liposarcoma

Clinical Features

Atypical and malignant adipocytic tumors of the vulva are rare, with less than 20 cases in the English literature [109]. They typically occur in middle-aged women (median age 52) and have a mean size of 6 cm. Most are superficial and mobile and are often misdiagnosed as a benign tumor.

Pathologic Features

The most common histologic type is atypical lipomatous tumor (formerly well-differentiated liposarcoma) [109, 110]. Only the lipomatous variant has been described in the vulvovaginal region; other types (spindle cell, sclerosing, and inflammatory) have not been reported. Atypical lipomatous tumor is typically lobulated and is composed of mature adipocytes of different sizes separated by cellular fibrous septa, which contain hyperchromatic atypical stromal cells. Lipoblasts may be present but are not a prerequisite for the diagnosis.

Myxoid/round cell liposarcoma is the second most common tumor type seen in the vulva [109]. This category includes tumors with variable degrees of lipoblastic differentiation from the well (myxoid) to the poorly differentiated (round cell). This morphologic spectrum can sometimes be appreciated within the same tumor. Myxoid tumors consist of nodular growths of myxoid stroma containing vacuolated adipocytic and spindle non-lipomatous cells. Round cell tumors are comprised of sheets of large cells with scant cytoplasm, round nuclei, and prominent nucleoli. Pleomorphic liposarcoma has only been documented in one patient to date [111].

Ancillary Studies

Atypical lipomatous tumor is characterized by amplification of the 12q13–15 locus, which includes the *MDM2*, *TSPAN31*, *CDK4*, and *HMGA2* genes [112]. Myxoid/round cell liposarcoma is characterized by recurrent rearrangements of *DDIT3* (most commonly *FUS-DDIT3* fusion, *EWSR1-DDIT3* fusion in a minority of cases) [112]. *MDM2* amplification and *FUS-DDIT3* rearrangements have also been demonstrated in examples of vulvar atypical lipomatous tumor and vulvar myxoid leiomyosarcoma, respectively [109].

Differential Diagnosis

Malignant lesions can be subtle and mimic lipoma both clinically and pathologically. Atypical lipomatous tumor can be distinguished from lipoma by the presence of atypical cells

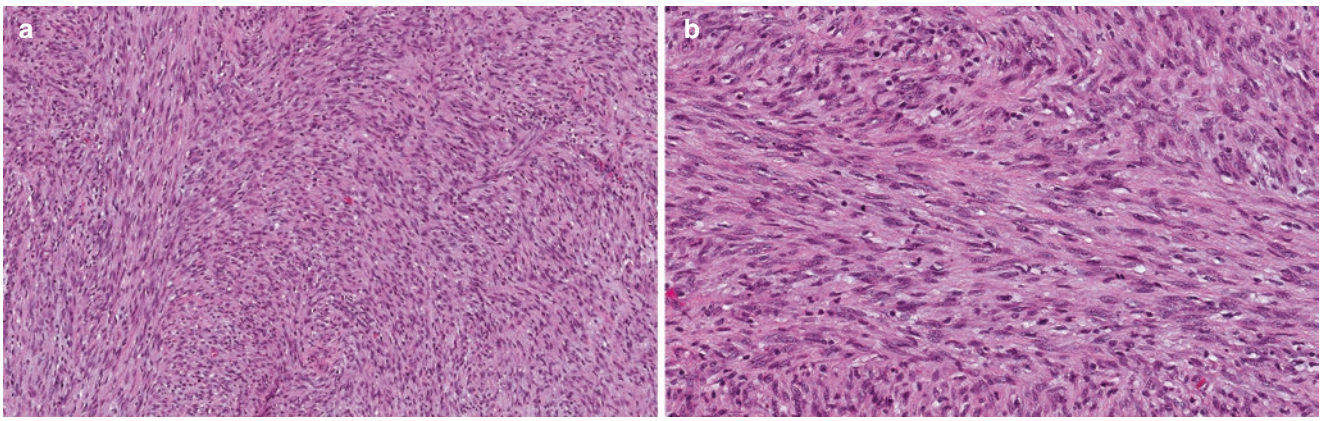

Fig. 8.16 Peripheral nerve sheath tumor. The picture depicts hypercellular areas of intersecting fascicles (**a**) composed of atypical spindle cells with pointed nuclei and conspicuous mitoses (**b**)

within fibrous septa and the variation in adipocyte size; if present, lipoblasts are also supportive of an atypical lipomatous tumor. In challenging cases, testing for 12q13–15 amplification can be of value. The differential diagnosis of myxoid liposarcoma of the vulva includes aggressive angiomyxoma, superficial angiomyxoma, and myxoid leiomyosarcoma. The presence of lipoblastic/adipocytic differentiation within the neoplastic/atypical population will argue against these possibilities and support liposarcoma. Testing for DDIT3 rearrangements should be considered in equivocal cases.

Prognosis and Management

Atypical lipomatous tumor is associated with local recurrence. Metastases have not been reported, except in tumors with a dedifferentiated component (a phenomenon not yet described in the vulvovaginal region). Myxoid liposarcomas tend to have an indolent outcome; conversely, round cell liposarcoma is an aggressive form [113]. Wide local excision with clear margins is the optimal treatment for vulvar liposarcoma, followed by close monitoring.

8.2.2.4 Malignant Peripheral Nerve Sheath Tumor

Clinical Features

This tumor is believed to originate in peripheral Schwann cells based on ultrastructural features indicative of Schwannian derivation. An association with neurofibromatosis type 1 is documented [114, 115]. Occurrence in the vulva and vagina is exceedingly rare [116–118]. The tumor appears predominantly in middle aged-women as a painful, rapid-growing mass which usually raises concern for malignancy.

Pathologic Features

The morphology of lower genital malignant peripheral nerve sheath tumor is identical to that described for extragenital sites. Alternating zones of hypercellularity and hypocellularity are characteristic, the latter being usually myxoid. The neoplastic population displays fusiform nuclei with pointed ends, hyperchromasia, pleomorphism, and conspicuous mitoses (>1 mitosis in 10 HPFs, Fig. 8.16). Peri- and intraneural invasion is common, sometimes with an evident plexiform pattern.

Ancillary Studies

S100 immunohistochemical expression is frequent (>80%) but usually focal; desmin and MDM2 expression is seen in a minority of tumors (~30%). The latter does not appear to correlate with *HMGA2* rearrangements [119]. Cytogenetic studies have revealed a complex tumor karyotype including structural abnormalities in chromosomes 17 and 22 [120].

Differential Diagnosis

Because the histologic appearance is usually nondescript, the differential diagnosis is wide, including benign (schwannoma) and malignant (fibrosarcoma, monophasic synovial sarcoma, leiomyosarcoma) conditions. The presence of cytologic atypia and mitotic activity should point against the possibility of schwannoma. In addition, S100 expression will be strong and diffuse in schwannoma and focal in peripheral nerve sheath tumor. Distinction from other types of sarcoma can be difficult; intimal tumor relationship with nerve structures and S100 expression in the absence of markers specific for other entities should raise the possibility of malignant peripheral nerve sheath tumor.

Prognosis and Management

Malignant peripheral nerve sheath tumors are aggressive neoplasms with high rates of recurrence and metastasis. Overall 5-year survival is ~40% [114]. Adverse prognostic features include high-grade morphology, personal diagnosis of neurofibromatosis type 1 syndrome, and positive margins on excision [115, 119].

8.2.2.5 Primitive Neuroectodermal Tumor

Clinical Features

Peripheral primitive neuroectodermal tumor is a round cell sarcoma of neuroectodermal derivation. Occurrence in the vulva and vagina is rare with small case series and single reports available in the English literature [121–123]. This tumor is more common in premenopausal women (median age 27 years).

Pathologic Features

Tumors tend to be small (mean size 5.8 cm) and superficial. The neoplasm is composed of large solid cellular aggregates of monomorphic round blue cells with hyperchromatic nuclei and scant cytoplasm (Fig. 8.17). Mitotic activity is usually high (over five mitoses per high-power field), and necrosis is frequent.

Ancillary Studies

Most cases show diffuse and strong membranous staining for CD99 and FLI-1 nuclear expression [123]. Synaptophysin and neuron-specific enolase are also positive [124]. The vast majority of tumors in the Ewing sarcoma/primitive neuroectodermal tumor family, including those in the vulvovaginal region, harbor a characteristic t(11;22)(q24;q12) translocation that results in a *EWS-FLI-1* fusion transcript [123].

Differential Diagnosis

The differential diagnosis is wide and includes other small round blue cell tumors (rhabdomyosarcoma, small cell carcinoma, melanoma). CD99 is highly sensitive for primitive neuroectodermal tumor but specific only when staining is strongly and diffusely membranous. In equivocal cases, detection of the *EWS-FLI1* translocation is keeping with primitive neuroectodermal tumor.

Prognosis and Management

Treatment involves wide surgical excision, chemotherapy, and/or radiation. The overall prognosis of lower genital primitive neuroectodermal tumor is largely dependent on the stage at presentation. Patients presenting with metastatic disease have a dismal prognosis [121, 122].

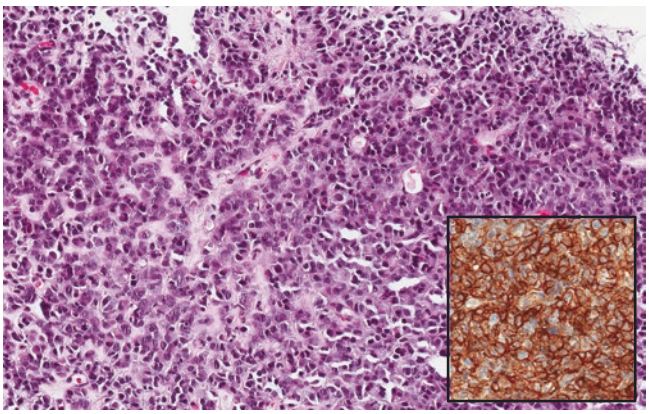

Fig. 8.17 Primitive neuroectodermal tumor. Monomorphic round blue cells with high nuclear-to-cytoplasmic ratio; CD99 expression is membranous, diffuse, and strong (insert)

8.2.2.6 Angiosarcoma

Only a few cases of angiosarcoma involving the vulvovaginal region are documented [125, 126]. Most are postmenopausal women presenting with a rapidly growing genital mass. Tumor size ranges from 1.5 to 8 cm (mean 3.5 cm). Microscopically, the tumor is composed of a deeply infiltrative malignant spindle and epithelioid cell population forming anastomosing vascular channels. Solid architecture and necrosis can be seen, particularly in poorly differentiated tumors (Fig. 8.18). Most patients reported had poor outcome with rapid recurrence and death of disease despite radical surgical treatment and radiation.

8.2.2.7 Dermatofibrosarcoma Protuberans

Clinical Features

Although this entity is commonly seen in the groin, cases restricted to the vulva are rare, with slightly over 50 cases reported in the English literature [127]. The lesion usually presents as a slow-growing nodule in the labium majus. Age at presentation is wide (mean 45 years).

Pathologic Features

The lesion is usually small (average 4 cm) [127]. Dermatofibrosarcoma protuberans can vary in appearance from a plaque or nodule to exophytic, multinodular growths which may be flesh colored or variably hypopigmented or hyperpigmented. Despite its name, the typical histologic appearance is bland, comprised of spindle cells with minimal to absent pleomorphism and low mitotic activity (less than 5 mitoses/10 PHFs), arranged in a storiform pattern (Fig. 8.19). Some cases contain areas of frank fibrosarcoma, characterized by pleomorphic and mitotically active spindle cells. The lesion is usually ill demarcated and infiltrates subcutaneous adipose tissue. The neoplasm is often separated from the normal-appearing epidermis by a rim of normal dermis.

Ancillary Studies

Immunohistochemically, tumors are diffusely and strongly positive for CD34 but negative for S100, C-KIT, factor XIII, smooth muscle, and epithelial markers, as well as hormone receptors. Positivity for PDGFR-α and β has been reported in vulvar lesions [128]. The tumor harbors a characteristic translocation t(17; 22)(q22; q13), generally in the form of a supernumerary ring chromosome, resulting in the formation of a chimeric fusion gene (*COL1A1*/*PDGFB*, i.e., collagen type I alpha I-platelet-derived growth factor beta) [129, 130].

Differential Diagnosis

An important distinction is with dermatofibroma (discussed above). Other benign entities frequently entertained in the

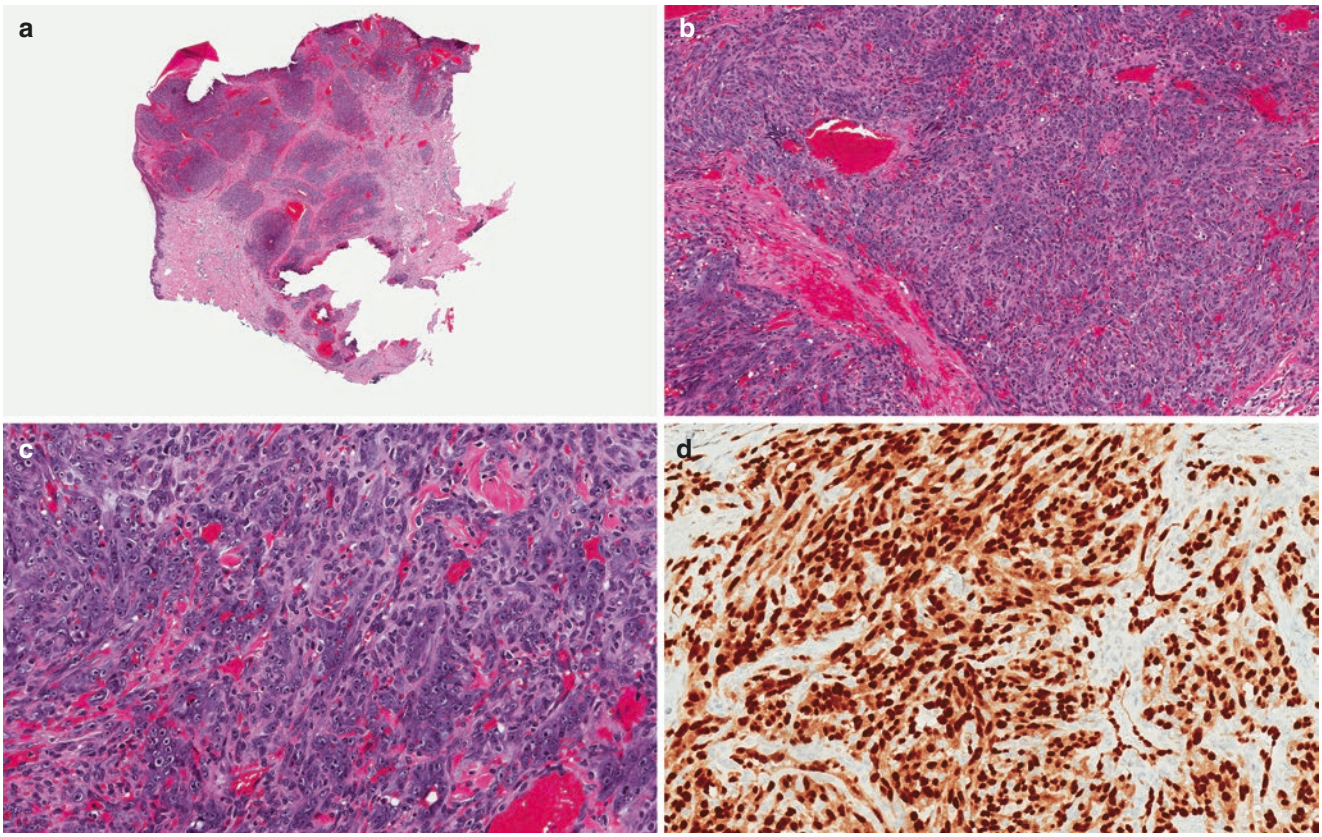

Fig. 8.18 Angiosarcoma. The lesion is infiltrative (**a**) and solid on low-power magnification (**b**). Poorly formed blood-filled channels and frankly atypical cells are noted on high-power magnification (**c**). Cells are diffusely positive for ERG (**d**)

differential are neurofibroma and schwannoma; S100 expression will be in favor of these and against dermatofibrosarcoma protuberans. Malignant peripheral nerve sheath tumor, another lesion of neural derivation, can also overlap with dermatofibrosarcoma and frequently express CD34; however, this tumor has a more peculiar appearance with alternating hypocellular and hypercellular areas [128].

Prognosis and Management

In contrast to dermatofibroma, dermatofibrosarcoma protuberans has significantly higher rates of local recurrence (50% of cases). Wide local excision is generally recommended. Since tumors frequently express PDGFR α and β, therapy with imatinib (Gleevec) is also a valid approach in recurrent or unresectable lesions, as evidenced in one case [128].

8.2.2.8 Myeloid Sarcoma

Clinical Features

Myeloid sarcoma (also known as granulocytic sarcoma, chloroma) is defined as immature myeloid cells forming a mass in an extramedullary location. Overall, most patients have a previous or concomitant history of a myeloid disorder in bone marrow and/or peripheral blood [131]. Interestingly, patients with female genital involvement frequently present only with the extramedullary mass and no evidence of leukemia [132, 133]. This represents a pitfall: in fact, up to 75% of non-leukemic cases are initially misdiagnosed as a lymphoma or non-hematopoietic malignancy [134]. Age ranges from 12 to 77 years (mean 39 years). Patients present with abnormal bleeding or a rapidly growing mass, most commonly centered in the vagina.

Pathologic Features

In most cases, the neoplastic population is composed of undifferentiated, large pleomorphic cells with a high nuclear-to-cytoplasmic ratio, apoptosis, and necrosis. When present, neutrophilic or eosinophilic precursors with lobulated nuclei and more abundant granular cytoplasm are helpful diagnostic clues. The proliferation is usually submucosal, seen as densely cellular aggregates that extend to the subepithelial stroma (but sparing the epithelium, Fig. 8.20).

Ancillary Studies

Immunohistochemistry is usually required to determine neoplastic lineage. Most lesions are granulocytic and express CD13, CD33, CD117, MPO, CD34, and/or CD38; they are either blastic (immature) or differentiated (promyelocytes and other mature forms). Monocytic/monoblastic (CD14, CD4, CD11b, CD64, lysozyme), erythroid (glycophorin A, blood group antigens), and megakaryoblastic (CD41, CD61, CD42) forms are less frequent [135].

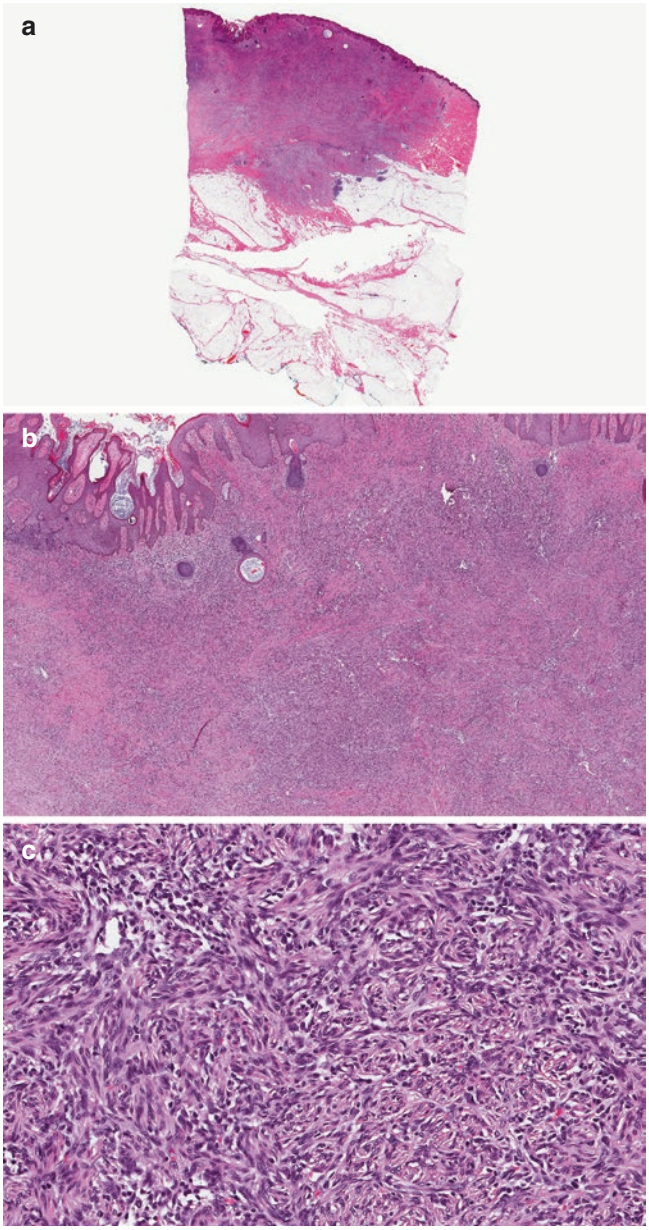

Fig. 8.19 Dermatofibrosarcoma protuberans. Multinodular and infiltrative growth (**a**) with uniform cellularity (**b**) and a storiform pattern on high power view; note the relative normocellularity of the neoplastic population (**c**)

Differential Diagnosis

The most important diagnostic considerations are poorly differentiated squamous cell carcinoma, rhabdomyosarcoma, primitive neuroectodermal tumor, melanoma, and lymphoma. Immunohistochemistry for myeloid, melanocytic, and epithelial markers is helpful in ascertaining the cell type and lineage.

Prognosis and Management

The prognosis of myeloid sarcoma is poor. 50% of non-leukemic patients will develop acute leukemia shortly after diagnosis. Most (70%) vaginal myeloid sarcoma patients reported died of disease within 3 years [135]. Local therapy (surgery, radiation) achieves remission in only 20% of patients. Therefore, systemic induction chemotherapy is the first line of treatment, followed by surgery and radiation in unresponsive patients or those requiring debulking for symptom control. Allogenic or autologous bone marrow transplantation offers higher chances of survival and cure [131].

8.2.2.9 SMARCB1-Deficient Tumors

The *SMARCB1* (*INI1/BAF47/SNF5*) gene is a member of the SWI/SNF chromatin-remodeling complex and regulates gene expression by uncoupling DNA from histones [136]. Alterations in this gene leading to loss of SMARCB1 expression were initially described in pediatric rhabdoid tumor and subsequently in proximal-type epithelioid sarcomas [137]. Other tumors found to harbor *SMARCB1* alterations include renal medullary carcinoma, epithelioid malignant peripheral nerve sheath tumor, myoepithelial carcinoma, and myxoid chondrosarcoma [138]. Lesions with myoepithelioma-like features have also been described within the spectrum of neoplasia with *SMARCB1* loss [139].

Clinical Features

Proximal-type epithelioid sarcoma is more frequent in the proximal extremities and pelvis. Primary vulvar involvement is rare with only 32 cases reported [140–142]. Similarly, there are 14 cases in the literature reported as malignant rhabdoid tumor of the vulva [143]. Both lesions present in young, premenopausal women (mean age at presentation 31–38 years).

Pathologic Features

Proximal-type epithelioid sarcoma and malignant rhabdoid tumor have strikingly similar pathologic features, and most authors consider them the same entity. Macroscopically, the tumor is firm to fleshy with frequent necrosis and hemorrhage. Microscopically, the tumor has a nodular arrangement. Rhabdoid differentiation, characterized by ovoid, polyhedral or spindle cell shape and eosinophilic cytoplasm, is seen in varying proportions (focal in epithelioid sarcoma, diffuse in rhabdoid tumor). Tumor cells have epithelioid to spindled shape, abundant cytoplasm and uniform nuclei with vesicular chromatin (Fig. 8.21). Conspicuous mitoses and necrosis are common. The tumor is variably myxoid (<5% to 95% of the tumor volume); non-myxoid areas have a diffuse fascicular or storiform architecture [136, 144].

Ancillary Studies

By immunohistochemistry, this family of lesions expresses epithelial membrane antigen and cytokeratins. Loss of SMARCB1/INI1 nuclear expression, which correlates with *SMARCB1* gene deletion at the 22q11.2 locus, is a

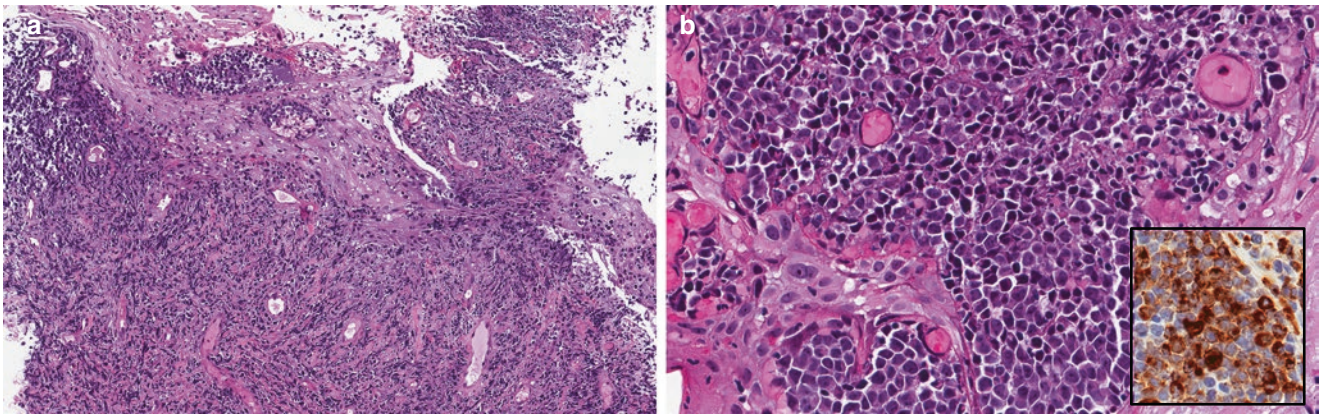

Fig. 8.20 Myeloid sarcoma. Dense proliferation of small, round blue cells in the subepithelial connective tissue (**a**). The population varies from immature (blastic) to maturing forms (**b**); strong expression of myeloperoxidase is in keeping with a myeloid lineage (insert)

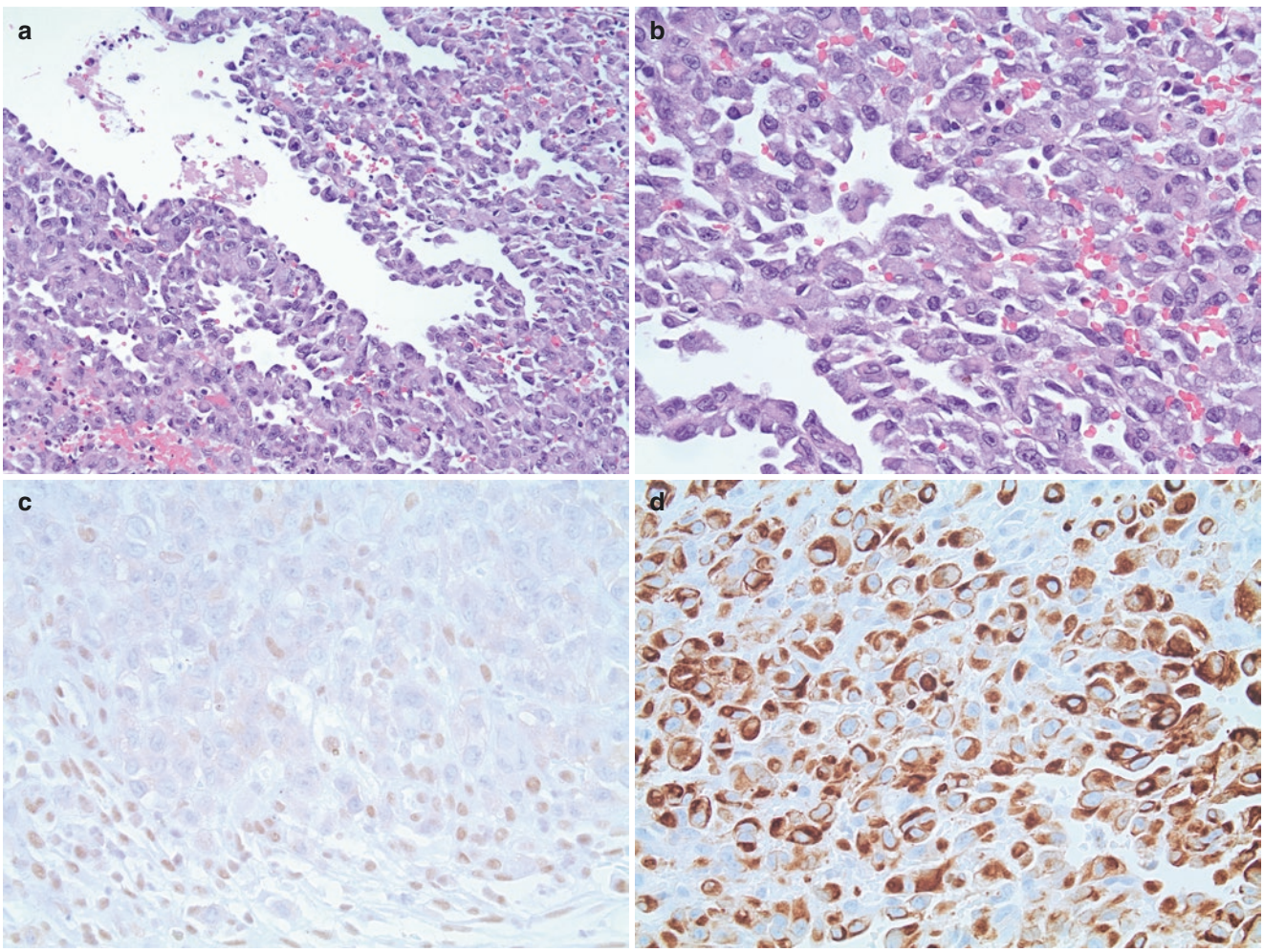

Fig. 8.21 *SMARCB1* deficient sarcoma. Tumor is usually multinodular and solid, sometimes with an "alveolar" pattern (**a**). Tumor cells display an epithelioid morphology with abundant eosinophilic cytoplasm and vesicular nuclei (**b**). Loss of nuclear INI1 expression, secondary to *SMARCB1* gene deletion, is characteristic (**c**). The tumor usually expresses cytokeratins (**d**). Courtesy of Dr. Oluwole Fadare (University of California, San Diego)

sensitive (>95% of cases) and specific finding in proximal-type epithelioid sarcoma [137, 145]. This characteristic feature has been also demonstrated, by immunohistochemistry and/or gene sequencing, in epithelioid sarcoma and myoepithelial neoplasms of the vulva [136, 139]. Myoepithelioma-like lesions also demonstrate negative S100 and CD34, as well as absence of *EWSR1*, *FUS*, and *NR4A3* rearrangements [139].

Differential Diagnosis

Given the epithelioid morphology and epithelial marker expression of this tumor type, it is important to distinguish it from a poorly differentiated squamous cell carcinoma. Identification of definitive epithelial features (cohesive nested areas, intercellular junctions), tumor connection with the surface, or an adjacent intraepithelial lesion should raise the possibility of carcinoma. INI1 immunohistochemistry must be considered in suspicious cases. The differential also includes other epithelioid mesenchymal neoplasms such as epithelioid smooth muscle tumors and angiomyofibroblastoma. Adequate sampling and identification of classic morphologic features for these entities can help.

Prognosis and Management

Tumors in this group demonstrate an aggressive behavior with 55% recurrence rate and fatality in 42–50% of patients [140, 143]. Treatment is primarily surgical aiming for complete resection; radiation therapy can be considered.

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