Vaginal Neoplasia

10

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Abstract

This chapter covers benign, premalignant, and malignant neoplasms of the vagina. The coverage includes epithelial, mixed epithelial/mesenchymal tumors, lymphoid and myeloid tumors, melanocytic tumors, and a variety of other primary and secondary neoplasms that may involve the vagina. Many of the tumors that arise in the vagina are also seen in other lower genital sites, but the clinical features occasionally differ at this site. Primary carcinoma of the vagina is rare and spread from cervical or vulvar primaries, or metastatic disease must always be considered in the differential diagnosis.

Keywords

Squamous papilloma · Müllerian papilloma
Fibroepithelial polyps · Vaginal adenoma
Vaginal intraepithelial neoplasia · Squamous cell carcinoma · Adenocarcinoma · Adenosquamous carcinoma · Adenoid cystic carcinoma
Adenoid basal carcinoma · Neuroendocrine carcinoma
Mixed tumor · Carcinosarcoma · Adenosarcoma

10.1 Epithelial Tumors of the Vagina

10.1.1 Benign Epithelial Tumors

10.1.1.1 Squamous Papilloma

A variety of polypoid lesions may arise in the vagina (Table 10.1). Squamous papillomas may be single or multiple. When multiple, this version is been called micropapillomatosis labialis (Fig. 10.1a). Micropapillomatosis labialis occurs at the introitus, involving the vestibule. It is considered a normal anatomic variant, unrelated to human papillomavirus, and does not require treatment [1]. It is grossly composed of multiple fingerlike projections of mucosa of normal color, each with a distinct base (Fig. 10.1a), distinguishing it from condyloma accuminatum, which has branching from a common base. Histologically the projections are composed of unremarkable or mildly thickened squamous epithelium devoid of koilocytosis or atypia lining fibrovascular tissue (Fig. 10.1b).

Table 10.1 Polypoid lesions of the vagina

Squamous papilloma
Fibroepithelial polyp
Müllerian papilloma
Vaginal adenoma
Condyloma accuminatum
Brenner tumor
Tubulosquamous vaginal polyp
Sarcoma botryoides
Yolk sac tumor
Adenocarcinoma
Müllerian adenosarcoma
Carcinosarcoma

10.1.1.2 Fibroepithelial Polyps

Fibroepithelial polyps, also known as mesodermal stromal polyps, occur across a wide age range, predominantly reproductive and midlife, but are seen in postmenopausal women as well. While often asymptomatic, the lesions may present with bleeding or local discomfort [2]. Fibroepithelial polyps are single lesions on a stalk, although grossly there may be some branching at the tip. Histologically, the lesions are composed of benign squamous mucosa lining a stroma which is usually of low cellularity (Fig. 10.2); however, there may be hypercellularity, mitotic activity, multinucleation, and atypia of stromal cells [3, 4], which should not be mistaken for malignancy. This finding has led to the term "pseudosarcoma botryoides," which should be avoided in clinical reports. Lack of a cambium layer of condensed stroma under

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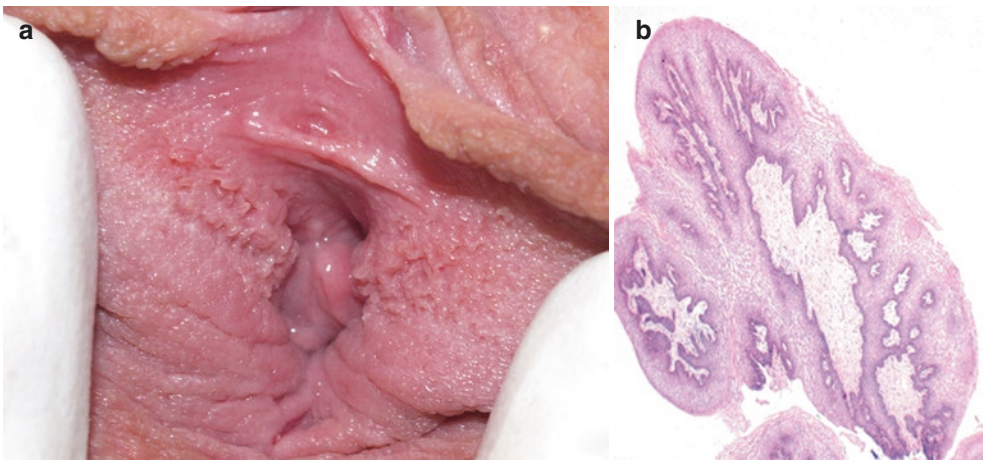

Fig. 10.1 (**a**) Micropapillomatosis labialis, composed of multiple fingerlike projections with individual bases, arising in the introitus. Copyright Libby Edwards, MD. Used with Permission. (**b**) Squamous papilloma. Fibrovascular core lined by benign squamous epithelium

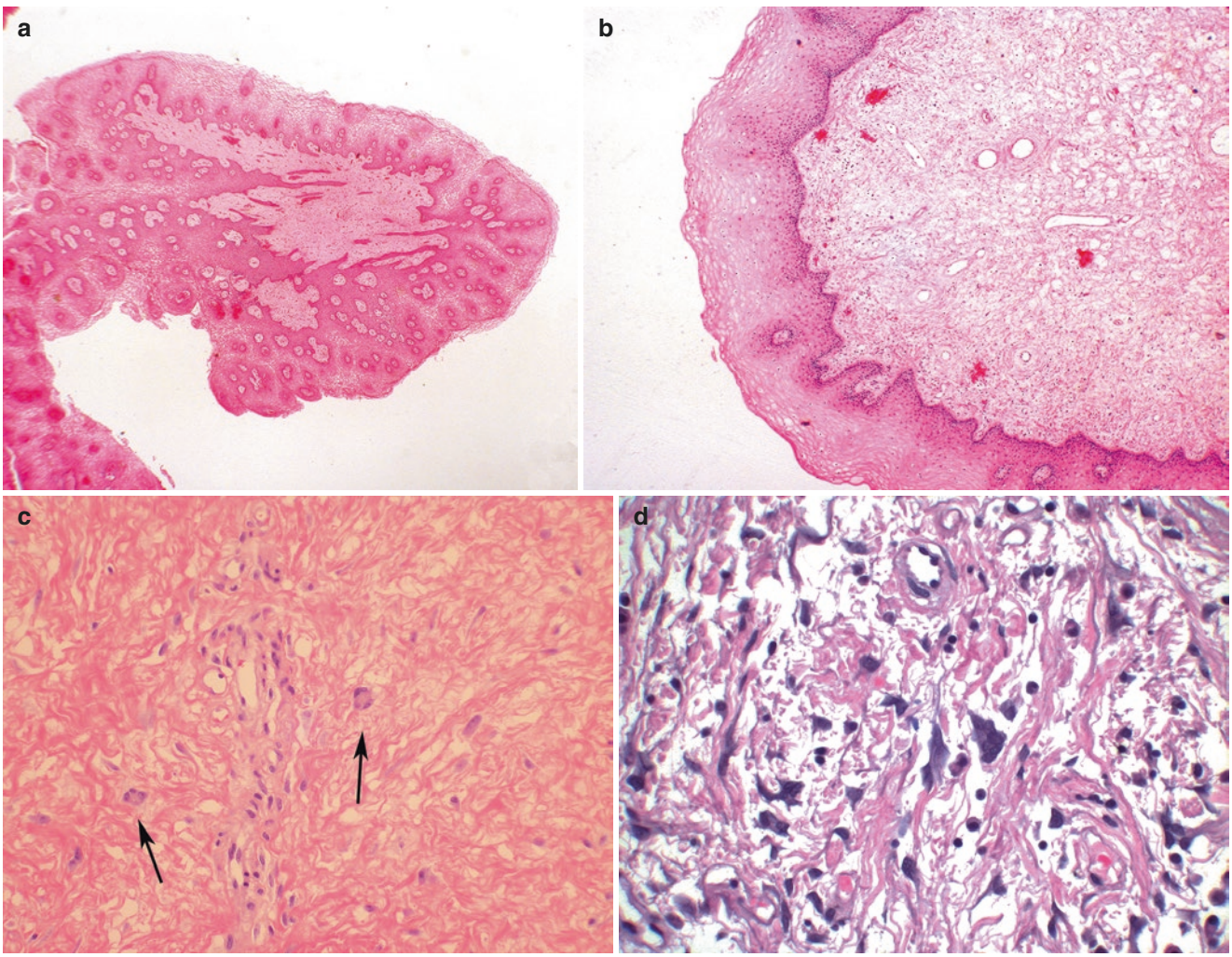

Fig. 10.2 Fibroepithelial polyp squamous lined fibroepithelial polyp on a stalk (**a**). At higher power (**b**), a low cellularity stroma is seen. Occasional rosettes (**c**) (arrows) and atypical stromal cells (**d**) may be seen and should not be mistaken for malignancy

the surface epithelium helps distinguish fibroepithelial polyps from true sarcoma botryoides. The stroma of fibroepithelial polyps is thought to contain myoepithelial cells, as well as estrogen and progesterone receptors [2, 5], and the lesion is frequently associated with pregnancy or hormone therapy [4]. Treatment is simple excision. They can

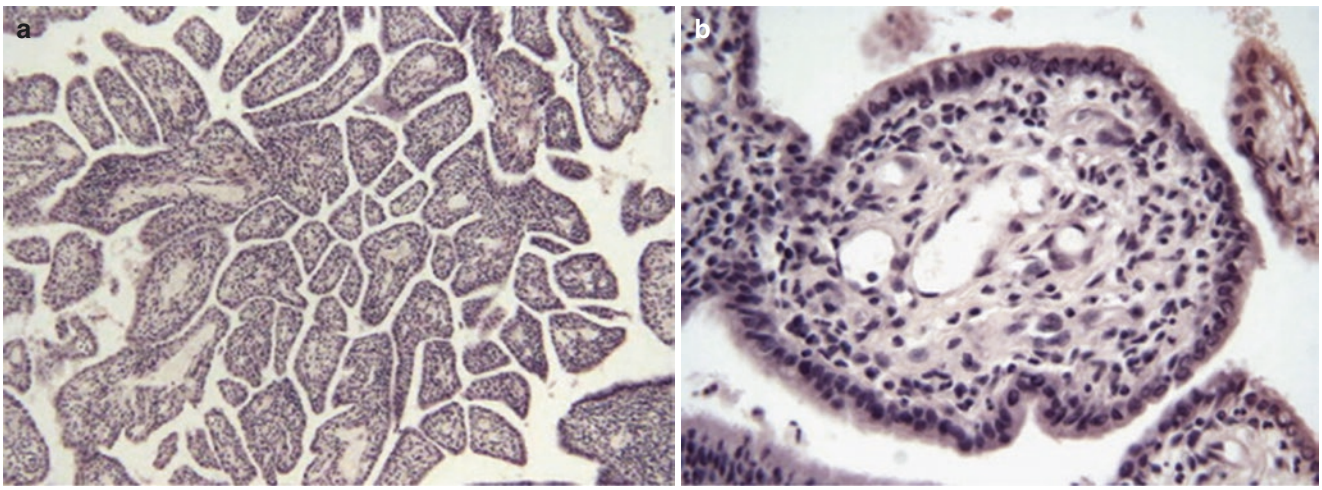

Fig. 10.3 Müllerian papilloma. The lesion is composed of multiple fronds (**a**), lined by a simple cuboidal epithelium (**b**). Reprinted from Journal of Pediatric and Adolescent Gynecology, Carlos A. Reck-Burneo, J Villanueva, FT Velcek. Vaginal Müllerian Papilloma: An Unusual Cause of Vaginal Bleeding in a Toddler. 2009 Oct;22(5):e124–6., with permission from Elsevier (**a**, **b**)

occasionally recur [3]. Fibroepithelial polyps are further discussed in Chaps. 8 and 9.

10.1.1.3 Müllerian Papilloma

Müllerian papillomas are rare benign polypoid neoplasms usually seen in children and adolescents, which may present with vaginal bleeding [6]. They can occur in the cervix as well as the vagina. They are composed of multiple complex branching fronds of fibrovascular tissue lined by a cuboidal to columnar epithelium (Fig. 10.3). Treatment is simple excision. These lesions can rarely recur [7]; however, one case, in a patient with cerebral palsy in a nursing home treated with numerous excisions, showed evolutionary changes over a 40-year period ranging from borderline to frank clear cell carcinoma [8].

10.1.1.4 Vaginal Adenoma

Polypoid lesions resembling colonic adenomatous polyps can occur in the vagina and may be tubular, villous, or tubulovillous. These lesions, common in the colon, are exceptionally rare in the vagina, with only a few case reports. They have similar histology to the intestinal lesions (Fig. 10.4). Reported cases have mostly occurred in the lower vagina of postmenopausal women, although younger patients have also been reported [9, 10], and may present with bleeding. Histologically, they are lined by enteric-type epithelium, which may have arisen from cloacal remnants [10]. The lesions should be considered premalignant, as there has been a report of an enteric-type vaginal adenocarcinoma arising in an adenoma [11], as well as a case with high-grade dysplasia [9], and so these should be excised. The differential diagnosis includes colonic adenocarcinoma, metastatic endocervical or endometrial carcinoma, prolapsed fallopian tube, and endometriosis [9]. Cytokeratin 7 and 20 expression profiles have been variable.

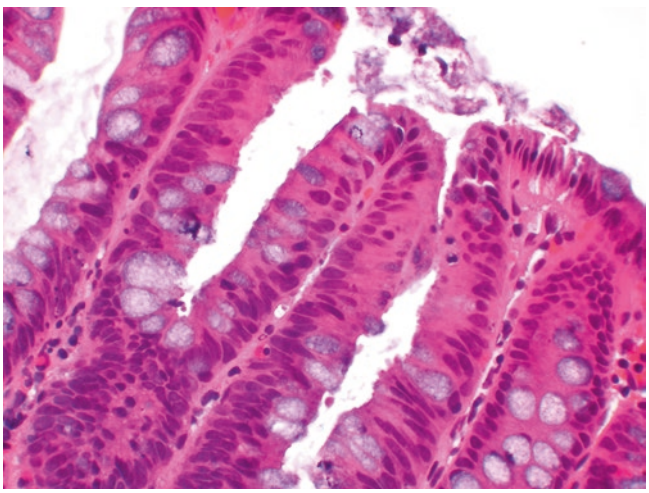

Fig. 10.4 Tubulovillous adenoma. This colonic lesion shows the typical architecture of tubules and villous structures lined by enteric-type tall columnar epithelium with goblet cells

10.1.1.5 Brenner Tumor

Brenner tumors represent about 1–2% of ovarian neoplasms, but only a few case reports describe a vaginal location for this benign neoplasm [12]. Most described cases have been small polypoid lesions found incidentally in elderly women and have been described at all levels of the vagina [12]. Histologically, the appearance is similar to the ovarian counterpart (Fig. 10.5), with nests of epithelium with squamo-transitional features, including nuclear grooves, embedded in a fibroconnective tissue stroma. Cystic spaces containing eosinophilic secretions can be seen in the epithelial nests. The origin of vaginal Brenner tumor is unknown, but it has been postulated that they arise from metaplasia of Müllerian epithelium [12]. A benign polypoid lesion in the upper

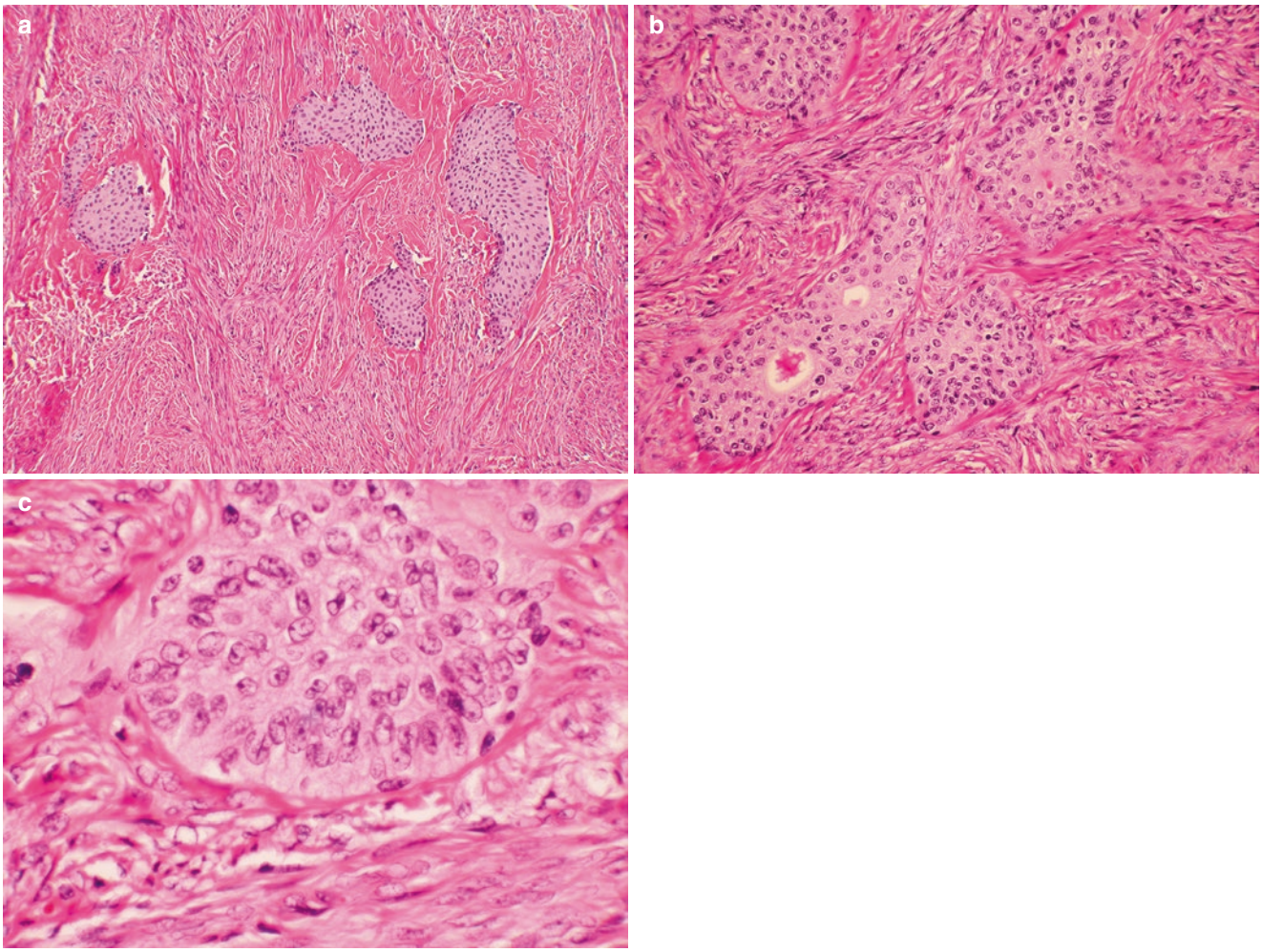

Fig. 10.5 Brenner tumor. The lesion shows nests of epithelial cells in a fibrous stroma (**a**). At higher power, the epithelium resembles squamotransitional epithelium, and the cells show nuclear grooves. Glandular lumens may be seen (**b**, **c**)

vagina of postmenopausal women termed the tubulosquamous vaginal polyp contains nests of cells with overlapping squamous and transitional cell features and may be the same lesion as some of the reported Brenner tumors [13, 14].

10.1.2 Premalignant Vaginal Tumors

10.1.2.1 Vaginal Intraepithelial Neoplasia

Low-Grade Squamous Intraepithelial Lesion (LSIL or Vaginal Intraepithelial Neoplasia [VaIN] 1)

Low-grade squamous intraepithelial lesions are less common in the vagina than the cervix; however, as HPV infection can affect the entire lower genital field, vaginal involvement must be considered in patients with HPV-related disease elsewhere in the lower genital tract. LSIL can be caused by both high-risk and low-risk HPV subtypes. As in other lower genital sites, LSIL is considered low risk for progression and often regresses. Hence, expectant management with follow-up is a reasonable option [15]. LSIL is often not grossly visible, but may be seen on colposcopy, and most often involves the upper vagina [16]. Grossly, the lesions are flat and may be multifocal. Similarly, histology shows that most of the lesions are flat, although condylomatous features are possible both grossly and microscopically. Morphologic changes are as described elsewhere in the lower female genital tract. There is koilocytosis, but maturation of the squamous epithelium is present (Fig. 10.6). In general, the composition of the vagina differs due to a relatively large amount of elastic tissue, when compared to the cervix. This imparts a corrugated architecture, especially when the tissue is removed by biopsy, which may mimic the papillary architecture seen in some dysplastic lesions; therefore, diagnosis of dysplasia requires well-defined nuclear atypia to avoid overcalling this normal finding.

High-Grade Squamous Intraepithelial Lesion (HSIL, VaIN 2/3)

HSIL (VaIN 2/3) of the vagina is considerably less common than HSIL of the cervix. It is seen in midlife and in older women, with a peak age in the 70s, and is frequently associated with lower genital tract neoplasia at other sites [15]. The most commonly associated HPV subtype is HPV 16 [15]. HSIL of the vagina is often discovered during the evaluation of an abnormal cervical cytology, evaluation of cervical HPV disease, or after an abnormal cytology in a woman with a prior hysterectomy related to HPV disease (HSIL or cancer). Usually vaginal HSIL is asymptomatic, although postcoital bleeding or discharge may be reported [15].

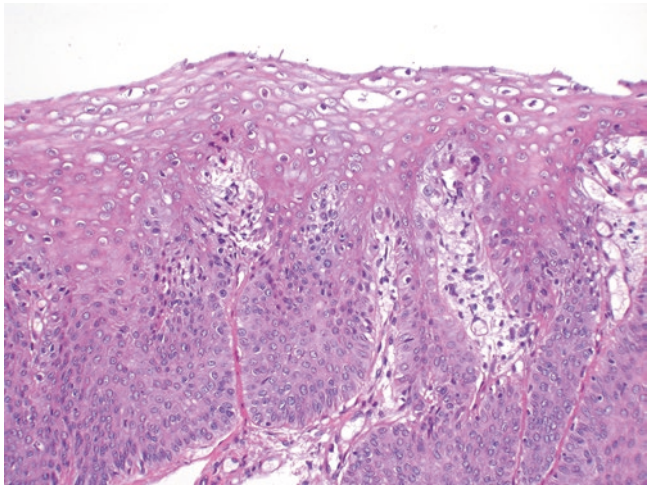

Fig. 10.6 Low-grade squamous intraepithelial lesion. Koilocytosis with epithelial maturation is present

As vaginal HSIL is considered preinvasive, therapy is indicated. Therapy is often individualized, and a variety of pharmacologic agents have been used, although they are not FDA-approved specifically for vaginal lesions, in addition to surgical excision or laser ablation [15]. The disease can be difficult to treat and can recur, particularly in immunosuppressed patients.

Histologically, HSIL of the vagina is similar in appearance to HSIL in other sites, with squamous maturation abnormality extending upward through at least two thirds of epithelium (Fig. 10.7). Some maturation is seen in VaIN 2 and generally none in VaIN 3; however, there is sufficient overlap, and the distinction between VaIN 2 and VaIN 3 is not reliably reproducible. Lesions may be pigmented and may show a predominantly basaloid or warty histology. The LAST project recommends the use of biomarkers for specific diagnostic scenarios, as opposed to routine or reflexive use [17]. P16, when diffusely block positive, is a surrogate marker of high-risk HPV and as such can be useful for distinguishing HSIL from benign mimics such as atrophy (Fig. 10.7e–g). Ki-67 activity above the basal layers is indicative of SIL; however, this does not correlate with grade (Table 10.2). The risk of developing an invasive carcinoma from VaIN is unknown [18].

Squamous neoplasia of the vagina is often associated with other lower genital tract squamous neoplasia, including the vulva, cervix, and anus. Human papillomavirus causes disease in a field effect, and hence, the entire region needs to be evaluated. This is particularly true in immunosuppressed patients, including those with HIV and status post organ transplantation.

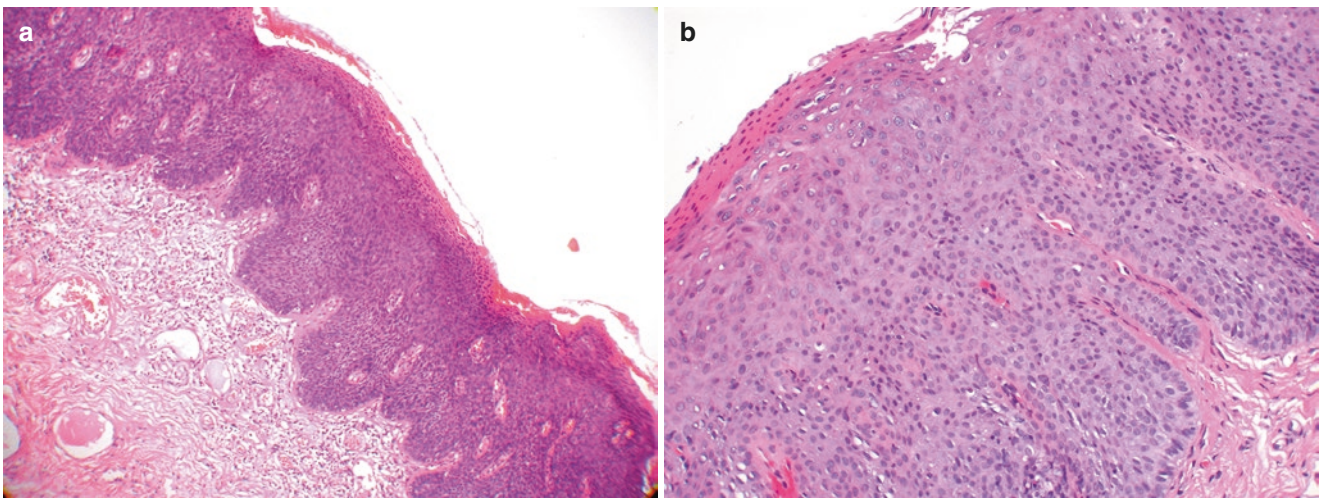

Fig. 10.7 High-grade squamous intraepithelial lesion. At low power (**a**), the epithelium is acanthotic, and parakeratosis is seen. Full thickness maturation abnormality is present (**b**, **c**). The lesions may be pigmented (**d**). There are times where it is difficult on H&E to separate HSIL from atrophy (**e**). This case was determined to be HSIL based on full thickness staining of Ki-67 (**f**) and block positivity for p16 (**g**)

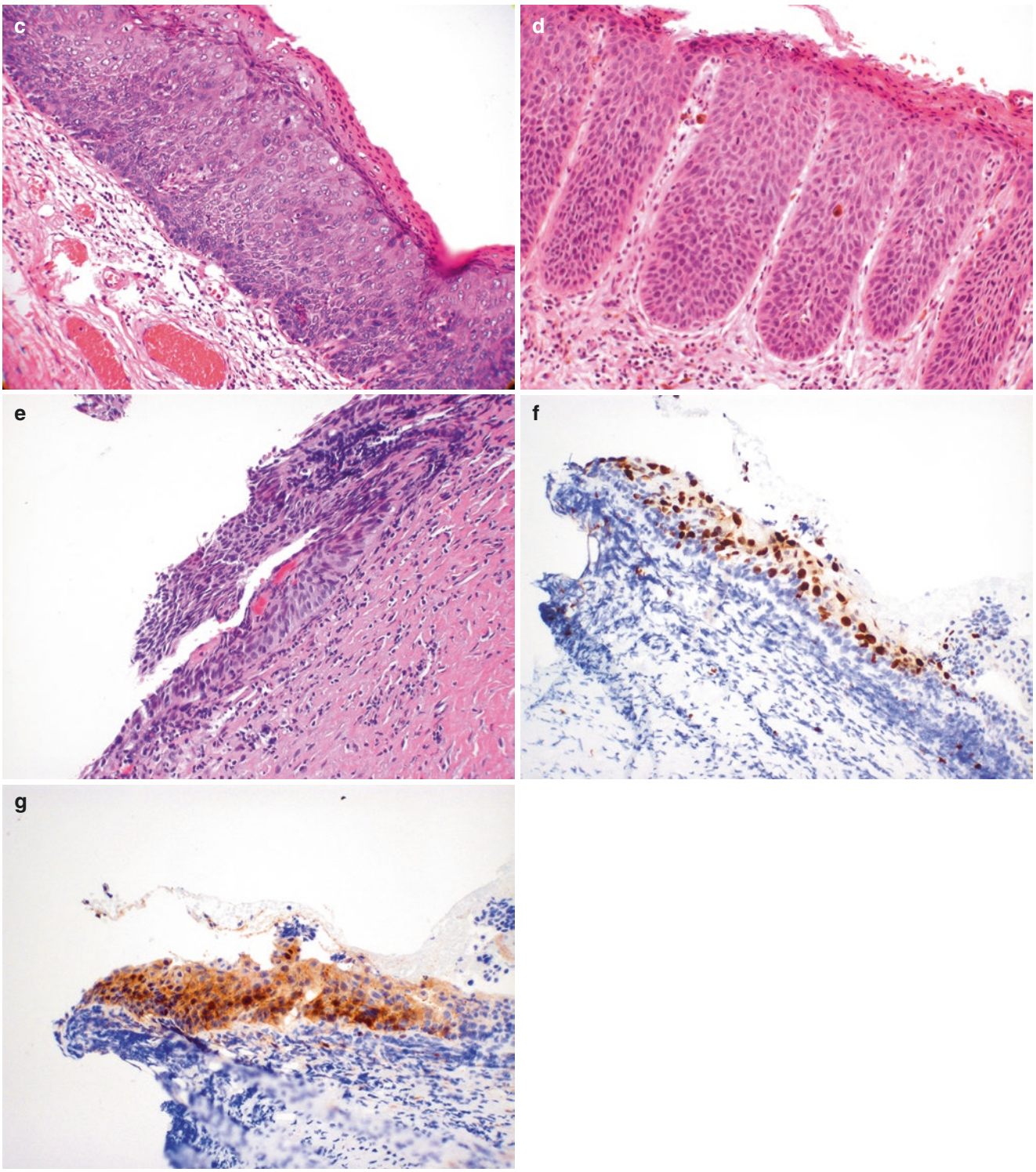

Fig. 10. 7 (continued)

Table 10.2 Immunohistochemistry of SIL (VaIN)

	P16	Ki-67
LSIL	+/−	Above basal layers
HSIL	Usually + diffusely (block positive)	Above basal layers
Atrophy	–	Confined to basal layers

10.1.3 Malignant Epithelial Tumors

10.1.3.1 Squamous Cell Carcinoma

Vaginal carcinoma represents about 2% of gynecologic malignancies for an incidence of about 3000 new cases per year in the USA [18]. Most lesions arise in the upper vagina of elderly women, although younger patients are occasionally affected. The vast majority of cases are squamous, and HPV is the causative agent in about 70–80% of cases [19] (most often HPV16) [20, 21]. Vaginal squamous cell carcinoma is considerably less frequent than cervical squamous cell carcinoma, and many patients with vaginal squamous cell carcinoma have a prior history of cervical disease, although it can be remote. As such, it is not always possible to diagnose a vaginal squamous cell carcinoma as a primary lesion.

While some attempts at defining superficially invasive squamous cell carcinoma of the vagina have been made, the LAST project made no recommendations on a definition for superficial invasion, as there was insufficient data in the group's opinion [17]. Some invasive carcinomas arise from HSIL, but the exact percentages are not known. Patients with invasive carcinoma tend to be about 10 years older than HSIL patients [18]. Interestingly, about half of vaginal carcinoma patients have had a prior hysterectomy [19].

Presenting symptoms of invasive vaginal carcinoma include bleeding, discharge, pain, or discomfort; however, the lesions may be asymptomatic [22]. Biopsy can be difficult, as it is technically challenging to acquire a deep enough biopsy to establish invasion (Fig. 10.8a, b). Histologically, the appearance is similar to squamous cell carcinoma in other lower genital tract locations and may sometimes appear warty or basaloid (Fig. 10.8c, d). Vaginal lesions are difficult to treat surgically, and thus, surgery is used predominantly for early lesions, with radiotherapy for more advanced disease, although treatment is variable [18, 22]. The increased benefit of chemotherapy is unclear, although it has been used with radiotherapy [19]. Stage is the most important prognostic factor [18]. Other poor indicators are size >4 cm, location outside the upper third of the vagina, and older age at presentation. The role of tumor grade is unclear. The presence of high-risk HPV appears to be associated with better clinical outcome [18]. Stage I disease has a 5-year survival rate of about 70% which drops rapidly with more advanced stage disease [22]. Staging is based on the 2009 FIGO system, which is clinical, as well as the AJCC TNM system, which incorporates pathologic findings [23, 24] (Table 10.3). The vagina has a rich lymphatic drainage system, which may be part of the explanation for the relatively poor prognosis. Upper vaginal lesions spread to iliac lymph nodes, and lower two thirds of the vagina lesions spread to inguinal nodes [20]. Distant metastases are uncommon, but the most common sites are the lung, liver, and bone [19].

A variant of squamous cell carcinoma, squamotransitional cell carcinoma, which may be papillary in architecture, and resembling the same neoplasm in the cervix, has been described [25]. It can be distinguished from a metastasis of a bladder primary transitional cell carcinoma by immunohistochemistry. Squamotransitional cell carcinomas of the vagina are typically CK7+/CK20- and stain for p16 reflecting association with high-risk HPV, while transitional cell carcinoma extending from bladder would be CK7+/CK20+, and does not demonstrate evidence of HPV infection [25].

10.1.3.2 Adenocarcinoma

Most vaginal carcinomas are squamous cell carcinomas, but adenocarcinoma represents about 2–10% of vaginal malignancies (Table 10.4) [18, 20]. Because of the rarity of these lesions, large case series are not available for treatment protocols and prognosis. In one series of mixed non-squamous cases, local control was achievable, but distant metastasis remained an issue [26]. In this series, many of the cases were clear cell adenocarcinoma, in spite of the lack of diethylstilbestrol (DES) exposure history [26]. Metastatic disease must be considered, as only about 20% of vaginal adenocarcinomas are primary [27]. Primary adenocarcinomas may be related to in utero exposure to DES or may be unrelated. Clear cell adenocarcinomas have most often arisen previously in association with DES exposure. This is becoming a less significant contributor to cases, as DES is no longer used in pregnancy, having been banned for use in pregnancy in 1971 [28]. Reported DES-associated clear cell adenocarcinomas usually occurred in younger women, in the anterior upper vaginal wall [21]. As many of these reported patients with DES-associated tumors were already under surveillance, their carcinomas were detected early and carried a good prognosis [21]. Late recur-

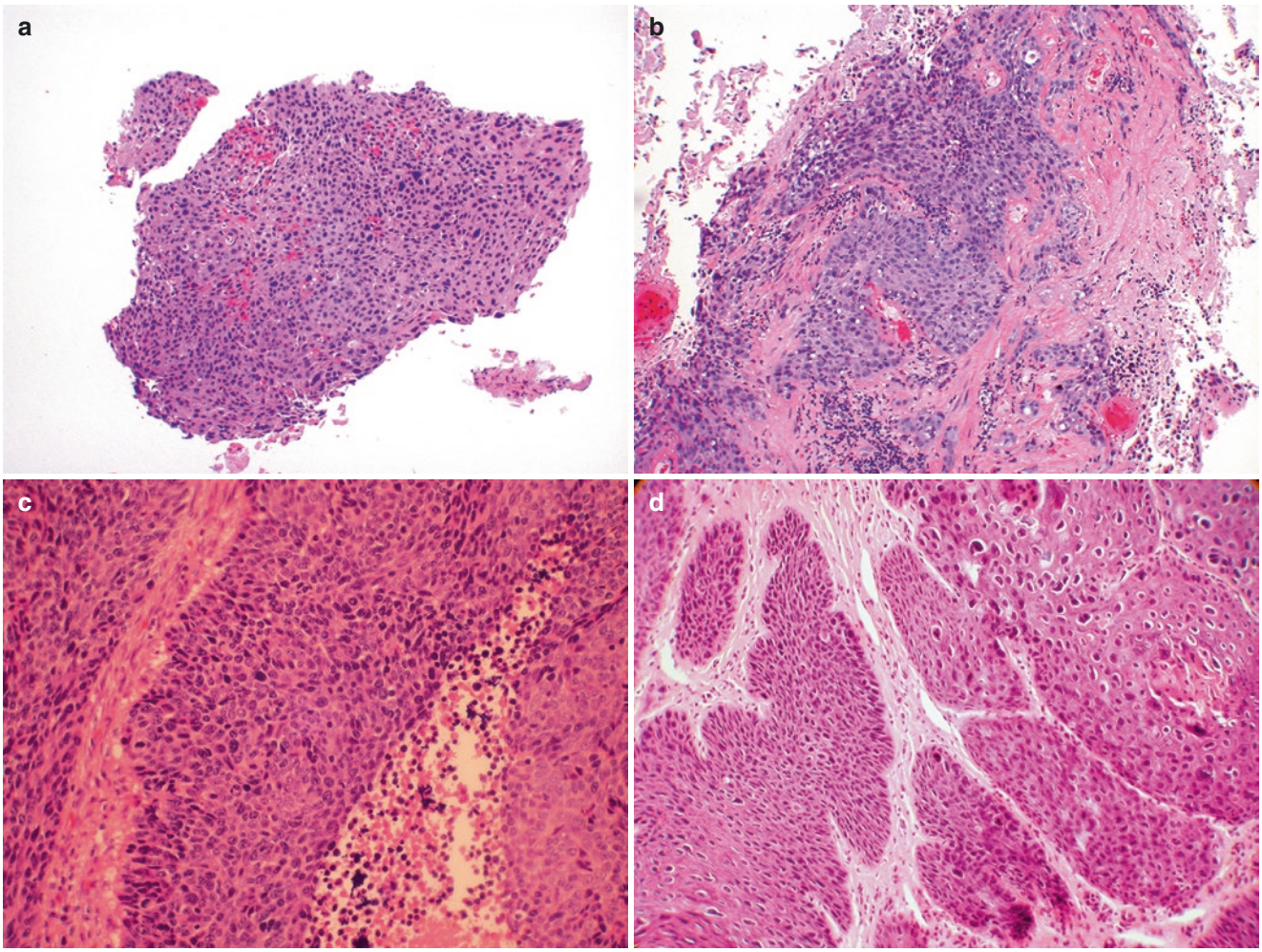

Fig. 10.8 Squamous cell carcinoma of the vagina. Superficial biopsies without underlying stroma may not be diagnostic (**a**), and a deep enough biopsy to show stromal invasion is needed (**b**). Some cases of squamous cell carcinoma may be basaloid (**c**) or warty (**d**)

Table 10.3 FIGO staging of carcinoma of the vagina[a]

FIGO stage	Description
I	The carcinoma is limited to the vaginal wall
II	The carcinoma has involved the subvaginal tissue but has not extended to the pelvic wall
III	The carcinoma has extended to the pelvic wall
IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum; bullous edema as such does not permit a case to be allotted to Stage IV
IVA	Tumor invades the bladder and/or rectal mucosa and/or direct extension beyond the true pelvis
IVB	Spread to distant organs

[a]From: Hacker NF, Eifel PJ, van der Velden J (2015). Cancer of the Vagina. Int J Gynaecol Obstet.131 Suppl 2:S84–7. doi: https://doi.org/10.1016/j.ijgo.2015.06.003

Table 10.4 Adenocarcinoma of the vagina

Primary
DES-associated
Clear cell adenocarcinoma
DES-unassociated
Clear cell adenocarcinoma
Mucinous adenocarcinoma
Intestinal type
Endocervical type
Endometrioid adenocarcinoma
Mesonephric adenocarcinoma
Serous adenocarcinoma
Metastatic

rences dictated prolonged follow-up [21]. Clear cell adenocarcinomas can arise in the absence of DES. Histologically, they appear similar to clear cell adenocarcinomas in other genital

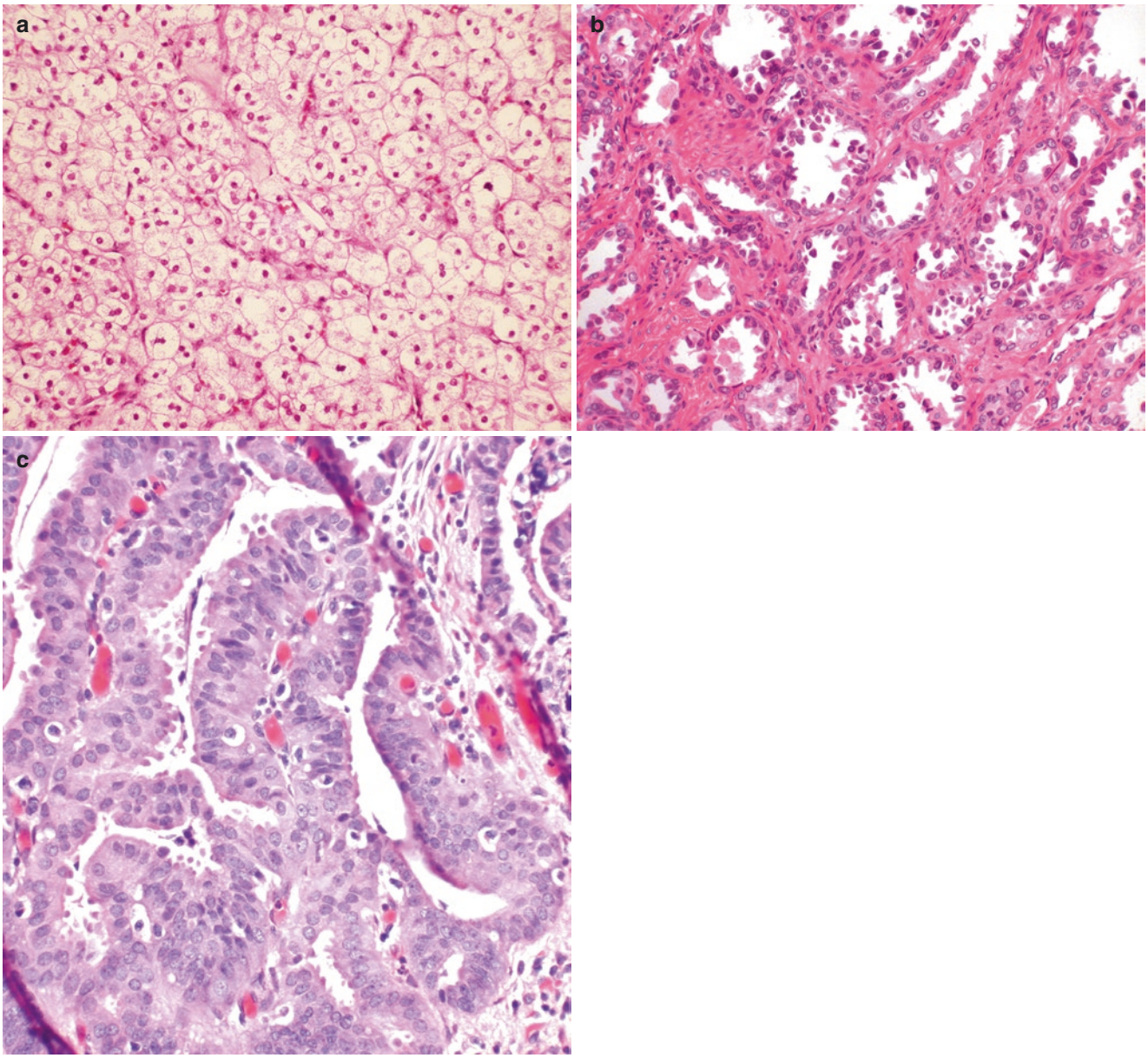

Fig. 10.9 Adenocarcinoma of the vagina. Clear cell adenocarcinoma may appear as sheets of cells with clear cytoplasm (**a**) or have a tubulopapillary architecture (**b**). Other types of adenocarcinoma include endometrioid (**c**), as well as endocervical and intestinal types (not shown)

sites and may have a clear cell or tubulopapillary appearance (Fig. 10.9). Adenocarcinoma can also rarely arise from endometriosis [20].

Adenocarcinomas not associated with DES have been reported in late reproductive and postmenopausal patients but can also occur in younger patients [11, 29]. Mucinous adenocarcinomas may be of endocervical or intestinal type. Primary vaginal adenocarcinoma of intestinal type is a rare tumor that must be distinguished from metastatic disease, particularly from the gastrointestinal tract [11]. This can be challenging, as the primary vaginal colonic-type lesions stain for CK20 and CEA, as well as CDX2 [30], but are negative for CK7, similar to a colonic neoplasms [11]. Theories of the origin of these lesions include gastrointestinal metaplasia, heterotopia, adenosis, mesonephric or cloacal remnants, or evolution from metaplastic endometriosis [11]. Endocervical-type adenocarcinoma has been theorized to arise from adenosis or endocervicosis [31]. Adenocarcinoma arising in the vagina may also be of the endometrioid type (Fig. 10.9c), as well as of serous, mucinous, or mesonephric types [26, 31–33]. The morphologic and immunophenotypic features of the various histotypes of primary vaginal adenocarcinomas are as described for these histotypes at other locations of the gynecologic tract.

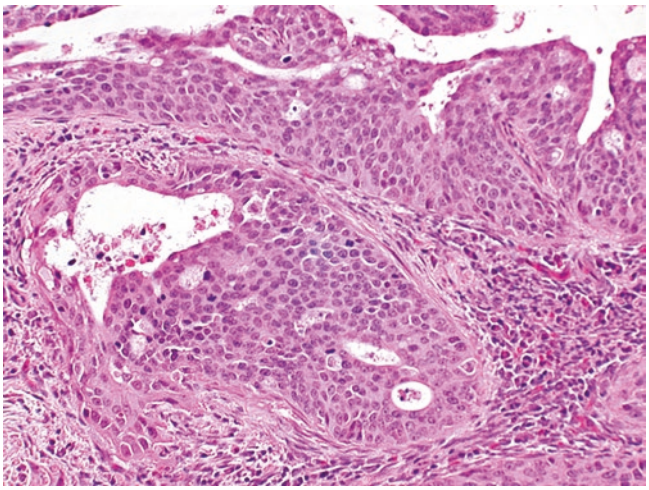

Fig. 10.10 Adenosquamous carcinoma, showing both squamous and glandular features

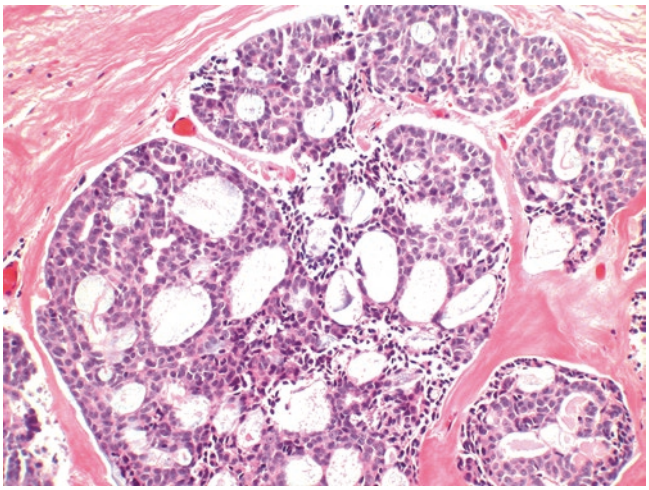

Fig. 10.11 Adenoid cystic carcinoma. The lesion is composed of "cookie cutter" round spaces in the epithelium, filled with basement membrane material

10.1.3.3 Adenosquamous Carcinoma

Adenosquamous carcinoma, containing both glandular and squamous differentiation (Fig. 10.10), has been reported as isolated cases [34, 35]. In one series, it represented about 4% of all primary vaginal cancers [35]. Lesions are most likely to arise on the anterior vagina [36]. The tumor has been described as locally aggressive with metastatic potential, as lung metastases have been described [35, 36]. Theories of origin have included adenosis, endometriosis, or growth from minor vestibular glands, misplaced Bartholin's glands, or glands of cloacogenic origin [36]. Glassy cell carcinoma, the most poorly differentiated aggressive form of adenosquamous carcinoma, which is usually seen in the cervix, has rarely been reported to arise primarily in the vagina [37].

10.1.3.4 Adenoid Cystic Carcinoma

Adenoid cystic carcinomas are classically described as tumors of the salivary glands, but rare cases have arisen in Bartholin's glands [38] and the vagina [39]. The tumors are composed of bland epithelial nests with cribriform architecture, embedded in an eosinophilic stroma composed of basement membrane material (Fig. 10.11). A tumor in the differential diagnosis of adenoid cystic carcinoma is polymorphous low-grade adenocarcinoma, another salivary gland neoplasm which has been reported to arise in the vulva and vagina [40]. It can be distinguished from adenoid cystic by its mixed pattern of cribriform (resembling adenoid cystic), papillary, and cystic growth [40]. Both lesions arise too infrequently in the vagina to establish prognosis; however, in the salivary glands, adenoid cystic carcinomas can metastasize, while polymorphous low-grade adenocarcinoma can recur locally [40].

10.1.3.5 Adenoid Basal Carcinoma

Adenoid basal carcinoma is a rare cervical lesion, with only sporadic case reports in the vagina [39, 41]. Nave's case [41] arose in the posterior upper third of the vagina in a 46-year-old woman who presented with abnormal bleeding. The lesions are composed of subepithelial nests of basaloid cells with no stromal reaction. The center of the nests may show glandular or squamous differentiation [36, 41](Fig. 10.12). A benign lesion in the differential diagnosis is a tubulosquamous vaginal polyp, which may contain abundant basaloid nests [14, 42]. However, tubulosquamous vaginal polyps can be differentiated from adenoid basal carcinoma by areas of frank squamous differentiation, as well as the presence of a tubular component. Basaloid nests, when present, are less likely to show prominent palisading in tubulosquamous vaginal polyps [42].

10.1.3.6 Neuroendocrine Carcinoma

Neuroendocrine carcinoma is more common in the cervix but can rarely arise in the vagina. The lesions may be of either small cell or large cell type.

Extrapulmonary small cell carcinoma is unusual. It can arise in the cervix, endometrium, ovary, vulva, and vagina [43]. Small cell neuroendocrine carcinoma of the vagina was first described by Scully et al. [44]. At the time of Bing's series, there were 25 described cases of small cell neuroendocrine carcinoma primary in the vagina [45]. Small cell neuroendocrine carcinoma is similar to the lung primary, with sheets of small cells with minimal cytoplasm, granular "salt and pepper" chromatin, and inconspicuous nucleoli [45]. There is often abundant necrosis and mitotic activity and a feature known as "crush artifact" (Fig. 10.13a, b).

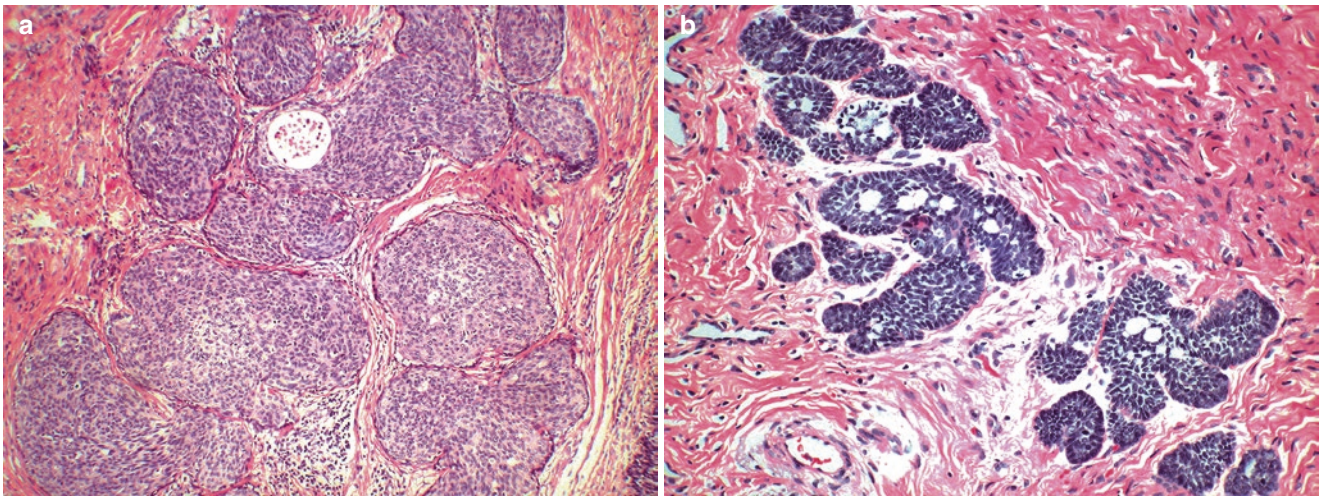

Fig. 10.12 Adenoid basal carcinoma. The lesion is composed of well-circumscribed nests of basaloid cells without a stromal reaction (**a**). Cystic spaces are often seen (**b**)

The tumors stain with neuroendocrine markers such as chromogranin and synaptophysin. Small cell carcinoma is a very aggressive tumor, typically presenting at an advanced stage with symptoms of bleeding, pain, and dysuria. A few cases have been associated with Cushing's syndrome due to ectopic ACTH production [46]. The lesions are often ulcerated and variable in size [36, 45]. Because of the rarity of the lesion, standardized therapy has not been established; however, they are typically treated with similar chemotherapeutic regimens as pulmonary tumors [47]. The origin of these tumors is not known; however, the lesion has been described with coexisting atypical adenosis of the vagina [48]. Coleman's case was described as having a Merkel cell carcinoma phenotype, based on positive CK20 staining, which was not investigated in many of the reported cases [49]. Merkel cell carcinoma is a neuroendocrine carcinoma of the skin.

Large cell neuroendocrine carcinoma (LNEC) is exceptionally rare, with only one case having been previously described [50]. The patient presented at an advanced stage, and histologically, the tumor was composed of sheets or organoid arrangements of poorly differentiated malignant cells with more cytoplasm that the small cell tumor. There was no nuclear molding, and nucleoli were prominent [50] (Fig. 10.13c–e). Neuroendocrine markers are expected to be positive as they are in the small cell variant.

10.1.3.7 Undifferentiated Carcinoma

Carcinomas lacking specific differentiation can occur in the vagina [39]. Undifferentiated carcinomas are composed of sheets of primitive undifferentiated cells with no evidence of specific phenotype by histology or immunohistochemistry.

10.2 Mixed Epithelial and Mesenchymal Tumors

10.2.1 Mixed Tumor

Mixed tumors of the vagina are rare benign lesions seen predominantly in premenopausal women and tend to occur in the lower vagina near the hymenal ring [14]. These lesions differ in appearance from the salivary gland tumors of the same name, which are thought to be of myoepithelial origin. Their origin in the vagina is unclear [51]. Vaginal mixed tumors are well circumscribed but not encapsulated [21]. The lesion is composed of both epithelial and stromal elements, with a mix of squamous, glandular, and spindle cells, which, although mesenchymal in appearance, stain with cytokeratin [14] (Fig. 10.14). In a series of cases, it was shown that these lesions have coexpression for epithelial and mesenchymal markers, without a specific immunoprofile, and therefore, diagnosis should rely on histology [51]. The authors felt the tumor may arise from pluripotential cells. Treatment is excision, although rarely these can recur [21].

10.2.2 Vaginal Adenosarcoma

Extrauterine adenosarcomas, including those arising in the vagina, are very rare lesions. Reported cases have occurred in midlife or postmenopausal women, with an association with prior hysterectomy [52]. Vaginal adenosarcoma has been proposed to arise from endometriosis [53, 54] or, alternatively, from pluripotential cells [53]. The tumors, like the uterine counterpart, are mixed epithelial-stromal tumors

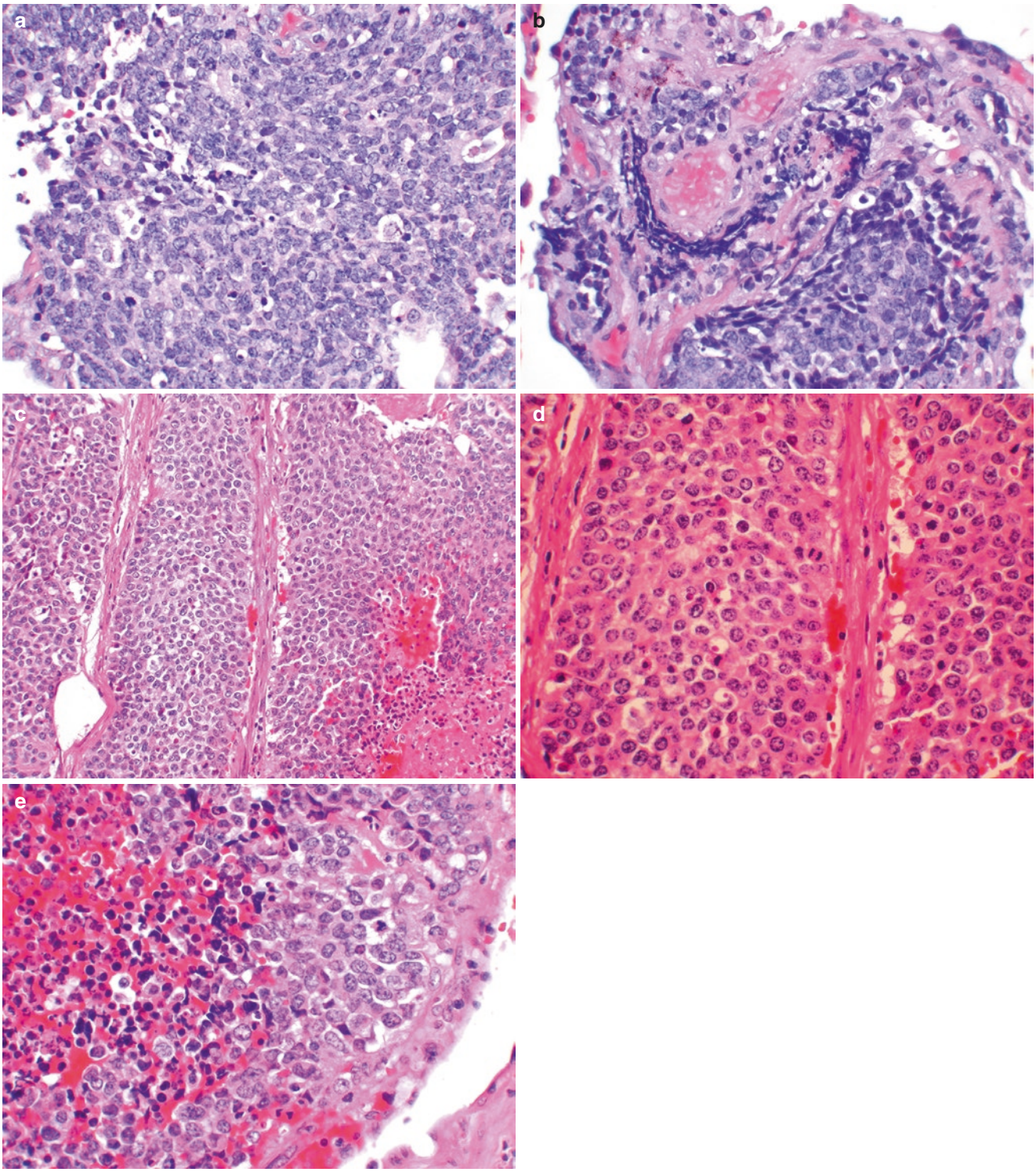

Fig. 10.13 Neuroendocrine carcinoma. The features of neuroendocrine carcinoma are demonstrated in these lung neoplasms. Small cell neuroendocrine carcinoma showing diffuse sheets of small cells with minimal cytoplasm and dispersed chromatin (**a**). Small cell carcinomas often show "crush artifact" (**b**). Large cell neuroendocrine carcinomas contain more cytoplasm than small cell neuroendocrine tumors (**c**–**e**) and may be arranged in organoid clusters (**c**, **d**) with areas of necrosis (**e**)

composed of benign glands in a malignant stroma. The lesions are often bulky and polypoid and may have a "phyllodes" (leaflike) architecture of epithelium lining sarcomatous projections. Histologically, the tumors are composed of benign-appearing endometrial-type glands and surface epithelium in a malignant spindle cell stroma, which has a

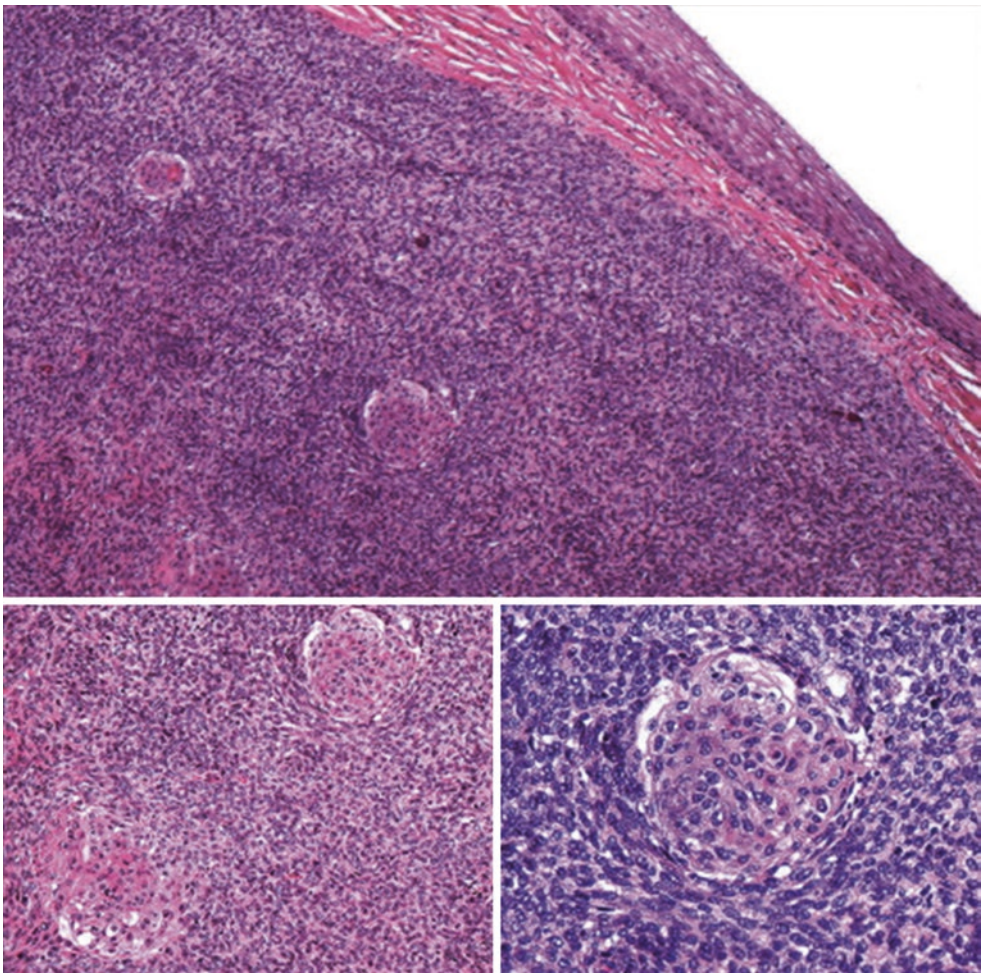

Fig. 10.14 Mixed tumor of the vagina. The lesion is composed of squamoid nests surrounded by spindle cells. The lesion is seen arising under the epithelium. Reprinted from Pathology Research and Practice 208(7) Mahe E, Bishara M, El Demellawy D, DeNardi F, Alowami S. The vaginal spindle cell epithelioma: A case report, review of the literature and discussion of potential histogenesis. p. 424–32, 2012 with permission from Elsevier

tendency to cuff around the glands under the surface in a "cambium" layer (Fig. 10.15). Heterologous elements such as rhabdomyosarcoma, chondrosarcoma, or liposarcoma can be present [55]. Although malignant, adenosarcomas usually are indolent; however, if sarcomatous overgrowth occurs, the tumor is aggressive with a poor prognosis [53].

10.2.3 Carcinosarcoma

Carcinosarcomas of the female genital tract usually arise from the endometrium of postmenopausal women. Primary vaginal carcinosarcomas are rare with only a few reports in the literature. They generally occur as a polypoid mass in postmenopausal women [56, 57]. The tumor is composed of malignant, high-grade epithelial and stromal elements, like its uterine counterpart; however, the epithelial component in vaginal tumors is more likely to be squamous as opposed to the more likely endometrioid epithelial component in the uterus (Fig. 10.16a) [56]. A previously described case was described as a polypoid lesion that was positive for HPV 31/33/51 by in situ hybridization in both the epithelial and mesenchymal components, favoring a metaplastic carcinoma for origin of the tumor [56]. Primary vaginal lesions appear to be aggressive [56, 57]. A diagnosis of carcinosarcoma should be made on the histologic presence of unequivocal, high-grade epithelial and mesenchymal components. This may be difficult in select cases, and immunohistochemistry may help; however, a diagnosis should never be made on immunohistochemical grounds alone. Sarcomatoid carcinoma is one of the most difficult entities to rule out in the differential diagnosis; however, sarcomatoid carcinoma (Fig. 10.16b) typically does not display vimentin expression as would be seen in the mesenchymal portion of carcinosarcoma [56].

10.2.4 Mixed Tumor Resembling Synovial Sarcoma

Synovial sarcoma is a soft tissue tumor that has overlapping epithelial and mesenchymal immunohistochemical markers. It may be monophasic with spindle cells, or biphasic, with a glandular or papillary epithelial component. Some cases may

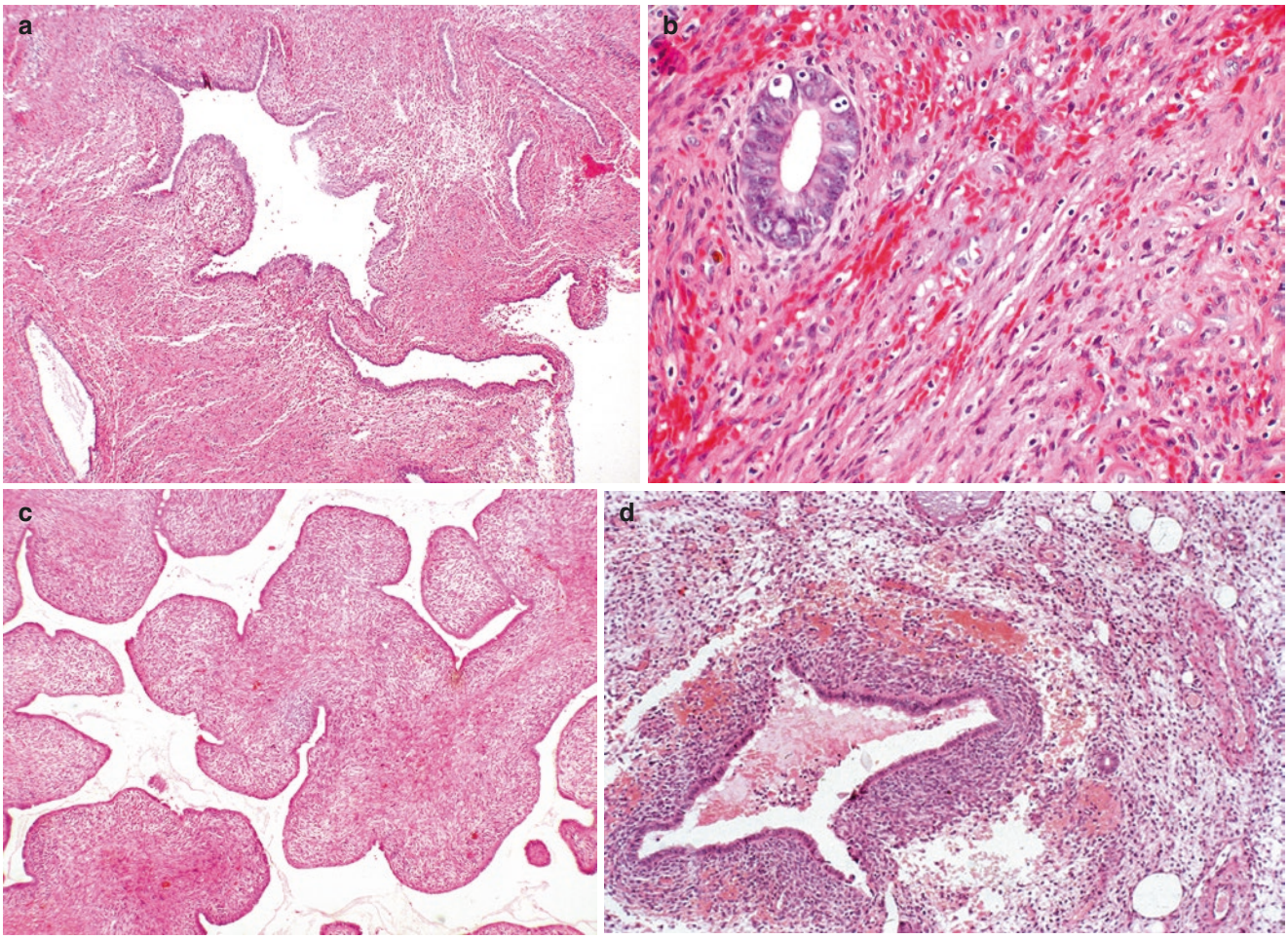

Fig. 10.15 Adenosarcoma. The lesions are composed of benign glands in a malignant stroma (**a**, **b**) and may have a leaflike (phyllodes) architecture (**c**). The malignant stromal cells may cuff under the glands in a "cambium" layer (**d**); (Part label **d** with permission from Heller DS, Handbook of Endometrial Pathology. London: JP Medical, 2012)

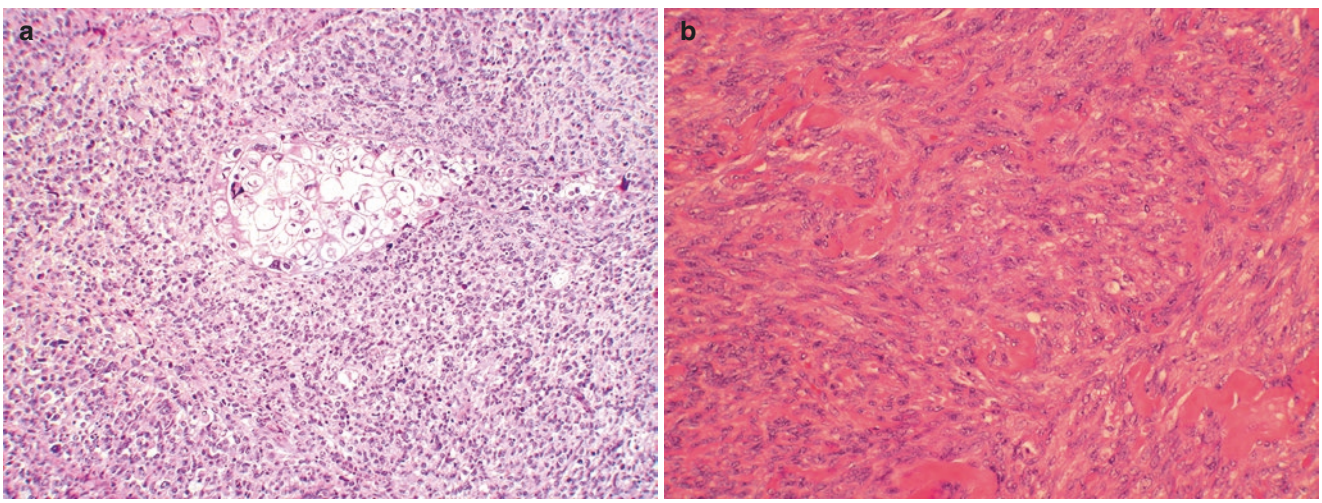

Fig. 10.16 Carcinosarcoma. Vaginal carcinosarcomas are more likely to have squamous epithelial elements rather than the endometrioid elements seen in the uterine counterpart (Part label **a**, With permission from Heller DS, Handbook of Endometrial Pathology. London: JP Medical, 2012). This needs to be distinguished from sarcomatoid carcinoma (**b**) which stains for keratins but not vimentin

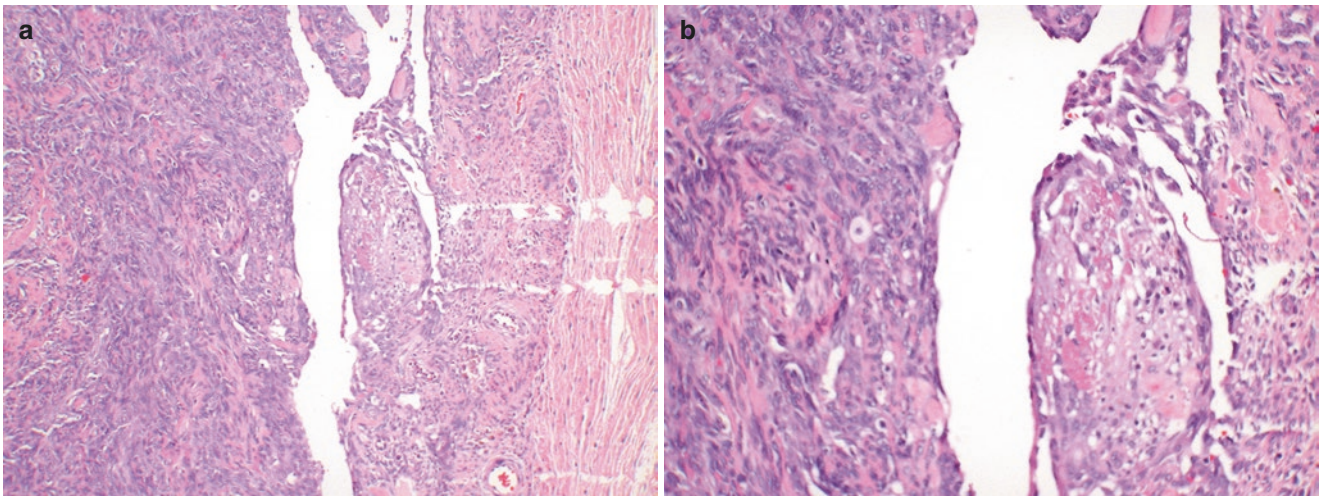

Fig. 10.17 Synovial sarcoma – this soft tissue lesion is spindle cell predominant, with only a minor epithelial component (**a**, **b**)

contain poorly differentiated sheets of pleomorphic tumor cells. In 1976, Okagaki et al. described a tumor arising in the upper vagina of a 24-year-old woman with a mixed pattern of tubular epithelial elements and spindle cell elements resembling fibrosarcoma, which they felt resembled synovial sarcoma [58]. They considered the tumor likely malignant, but did not provide follow-up. Since then, rare case reports of vaginal synovial sarcomas have appeared, with some of them having confirmatory molecular testing showing the characteristic X;18 translocation, as well as the overlapping immunoprofile of vimentin, cytokeratin, and epithelial membrane antigen [59]. Malignant behavior has been demonstrated, as proven in one case, where the patient developed lung metastases 11 months after initial surgery [60]. Additionally, another reported patient suffered multiple local recurrences and eventually died of disease 8 years after diagnosis [59]. The differential diagnosis of this lesion includes carcinosarcoma. Synovial sarcoma arising in the vagina has been described in younger women than carcinosarcoma, with one patient in her 20s and two in their 40s [58–60]. Additionally, the epithelial and mesenchymal components of carcinosarcoma are usually of higher grade than synovial sarcoma [59], which is often predominantly composed of a bland spindle cell proliferation (Fig. 10.17). This distinction, however, may be difficult, as both neoplasms tend to show sharp demarcation of epithelial and mesenchymal elements, overlapping immunoprofiles, and both may have heterologous elements [59]. Mixed tumor of the vagina is also in the differential diagnosis but usually has both squamous and glandular epithelial elements, with a spindle cell component that is usually bland with no mitotic activity. Mixed tumors are more likely to be diffusely positive for cytokeratin, while the spindle cell component of synovial sarcoma is usually focally positive for cytokeratin [59]. Monophasic spindle cell synovial sarcoma raises a wide differential of spindle cell lesions that can occur in the vagina, which can be distinguished by immunohistochemistry and molecular genetic studies.

10.3 Other Rare Tumors

10.3.1 Melanocytic Lesions

10.3.1.1 Melanocytic Nevus

The vagina does not usually contain melanocytes; however, rare benign pigmentation of the vagina has been reported [61]. Although theoretically possible, no well-documented melanocytic nevus has been reported in the literature [36]. Melanocytic nevi are composed of nests of melanocytes, which may be intradermal, junctional, or compound, based on the location of the cells.

10.3.1.2 Blue Nevus

Blue nevi are so termed because grossly they display a blue hue. This gross feature is because of the clusters of spindle-shaped dendritic melanocytes that comprise these lesions that are located deep in the dermis [36] with no junctional activity. Vaginal blue nevi have been occasionally reported [62]. These benign lesions may be biopsied over concern of melanoma (Fig. 10.18).

10.3.1.3 Malignant Melanoma

Vaginal melanoma represents about 3% of malignant vaginal tumors [28]. This aggressive neoplasm is usually diagnosed late, with poor outcome, presenting symptoms including bleeding, mass, or discharge [22]. In one reported case, the patient developed a paraneoplastic syndrome comprised of paraneoplastic cerebellar degeneration with opsoclonus myoclonus [63]. The lesions tend to arise in the lower vagina,

and most have occurred in postmenopausal women [22]. As in other areas of the body, mucosal melanomas tend to be more aggressive than their cutaneous counterparts; hence, vaginal melanoma typically behaves more aggressively than the more common vulvar melanoma [22]. Compared with an overall 50–60% 5-year survival in vulvar melanoma, vaginal melanoma has an overall 15% 5-year survival, with frequent local recurrences and distant metastasis (lung and liver) [63]. Because of the rarity of the lesion, treatment has been individualized. Radical surgery has not been shown to improve outcomes [64]; however, surgical excision as primary treatment seems to be the best option when possible, with radiotherapy sometimes used in nonresectable disease [65]. Adjunctive chemotherapy and immunotherapy are also used. In evaluation of a vaginal melanoma excised specimen, tumor size and Breslow thickness should be provided, as they are with the vulvar tumor. Tumor thickness has been described as an indicator of disease-free interval but not survival in one meta-analysis, with size less than 3 cm a significant survival factor [66]. Fortunately, most vaginal melanomas are pigmented [64]. Histologically, vaginal melanoma is similar to other locations, with either an epithelioid, spindle cell, or mixed histology (Fig. 10.19). Prominent nucleoli are often seen in epithelioid lesions, as well as scattered mitotic figures and a loss of cellular maturation in the submucosal connective tissue. Tumors are immunoreactive for melanocytic markers such as S100, HMB 45, SOX10, tyrosinase, miTF, and Melan-A.

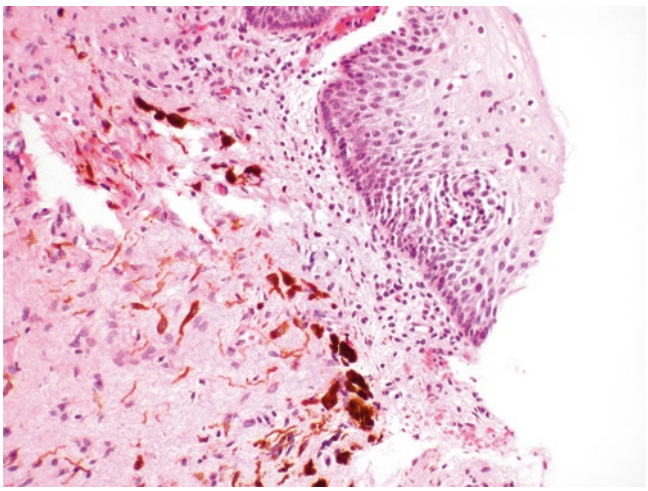

Fig. 10.18 Blue nevus. Dendritic melanocytes are seen in the submucosa

10.3.2 Germ Cell Tumors

10.3.2.1 Dermoid Cyst

Vaginal dermoid cysts are rare, although they have been known since biblical times [67]. The term is used as it is in cutaneous dermoids, rather than as it is for ovarian "dermoids" which are composed of all three germ cell layers. In skin and vaginal dermoids, ectodermal cells are entrapped during embryogenesis [68]. The differential diagnosis includes vaginal cysts, paravaginal cysts including embryologic remnants (Gartner's duct and Müllerian cysts), and epidermal inclusion cysts [69], the last two of which are similar on ultrasound [70]. As several of the reported cases of dermoid cyst of the vagina occurred in women with prior episiotomy, it is possible that dermal appendages became entrapped and that dermoid cysts are actually a type of epidermal inclusion cyst [70].

10.3.2.2 Yolk Sac Tumor or Endodermal Sinus Tumor

Extragonadal yolk sac tumor (endodermal sinus tumor) most commonly arises in the vagina [21], but it is an uncommon lesion with less than 100 cases reported [71]. The clinical differential diagnosis includes the more common rhabdomyosarcoma, which can be distinguished on histopathology. Yolk sac tumor is usually seen in girls under 3 years of age,

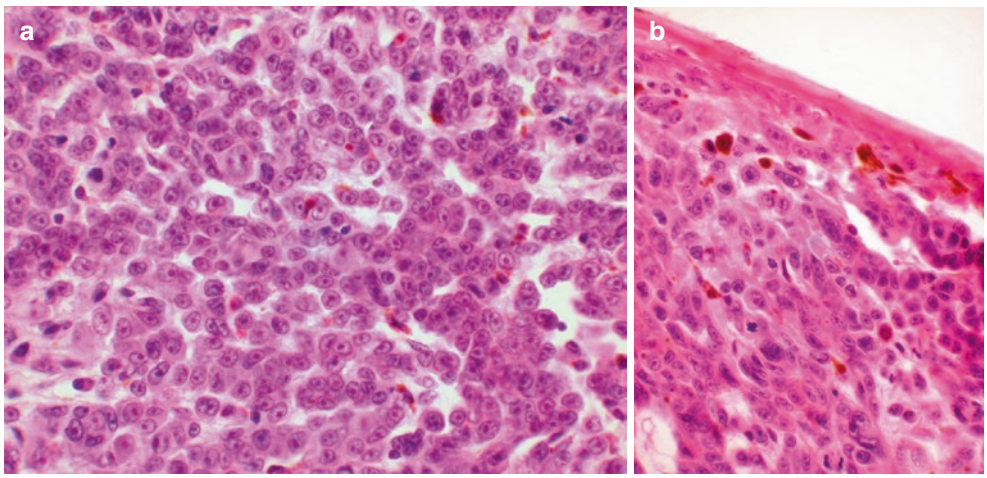

Fig. 10.19 Melanoma. Sheets of cells with prominent nucleoli (**a**, **b**) and melanin pigment (**b**) are seen

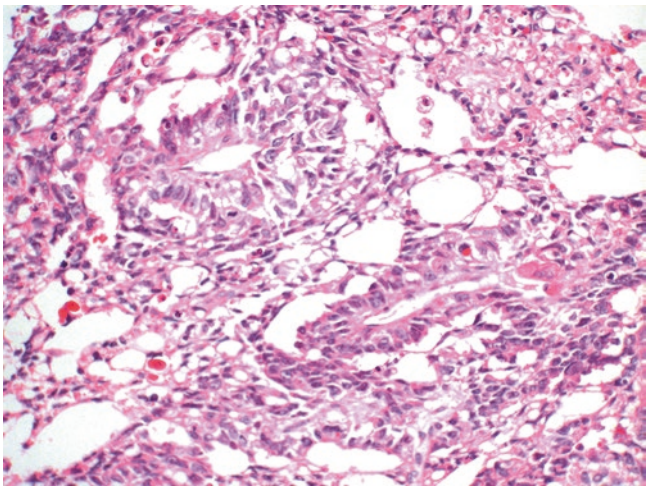

Fig. 10.20 Yolk sac tumor. The lesion is comprised of a reticular pattern. Two Schiller-Duval bodies are seen. Eosinophilic globules positive for AFP (not shown) are often present

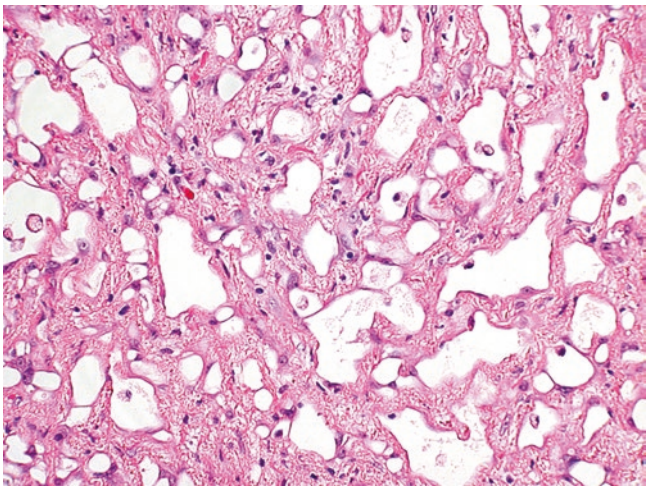

Fig. 10.21 Adenomatoid tumor, comprised of tubules lined by flattened mesothelial cells

presenting as a polypoid lesion [21, 72]. With improved chemotherapy, survival is much improved, and there has been a move away from radical surgery and toward either conservative surgery with chemotherapy or sometimes chemotherapy alone [71, 72]. Histologically, the tumor is similar to the ovarian counterpart, with a reticular pattern containing Schiller-Duval bodies and PAS- and AFP-positive globules (Fig. 10.20).

10.3.3 Other Tumors

10.3.3.1 Adenomatoid Tumor

Adenomatoid tumors are benign neoplasms occasionally seen as incidental findings in the uterus or fallopian tubes. Rarely, they can arise in the vagina (Fig. 10.21). They are of mesothelial origin and hence stain for mesothelial markers such as calretinin, D2-40, and WT-1 [73]. The lesions are composed of tubules lined by a flattened epithelium.

10.3.3.2 Neuroectodermal Tumors

Neuroectodermal tumors (peripheral neuroectodermal tumor (PNET), Ewing's sarcoma) are most often lesions of the bone and soft tissue, but rare cases have been reported in the vagina [74, 75]. These lesions fall under the category of small round blue cell tumors, requiring immunohistochemistry and molecular studies to establish the diagnosis. Membranous CD99 and Fli-1 immunostaining are expected, but may not be specific. Epithelial and neuroendocrine markers may be positive. A characteristic t11;22 (q24;q12) translocation is seen in most of these lesions [74, 75] and serves to confirm the diagnosis. In one series of seven cases [74], patient age ranged from 28 to 47 years. Lesions presented as masses of variable size, with vaginal bleeding in some cases.

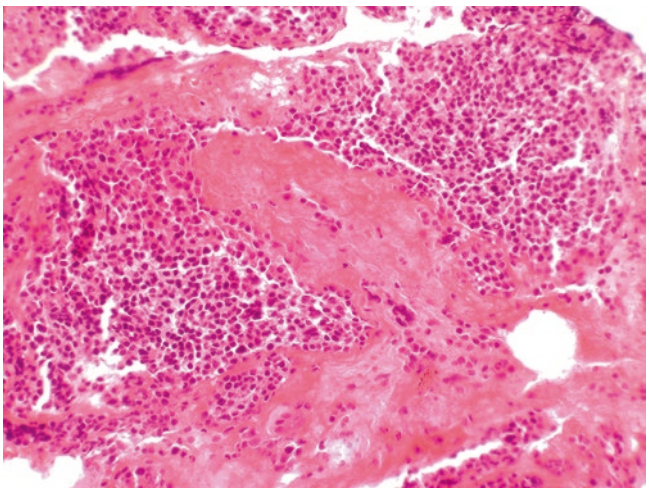

Fig. 10.22 Ewing's sarcoma. This lesion of the bone shows the characteristic sheets of small blue cells with minimal cytoplasm

All patients were alive 3–48 months after diagnosis. Histologically the tumors are composed of lobulated sheets of small blue cells with coarse chromatin and small nucleoli [75] (Fig. 10.22).

10.3.3.3 Lymphoma and Leukemia

Primary vaginal lymphoma is exceptionally rare, although it is not an unusual site in disseminated disease [76]. Presenting symptoms of primary vaginal lymphoma have included pain, bleeding, discharge, and a mass lesion, although they may be asymptomatic. Most cases are composed of diffuse large B cell lymphoma, which may present as multiple subepithelial nodules [76]. Histologically the lesions are similar to lymphomas elsewhere in the body (Fig. 10.23a), and adjunctive studies including cytogenetics, FISH, flow cytometry, and

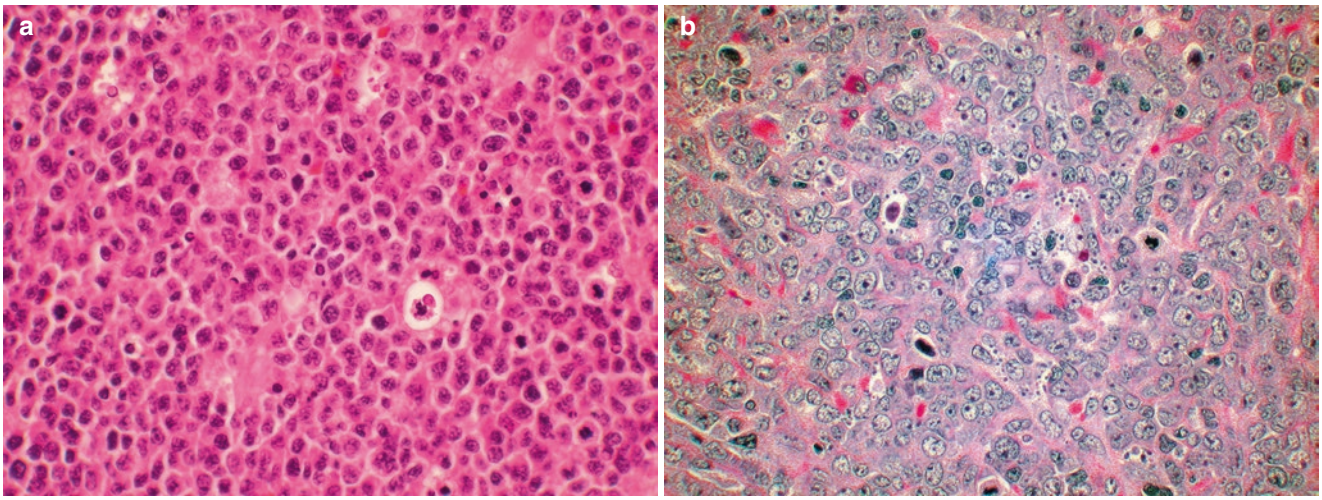

Fig. 10.23 Hematologic neoplasms. The vagina is a rare site for lymphoma (**a**) and myeloid sarcoma (**b**), both falling under the small round blue cell tumor category, requiring adjunct studies to elucidate the lineage

immunohistochemistry are useful adjuncts in the workup of such a lesion. Therapy is nonsurgical and utilizes chemotherapy [76]. Distinguishing lymphoma from other small blue cell lesions that can occur in the vagina, such as small cell neuroendocrine carcinoma, is critical as treatment modalities differ drastically between most of the tumors in this differential diagnosis.

Myeloid (granulocytic) sarcomas are solid masses composed of myeloid precursor cells and may be associated with a myeloproliferative disorder or rarely predate a leukemia [77]. Its occurrence in the vagina is exceptionally rare, with one case presenting with vaginal bleeding [77]. Historically, these tumors were termed "chloroma" referring to the green color that can be seen grossly due to myeloperoxidase. The lesions usually arise as submucosal nodules. The tumor is composed of sheets of mononuclear cells (Fig. 10.23b) and falls into the small round blue cell category. It has been suggested that therapy be individualized in these rare cases [77]. Overall prognosis is poor [78].

10.3.3.4 Secondary Tumors

80–90% of vaginal malignancies are secondary to metastatic disease, with primaries arising from the vulva, cervix, bladder, or rectum [20]. Metastatic disease may be from both genital tract and extragenital primaries [79]. Metastatic diseases from endometrial and ovarian primaries are not infrequent. According to one study, the most common primary site of metastatic carcinoma is the cervix, followed by the endometrium, colon, ovary, vulva, and urinary tract [27]; however, another series [79] found that the most common primary sites were the colon and rectum (Fig. 10.24). It is important to have the patient's prior history and to employ adjunctive immunohistochemistry in these cases to avoid errors in diagnosis and therapy.

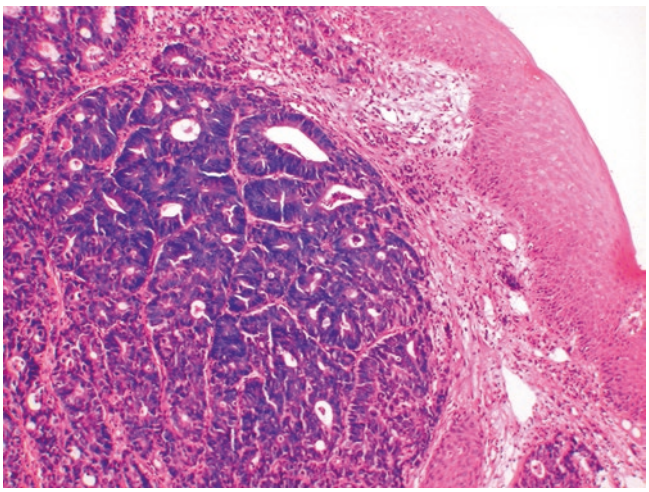

Fig. 10.24 Colonic adenocarcinoma metastatic to vaginal submucosa

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