9 Epithelial Malignant Tumors of the Cervix: Other Epithelial Tumors (Adenosquamous Carcinoma, Adenoid Basal Carcinoma, Carcinoma with Adenoid Cystic-like Features, Undifferentiated Carcinoma)

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Contents

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9.1 Adenosquamous Carcinoma

9.1.1 Definition

According to the 2014 WHO Classification of Tumours of the Female Reproductive Organs, both unequivocal malignant glandular and squamous elements must be present in order to make a diagnosis of cervical adenosquamous carcinoma [1]. These tumors are relatively uncommon neoplasms, and although the diagnostic criteria for this entity are relatively strict, varied application has led to a wide-ranging reported prevalence for this tumor type.

9.1.2 Synonyms

Originally called "mixed carcinoma" [2], however this term is no longer applied when dealing with this entity.

9.1.3 Etiology

Most but not all cervical adenosquamous carcinomas are associated with high-risk human papillomavirus infection [3–7]. It has been postulated that these neoplasms arise from cervical subcolumnar pluripotential reserve cells, which have the capacity to differentiate into both endocervical and squamous epithelium [8]. Interestingly, it has been shown that both tumor components of adenosquamous carcinoma—that is, both malignant glandular and squamous elements—appear to be monoclonal in origin and show identical patterns of X chromosome inactivation in addition to human papillomavirus type and physical status [9]. A subset of these tumors has been shown to demonstrate loss of ARID1A protein expression, but the significance of this finding and its role in tumor pathogenesis is not well understood in this tumor type [10].

9.1.4 Macroscopy

Adenosquamous carcinoma may present as a nodular enlargement of the cervix or as a frank exophytic mass; ulceration, hemorrhage, and necrosis also may be seen.

9.1.5 Microscopy

In order to make the diagnosis of adenosquamous carcinoma, the tumor must display unequivocal and overtly malignant glandular and squamous elements (often intimately admixed). Both elements should be morphologically distinguishable and recognizable, and both low-grade and high-grade morphology may be seen for both glandular and squamous components. High-grade glandular morphology usually takes the form of solid growth and diffuse high-grade nuclear atypia. High-grade squamous morphology typically exhibits sheet-like growth, high nuclear-to-cytoplasmic ratios, and lack of keratinization. Human papillomavirus infection-related features may be identified in the glandular component (which is most commonly of the "usual" type) while the squamous component may exhibit keratinization. Of note, precursor lesions, including high-grade squamous intraepithelial lesion, adenocarcinoma in situ, and stratified mucin-producing intraepithelial lesion, may be identified in association with the invasive adenosquamous carcinoma component.

From an ancillary test point of view, mucin histochemical stains may be used to confirm the presence of a morphologically evident glandular component. Immunohistochemically, block-like nuclear and cytoplasmic expression of p16 and positivity for high-risk human papillomavirus by in situ hybridization is seen in the majority of cases. Immunoexpression of other markers including cytokeratin 7, PAX8, p63, p40, MUC6, carbonic anhydrase IX, and HNF-1β may be variably seen in a subset of cases.

In cervical cytological preparations, malignant glandular and/or squamous elements are present (with features identical to invasive adenocarcinoma and squamous cell carcinoma, respectively), often in a necrotic and inflammatory background. Practically speaking, a definitive diagnosis of adenosquamous carcinoma is often difficult to make on cytological material alone.

Diagnostic Highlights

- Unequivocal malignant glandular and squamous elements should be morphologically identifiable
- A range of associated precursor lesions may be seen
- These tumors tend to be associated with high-risk human papillomavirus infection and thus frequently demonstrate block-like p16 expression and positivity for human papillomavirus by in situ hybridization
- Glassy cell carcinomas and mucoepidermoid carcinomas of the cervix are probably unrelated to true adenosquamous carcinomas of the cervix (*See* Differential diagnosis)

9.1.6 Differential Diagnosis

A number of lesions may be considered in the morphological differential diagnosis of cervical adenosquamous carcinoma (Table 9.1).

- *Tumors with squamous and glandular differentiation.* The presence of mucin in an otherwise typical squamous cell carcinoma does not warrant the designation of adenosquamous carcinoma. Likewise, a typical usual-type endocervical adenocarcinoma with benign squamous metaplasia also should not be classified as an adenosquamous carcinoma. Endometrioid adenocarcinoma of the cervix with squamous metaplasia has historically been considered in the differential diagnosis of adenosquamous carcinoma, but it is now recognized that endometrioid carcinoma of the cervix is exceedingly rare and is not associated with human papillomavirus infection. Although "clear cell adenosquamous carcinoma" was previously described [11], tumors fitting this description often do not meet the stringent criteria for a diagnosis of adenosquamous carcinoma.
- *Invasive stratified mucin-producing carcinoma*. This recently described neoplasm is a human papillomavirus–associated endocervical adenocarcinoma subtype which displays a relatively characteristic morphology that includes peripherally palisaded nests composed of stratified tumor cells with variable amounts of cytoplasmic mucin. Interestingly, a retrospective review of a cohort of cases originally classified as adenosquamous carcinoma demonstrated that a number of tumors in fact showed a morphology that was more consistent with the diagnosis of invasive stratified mucin-producing carcinoma.
- *Mucoepidermoid carcinoma and glassy cell carcinoma*. Historically, a number of different cervical tumors have been classified under the cervical adenosquamous umbrella, including glassy cell carcinoma and mucoepidermoid carcinoma. So-called glassy cell carcinomas are described as being characteristically composed of sheets of tumor cells with abundant "ground glass" eosinophilic cytoplasm, distinct cell borders, and enlarged nuclei with prominent nucleoli; necrosis and a prominent eosinophilic and/or neutrophilic infiltrate also are often seen. Given that glassy cell carcinomas do not exhibit definitive morphologic evidence of both squamous and glandular elements, it is thought by some that these tumors should not be classified under the adenosquamous carcinoma umbrella. A recent study evaluating the histological, immunohistochemical, and clinicopathological features of a cohort of adenosquamous carcinomas included two tumors originally classified as glassy cell carcinoma. Both of these tumors were reclassified as poorly differentiated adenocarcinomas, given the lack of overt glandular or squamous differentiation and the lack of immunohistochemical expression of p63 and p40. Overall, the diagnosis of glassy cell carcinoma should be used very sparingly, if at all. Cervical mucoepidermoid carcinomas are described as being morphologically identical to those arising in salivary gland–type tissue; that is, they are classically composed of three cell types—squamoid cells, intermediate cells, and mucous cells—that do not exhibit overt glandular formation. Architecturally, they may be solid or cystic. Importantly (and in contrast to true adenosquamous carcinomas of the cervix), these tumors have not been shown to be associated with human papillomavirus infection, and they commonly harbor genetic alterations in the genes (*CRTC1, MAML2*) that are characteristically altered in mucoepidermoid carcinomas at other sites [12]. Thus it is thought that these tumors may in fact be a distinct entity, separate from true adenosquamous carcinomas.

Table 9.1 Differential Diagnosis of Cervical Adenosquamous Carcinoma

	Adenosquamous carcinoma	Invasive stratified mucin-producing carcinoma	HPV-associated adenocarcinoma with benign squamous metaplasia	Squamous cell carcinoma with mucin production
Morphology	Unequivocal malignant glandular and squamous components	Stratified and palisaded nests of tumor cells which display HPV-associated features and have variable intracytoplasmic mucin	Malignant glands with HPV-associated features and (often abrupt) benign-appearing squamous differentiation	Typical squamous cell carcinoma with intracytoplasmic mucin (usually focal); no evident glandular formation
Association with HPV	Most	Yes	Yes	Yes
Immunohistochemistry	Variable immunoexpression of cytokeratin 7, PAX8, p63, p40, MUC6, carbonic anhydrase IX, and HNF-1β; diffuse and block-like p16 expression and positive HPV in situ hybridization in the majority of cases	Cytokeratin 7 in all cases; p63/p40 expression in peripherally palisaded cells; PAX8 and abnormal p53 expression in a subset of cases	Variable immunoexpression of cytokeratin 7, PAX8, HNF-1β and napsin-A, rare estrogen and progesterone receptor expression. Areas with squamous differentiation frequently show p63/p40 expression	Positivity for high-molecular-weight keratin, cytokeratin 5/6, p63/p40, p16 (diffuse, block-like), and HPV in situ hybridization

HPV—human papillomavirus

9.1.7 Prognosis

Some studies have suggested that cervical adenosquamous carcinomas may behave more aggressively than pure cervical glandular or squamous malignancies [13], but others have refuted this idea [14]. In a recent study that compared adenosquamous carcinomas to some of its invasive glandular mimics in the cervix, there was no significant difference between these groups [3].

9.1.8 Cases

1. A 59-year-old woman undergoes a hysterectomy after a cervical biopsy demonstrates the presence of a malignant tumor with both glandular and squamous differentiation (Fig. 9.1)
2. A 56-year-old woman undergoes a biopsy of a large cervical tumor (Fig. 9.2)
3. A 71-year-old woman undergoes a hysterectomy after initially presenting with vaginal bleeding; a large cervical mass was detected and a cervical biopsy showed a poorly differentiated neoplasm with a prominent inflammatory infiltrate (Fig. 9.3)
4. A small cervical mass was identified in a 49-year-old woman who presented with post-coital bleeding; hysterectomy was performed after a biopsy demonstrated a neoplasm with distinctive morphological variability including areas of both squamous and mucinous differentiation (Fig. 9.4)

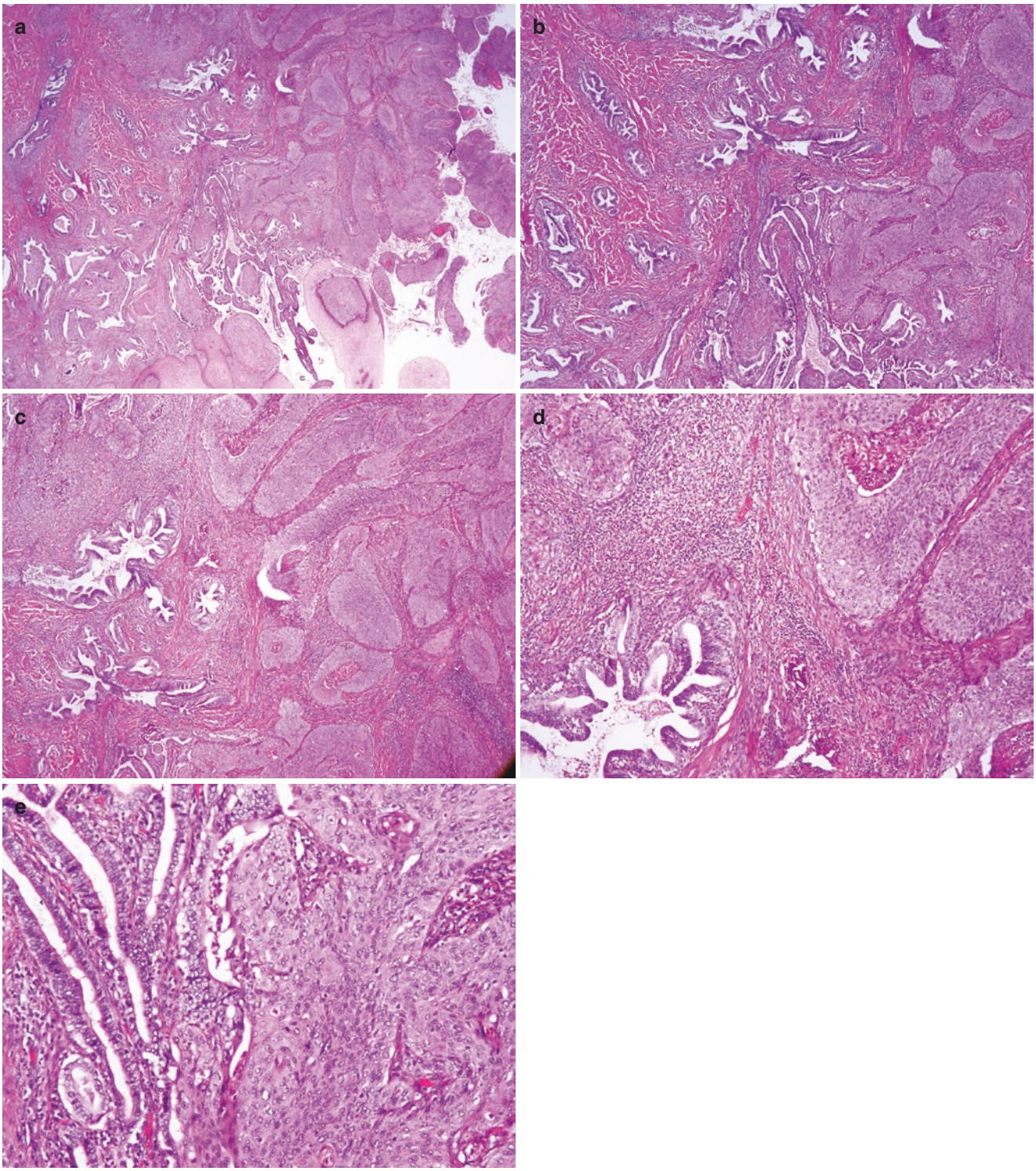

Fig. 9.1 Adenosquamous carcinoma. (**a**) Low-power examination shows the glandular component of the tumor on the left, adjacent to the squamous component on the right. (**b**) The glandular and squamous elements are mostly separate but show some intermixing towards the bottom right of the image. (**c**) Both components infiltrate into the cervical stroma. (**d**) Malignant glands and squamous elements. Note the comedo-necrosis in the center of the large squamous nest at the top right of the image. (**e**) High-power morphological comparison between the glandular component on the left and the squamous component on the right (*Courtesy* of Dr. Simona Stolnicu)

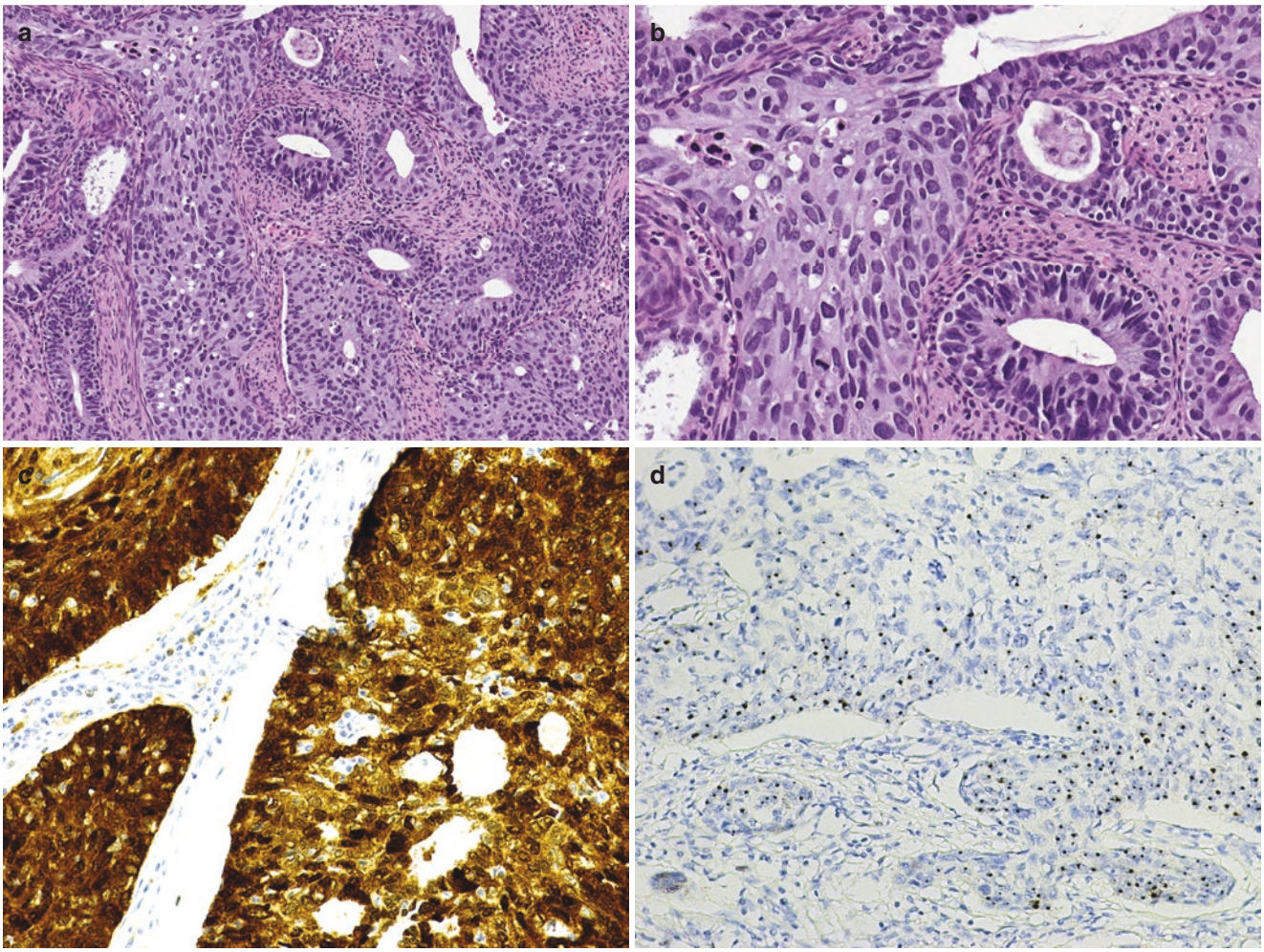

Fig. 9.2 Adenosquamous carcinoma associated with high-risk human papillomavirus infection. (**a**) Malignant glandular elements are seen in close proximity to malignant squamous elements. (**b**) Squamous and glandular components are intimately admixed; note the human papillomavirus infection-related features (luminal mitoses and apoptosis) seen in the glandular component. (**c**) Diffuse and block-like expression of p16. (**d**) Positivity for human papillomavirus by in situ hybridization for high-risk virus types. *Final remarks*: Although morphological malignant squamous and glandular elements should be present in order to make the diagnosis of adenosquamous carcinoma, different components may be difficult to distinguish when the tumor is poorly differentiated

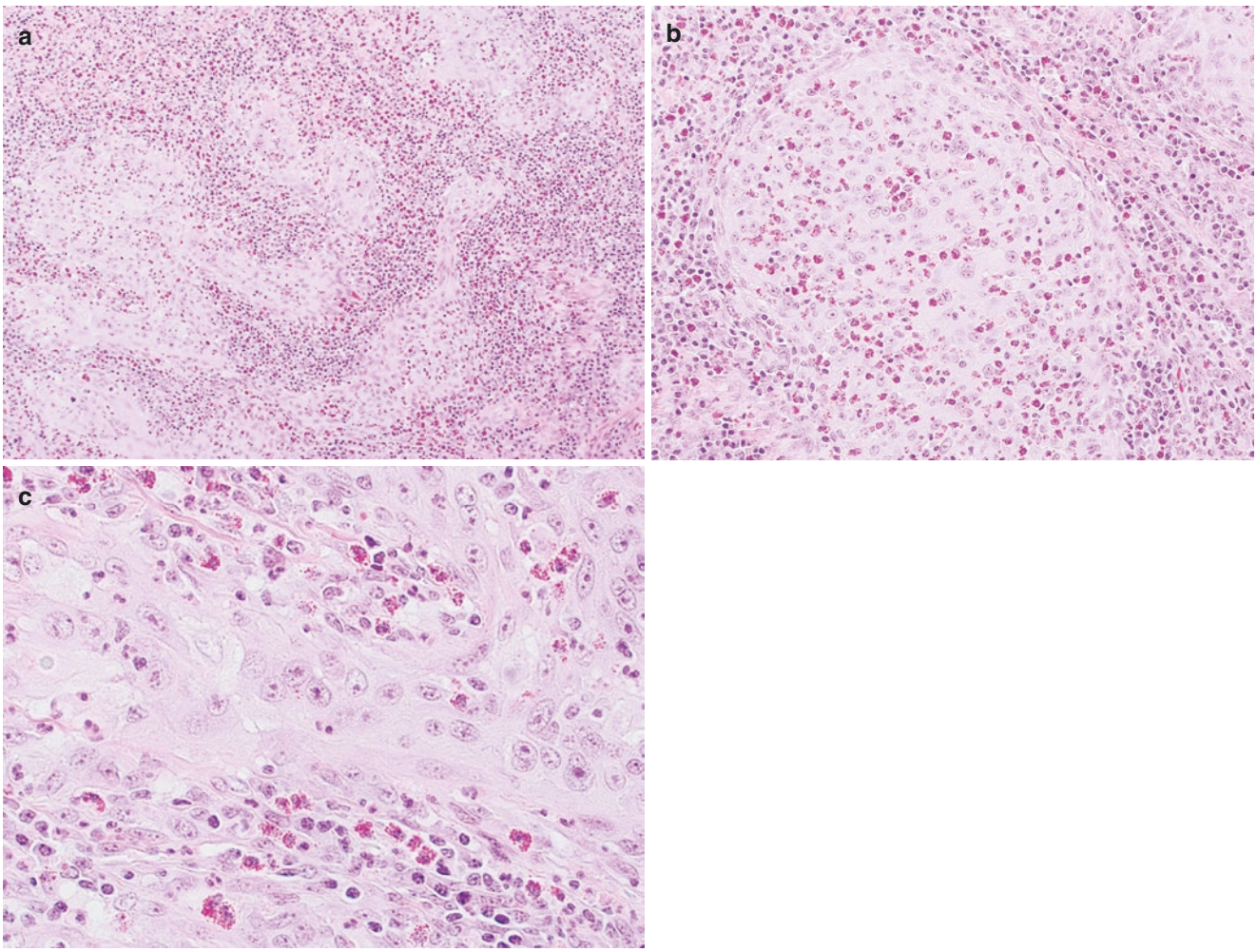

Fig. 9.3 So-called glassy cell carcinoma. (**a**) Large, irregular nests of tumor cells are surrounded and infiltrated by an inflammatory infiltrate rich in plasma cells and eosinophils. (**b**) The tumor cells have abundant "ground glass" eosinophilic cytoplasm and irregular nuclei with prominent single nucleoli. (**c**) Nuclear irregularity is evident at high power; note the inflammatory infiltrate surrounding and within the tumor. *Final remarks:* The diagnosis of glassy cell carcinoma of the cervix should be used very sparingly, if at all

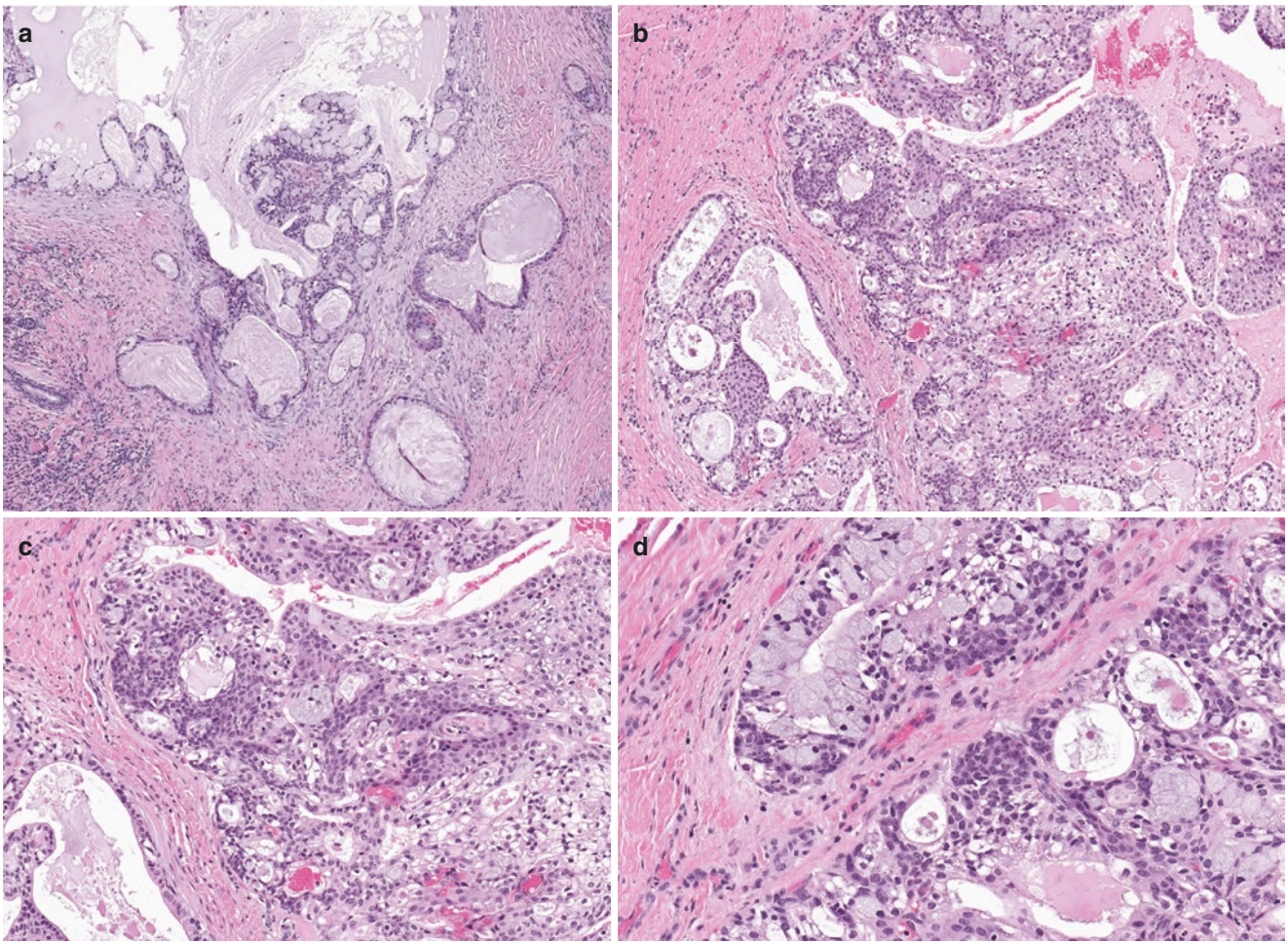

Fig. 9.4 Mucoepidermoid carcinoma of the cervix. (**a**) Low-grade tumors typically have abundant cystic spaces. (**b**) Closer examination may be necessary in order to appreciate the triphasic nature of the tumor. (**c**) Squamoid and intermediate cells may predominate. (**d**) Mucous cells may be sparse or difficult to appreciate. In this case, they were numerous and easily identified; note the abundant foamy cytoplasm in the cells towards the top of the image. *Final remarks:* True mucoepidermoid carcinoma of the cervix is exceedingly rare and appears to be a distinct entity from cervical adenosquamous carcinoma. Molecular testing to identify rearrangements involving the characteristic genes (*MAML2, CRTC1*) can be used to confirm the diagnosis

9.2 Adenoid Basal Carcinoma

9.2.1 Definition

Adenoid basal carcinoma is a rare low-grade carcinoma most commonly occurring in women older than 50 years of age [15], but these tumors have been reported in women as young as 20 years of age [16]. These tumors are frequently seen in association with high-grade squamous intraepithelial lesion and may occur in pure form or can be admixed with another carcinoma subtype such as carcinoma with adenoid cystic-like differentiation, squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and small cell carcinoma.

9.2.2 Synonyms

"Adenoid basal epithelioma" has been proposed for pure tumors without significant nuclear atypia or a stromal reaction to invasion [15, 17], but this term is not widely accepted.

9.2.3 Etiology

It has been postulated that adenoid basal carcinomas arise from pluripotential subcolumnar reserve cells. High-risk human papillomavirus infection is implicated in the pathogenesis of most tumors [18–21]. Some authors have postulated that adenoid basal lesions may be precursors to cervical

"adenoid cystic carcinoma", given that these two tumors appear to exist along a morphological continuum and often co-exist [18]. In addition, both tumor types are often identified with other carcinoma subtypes.

9.2.4 Macroscopy

Pure adenoid basal carcinomas are most commonly clinically occult (asymptomatic, no cervical mass) and are identified only at the time of microscopic examination. When admixed with another carcinoma subtype, cervical enlargement or a frank cervical mass may be identified.

9.2.5 Microscopy

Adenoid basal carcinomas are typically composed of rounded/lobulated small or large tumor nests and cords infiltrating into the cervical wall without a desmoplastic stromal reaction. The nests and cords are composed of peripherally palisaded small and uniform basaloid tumor cells with regular oval nuclei, inconspicuous or no nucleoli, and minimal mitotic activity. Glandular and squamous differentiation may be evident and central lumina with cystic dilatation and debris may be seen in some nests. Necrosis, lymphovascular invasion, and perineural invasion should not be seen in pure tumors. These neoplasms are often seen in association with high-grade squamous intraepithelial lesion and other carcinoma subtypes, especially squamous cell carcinoma. Immunohistochemically, the basaloid tumor cells should exhibit positivity for low-molecular-weight keratin, p63/p40, and p16 (nuclear and cytoplasmic expression in diffuse block-like pattern). CD117 expression, if present, should be only weak and focal. The Ki-67 proliferation index is variable, depending on the phenotype of tumor cells [22, 23]. The presence of human papillomavirus genetic material may be detected by in situ hybridization or polymerase chain reaction.

Adenoid basal carcinomas are not typically identified in cervical cytological preparations, as it usually does not involve the surface, but high-grade squamous intraepithelial lesion can be seen [24].

Diagnostic Highlights

- Low-grade basaloid-appearing carcinoma arranged in solid or cystic nests/cords, invading into the cervical wall without a stromal response to invasion
- Frequently associated with high-risk human papillomavirus infection and often seen underlying high-grade squamous intraepithelial lesion involving the cervical surface epithelium
- May be seen in association with a more aggressive neoplasm therefore, sampling is critically important

9.2.6 Differential Diagnosis

Both benign and malignant lesions may enter into the differential diagnosis of adenoid basal carcinoma; care should be taken to distinguish a pure adenoid basal lesion from a more aggressive tumor with an adenoid basal component.

- *Adenoid basal hyperplasia.* Adenoid basal hyperplasia shows morphological features similar to those of adenoid basal carcinoma, but it is differentiated from its invasive counterpart by its small size and superficial location [25].
- *"Adenoid cystic carcinoma".* Cervical tumors with adenoid basal and adenoid cystic differentiation share a common putative precursor and are both pathogenetically driven by high risk human papillomavirus infection. Modern studies have shown that pure adenoid cystic carcinomas of the cervix are very rare, and that it is more common for tumors with "adenoid cystic-like differentiation" to occur with other HPV-associated carcinoma types, including adenoid basal carcinoma (*See* Adenoid cystic carcinoma below).
- *Tumors with squamous and/or glandular differentiation.* Care should be taken to distinguish an adenoid basal carcinoma with squamous or glandular differentiation from an invasive squamous cell carcinoma or adenosquamous carcinoma. Adenoid basal carcinomas most commonly form rounded tumor nests, exhibit banal nuclear features, and do not elicit a desmoplastic stromal response, whereas squamous cell and adenosquamous carcinomas are expected to more commonly infiltrate a desmoplastic stroma in irregular or jagged nests and demonstrate greater nuclear atypia. As with tumors with adenoid cystic-like differentiation, adenoid basal carcinoma may co-occur with other invasive carcinoma subtypes. Immunohistochemistry may be of some value in the evaluation of difficult cases, as residual low-molecular-weight keratin–positive basaloid cells will be evident around the periphery of adenoid basal carcinoma tumor nests with abundant squamous differentiation, whereas a true squamous cell carcinoma will lack these. In addition, the basaloid cells of adenoid basal carcinoma are expected to lack cytokeratin 7 expression, whereas the cells of an adenosquamous carcinoma should express cytokeratin 7.
- *Well-differentiated neuroendocrine tumors.* Adenoid basal carcinomas with compact nest-like architecture may also be confused with primary well-differentiated neuro-

endocrine tumors (carcinoids) arising in the cervix. Metastatic neuroendocrine tumors also must be excluded. Both primary and metastatic neuroendocrine tumors exhibit immunopositivity for neuroendocrine markers including synaptophysin and chromogranin A; adenoid basal carcinomas do not.

- *Ectopic prostate tissue.* Because it may exhibit squamous differentiation, ectopic prostate tissue may also mimic an adenoid basal carcinoma, but this lesion is usually superficial and does not infiltrate into the cervical stroma. Immunohistochemical stains including NKX3.1, prostate specific antigen and/or prostate specific acid phosphatase can be expressed in both ectopic prostate tissue and adenoid basal carcinoma and, therefore, cannot be used to differentiate between the two lesions.

9.2.7 Prognosis

When completely excised, pure adenoid basal carcinomas behave in an essentially benign fashion, and the overall prognosis is extremely favorable [1]. As such, conservative treatment is usually employed. In contrast, when admixed with another carcinoma subtype, tumor aggressiveness is largely determined by the non–adenoid basal carcinoma component.

9.2.8 Cases

1. A 45-year-old woman with history of high-grade squamous intraepithelial lesion (diagnosed by cytological examination of Pap smear material) undergoes a cone biopsy (Fig. 9.5)
2. A 43-year-old woman underwent a hysterectomy for the treatment of abnormal uterine bleeding attributed to multiple uterine fibroids (Fig. 9.6)

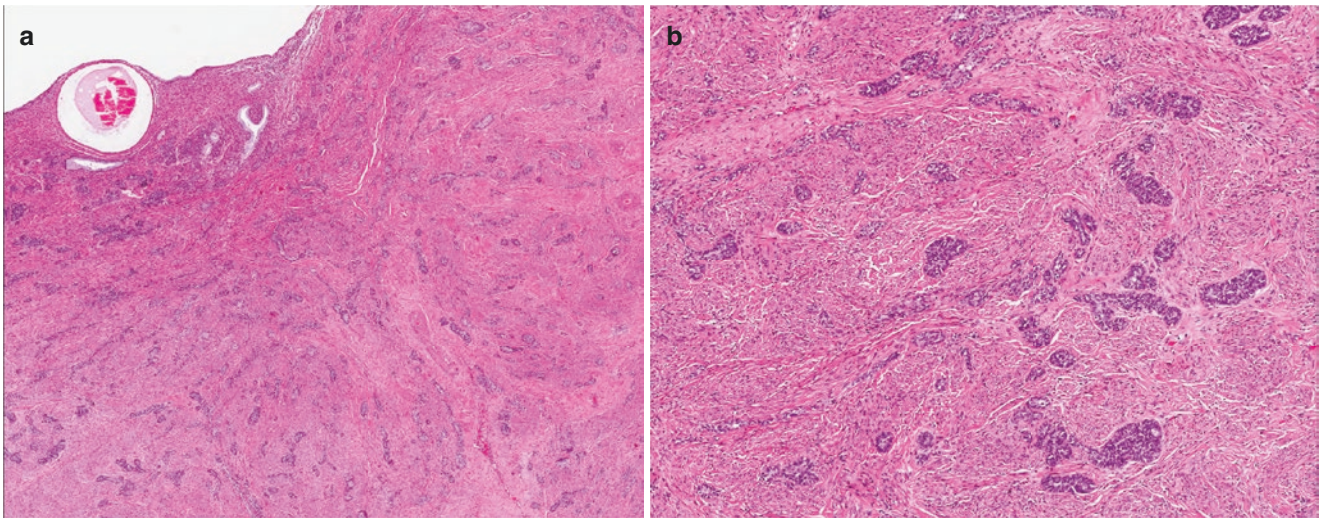

Fig. 9.5 Adenoid basal carcinoma of the cervix associated with high-grade squamous intraepithelial lesion and focal squamous cell carcinoma. (**a**) At low power, a nested proliferation is seen infiltrating the cervical stroma; note the benign endocervical glands at the top left of the image. (**b**) Rounded and partially lobulated basaloid tumor nests are seen embedded within in a nonreactive cervical stroma. (**c**) High-grade squamous intraepithelial lesion is seen overlying basaloid tumor nests. (**d**) In some foci, banal-appearing basaloid tumor nests (right) were seen adjacent to larger nests composed of cells with abundant eosinophilic cytoplasm, abrupt keratinization, and highly irregular nuclei with evident mitotic activity (left), compatible with squamous cell carcinoma. (**e**) High-power examination shows rounded tumor nests composed of basaloid cells with regular, oval-shaped nuclei and pinpoint nucleoli; mitotic activity is not appreciated. (**f**) p16 expression was diffuse and block-like in all tumor cells

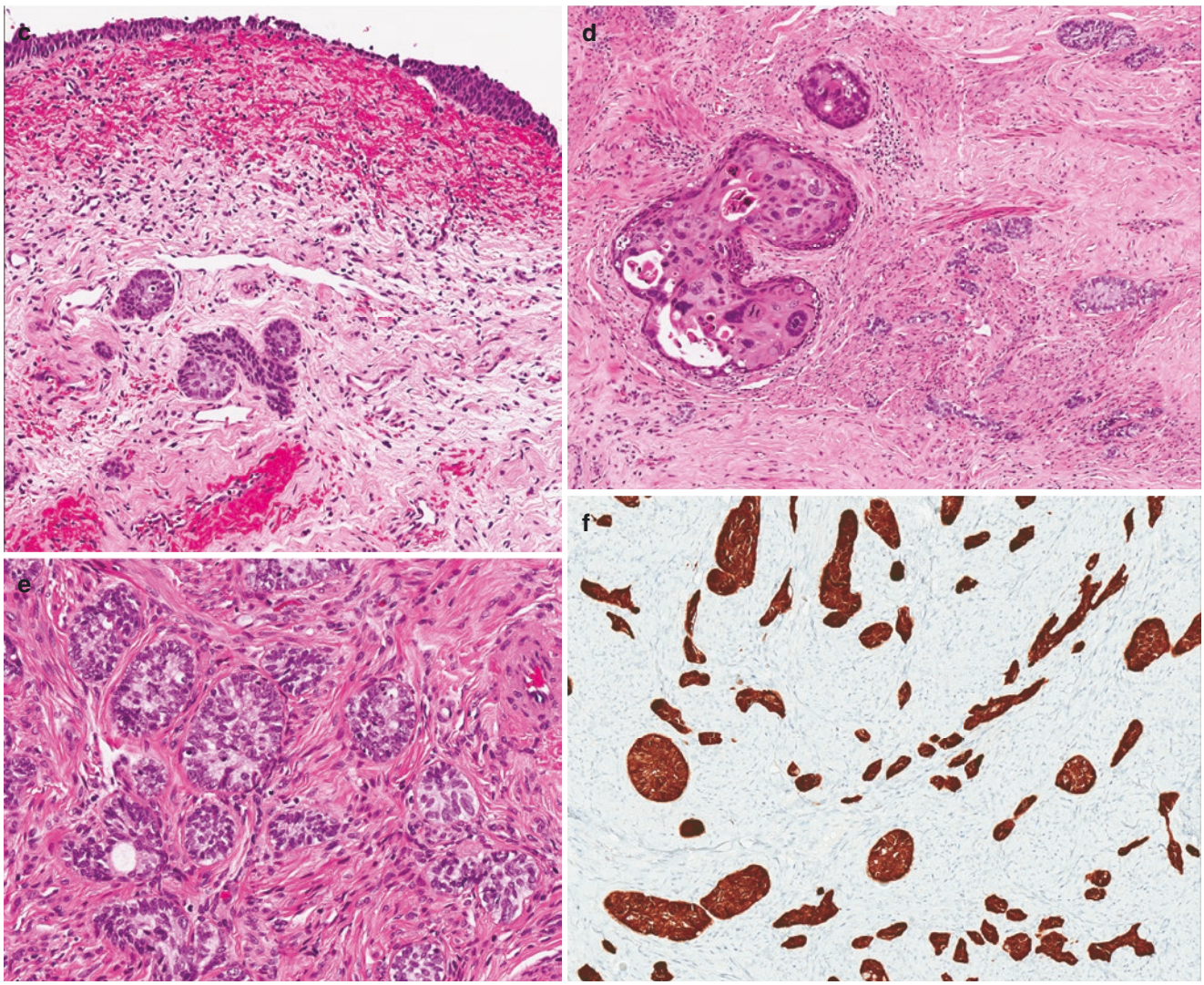

Fig. 9.5 (continued)

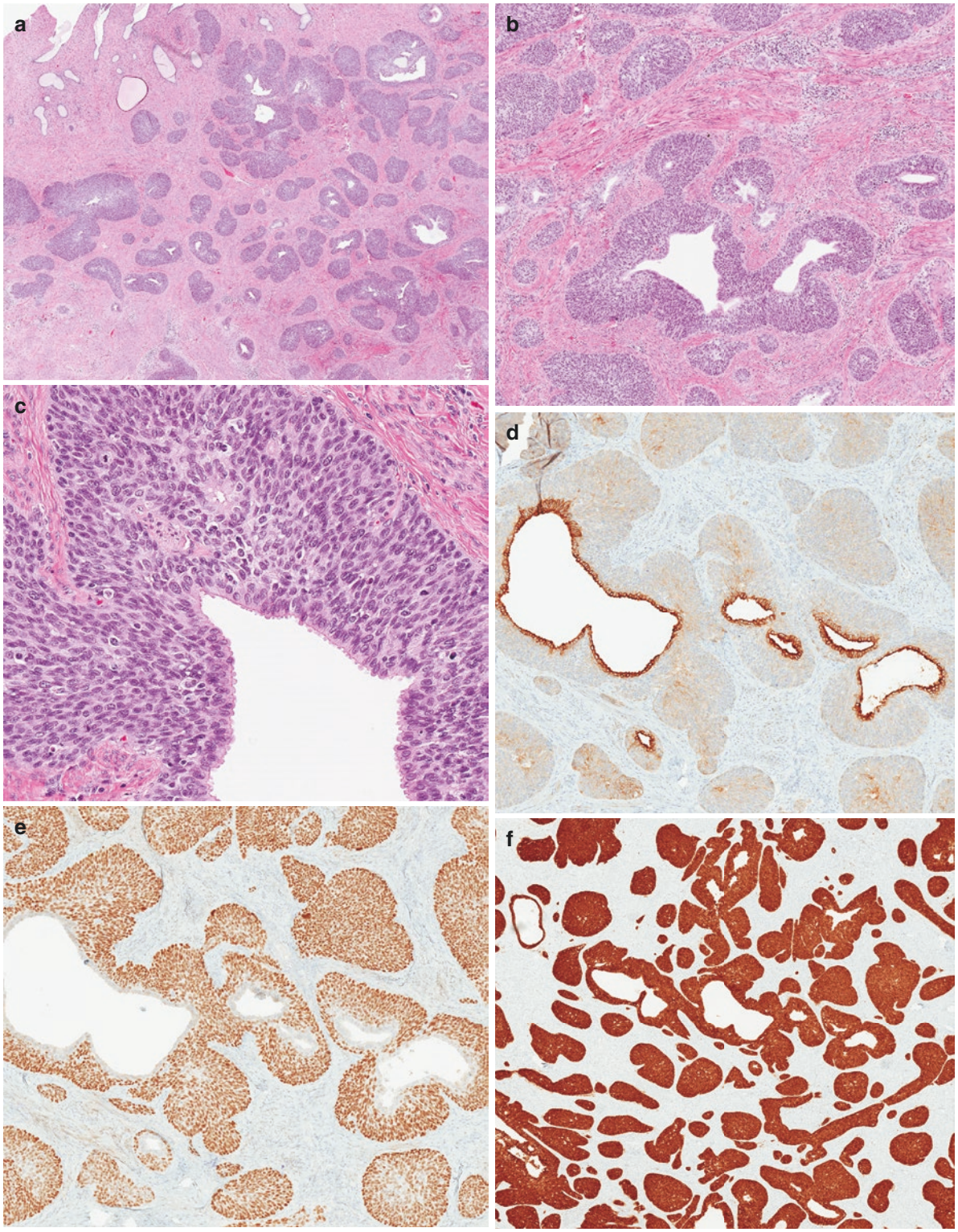

Fig. 9.6 Adenoid basal carcinoma with large nests and cystic spaces. (**a**) Within the cervix, a basaloid-appearing infiltration was seen extending deep into the cervical wall; note the normal endocervical glandular epithelium at the surface and the cystic spaces within some of the tumor nests. (**b**) Tumor nest size variability was evident. (**c**) High-power examination shows bland and monotonous basaloid tumor cells surrounding a central cystic space lined by cells with apical snouts; scattered mitotic activity is appreciated. (**d**) Low-molecular-weight keratin expression is seen in both glandular and basaloid components, although expression is strongest in the cells lining the cystic spaces. (**e**) p63 was strongly expressed in the basaloid component of the tumor nests; note the distinct lack of expression in the glandular cells lining the cystic spaces within the center of the nests. (**f**) p16 expression was diffuse and block-like in all tumor cells. *Final remarks:* Adenoid basal carcinomas of the cervix are often incidentally discovered but are frequently seen in association with epithelial in situ lesions. Diligent care should be taken to ensure that another, more aggressive tumor component is not present

9.3 Carcinoma with Adenoid Cystic-Like Features

9.3.1 Definition

True adenoid cystic carcinoma of the cervix likely does not exist and is no longer recognized as a distinct entity in the 2020 WHO Classification of Tumors of the Female Genital Tract. Rather, tumors can show adenoid cystic-like features. These are rare tumors and have been reported to most often occur in women older than 40 years of age, with an average age of diagnosis between 60 and 70 years [26]. Adenoid cystic-like morphology may be very rarely pure or, more commonly, be admixed with another carcinoma subtype ("mixed carcinoma with adenoid cystic-like differentiation") [27].

9.3.2 Synonyms

Not applicable.

9.3.3 Etiology

Like their adenoid basal carcinoma counterpart, cervical carcinoma with adenoid cystic-like features are thought to arise from cervical pluripotential subcolumnar reserve cells [18]. This putative shared origin explains why cervical tumors with adenoid cystic-like differentiation may co-occur with adenoid basal carcinomas, in addition to other carcinoma subtypes. High-risk human papillomavirus infection is thought to play a pathogenic role in most tumors, particularly those that co-occur in a mixed fashion with other tumor types [28]. "True" adenoid cystic carcinomas lack this association with human papillomavirus [27] but, have the characteristic (t6;9)(*MYB-NFIB*) gene fusion seen in adenoid cystic carcinomas of the salivary gland, breast, and even vulva [29]. Interestingly, HPV-related carcinomas with adenoid cystic-like features that show a varied morphology and lack the characteristic *MYB-NFIB* fusion have also been described in the sinonasal tract ("HPV-related multiphenotypic sinonasal carcinoma"). Although they may be morphologically similar, cervical adenoid cystic-like carcinomas are, in fact, biologically distinct from their "true" counterparts occurring in other parts of the body.

9.3.4 Macroscopy

These tumors have most often been reported to present as a palpable, hard mass. The tumor may be ulcerated or friable.

9.3.5 Microscopy

Tumors with adenoid cystic-like features commonly show the prototypical features associated with adenoid cystic carcinomas occurring outside of the genital tract. These tumors are composed of heterogeneous tubular and cribriform ("punched out" or "sieve-like") arrangements with eosinophilic hyaline (basement membrane) or basophilic/myxoid-appearing material. Solid architecture and/or peripheral palisading may be prominent [30]. The tumor cells are basaloid and display hyperchromatic and angulated nuclei without obvious nucleoli. In contrast to their counterpart in the salivary gland, cervical carcinomas with adenoid cystic-like features may lack or show minimal myoepithelial cells. Necrosis, perineural invasion, and lymphovascular invasion may be prominent. Tumors may be seen in association with high-grade squamous intraepithelial lesion and may occur as a component of a mixed carcinoma with adenoid basal carcinoma, squamous cell carcinoma, small cell carcinoma, and others.

From an ancillary testing point of view, a Periodic acid-Schiff histochemical stain may be used to highlight the basement membrane material. Immunohistochemically, the tumor cells may variably express epithelial membrane antigen, low-molecular-weight keratin, and S100. CD117 expression has been reported in some tumors, particular those existing as a component of a mixed carcinoma [31]. Collagen IV and laminin immunohistochemistry may be used to highlight the extracellular basement membrane material. MYB immunopositivity has been reported in some mixed carcinomas [32]. Block-like nuclear and cytoplasmic expression of p16 and positivity for human papillomavirus by in situ hybridization will be seen in tumors with adenoid cystic-like differentiation, in contrast to pure adenoid cystic carcinomas [27]. Cytologically, these may be challenging to identify, as they typically do not involve the surface; high-grade squamous intraepithelial lesions may be seen in addition to three-dimensional cell clusters with acini-like architecture and irregular, angulated nuclei with coarse and granular chromatin [33].

Diagnostic Highlights

- Basaloid tumor cells with cribriform, tubular, or solid architecture and extracellular eosinophilic (basement membrane) and/or basophilic/myxoid-appearing material
- May occur as a component of a mixed carcinoma; human papillomavirus plays a pathogenetic role in mixed carcinomas which show adenoid cystic-like differentiation

9.3.6 Differential Diagnosis

As previously discussed, carcinoma of the cervix with adenoid cystic-like features may occur in pure form or as a component of a mixed carcinoma ("mixed carcinoma with adenoid cystic-like features"); adequate sampling and diligent microscopic examination are needed to distinguish these biologically distinct entities.

- *Basaloid-appearing neoplasms.* Given that tumors with adenoid cystic-like differentiation exhibit a predominant basaloid morphology, a number of other basaloid-appearing neoplasms should be kept in the differential diagnosis including adenoid basal carcinoma, basaloid squamous cell carcinoma, and high-grade neuroendocrine carcinoma (Table 9.2) [34]. Of course, tumors in the differential diagnosis may all co-occur in the context of adenoid cystic-like differentiation. Immunohistochemical evaluation may be necessary to distinguish a tumor with adenoid cystic-like differentiation with solid architecture from basaloid squamous cell carcinoma or high-grade neuroendocrine carcinoma (both small-cell and large-cell types). Depending on the clinical scenario, basaloid-appearing metastases and some exceedingly rare primary tumors (such as extrarenal Wilms tumor) should also be considered [35].

9.3.7 Prognosis

These tumors behave aggressively and often display a propensity for local recurrence and distant metastases.

9.3.8 Cases

1. A 71-year-old woman presents with a 2-month history of vaginal bleeding. Bimanual examination revealed an enlarged and firm cervix, and speculum examination showed that the cervix was mostly replaced by an ulcerated mass. The patient was sent for urgent colposcopic examination and biopsy (Fig. 9.7)
2. A 68-year-old woman underwent hysterectomy after a cervical biopsy revealed the presence of an infiltrative basaloid neoplasm (Fig. 9.8)

Table 9.2 Main differential diagnoses for high-grade basaloid carcinoma occurring in the cervix

	Carcinoma with adenoid cystic-like features	Basaloid squamous cell carcinoma	High-grade neuroendocrine carcinoma
Basaloid morphology	Yes	Yes	Yes
"Punched out" or "sieve-like" architecture	Yes	No	No
Solid architecture	Yes	Yes	Yes
Keratinization	May be present	May be present	No
Extracellular hyaline material	Yes	No	No
Immunohistochemical expression of p63 and p40	Possible	Yes	No
Immunohistochemical expression of collagen IV and laminin	Yes	No	No
Immunohistochemical expression of neuroendocrine markers	No	No	Yes

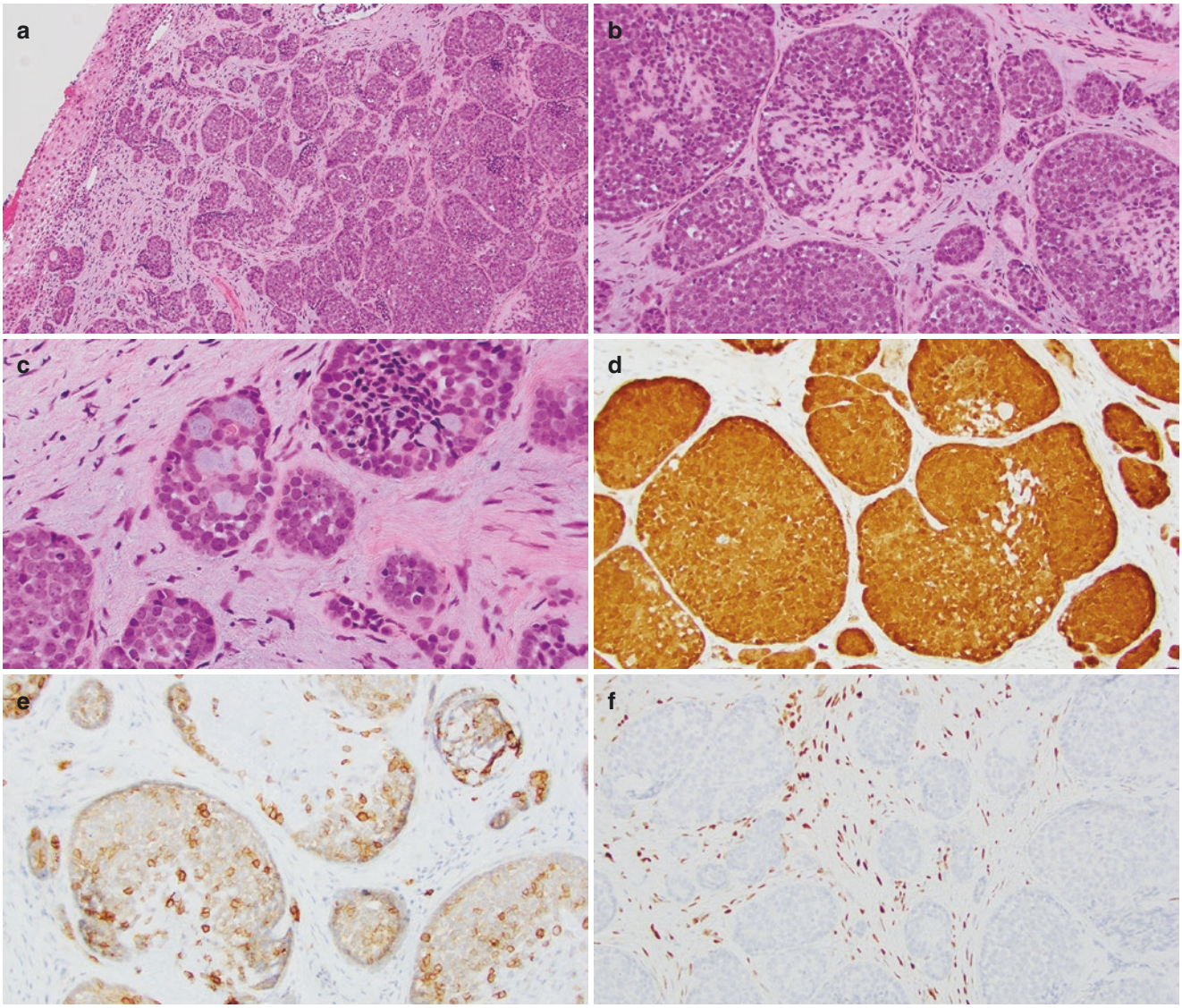

Fig. 9.7 Carcinoma with adenoid cystic-like features, identified at the time of cervical biopsy. (**a**) Cervical squamous epithelium overlies a proliferation composed of basaloid nests of varying sizes. (**b**) Variably sized, rounded tumor nests are composed of basaloid tumor cells; note the peripheral palisading and extracellular eosinophilic hyaline material. (**c**) High-power examination demonstrates nuclear atypia and evident cylinders of lightly basophilic material; note the background desmoplastic cervical stroma. (**d**) p16 expression was diffuse and block-like in all tumor cells. (**e**) CD117 (c-kit) expression was seen in most tumor cells, but staining intensity was highly variable. (**f**) Estrogen receptor was not expressed in the tumor cells; note the background stromal cell expression

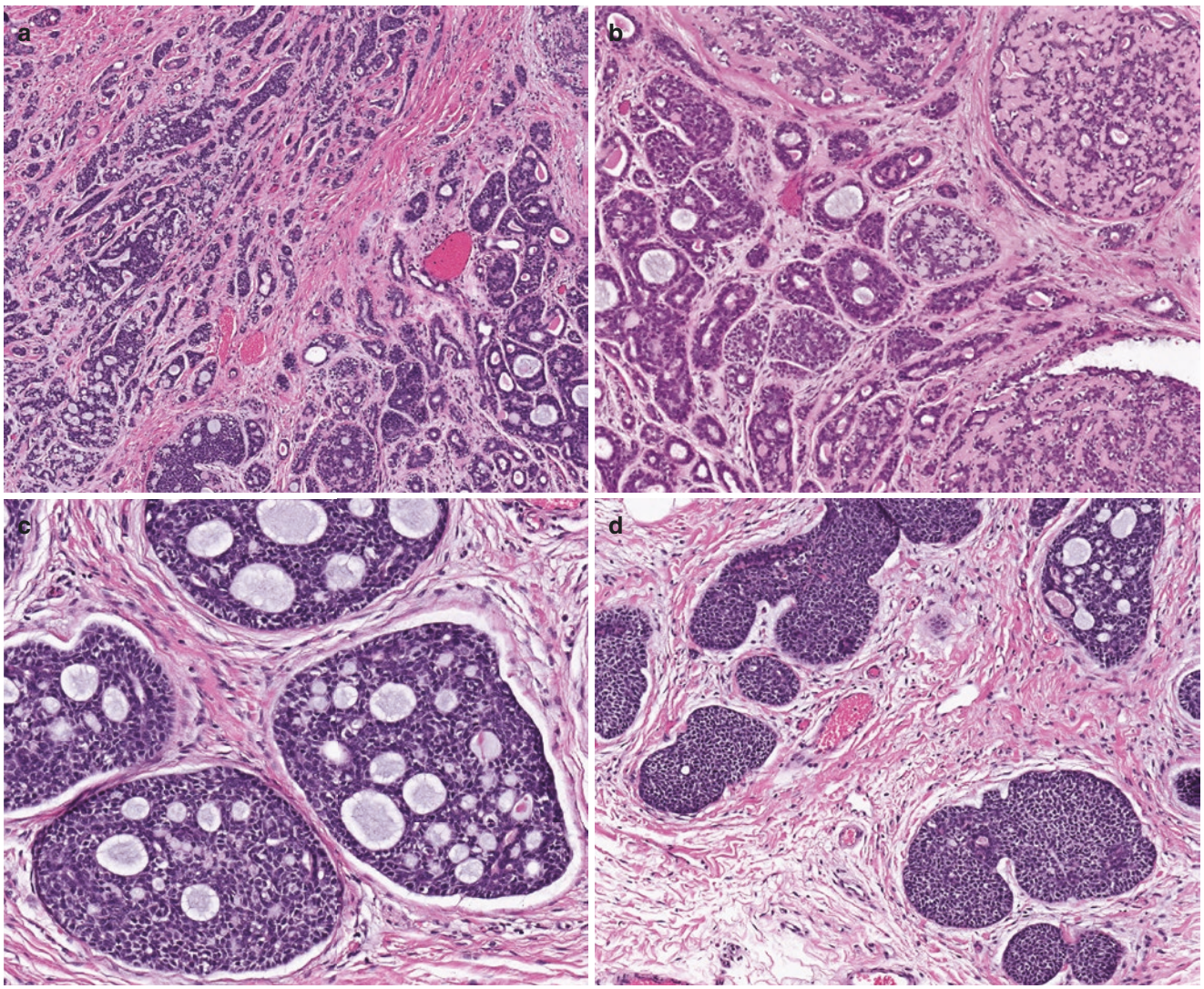

Fig. 9.8 Carcinoma with adenoid cystic-like features with variable architectural patterns. (**a**) The tumor was architecturally heterogeneous; in this field, small nests and compressed cords are readily apparent. (**b**) Other areas showed larger nests with "punched out" spaces (left) and foci rich in extracellular hyaline material (right, top and bottom). (**c**) Note the rigid, cyst-like spaces and basaloid appearance of the tumor cells. (**d**) Focally, larger solid tumor nests were identified. *Final remarks:* "True Adenoid cystic carcinoma" of the cervix occurs only very rarely. More commonly, adenoid cystic-like differentiation is associated with one or more carcinoma subtypes. When classic cribriform architecture and basement membrane material is not readily apparent, it may be difficult to distinguish this neoplasm from some of its high-grade basaloid-appearing mimics, including basaloid squamous cell carcinoma and high-grade neuroendocrine carcinoma

9.4 Undifferentiated Carcinoma

9.4.1 Definition

Undifferentiated carcinoma of the cervix is a very rare lesion [1], and little has been described in the literature concerning this entity. As its name suggests, this tumor is an undifferentiated epithelial neoplasm that does not show any evidence of glandular, squamous, or neuroendocrine differentiation, either morphologically or by immunohistochemical evaluation. These neoplasms may occur in isolation or can be associated with a more well-differentiated tumor component.

9.4.2 Synonyms

Not applicable.

9.4.3 Etiology

Undifferentiated carcinomas of the cervix are of epithelial origin and may represent a "de-differentiated" component of a more well-differentiated carcinoma. Most will be associated with oncogenic human papillomavirus infection [36].

9.4.4 Macroscopy

The cervix may be bulky or may be involved by a frank mass; ulceration, hemorrhage, and necrosis may be prominent.

9.4.5 Microscopy

Undifferentiated carcinomas are composed of sheets of often discohesive enlarged cells with variable amounts of cytoplasm, highly irregular nuclei, and often prominent nucleoli. True glandular, squamous, and neuroendocrine differentiation should not be morphologically evident. No evident mucin should be identified by routine examination or by evaluation with mucin histochemical stains. These tumors may be seen in isolation, adjacent to or as a component of a more well-differentiated carcinoma, or as a component of a carcinosarcoma. A background inflammatory infiltrate may be prominent [37].

Epithelial origin should be confirmed by epithelial membrane antigen and cytokeratin expression; expression may be focal and/or weak. Block-like nuclear and cytoplasmic expression of p16 and positivity for human papillomavirus DNA or RNA by in situ hybridization may be used to definitively localize the tumor to the cervix. Distinct lack of expression for markers of squamous differentiation (34βE12, cytokeratin 5/6, p63, p40) or neuroendocrine differentiation (synaptophysin, chromogranin A) is typical.

Diagnostic Highlights

- Undifferentiated carcinoma is rare in the cervix and is essentially a diagnosis of exclusion; a primary tumor in the uterine corpus or lower uterine segement should be excluded
- May be a component of a "de-differentiated" carcinoma
- Expression of epithelial membrane antigen and cytokeratins may be focal and weak
- p16/human papillomavirus positivity can be used to localize the tumor to the cervix; otherwise, involvement of the cervix by a tumor centered in the corpus/lower uterine segment or other various high grade and/or undifferentiated neoplasms should be considered (*See* Differential diagnosis)

9.4.6 Differential Diagnosis

- *Various high-grade and/or undifferentiated neoplasms.* Given the undifferentiated and high-grade nature of undifferentiated carcinoma of the cervix, a number of malignant neoplasms may enter the differential diagnosis, including primary poorly differentiated carcinomas of squamous, glandular, or neuroendocrine origin; mesenchymal neoplasms; malignant melanoma; and neoplasms of hematolymphoid origin, such as high-grade lymphomas, plasma cell neoplasms, or myeloid neoplasms. Cervical involvement by upper tract drop metastases or direct involvement by undifferentiated endometrial carcinoma should also be considered, in addition to metastases to the cervix arising from non-gynecological organs. As such, the diagnosis of undifferentiated carcinoma of the cervix is essentially a diagnosis of exclusion.

9.4.7 Prognosis

Undifferentiated carcinomas are expected to behave aggressively.

9.4.8 Cases

1. A 64-year-old woman with no prior history of cervical screening presents with vaginal bleeding; speculum examination shows a large, ulcerated tumor. Staging investigations showed that the tumor was confined to the cervix and that no other lesions were present (Fig. 9.9).

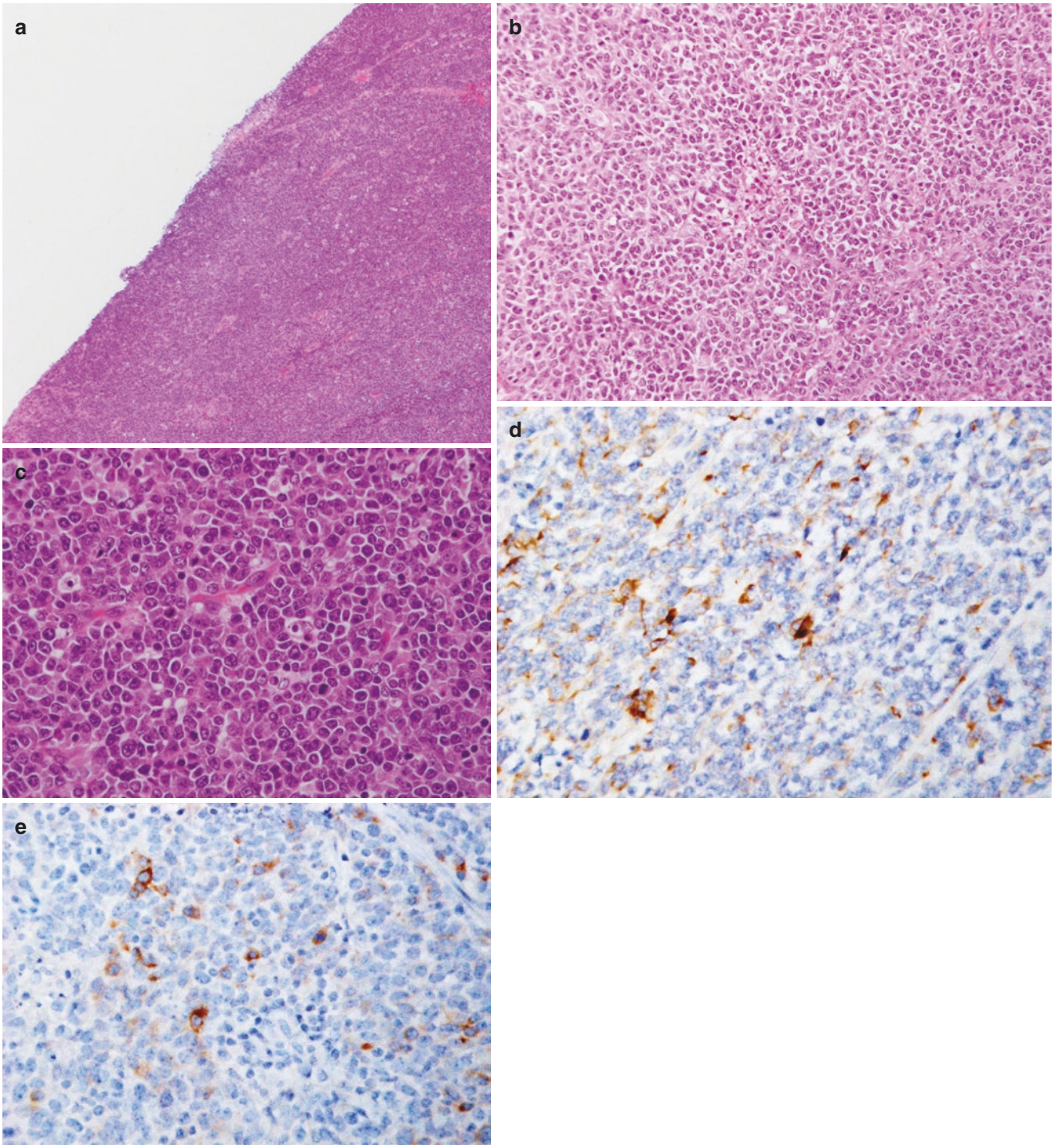

Fig. 9.9 Undifferentiated carcinoma of the cervix. (**a**) At low power, a diffuse, sheet-like proliferation is seen below an entirely ulcerated surface. (**b**) The tumor cells exhibit evident discohesion. Note the focus of incipient necrosis seen in the middle of the field. (**c**) Discohesive tumor cells with a plasmacytoid morphology. Nuclear atypia, nucleoli, and mitotic activity are easily appreciated. (**d**) Patchy pankeratin expression was seen throughout the tumor. (**e**) Epithelial membrane antigen expression was focal and weak. *Final remarks:* Undifferentiated carcinomas of the cervix should be distinguished from other primary, poorly differentiated epithelial tumors, in addition to non-epithelial malignancies and metastases to the cervix. A more well-differentiated component may be present

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