Metastases to the Cervix

13

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Metastases to the gynecologic tract involve the ovaries and vagina in approximately 80% of cases; the uterine cervix is affected in less than 2% [1, 2]. The low incidence of cervical involvement has been attributed to various factors, such as the relatively small size of the cervix, which has abundant fibromuscular stroma containing scarce vasculature and a centrifugally draining lymphatic network [3]. The potential routes of metastatic spread are retrograde lymphatic, hematogenous, and transperitoneal (transtubal or direct extension from the cul-de-sac) [1, 4]. Patients may present with either widespread disease or isolated involvement of the cervix, which may occur simultaneously or following the diagnosis of primary tumor. In some tumors, such as urothelial carcinoma, involvement of the gynecologic tract may be the first manifestation of disease [5].

Clinical presentations may be similar to primary cervical tumors (abnormal bleeding, cervical mass, abnormal cervical cytology) [2, 6]. In addition, metastases may closely mimic primary neoplasms radiologically and pathologically because of overlapping morphologic and immunophenotypic features. Therefore, review of the clinical history and careful histologic examination and ancillary studies, when appropriate, are paramount in the differential diagnosis, to ensure optimal treatment and accurate prognostication [7, 8]. A high level of suspicion is often crucial for initiating the additional work-up, which in turn requires awareness of the characteristic pathologic findings discussed below. The key features of secondary cervical involvement by epithelial, melanocytic and hematolymphoid neoplasms are summarized in Table 13.1. Local extension by uterine corpus sarcomas to the cervix is discussed in Chap. 11.

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R. A. Soslow et al. (eds.), *Atlas of Diagnostic Pathology of the Cervix*, https://doi.org/10.1007/978-3-030-49954-9_13

Table 13.1 Key features of metastatic tumors to the cervix

Clinical presentation
• Rare (2% of metastases to gynecologic tract)
• Nonspecific presentation
– Asymptomatic
– Abnormal cervical cytology
– Abnormal bleeding
– Cervical mass
• Presents simultaneously, before, or after diagnosis of primary tumor
• Most common metastatic tumors: Carcinomas
• Most common carcinomas: Gynecologic
• Most common non-gynecologic carcinomas: Gastrointestinal and mammary
Macroscopy
• Normal appearance
• Diffuse enlargement
• Well defined mass
• Poorly defined mass
• Ulcerated and/or indurated mass
Microscopy
• Lack of a cervical precursor lesion (HSIL, AIS)
• Replacement of preexisting epithelium without stromal reaction
• Permeative growth surrounding benign endocervical glands
• Cervical stromal invasion (superficial or deep)
• Predominant involvement of outer cervical wall
• Multifocal or multinodular growth
• Extensive LVSI
• Signet ring cells in some carcinomas

AIS adenocarcinoma in situ, *HSIL* high-grade squamous intraepithelial lesion, *LVSI* lymphovascular space invasion

13.1 Definition

Secondary involvement of the uterine cervix by tumors originating outside of the cervix.

13.2 Synonyms

Secondary neoplasms.

13.3 Etiology

A variety of epithelial and non-epithelial neoplasms have been reported to metastasize to the uterine cervix. The most common are carcinomas. Metastatic tumors most frequently represent contiguous extension of primary endometrial carcinomas and colorectal carcinomas, or "drop" metastases from adnexal carcinomas [4, 9]. The most common non-gynecologic primary sites of origin are the gastrointestinal tract and breast [2, 10–12]. A single-institution study of 144 patients reported lymphomas (5.5%) and breast carcinomas (2.8%) as the most common non-gynecologic tumors, accounting for 14% of metastatic cervical neoplasms [13]. Other rare primary sites of origin for carcinomas (in decreasing order of frequency) include the urinary bladder, pancreatobiliary tract, lung, and kidney [2, 5, 6, 11, 13–21]. Metastatic involvement of the cervix by cutaneous malignant melanoma is extremely rare [1, 13, 22–25]. Uterine corpus sarcomas may also extend to the cervix (*see* Chap. 11).

13.4 Macroscopy

Macroscopic appearances are variable, ranging from an unremarkable cervix to diffuse enlargement, or a well defined or poorly defined mass with or without ulceration and induration [2, 6, 9, 26].

13.5 Microscopy

13.5.1 Histology

Metastatic tumors may replace the preexisting benign cervical epithelium without associated stromal desmoplastic reaction, thereby mimicking cervical precursor lesions, either high-grade squamous intraepithelial lesion (HSIL) or adenocarcinoma in situ (AIS). Metastases with an infiltrative growth pattern may resemble invasive endocervical adenocarcinoma or squamous cell carcinoma. The tumors most likely to colonize cervical mucosa include endometrial and urothelial carcinomas, although adnexal, primary peritoneal, and even pancreatic carcinomas can present with cervical mucosal metastasis [10]. Cervical stromal involvement, when present, may be either superficial or deep. Metastases, particularly those from ovarian and colorectal carcinomas, may be centered in the outer half of the cervical wall. Generally, features suggestive of secondary involvement by carcinomas include a permeative growth surrounding benign endocervical glands, multifocal or multinodular growth pattern, extensive lymphovascular space invasion (LVSI), signet ring cells, and the absence of a cervical precursor lesion [2, 4, 6, 13, 17, 27]. Additional specific features vary depending on the primary site of origin. Below are the histologic and immunophenotypic characteristics of the relatively common subtypes.

Adnexal high-grade serous carcinomas exhibit a variety of growth patterns (glandular, papillary, solid, pseudoendometrioid, transitional cell carcinoma–like) with high-grade nuclei and brisk mitotic activity. Mucosal metastases may be confused with "primary cervical serous carcinoma," which is no longer thought to exist. Psammoma bodies and tumor-infiltrating lymphocytes may be seen. Immunohistochemically, the tumor cells are positive for WT1 (strong, diffuse), PAX8, CK7 (cytokeratin 7), p16 (diffuse, block-like), and ER and

PR (estrogen and progesterone receptors), with aberrant expression of p53 (strong, diffuse staining in >80% of nuclei; complete absence of staining, also known as *null-phenotype*; or strong cytoplasmic staining that may be accompanied by nuclear staining). The cells are negative for napsin-A and HNF1β (hepatocyte nuclear factor 1β) (Fig. 13.1) [28].

Endometrial neoplasms can present with cervical stromal involvement (pT2 disease) or cervical mucosal involvement. Most frequent are endometrioid adenocarcinomas; other relatively common subtypes include clear cell carcinoma and serous carcinoma.

- *Endometrioid adenocarcinomas* are composed of back-to-back endometrial-type glands of varying differentiation, often with foci of squamous metaplasia and/or mucinous features (FIGO grade 1: <5% non-squamous solid growth; FIGO grade 2: 6–50% non-squamous solid growth; FIGO grade 3: >50% non-squamous solid growth) (Fig. 13.2). In some cases, neoplastic glands involving the lower uterine segment and cervix may look deceptively bland and can be misinterpreted as benign glands [9] (Fig. 13.3). Immunohistochemically, endometrioid adenocarcinoma is typically positive for PAX8, CK7, vimentin, ER and PR, and negative for WT and napsin-A, with patchy staining for p16 and normal/wild-type pattern for p53 (heterogeneous staining with an admixture of negative cells, weakly positive cells, and strongly positive cells). Aberrant p53 expression is seen in 10% of low-grade tumors and 30% of high-grade tumors. Approximately 50% of cases may show loss of PTEN or ARID1a. Abnormal expression of DNA mismatch repair proteins (MLH1, PMS2, MSH2, MSH6) may be seen in 20–30% of cases.
- *Clear cell carcinomas* usually show an admixture of papillary, tubulocystic, and solid architectural patterns with enlarged round, cuboidal, flattened, or hobnail nuclei with prominent nucleoli, typically low mitotic count, and clear to eosinophilic (oxyphilic) cytoplasm. Intracytoplasmic mucinous material or hyaline bodies may be seen. Immunohistochemically, these carcinomas may be positive for HNF1β, napsin-A and racemase, and negative for ER and PR. Aberrant p53 expression and diffuse p16 positivity may be present in approximately 30% of cases, with loss of ARID1a in 20% of cases. Abnormal expression of DNA mismatch repair proteins may be seen (Fig. 13.4).
- *Serous carcinoma* resembles adnexal high-grade serous carcinoma both morphologically and immunophenotypically, except for weak positivity or negativity for ER, PR, and WT1. Strong and diffuse p16 staining, present in serous carcinomas, may be misleading since this immunophenotype is shared with HPV-associated neoplasia.

Metastatic breast tumors to the cervix predominantly represent *invasive lobular carcinoma*, but *invasive ductal carcinoma of no special type* may also be found [11, 13, 29–36]. The most common *classic variant of lobular carcinoma* shows a characteristic dyscohesive growth pattern in single linear files or individually dispersed cells (Fig. 13.5), due to loss of the intercellular adhesion molecule E-cadherin [37]. The tumor cells show mild to moderate nuclear atypia, central or eccentric nuclei, and inconspicuous mitotic activity, sometimes with intracytoplasmic mucin. A *signet ring cell variant* exhibits signet ring cells, whereas a *pleomorphic variant* shows large pleomorphic nuclei, prominent nucleoli, and mitotic figures. Immunohistochemically, lobular carcinomas are usually positive for GATA3, CK7, ER, PR, mammaglobin, GCDFP-15 (gross cystic disease fluid protein 15), and are negative for PAX8 and E-cadherin. HER2 overexpression may be seen in up to 30% of pleomorphic or grade 3 tumors.

Invasive ductal carcinoma forms tubular structures, nests, or sheets of cells without specific growth patterns (Fig. 13.6). The immunophenotype is similar to that of lobular carcinoma, except for E-cadherin, which demonstrates retained membranous expression in invasive ductal carcinoma. Triple-negative (lacking ER, PR, and HER2 expression) tumors are also positive for SOX10 in 70% of cases [38].

Gastrointestinal carcinomas: *Colorectal carcinoma* shows varying degrees of gland formation, usually lined by pseudostratified columnar cells and often associated with intraglandular necrotic debris ("dirty" necrosis) (Fig. 13.7). Mucin production, including goblet cells, is not uncommon. Poorly differentiated variants may exhibit small clusters or individually dispersed signet ring cells with intracytoplasmic mucin and eccentric nuclei (Fig. 13.8). Immunohistochemically, colorectal carcinoma is positive for CK20 (cytokeratin 20), CDX2, and SATB2 (Special AT-Rich Sequence-Binding Protein 2), and is negative for PAX8, CK7, ER, and PR. *Small bowel carcinomas* are nearly identical to colorectal carcinoma. *Gastric adenocarcinomas* are divided into gland-forming intestinal type and poorly cohesive (diffuse) variants. The *intestinal variant* shows glandular, tubular, or papillary structures of varying degrees of differentiation, whereas the *diffuse variant* is composed of dyscohesive cells with plasmacytoid, histiocytic, eosinophilic, or signet ring morphology (Fig. 13.9). There are no specific immunohistochemical markers. Variable expression of CK7, CK20, and CDX2 may be seen, with rare SATB2 positivity [39].

Urothelial carcinomas may show a papillary growth pattern, flat in situ growth pattern (pagetoid growth along the cervical epithelium), or an invasive growth pattern. *Low-grade tumors* are characterized by abundant eosinophilic cytoplasm; *high-grade tumors* have enlarged, hyperchromatic, irregular nuclei [5]. Immunohistochemically, the tumor cells are positive for CK7, CK20 (CK7 + CK20+ in

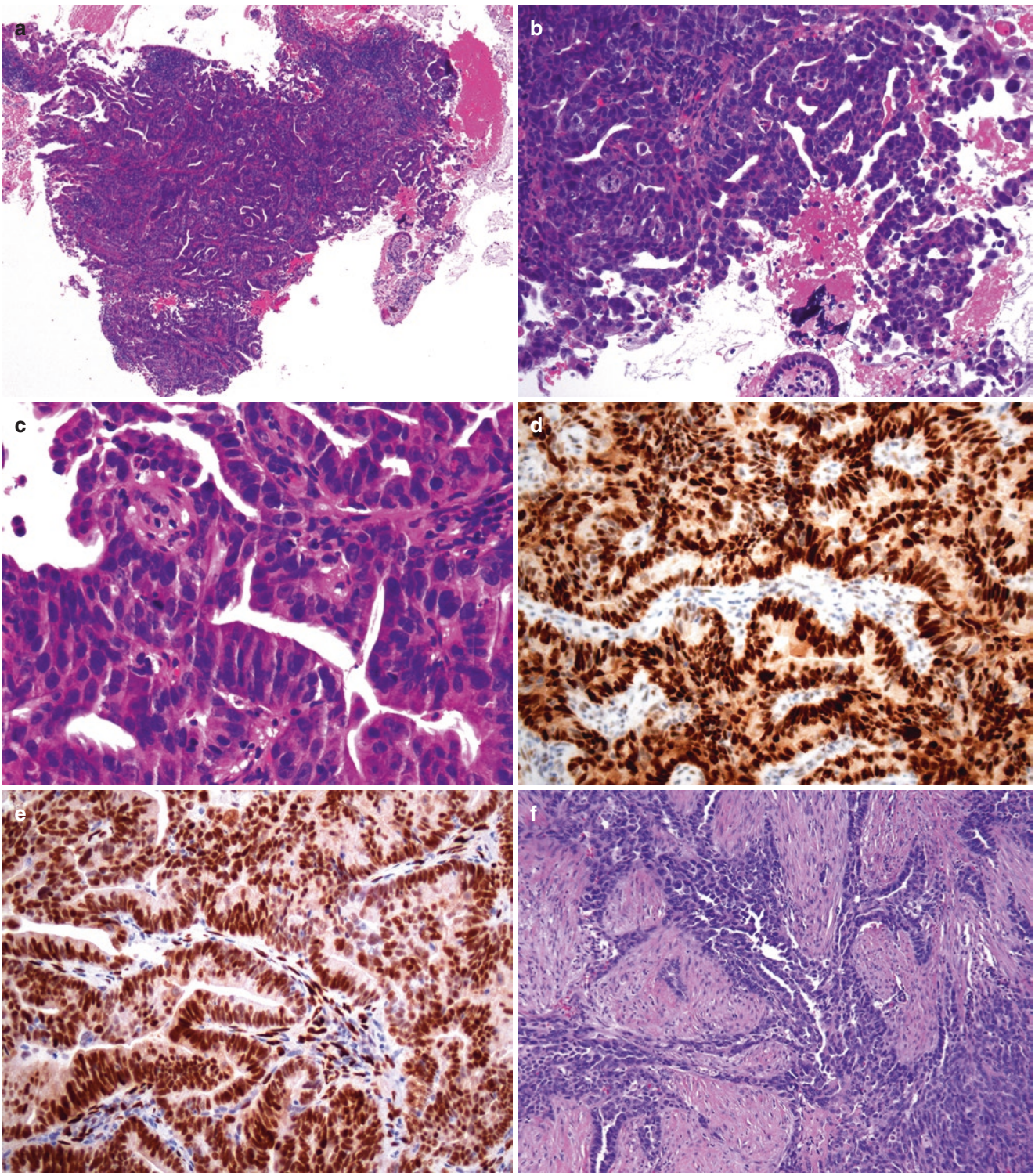


Fig. 13.1 Adnexal high-grade serous carcinoma. (**a–c**), Endocervical curettings with a fragment of high-grade adenocarcinoma with glandular growth pattern, high nuclear grade, brisk mitotic activity, and apoptotic bodies (H&E). Fragments of benign endocervical tissue are also seen in (**a**) and (**b**). Immunohistochemical stains show diffuse, strong staining for p53 (aberrant expression) (**d**) and WT1 (**e**), consistent with adnexal/primary peritoneal origin. (**f**), Examination of a bilateral salpingo-oophorectomy specimen confirms the diagnosis of tubo-ovarian high-grade serous carcinoma (H&E)

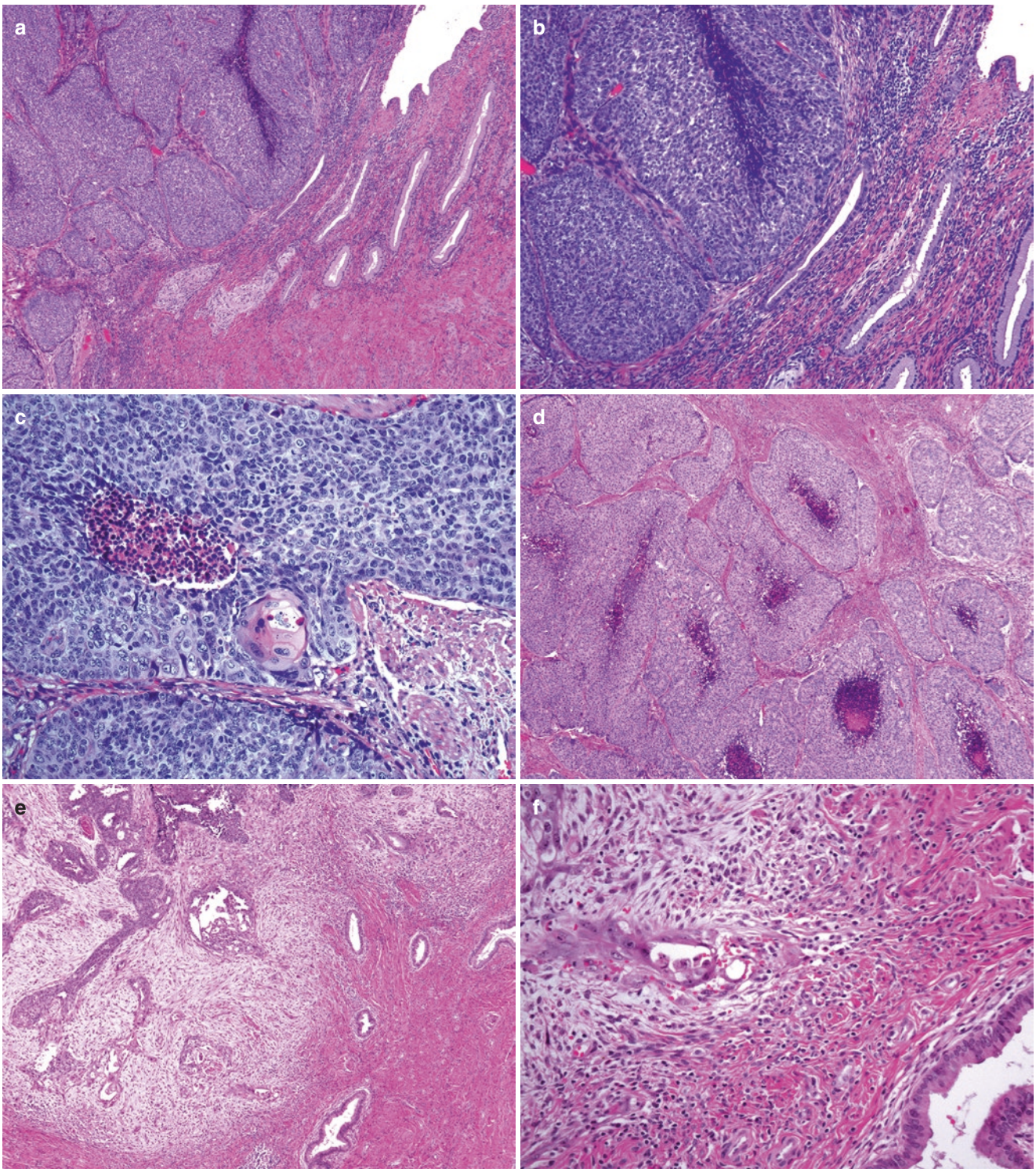
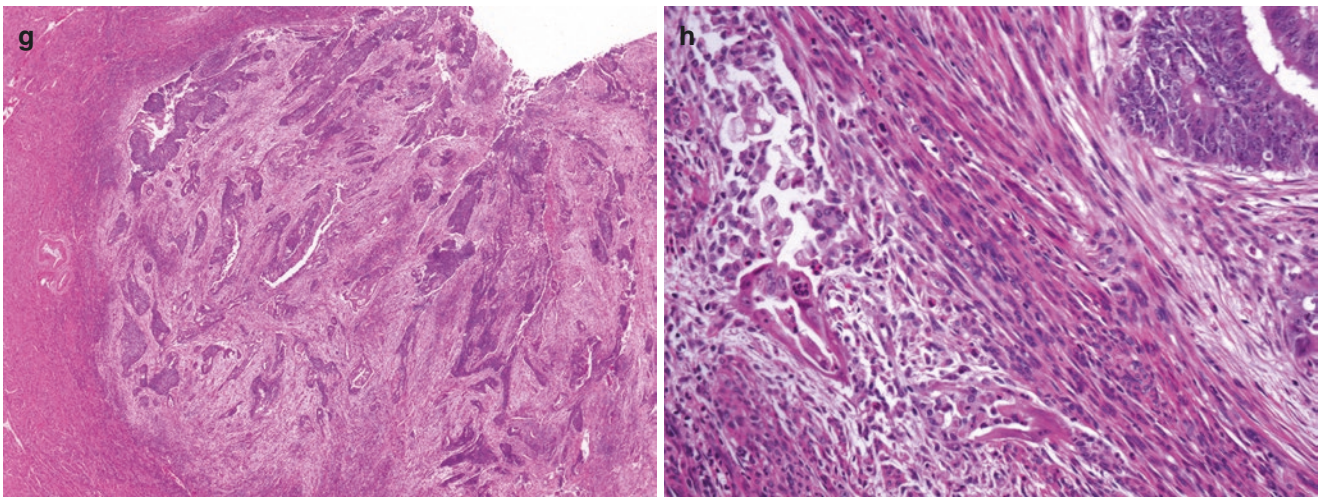


Fig. 13.2 Endometrial endometrioid adenocarcinoma. (**a–d**), Total hysterectomy specimen with a FIGO grade 3 endometrioid adenocarcinoma (H&E). The tumor involves endocervical mucosa (**a, b**) and exhibits solid growth pattern with focal squamous differentiation (**c**) suggestive of endometrioid morphology. The tumor is endometrium-based, with <50% myometrial invasion (**d**). (**e–h**), Total hysterectomy specimen with a FIGO grade 1 endometrioid adenocarcinoma (H&E). The tumor involves cervical stroma and is associated with desmoplastic stromal reaction (**e, f**). There is a MELF (Microcystic, Elongated and Fragmented) pattern of invasion in the inner half of the myometrium (**g, h**)



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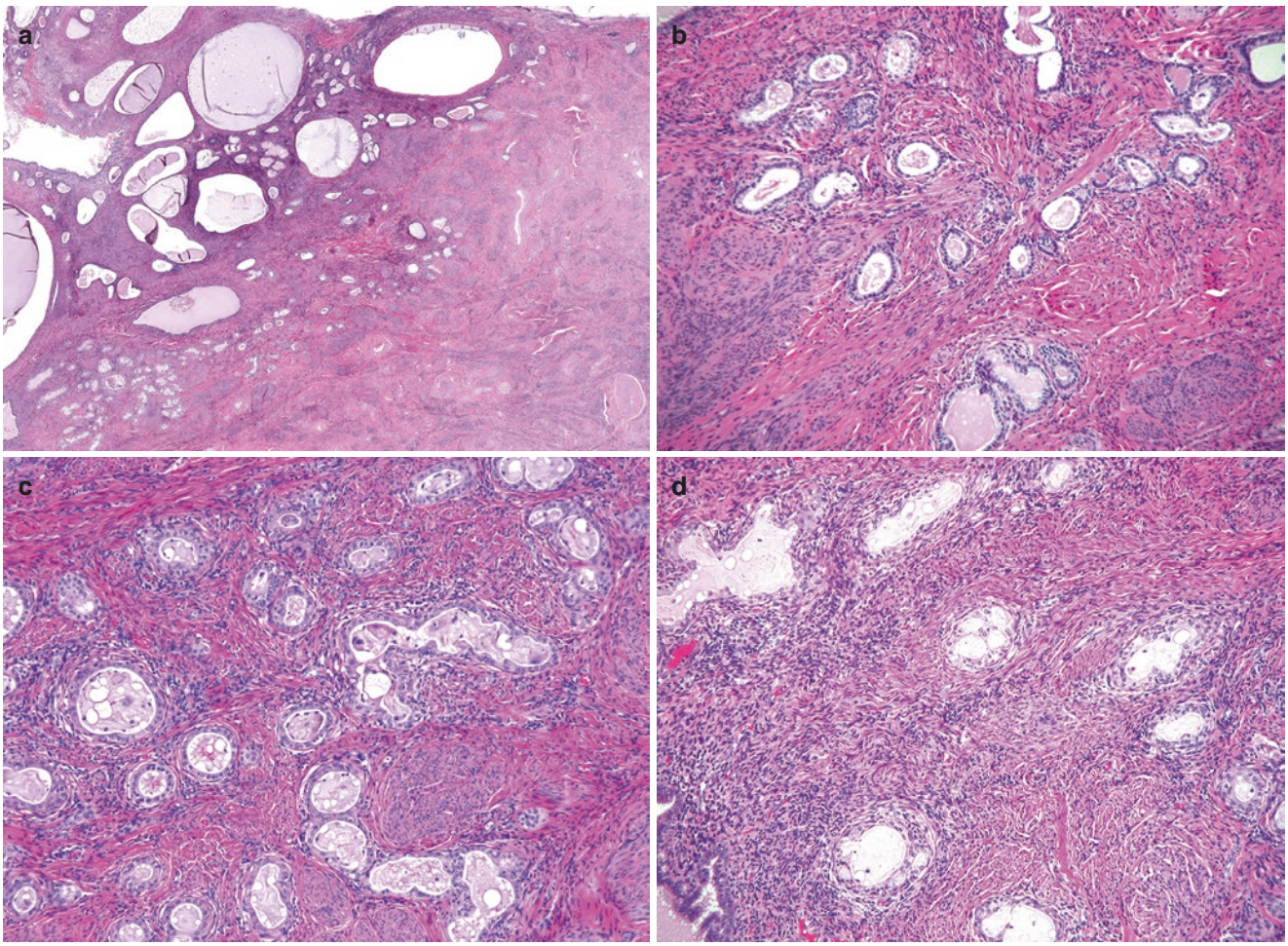
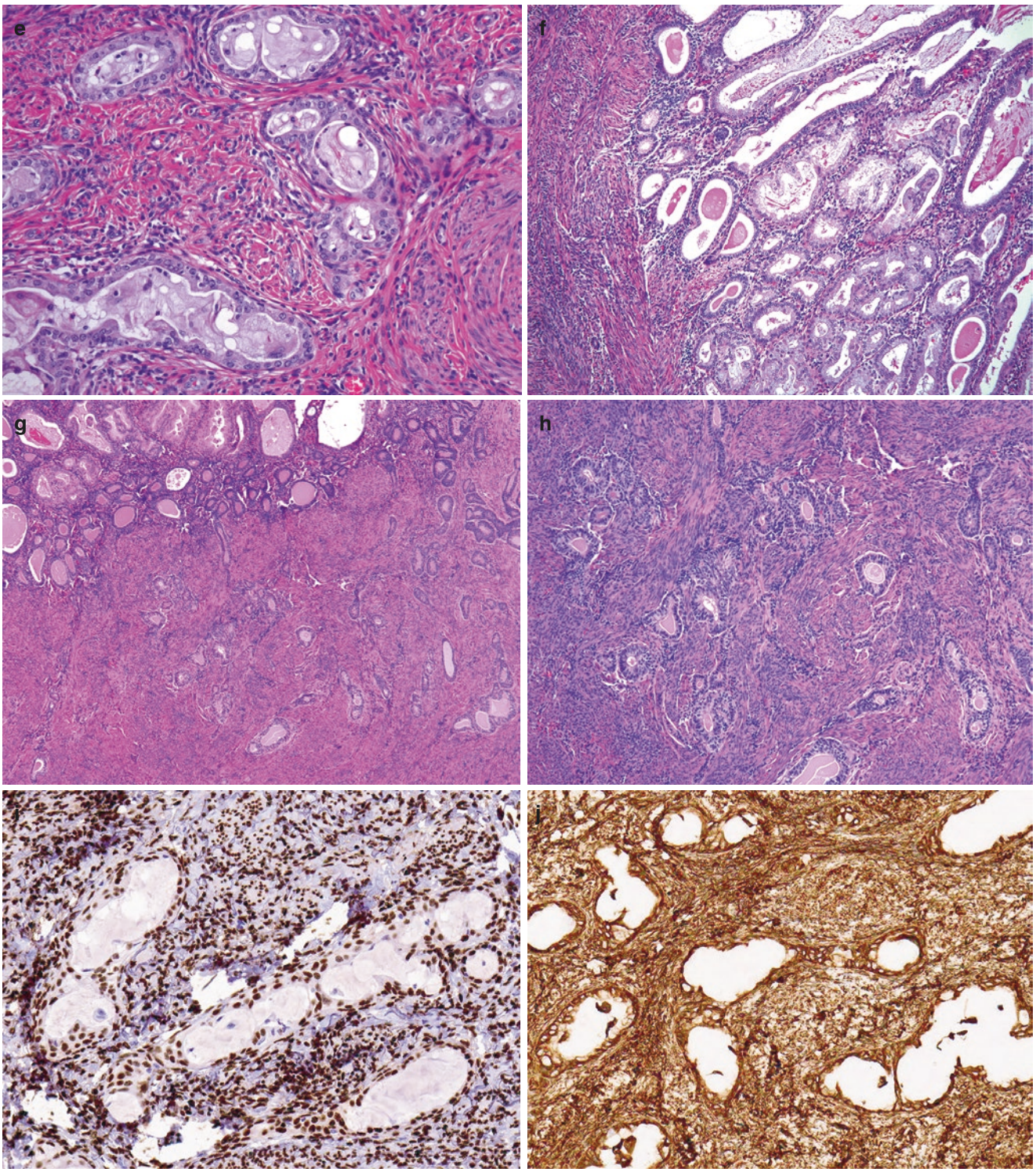


Fig. 13.3 Endometrial endometrioid adenocarcinoma. (**a–e**) Total hysterectomy specimen with small, variably sized and shaped glands infiltrating within the cervical wall (H&E). There are tubular glands with eosinophilic luminal material resembling mesonephric remnants (**b**) or more basophilic mucinous material (**c–e**), as well as focal cribriforming (**d, e**). There is no stromal reaction around these glands. (**f–h**) Endometrioid adenocarcinoma in the endometrium with similar morphology (**f**) invading as separated, small glands without stromal reaction (**g, h**). (**i** and **j**), Immunohistochemical stains show strong, diffuse staining for estrogen receptor (**i**), progesterone receptor, and vimentin (**j**), and no immunoreactivity for CEA, GATA3, and TTF-1 in the small glands involving the cervix, ruling out a mesonephric process



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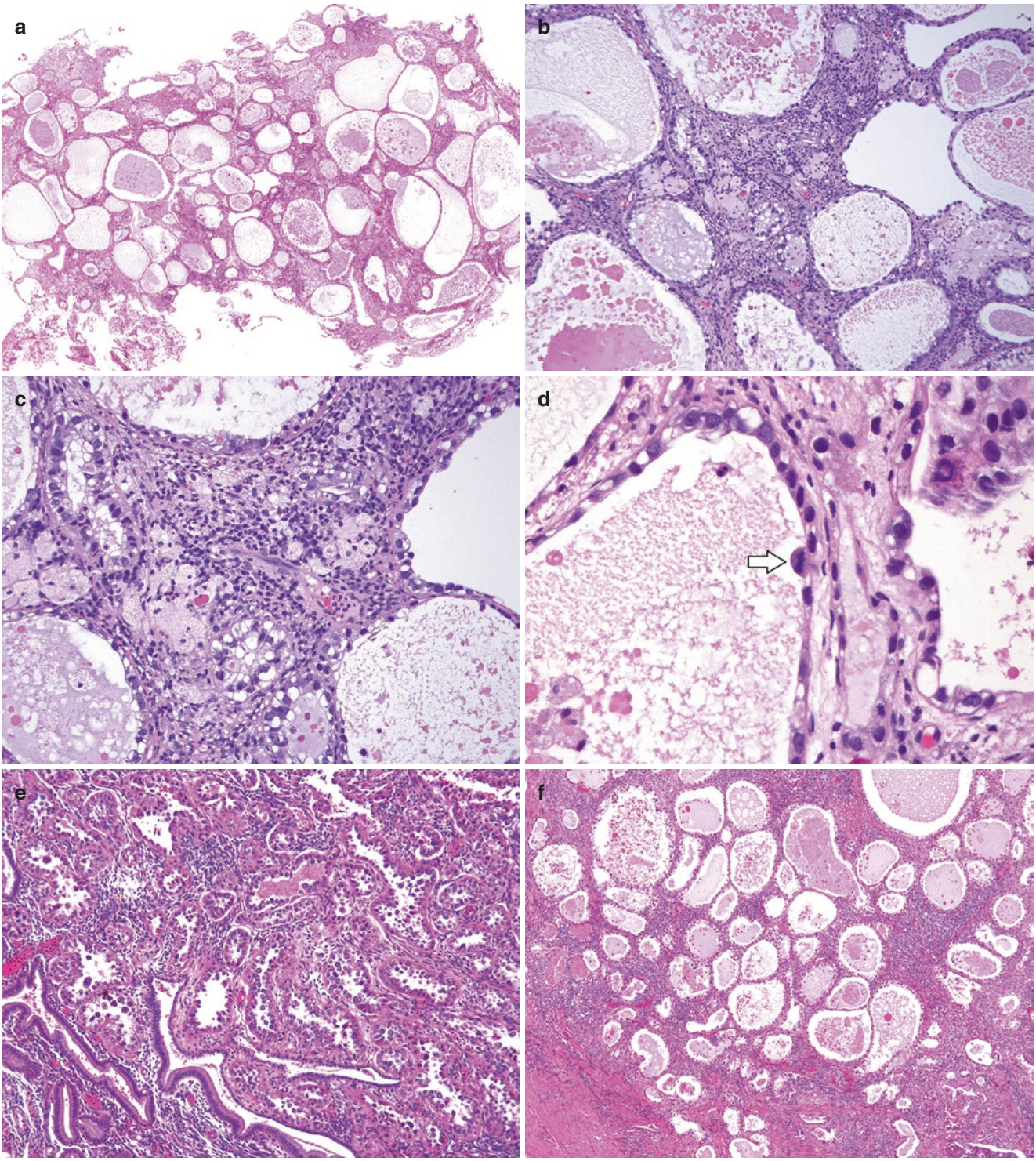


Fig. 13.4 Endometrial clear cell carcinoma. (**a–d**), Cervical biopsy with a fragment of a tubulocystic proliferation (H&E). The tubulocystic structures are lined by one layer to several layers of cells with uniform, but atypical nuclei, clear to eosinophilic cytoplasm, and rare mitotic figures (*arrow* in **d**). (**e** and **f**), Examination of the hysterectomy specimen reveals cervical stromal involvement (**e**) by endometrial clear cell carcinoma (**f**). Note benign endocervical glands in (**e**)

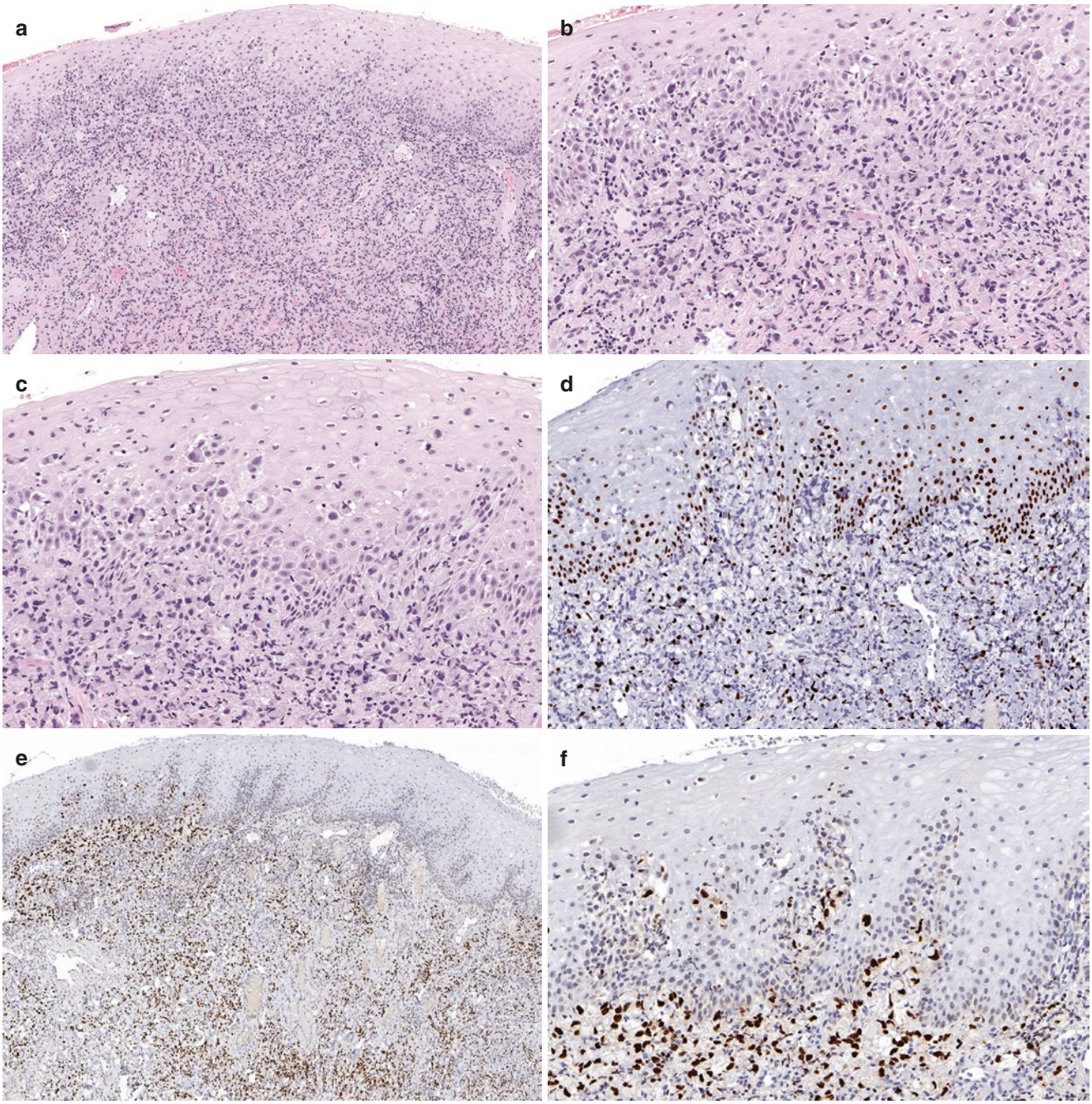


Fig. 13.5 Metastatic lobular carcinoma of the breast. (**a–c**), Cervical biopsy with a neoplastic proliferation ranging from infiltrating to pagetoid growth patterns (H&E). The tumor cells infiltrate in single files (**a**) within the subepithelial stroma and extend into the overlying squamous epithelium (**b, c**). (**d–f**), Immunohistochemical stains show the tumor to be positive for estrogen receptor (**d**), progesterone receptor, and GATA3 (**e, f**), and negative for PAX8, melanocytic markers, and p63, supporting mammary origin. The patient has a prior history of invasive lobular carcinoma of the breast

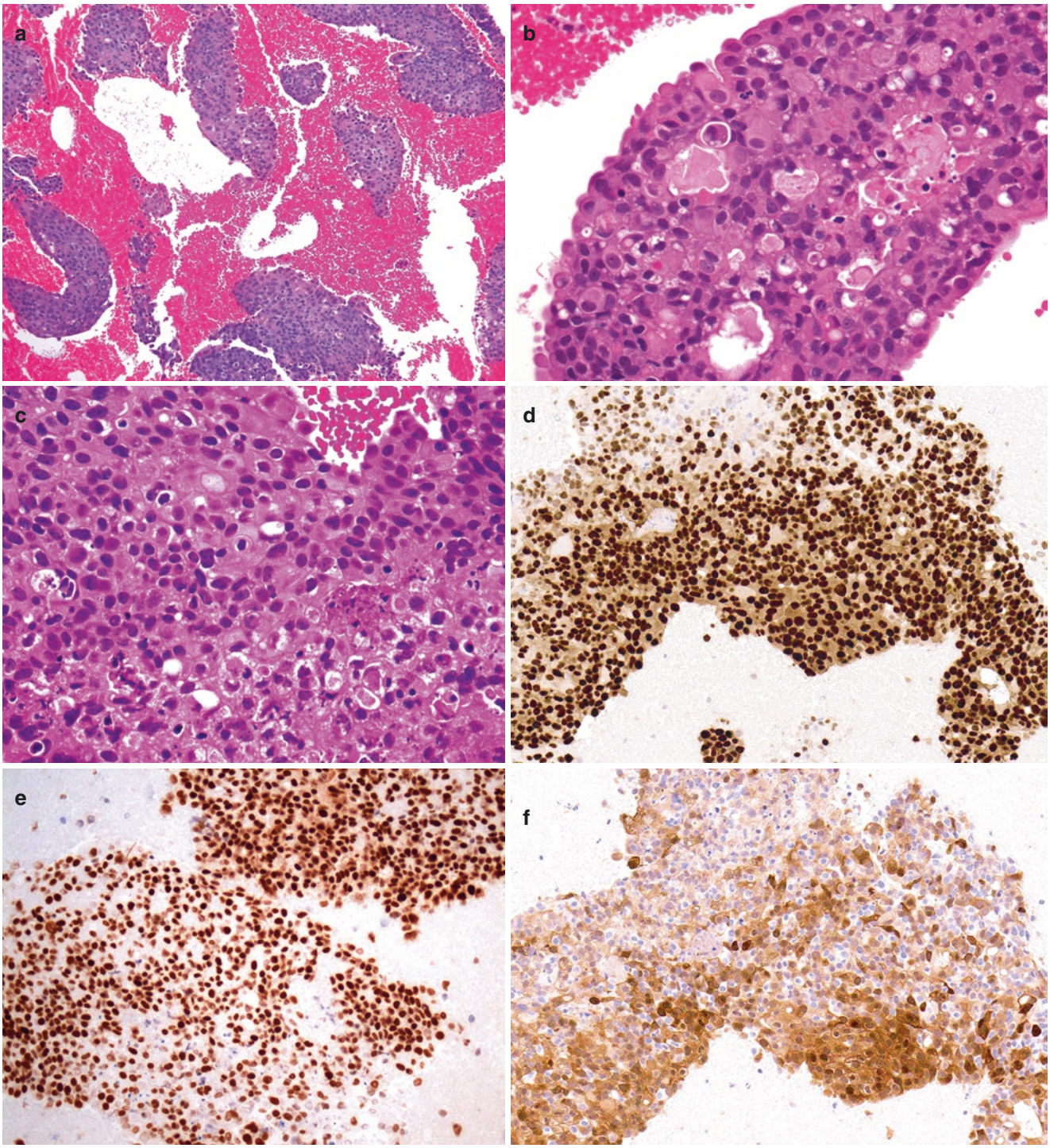


Fig. 13.6 Invasive ductal carcinoma of no special type. (**a–c**), Cervical biopsy with fragments of a poorly differentiated carcinoma (H&E). The tumor is composed of solid sheets of highly atypical tumor cells with focal glandular differentiation (**b**). (**d–f**), Immunohistochemical stains show the tumor to be diffusely and strongly positive for estrogen receptor (**d**), progesterone receptor, and GATA3 (**e**), patchy positive for p16 (**f**), and negative for PAX8 and p63, supporting mammary origin. The patient has a prior history of invasive ductal carcinoma of the breast

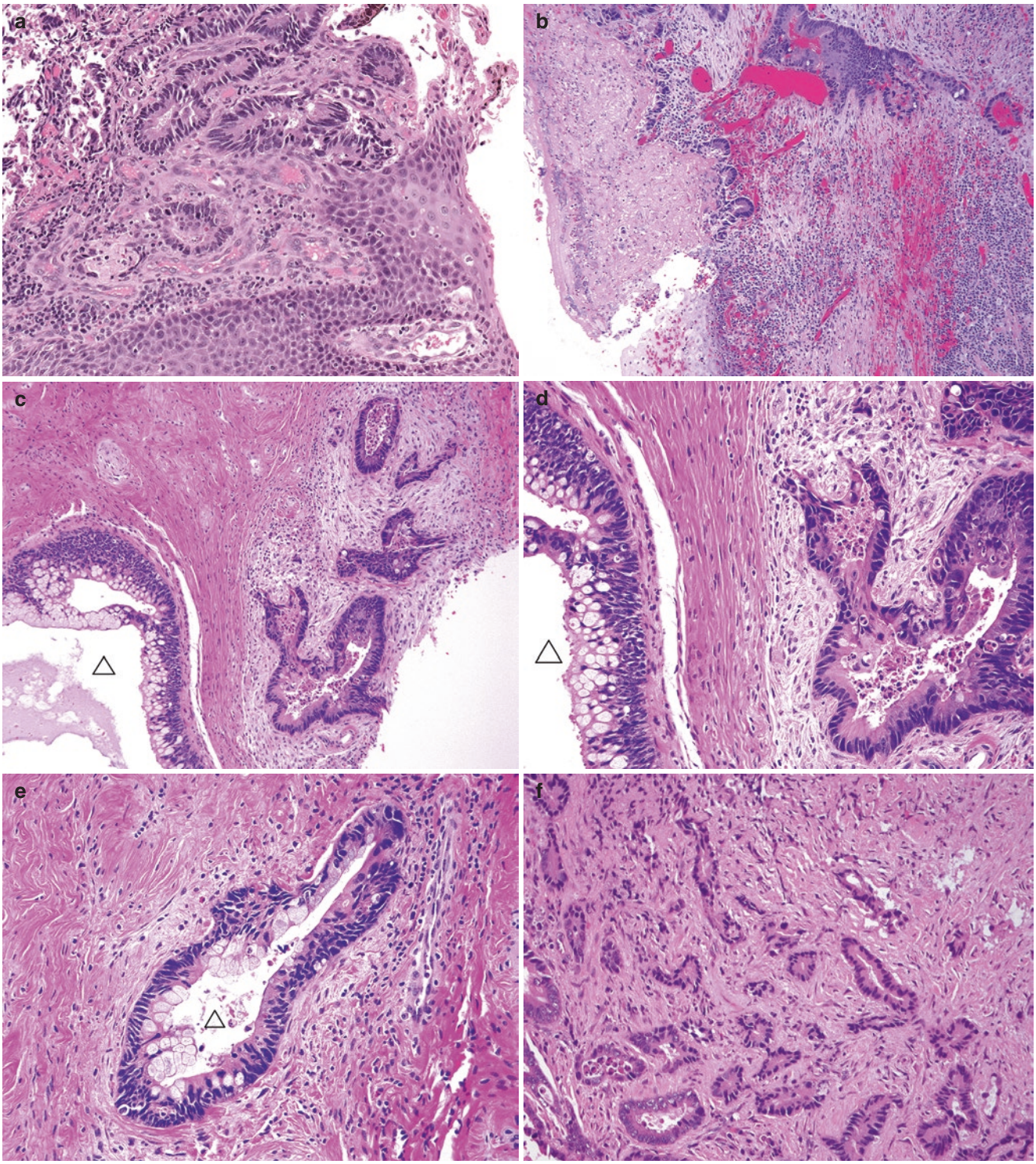
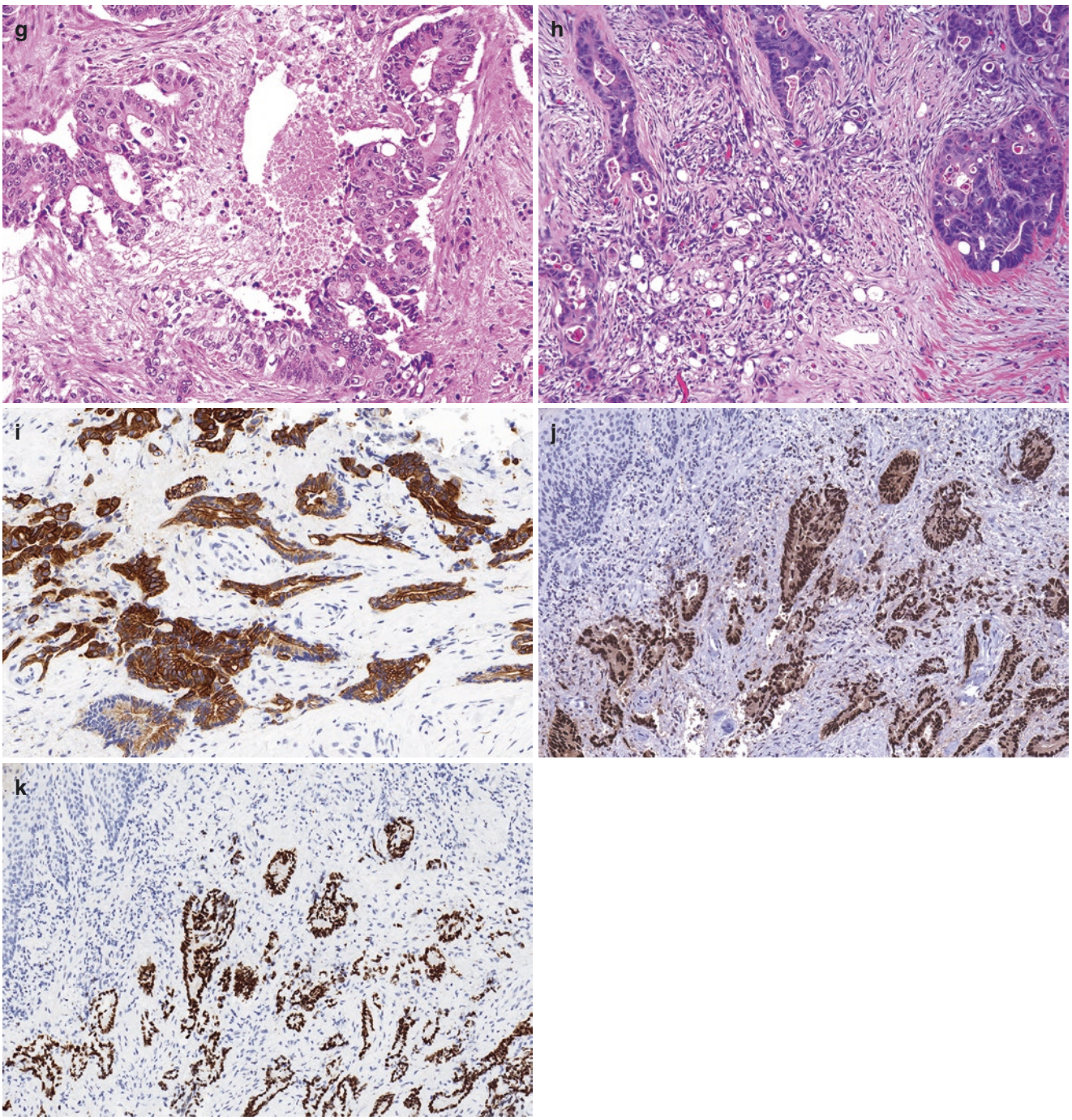


Fig. 13.7 Colorectal carcinoma. (**a–h**), Total hysterectomy with an adenocarcinoma of varying degrees of differentiation (H&E). The tumor undermines the benign cervical squamous epithelium (**a**) with ulceration (**b**). There are infiltrating neoplastic glands (**c, d, f–h**), as well as variably sized glands with a pattern resembling adenocarcinoma in situ (*triangle* in **c–e**). Note "dirty necrosis" within the lumina of neoplastic glands (**g**). Focal signet ring cells are also seen (**h**). (**i–k**), Immunohistochemical stains show the tumor to be positive for CK20 (**i**), CDX2 (**j**), and SATB2 (**k**), and negative for CK7 and PAX8, supporting colorectal origin. Note the overlying benign squamous epithelium in (**j**) and (**k**). The patient has a recent diagnosis of stage IV colon cancer



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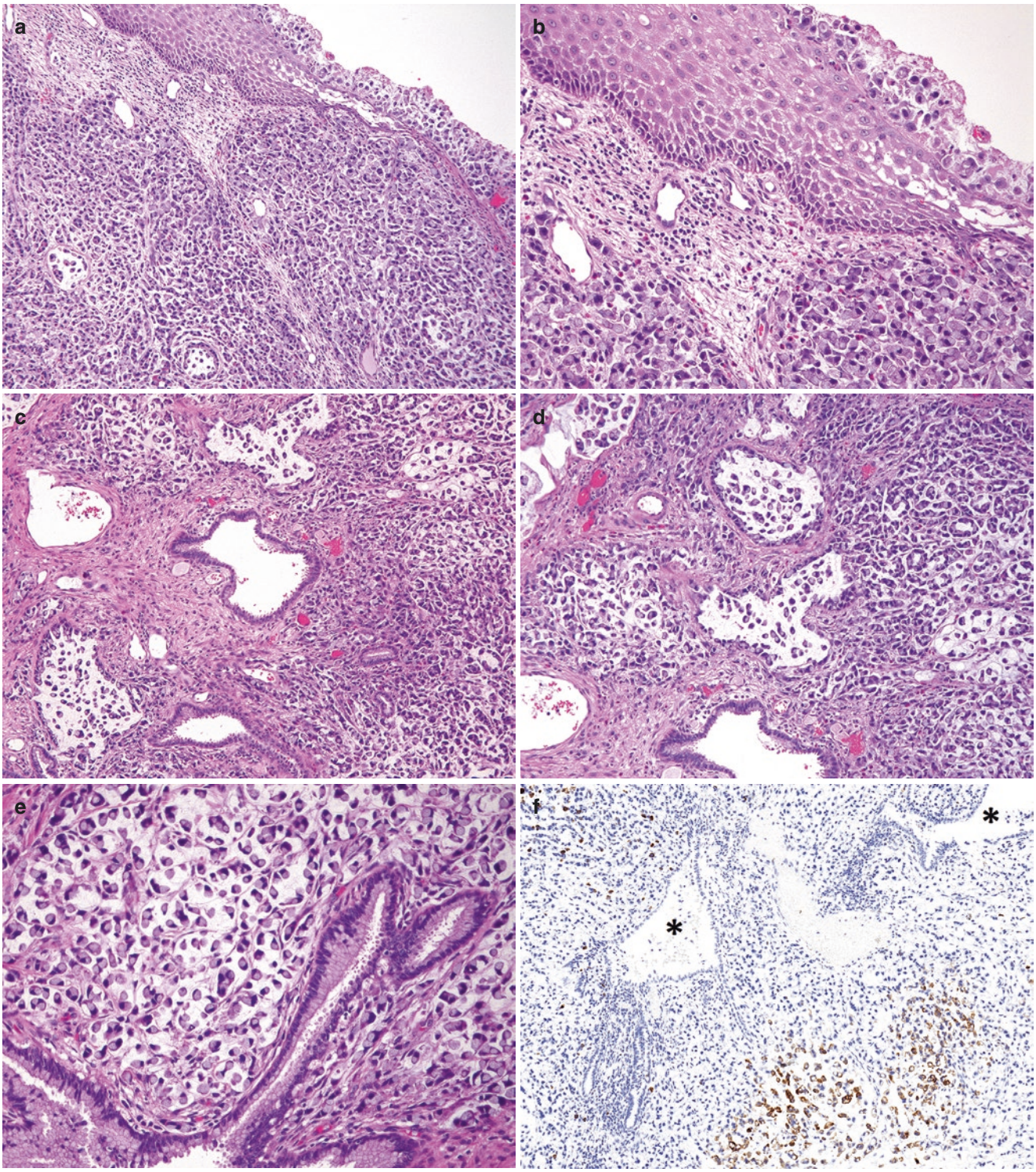
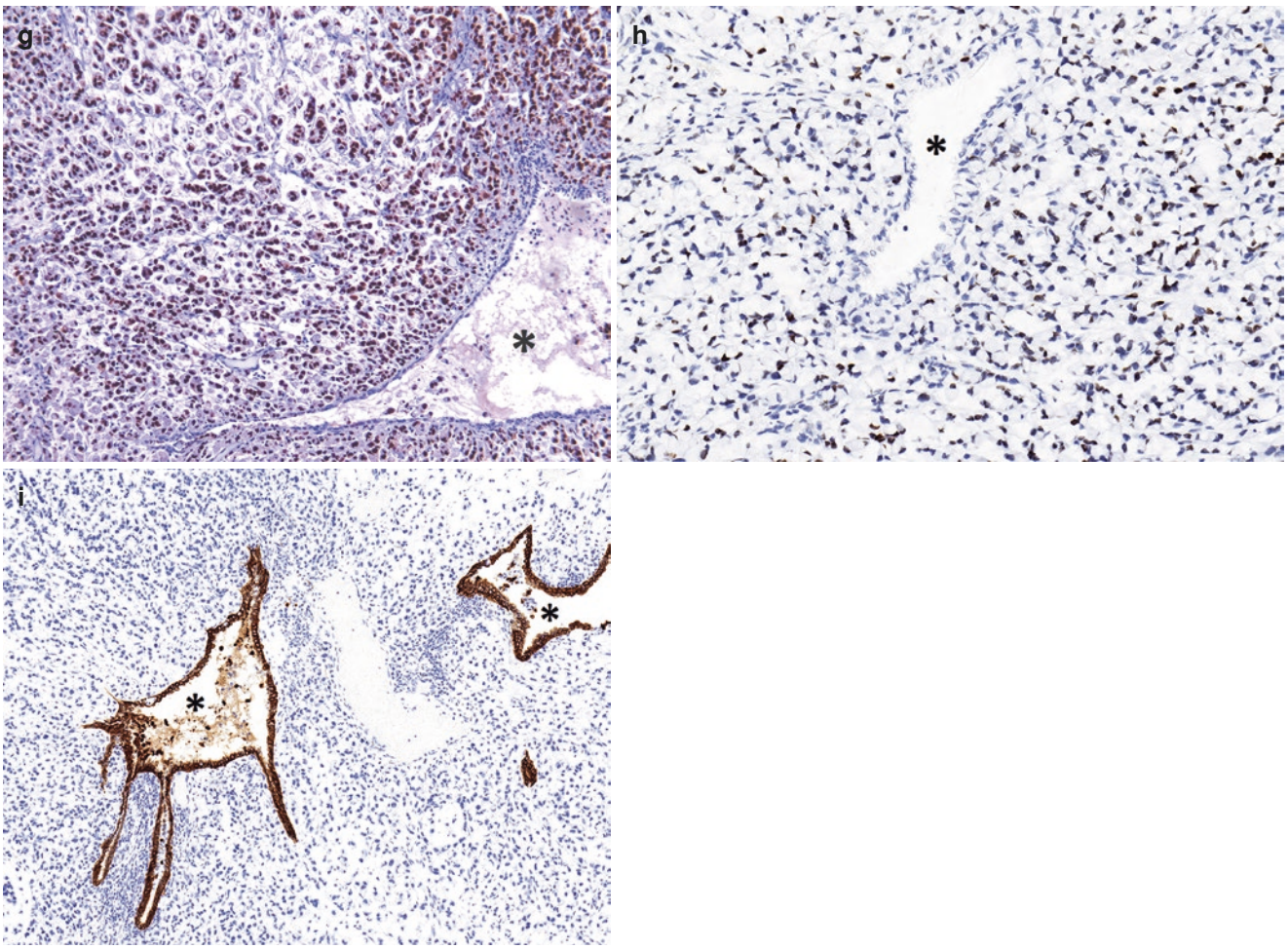


Fig. 13.8 Colonic signet ring cell adenocarcinoma. (**a–e**), Total hysterectomy with a poorly differentiated adenocarcinoma composed of signet ring cells (H&E). The tumor shows both infiltrative and pagetoid growth patterns in the ectocervix (**a, b**) and permeates around benign endocervical glands in the endocervix (**c–e**). (**f–i**), Immunohistochemical stains show the tumor to be positive for CK20 (**f**), CDX2 (**g**), and SATB2 (**h**), and negative for CK7 (**i**) and PAX8, supporting colorectal origin. Note benign endocervical glands (*asterisks*), which are negative for CK20, CDX2, and SATB2 (**f–h**), and positive for CK7 (**i**). The patient has a prior history of poorly differentiated colorectal carcinoma



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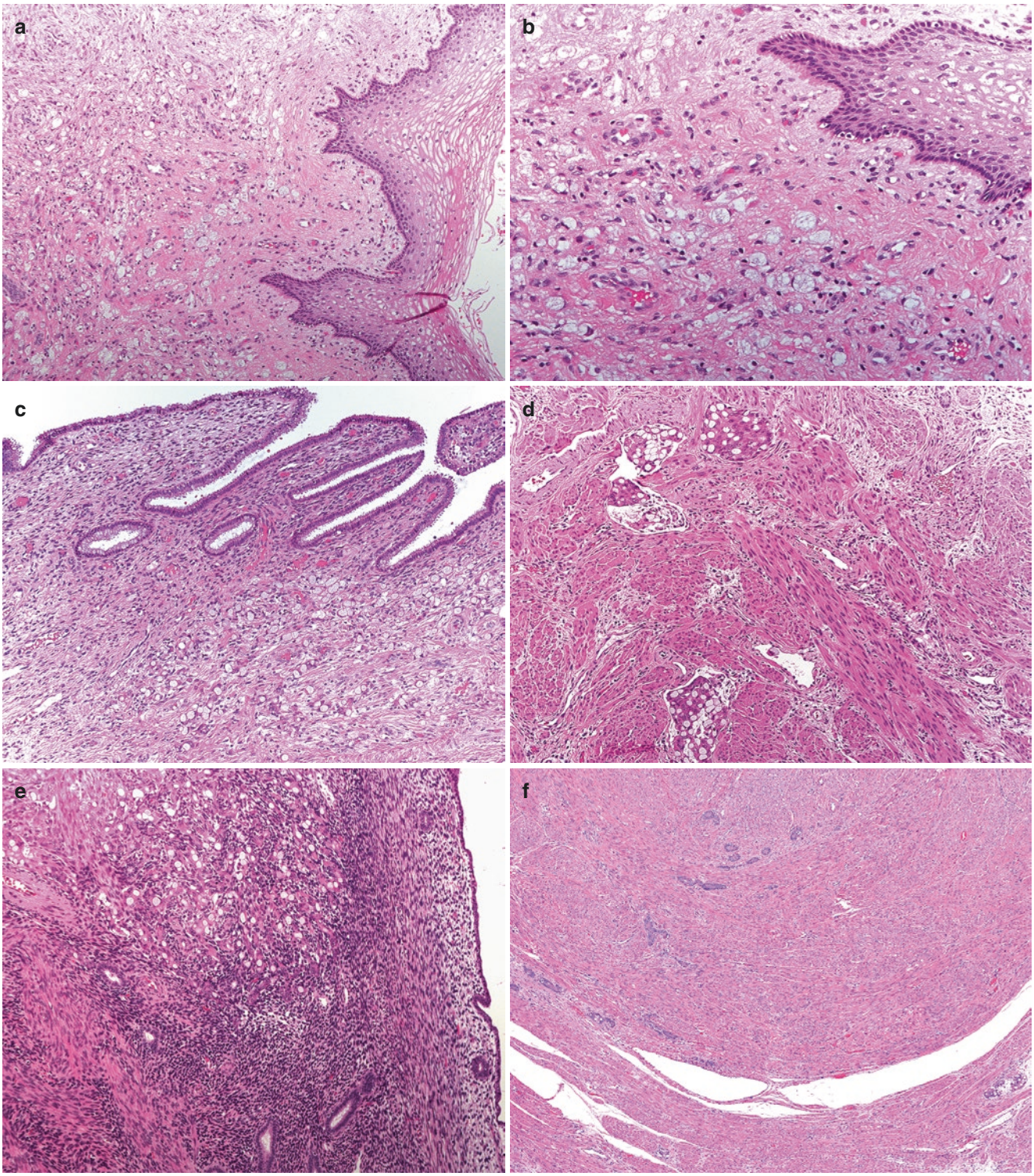

Fig. 13.9 Gastric signet ring cell adenocarcinoma. (**a–f**), Total hysterectomy with a poorly differentiated adenocarcinoma composed of signet ring cells (H&E). The tumor approaches the benign cervical squamous epithelium (**a, b**) and endocervical surface epithelium (**c**). Extensive lymphovascular invasion is identified in the lower uterine segment (**d**). The tumor also involves the endometrium (**e**) and myometrial leiomyoma (**f**). Immunohistochemistry is not very helpful for establishing gastric origin with certainty. The tumor shows patchy positivity for both CK20 and CK7, and is negative for CDX2, SATB2, and PAX8. The patient has a recent diagnosis of diffuse-type gastric cancer

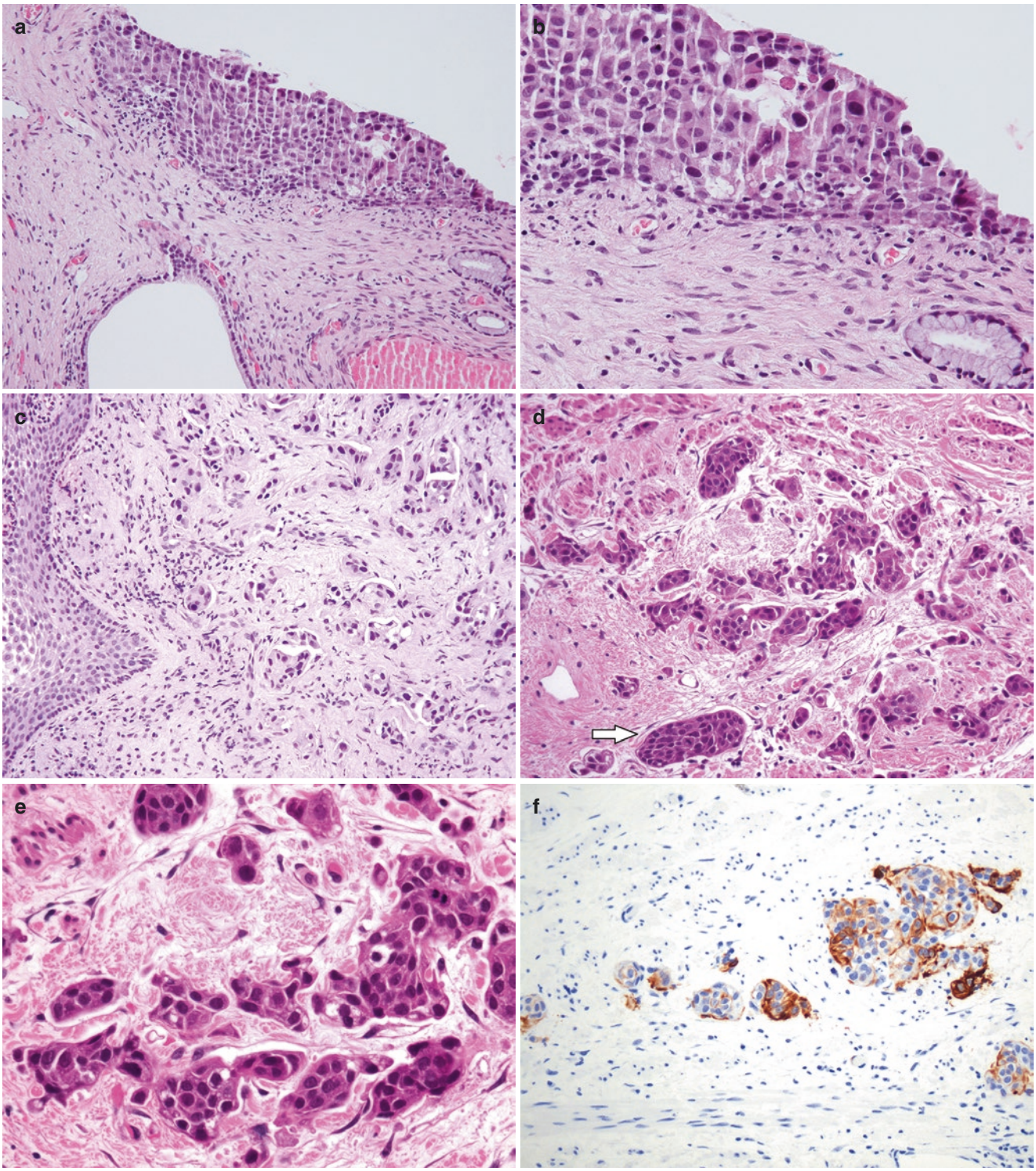

Fig. 13.10 Urothelial carcinoma. (**a–c**), Cervical biopsy specimen with atypical surface epithelium (H&E) showing pagetoid involvement of squamous epithelium with dyscohesive tumor cells resembling cervical high-grade squamous intraepithelial lesion (**a, b**), and another biopsy specimen with variably sized nests of invasive urothelial carcinoma involving the subepithelial stroma (**c**). (**d** and **e**), Total hysterectomy with infiltrating nests of urothelial carcinoma (H&E). The tumor cells exhibit round to oval nuclei with conspicuous mitotic activity and eosinophilic cytoplasm, resembling squamous cell carcinoma. Lymphovascular invasion is present (*arrow* in **d**). (**f–h**), Immunohistochemical stains show the tumor to be positive for CK7 (**f**), CK20 (**g**), GATA3 (**h**), and cytokeratin 5, and negative for p63, p40, and PAX8, supporting urothelial differentiation. The patient has a prior history of invasive urothelial carcinoma

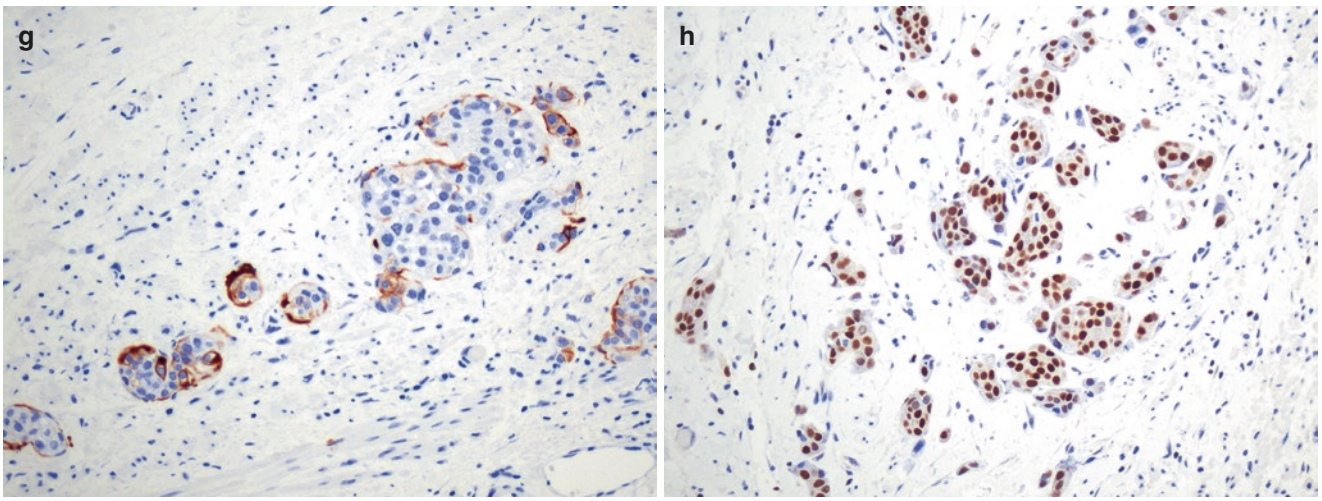

Fig. 13.10 (continued)

65% of cases), HMWK (high molecular weight keratin), GATA3, and uroplakin; they are variably positive for p63, and negative for PAX8, ER, and PR (Fig. 13.10).

Cutaneous malignant melanoma shows infiltration by highly atypical epithelioid or spindle-shaped cells with enlarged nuclei, prominent nucleoli, and mitotic figures. Melanin pigment may be present, although amelanotic variants are not uncommon. Immunohistochemically, it is positive for melanocytic markers such as S100, HMB-45 (Human Melanoma Black 45), melan-A/MART-1 (melanoma antigen recognized by T cells), SOX10, MITF (microphthalmia transcription factor), and is negative for epithelial markers and PAX8 (Fig. 13.11).

Systemic hematolymphoid tumors have morphologic and immunophenotypic features similar to those of primary cervical hematolymphoid neoplasms (*see* Chap. 12).

Diagnostic Highlights of Metastatic Carcinomas

- Lack of a cervical precursor lesion (HSIL, AIS)
- Replacement of preexisting epithelium without stromal reaction (pagetoid growth)
- Permeative growth surrounding benign endocervical glands
- Cervical stromal invasion (superficial or deep)
- Predominant involvement of outer cervical wall
- Multifocal or multinodular growth
- Extensive LVSI
- Signet ring cells in some carcinomas
- Absence of junctional activity in in most metastatic melanomas

13.5.2 Cytology

Adnexal high-grade serous carcinoma shows three-dimensional clusters with high nuclear-cytoplasmic ratio, irregular nuclear contours, vesicular chromatin, prominent nucleoli, and scant cytoplasm, and may be associated with psammoma bodies and bloody or subtle clinging diathesis. Cytologic diagnosis in cervical cytology preparations is usually "adenocarcinoma," "atypical endometrial cells," or "atypical glandular cells favor neoplastic."

Endometrial carcinomas: *Endometrioid adenocarcinomas* typically show low cellularity and form small groups of cohesive cells with mild nuclear atypia and degenerative changes in a clean background. The nuclear features include enlargement two to three times that of normal endometrial cell nuclei, open chromatin, and small nucleoli. Intracytoplasmic neutrophils may be seen. Cytologic diagnosis in cervical cytology preparations is usually "atypical endometrial cells" or "atypical glandular cells." *Clear cell carcinoma* is composed of loose clusters of malignant cells with enlarged nuclei, prominent in a background of necrotic debris (tumor diathesis). Intracytoplasmic neutrophils may be seen. Cytologic diagnosis in cervical cytology preparations is usually "adenocarcinoma," "atypical endometrial cells," or "atypical glandular cells favor neoplastic." *Serous carcinoma* resembles adnexal high-grade serous carcinoma.

Breast carcinomas: The classic variant of *lobular carcinoma* shows small tumor cells forming loose clusters or single files, or distributed singly. The tumor cells have a

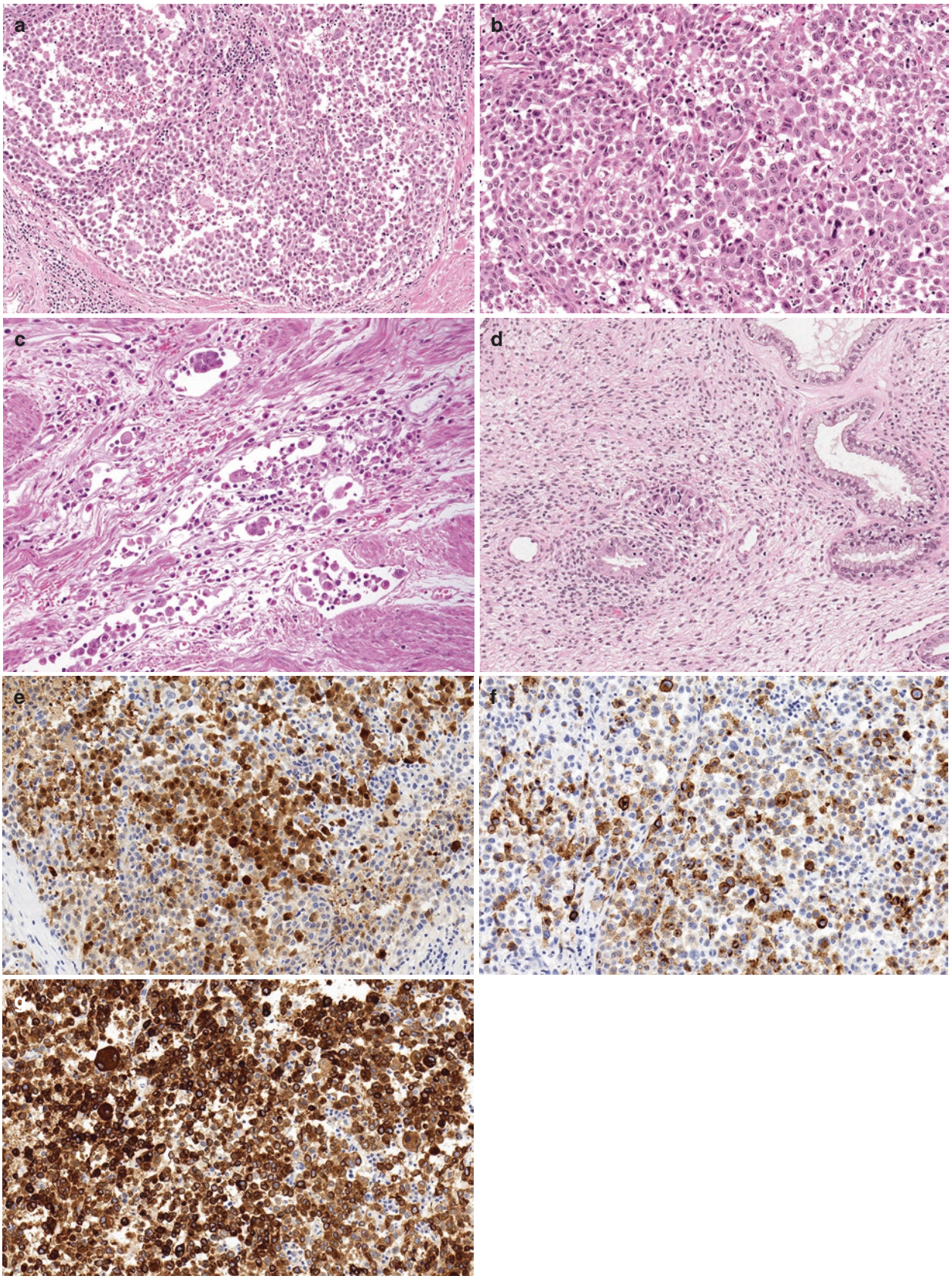

Fig. 13.11 Malignant melanoma. (**a–d**), Total hysterectomy with a neoplastic nodule involving the outer half of the cervical wall (H&E). The tumor cells are epithelioid and exhibit large, vesicular nuclei with prominent nucleoli and occasional binucleated forms (**a, b**). Extensive lymphovascular space invasion is present (**c, d**). No melanin pigment is identified (amelanotic variant). There is no junctional activity in the cervical epithelium. (**e–g**), Immunohistochemical stains show the tumor to be positive for S100 (**e**), SOX10, HMB-45 (**f**), and melan-A (**g**), and negative for cytokeratins, p63, and p40, supporting melanocytic differentiation. The patient has a prior history of cutaneous malignant melanoma

plasmacytoid appearance with central or eccentric round nuclei, fine chromatin, and cytoplasmic mucin vacuoles. The signet ring cell variant includes signet ring cells, whereas the pleomorphic variant shows larger cells with greater nuclear pleomorphism, often with prominent nucleoli and conspicuous mitotic activity. *Invasive ductal carcinoma of no special type* is composed of loosely cohesive, three-dimensional clusters and sheets as well as single tumor cells with central or eccentric nuclei, varying grades of nuclear atypia, coarse nuclear chromatin, and prominent nucleoli.

Gastrointestinal carcinomas: *Colorectal carcinoma and intestinal-type gastric adenocarcinoma* show tumor cells forming glands and/or rosettes in a background of tumor diathesis. Poorly differentiated tumors with signet ring cells demonstrate single cells with signet ring appearance due to intracytoplasmic mucin and eccentric nuclei in a background of tumor diathesis.

Urothelial carcinoma: *High-grade lesions* demonstrate increased nuclear-cytoplasmic ratio with focal cytoplasmic vacuolization, nuclear hyperchromasia, irregular nuclear membranes, and coarse chromatin, sometimes with nucleoli and mitotic activity. Tumor diathesis may be seen. *Low-grade lesions* show fewer single cells, more papillary clusters, and less nuclear pleomorphism, with finer chromatin and less nuclear membrane irregularity. Loosely cohesive clusters of cells with eccentric nuclei and tail-like cytoplasmic extensions may be seen.

Malignant melanoma shows variable cytologic features including epithelioid, spindled, and pleomorphic appearances, generally high nuclear-cytoplasmic ratio, nuclear contour cerebrations, intranuclear cytoplasmic inclusions, prominent nucleoli, and mitotic figures in a bloody background. The cells may be plasmacytoid and resemble HSIL or carcinoma. Binucleated and multinucleated forms may be present. Intracytoplasmic melanin pigment is often seen.

Systemic hematolymphoid tumors have cytologic features similar to those of primary cervical hematolymphoid neoplasms (*see* Chap. 12).

13.6 Differential Diagnosis

Metastatic tumors frequently pose diagnostic challenges, as they may be mistaken for benign proliferations as well as in situ or invasive primary cervical neoplasms, especially in the absence of a prior pertinent clinical history [2, 4, 6, 10, 13, 26, 27].

Table 13.2 outlines the main differential diagnostic considerations:

- ***Primary invasive or in situ endocervical adenocarcinoma***:
  - *Usual-type endocervical adenocarcinoma* (human papillomavirus [HPV] associated) should be differentiated from endometrioid or serous carcinoma of the endometrium, adnexal high-grade serous carcinoma, invasive ductal carcinoma of the breast, and pulmonary adenocarcinoma. Consider the history of endometrial, ovarian, breast, or pulmonary adenocarcinoma. Tumors from each of these sites are negative for high-risk HPV subtypes. Endometrial endometrioid adenocarcinomas are positive for ER, PR, and vimentin; focally positive or negative for p16 and CEA (carcinoembryonic antigen); and may show loss of PTEN, ARID1a, and DNA mismatch repair proteins. Endometrial serous carcinomas show aberrant expression of p53 and p16 in most cases and may be positive for ER and PR. In addition to aberrant p53, adnexal high-grade serous carcinomas typically show diffuse, strong staining for WT1, ER, and PR. Most breast carcinomas are positive for GATA3, ER, and PR; overexpress HER2 protein in approximately 25% of cases (similar to endometrial serous carcinomas); and may be positive for GATA3 (less often) and SOX10 (more often) in triple-negative cases. Pulmonary adenocarcinomas are typically positive for TTF-1 and/or napsin-A.
  - *Intestinal-type endocervical adenocarcinoma* should be differentiated from colorectal carcinoma and urachal adenocarcinoma by clinical history, an intramural mass sparing the mucosal surface, and invasion of the cervical wall from the outside towards the mucosal surface. "Dirty necrosis" is helpful when present. Immunohistochemistry may be useful, as endocervical adenocarcinomas are usually PAX8 and CK7 positive; however, CK20, CDX2 and SATB2 may also be expressed. HPV testing might help as most intestinal-type endocervical adenocarcinomas are positive for HPV, the exception being gastric-type carcinomas containing goblet cells. Rare HPV-negative intestinal-type adenocarcinomas, identical to colorectal carcinomas, can also arise in the cervicovaginal region and can be confidently diagnosed as such when metastasis from the intestines is excluded and a precursor lesion (villous adenoma of cervix/vagina) is present.
  - *Gastric-type endocervical adenocarcinoma* should be differentiated from gastric carcinoma by a history of gastric carcinoma. Both show columnar cells with eosinophilic or foamy cytoplasm containing HIK1083-positive gastric-type mucin and basally located nuclei with inconspicuous mitotic activity [40, 41]. It should also be differentiated from pancreato-biliary carcinomas, including carcinoma of the gallbladder, by history; immunohistochemistry is not useful, as both are positive for CK7 and CK20, and negative for p16. Approximately 30% of cervical gastric-type adenocarcinomas are PAX8 negative [42]. Loss of SMAD4 expression, see in approximately 50% of pancreatic ductal carcinoma and less commonly in other gastrointestinal carcinomas, could be informative, although

Table 13.2 Differential diagnosis of metastatic tumors to the cervix[a]

	Clinical history	Microscopy	Ancillary studies	
			Positive	Negative
Endocervical adenocarcinoma, usual-type (HPV-associated)	No other primary tumor	Glandular, cribriform, microglandular, papillary, microcystic or solid growth; variable amounts of apical mucinous cytoplasm; enlarged, pseudostratified hyperchromatic nuclei with apical mitoses and apoptotic bodies	CK7, PAX8, CEA, diffuse p16, high-risk HPV	Vimentin, CK20, WT1, ER/PR, TTF-1, napsin-A
Endocervical adenocarcinoma, intestinal-type (HPV-associated)	No other primary tumor	Well to poorly formed glands, solid nests, signet ring cells or goblet cells	CK7, PAX8, CEA, diffuse p16, high-risk HPV; ±CK20, CDX2, SATB2 (5%)	Vimentin, WT1, ER/PR, TTF-1, napsin-A
Endocervical adenocarcinoma, gastric-type	No other primary tumor	Columnar cells with eosinophilic or foamy cytoplasm with gastric-type mucin and basally located nuclei with inconspicuous apical mitotic figures	CK7, PAX8 (70%), HIK1083; ±CK20, CEA, aberrant p53	p16 (or patchy), vimentin, WT1, ER/PR, TTF-1
Cervical adenosquamous cell carcinoma	No other primary tumor	Admixed malignant squamous and glandular elements	CK7, PAX8, p63, p40, MUC6, carbonic anhydrase IX, HNF1β, diffuse p16, high-risk HPV	CK20, WT1, ER/PR, TTF-1, napsin-A
Cervical squamous cell carcinoma	No other primary tumor	Irregularly shaped and sized tumor nests with at least focal evidence of keratinization	p63, p40, HMWK, CK7, diffuse p16, high-risk HPV; ±GATA3 (focal, weak to moderate)	CK20, WT1, ER/PR, TTF-1, napsin-A
Endometrioid carcinoma	Endometrial endometrioid adenocarcinoma	Back-to-back endometrial-type glands of varying differentiation, often with foci of squamous metaplasia or mucinous features	PAX8, CK7, vimentin, ER/PR, aberrant p53 in ~30% of high-grade tumors and 10% of low-grade tumors	CK20, p16 (or patchy), loss of PTEN or ARID1a in ~50%; ±MMR deficiency, TTF-1, napsin-A, high-risk HPV
Serous carcinoma	Adnexal high-grade or endometrial serous carcinoma	Glandular, papillary, micropapillary, solid, pseudo-endometrioid or transitional cell carcinoma-like (SET features, adnexal) growth patterns with high-grade nuclei and brisk mitotic activity	*Endometrial:* Variable ER/PR, focal WT1 *Adnexal:* Diffuse WT1, ER and PR *Both:* Aberrant p53, diffuse p16 (most cases but not all), PAX8, CK7	CK20, TTF-1, napsin-A, high-risk HPV
Clear cell carcinoma	Endometrial clear cell carcinoma	Papillary, tubulocystic, or solid architecture with enlarged round, cuboidal, flattened, or hobnail nuclei; prominent nucleoli; low mitotic activity; clear to eosinophilic cytoplasm	HNF1β, napsin-A, racemase; ~30% with aberrant p53 and diffuse p16	ER/PR, 20% with loss of ARID1a; ±MMR deficiency, TTF-1, high-risk HPV
Pancreato-biliary carcinoma	Pancreato-biliary carcinoma	Glands, solid nests, cords, or papillary structures; columnar to cuboidal cells with eosinophilic and granular cytoplasm; often desmoplastic stromal reaction	CK7, CK19, CEA; ±CK20	p16 (or patchy), PAX8, SATB2, GATA3, ER/PR, TTF-1, napsin-A, high-risk HPV, loss of SMAD4 in 50% of pancreatic ductal carcinoma
Pulmonary carcinoma	Pulmonary adenocarcinoma	Acinar, solid, papillary, or mixed growth patterns; variable cytologic atypia	CK7, TTF-1, napsin-A; ±GCDFP-15, mammaglobin, ER/PR (8%)	PAX8, WT1, CK20, CDX2, SATB2, GATA3, high-risk HPV

Table 13.2 (continued)

	Clinical history	Microscopy	Ancillary studies	
			Positive	Negative
Breast carcinoma, invasive lobular	Invasive lobular carcinoma of the breast	*Classic variant:* Dyscohesive growth pattern in single linear files or individual cells with mild to moderate nuclear atypia, central or eccentric nuclei, rare mitoses; sometimes with intracytoplasmic mucin *Signet ring cell variant:* Signet ring cells *Pleomorphic variant:* Pleomorphic nuclei, prominent nucleoli, mitoses	CK7, GATA3, ER/PR (>90%); ±GCDFP-15, mammaglobin, HER2 (up to 30% of pleomorphic or grade 3 tumors)	E-cadherin, PAX8, WT1, CK20, CDX2, SATB2, TTF-1, napsin-A, high-risk HPV
Breast carcinoma, invasive ductal	Invasive ductal carcinoma of the breast	Tubular structures, nests or sheets of cells without specific growth patterns	CK7, GATA3, ER and PR (75%), HER2 (25%); ±GCDFP-15, mammaglobin; napsin-A in tumors with apocrine features; rarely TTF-1	Same as lobular carcinoma except for retained E-cadherin
Gastric adenocarcinoma	Gastrointestinal carcinoma	Intestinal variant with glandular, tubular, or papillary structures of various degrees of differentiation Poorly cohesive (diffuse) variant with dyscohesive cells of plasmacytoid, histiocytic, eosinophilic, or signet ring cell type	CK7 may predominate over CK20; CDX2, HIK1083	PAX8, ER/PR, WT1, TTF-1, napsin-A, high-risk HPV
Colorectal carcinoma	Gastrointestinal carcinoma	Neoplastic glands with pseudostratified columnar cells; often intraglandular necrotic debris (“dirty” necrosis)	CK20, CDX2, SATB2	PAX8, ER/PR, CK7, WT1, TTF-1, napsin-A, high-risk HPV
Small bowel carcinoma	Gastrointestinal carcinoma	Nearly identical to colorectal carcinoma Signet ring cells in poorly differentiated variants in all sites	CK7 may predominate over CK20; Intestinal or gastric phenotype in duodenal tumors	Intestinal or gastric phenotype in duodenal tumors
Urothelial carcinoma	Non-invasive or invasive urothelial carcinoma	Papillary, flat in situ (pagetoid growth) and invasive patterns *Low-grade tumors:* Abundant eosinophilic cytoplasm *High-grade tumors:* Enlarged, hyperchromatic, irregular nuclei	GATA3, CK7, CK20, HMWK, uroplakin; ±p63	PAX8, ER/PR, TTF-1, napsin-A, high-risk HPV
Malignant melanoma	Cutaneous melanoma	Atypical epithelioid or spindled cells with enlarged nuclei, prominent nucleoli, and melanin pigment; no junctional activity in cervical epithelium	Melanocytic markers (S100, SOX10, HMB-45, melan-A, MITF)	Cytokeratins (pan-cytokeratin may be positive), high-risk HPV
Lymphomas	Systemic lymphoma	Variable depending on subtype (*see* Chap. 12)	CD45, CD20, CD5, CD23, PAX5, CD15, CD30, Bcl-2, Bcl-6 (depending on subtype)	Cytokeratins and melanocytic markers, high-risk HPV

AIS adenocarcinoma in situ, *ARID1A* AT-rich interaction domain 1A, *CDX2* caudal type homeobox 2, *CEA* carcinoembryonic antigen, *CK7* cytokeratin 7, *CK19* cytokeratin 19, *CK20* cytokeratin 20, *ER* estrogen receptor, *GCDFP-15* gross cystic disease fluid protein 15, *HMWK* high molecular weight keratin, *HNF1β* hepatocyte nuclear factor 1β, *HPV* human papillomavirus, *HSIL* high-grade squamous intraepithelial lesion, *GATA3* GATA binding protein 3, *HMB-45* Human Melanoma Black, *HPV* human papillomavirus, *LVSI* lymphovascular space invasion, *MART-1* melanoma antigen recognized by T cells, *MITF* microphthalmia transcription factor, *MMR* mismatch repair, *MUC6* mucin 6, *PAX8* paired box 8, *PR* progesterone receptor, *PTEN* phosphatase and tensin homolog, *SATB2* special AT-rich sequence-binding protein 2, *TTF1* thyroid transcription factor-1, *WT1* Wilms tumor 1

[a]This table describes common immunoprofiles for each tumor type; unexpected and/or rare expression patterns may occur and, therefore, none of these markers should be used in isolation but always as part of the Triple Test approach based on clinical examination, radiologic findings, and pathologic and immunophenotypic features

comprehensive studies of SMAD4 expression in gastric-type endocervical carcinomas are lacking.

- *Endocervical adenocarcinoma with signet ring cells* requires consideration of the patient's history of gastrointestinal, breast, bladder, colorectal, or lung carcinoma. Most signet ring cell carcinomas of the cervix are HPV-positive, with the exception of poorly differentiated gastric-type carcinomas. Diffuse-type gastric adenocarcinoma is most common; appendiceal adenocarcinoma ex goblet cell carcinoid is rare [13, 43, 44]. Immunohistochemical stains may be helpful and include CK7, TTF-1, and napsin-A for pulmonary; CK7 with or without CK20 for gastric (nonspecific); GATA3, ER, PR, and SOX10 for mammary; CK7, CK20, and GATA3 for bladder; and CK20, CDX2, and SATB2 for colorectal origin [39, 45].
- *Primary usual-type endocervical adenocarcinoma (HPV-associated) with serous-like morphology* should be differentiated from adnexal high-grade serous carcinoma and endometrial serous carcinoma by identifying a history of the latter two tumors; primary cervical serous carcinoma is exceedingly rare and may not exist [41]. Adnexal high-grade serous carcinoma typically shows diffuse, strong staining for WT1, ER, and PR. p16 expression can be found in both metastatic serous carcinomas and HPV-associated usual-type endocervical adenocarcinoma.

- ***Primary cervical squamous cell carcinoma with acantholytic changes*** should be differentiated from invasive lobular carcinoma of the breast, as it may undergo dedifferentiation mimicking the single files of lobular carcinoma. Metastatic mammary carcinoma would be favored with a pertinent clinical history, positivity for GATA3, ER, and PR; negativity for p63, p40, high molecular weight keratin, p16 and high-risk HPV subtypes [46, 47].
- ***Endocervical adenosquamous carcinoma*** should be differentiated from endometrial endometrioid adenocarcinoma with squamous differentiation, by identifying an endometrium-based mass; negativity or patchy positivity for p16 and high-risk HPV subtypes; and positivity for ER and PR in endometrial endometrioid carcinoma.
- ***Primary cervical squamous lesions,*** both HSIL and invasive carcinoma, may be confused with urothelial carcinoma, identified with a clinical history of either non-invasive or invasive urothelial carcinoma, or by an HSIL-like lesion with dyscohesive cells, co-expressing CK20 and GATA3 [5, 16, 48–51].
- *Primary cervical melanoma* should be differentiated from metastatic cutaneous malignant melanoma, looking for a clinical history of cutaneous melanoma and an absence of junctional activity; *see also* Chap. 12 [1, 13, 22–25, 52–56].
- ***Lymphoid and myeloid tumors*** are suggested by a history of prior diagnosis and systemic involvement, with histology and immunophenotype identical to primary cervical lymphoid and myeloid tumors. *See also* Chap. 12.

13.7 Prognosis

Prognosis depends largely on the primary tumor stage at diagnosis. Widespread disease is usually associated with unfavorable clinical outcomes. Direct extension from endometrial endometrioid carcinoma typically carries a relatively good prognosis compared to cases where the cervix represents a site of distant metastasis. Clinical outcome of metastatic breast cancer is poor, with survival ranging from 2 months to 12 years (mean, 28 months) [22, 30, 31, 33, 35, 57]. Favorable prognosis of lung adenocarcinoma depends on the presence of *EGFR* (epidermal growth factor receptor) mutations or low-grade histology [58]. Metastatic cholangiocarcinoma is usually diagnosed at an advanced stage with visceral metastases; it has a very poor prognosis, with 5-year survival rates less than 5% [6, 14, 15, 59–62].

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