Cancer of Other Origin

7

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Introduction

The list of malignant tumors that may affect the serosal cavities in the form of malignant effusions is essentially as long as the list of existing cancers, as almost any type of malignancy has been described at this anatomic site. There are, however, considerable variations in terms of incidence that must be taken into account. The previous chapters in this section focused on five of the more commonly diagnosed entities in effusion diagnosis—breast, lung, and ovarian carcinoma, malignant mesothelioma, and hematological cancers. The frequency with which one may diagnose any of the remaining cancers depends on the type of institution and diagnostic service one works in, as well as on geographic factors. Nevertheless, the most frequently encountered tumors among those discussed in this chapter are undoubtedly those originating from the gastrointestinal tract, followed by metastases from uterine (endometrial and cervical) carcinomas, with the remaining entities ranging from infrequent to exceedingly rare. It should be noted that papers cited in this chapter are limited to those in which unequivocal presence of tumor cells has been documented in the effusion based on cytological evaluation. Reports in which effusions have been described as "malignant" based on the fact that the patient had documented metastasis to the same anatomic compartment that has been diagnosed in biopsy material have not been included in this discussion.

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Gastrointestinal Cancers

The most common gastrointestinal organs of origin for metastases in effusions are the stomach, pancreas, liver, colon and rectum, and esophagus. In addition, dissemination from a primary in the appendix, and less frequently from a colonic, ovarian, or other origin, in the form of pseudomyxoma peritonei deserves discussion, as it represents a distinct clinical entity.

The clinical and morphological characteristics of these tumors will be discussed separately, followed by a joint discussion on their immunohistochemical profile and the differential diagnosis, as several markers are expressed by the majority or all of these cancers.

Gastric Carcinoma

Globally, gastric cancer, constituting predominantly of adenocarcinoma, is the fourth and fifth most commonly diagnosed cancer in men and women, respectively, and ranks third and fifth in cancer-associated mortality in the two genders, making it a major health problem [1]. Considerable geographic variation exists, with highest disease incidence in Eastern Europe, Asia, and Central and South America [2]. *Helicobacter pylori* is a major causative agent. Mass screening for gastric cancer in Japan and South Korea has led to detection of smaller tumors at an earlier disease stage, resulting in improved survival. However, screening has not been implemented in the majority of countries, resulting frequently in late diagnosis, with 5-year survival at 25–30% for all stages [2]. Malignant ascites is present in 10% of gastric cancer patients and is associated with poor outcome [3].

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Surgery at early stage remains the only curative approach. However, treatment is multidisciplinary, with combination of surgery with chemotherapy or chemoradiotherapy in patients with resectable disease or the use of the latter modalities in the non-resectable setting. Intraabdominal chemotherapy has been assessed as therapeutic modality, with generally disappointing results. Targeted therapy using trastuzumab is used in patients with HER2-overexpressing tumors, and several other therapeutic targets are currently being assessed in clinical trials [2]. Analysis of 72 patient-matched primary and metastatic gastric carcinomas, including 15 effusions, showed good agreement with respect to HER2 status by both FISH (98.5%) and IHC (94.9%) [4]. The feasibility of assessing HER2 status in effusion specimens was confirmed in a more recent study of 46 gastric carcinoma effusions [5].

Gastric carcinoma effusions are often highly cellular (Fig. 7.1a). Tumor cells in effusions most often originate from diffuse infiltrating carcinomas and consequently tend to disseminate in the form of single cells (Fig. 7.1b, c), although more cohesive groups, occasionally with acinar form, may be seen (Fig. 7.1d). Tumor cells have variable size but are generally medium-sized, with high n/c ratio, markedly atypical nuclei with coarse chromatin, and conspicuous nucleoli (Fig. 7.1e, f). Signet ring morphology is common and intracytoplasmic vacuoles are easily detected (Fig. 7.1e–g). Binucleate or multinucleate cells may be seen (Fig. 7.1h). Mitotic figures are easily found (Fig. 7.1g, i).

Cells that have spread from gastric carcinomas of intestinal type tend to be more cylindrical and less atypical and form more cohesive groups [6].

Pancreatic Carcinoma

Pancreatic cancer, predominantly adenocarcinoma, is a highly lethal malignancy which is more prevalent in developed countries, in which it is the ninth and eighth most commonly diagnosed cancer in men and women, respectively. The aggressiveness of pancreatic cancer is clearly reflected in the fact that it ranks fifth and fourth in cancer-associated mortality in the two genders, with 5-year survival for all stages at 8%. The disease is predicted to become the second most common cancer by 2030 [1, 7].

Pancreatic cancer usually presents as locally advanced or metastatic disease, with only 15–20% of patients deemed eligible for upfront surgery [8]. For the remaining patients, chemotherapy is the mainstay of treatment. However, few patients achieve long-term survival, and data from trials applying targeted therapy have generally been disappointing to date [7].

Individuals with family history of pancreatic cancer are at increased risk of developing the disease, as are those with genetic syndromes, including hereditary pancreatitis, familial atypical mole and multiple melanoma, Peutz-Jeghers syndrome, Lynch syndrome, and Li-Fraumeni syndrome, as well as those carrying *BRCA* mutations [9]. Effective screening is unavailable to date [9, 10].

The presence of malignant ascites, either at diagnosis or at new onset, is associated with extremely poor survival [11–13]. In a recent study of 180 patients, median survival after development of ascites was 1.8 months [14]. Therapeutic approaches that have been considered in this setting are administration of paclitaxel after failed treatment with gemcitabine, the drug of choice in treating pancreatic cancer [15], and combined regimen of 5-FU and cisplatin [16], the latter with disappointing results.

Warshaw analyzed peritoneal washings from 40 patients diagnosed with pancreatic carcinoma of the head ($n = 35$) or body (=5). Tumor cells were found in 12 cases (30%), and their presence was associated with the presence of non-resectable tumors and shorter survival [17]. In contrast, only three positive specimens were found in analysis of peritoneal washings and ascites specimens from 36 patients with biopsy-proven pancreatic carcinoma, all three from patients with peritoneal carcinomatosis [18].

The morphology of pancreatic carcinoma in effusions depends on the histological type of the primary tumor (serous vs. mucinous) and the degree of differentiation. Di Bonito et al. studied 26 effusions from 20 patients with pancreatic carcinoma of ductal type, of which 18 were peritoneal and 8 pleural. The authors found Indian file formation with nuclear molding to be the most prominent morphological feature. Other non-specific features included eccentric hyperchromatic nuclei, abundant vacuolated cytoplasm, and a reactive background [19].

Spieler and Gloor describe two types of cells in well-differentiated pancreatic and biliary duct carcinoma-small cylindrical cells forming smooth, round, or papilliform clusters and larger cells with abundant vacuolated cytoplasm. Less differentiated cells were difficult to distinguish from adenocarcinomas of other origin [6].

Cases seen by the authors of this chapter encompass a fairly wide morphological spectrum. Pancreatic carcinoma cells may form papillary groups that are indistinguishable from serous carcinoma of the ovary or peritoneum (Fig. 7.2a–c). Vacuolization may be prominent (Fig. 7.2a, d), occasionally encroaching on the nucleus (Fig. 7.2e). Acinar structures may be seen, with nuclear molding (Fig. 7.2f), as well as nondescript groups of various size (Fig. 7.2g, h). Cells have variable n/c ratio and degree of atypia, but the latter may be pronounced (Fig. 7.2i), occasionally with the formation of giant cells, both mononucleated and multinucleated (Fig. 7.2j, k). Tumors with dissociated cells, occasionally with intracytoplasmic vacuoles, which are indistinguishable from gastric carcinoma or lobular breast carcinoma, may be seen (Fig. 7.2m).

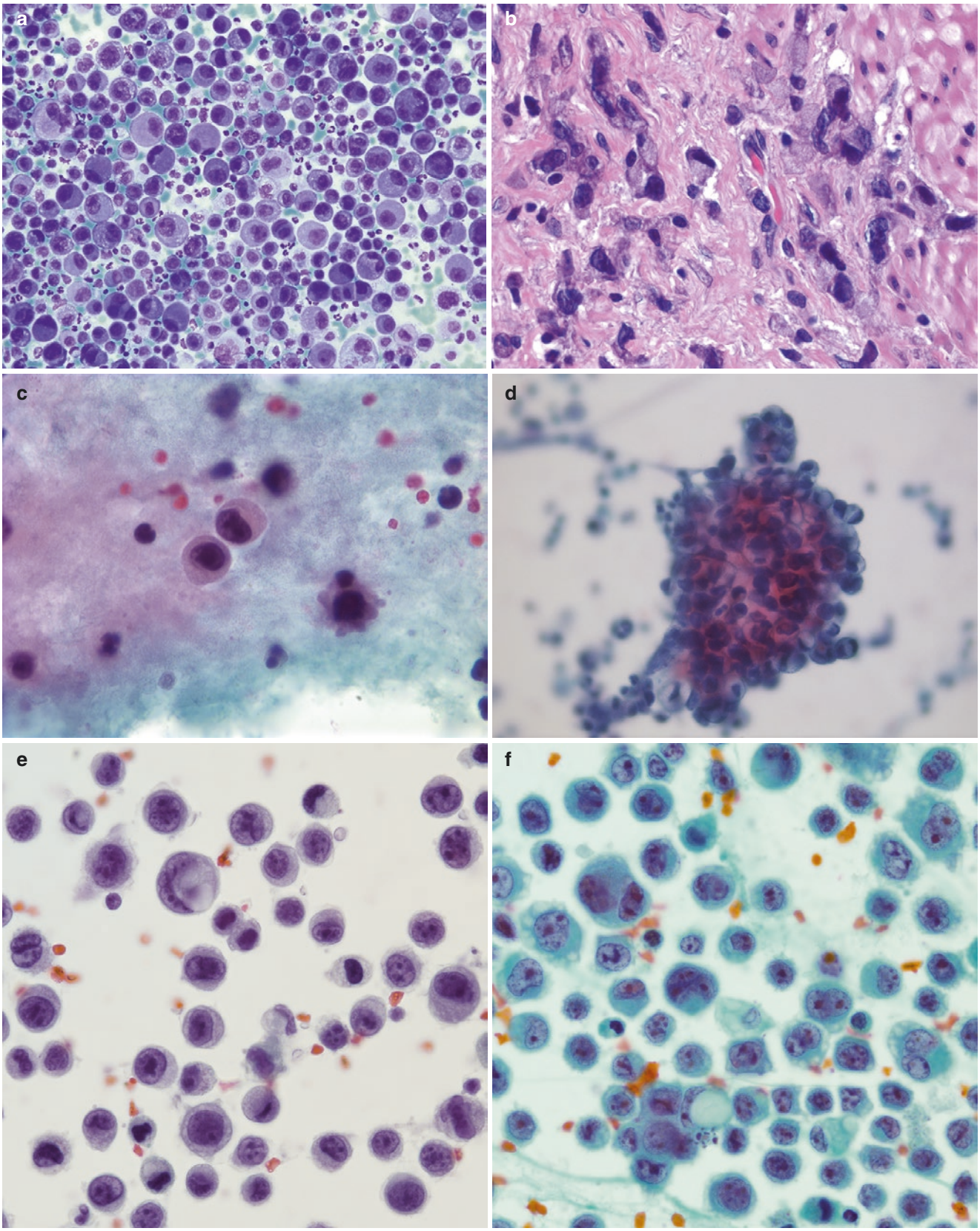


Fig. 7.1 Gastric carcinoma: (**a**) highly cellular specimen with dissociated tumor cells; (**b** and **c**), matched effusion (**b**) and gastric resection (**c**) from a patient with adenocarcinoma of the diffuse infiltrating type; (**d**) cohesive cell group; (**e** and **f**) prominent atypia; (**g**) signet ring cells; (**h**) binucleation; (**i**) mitosis. (**a**) MGG/Diff-Quik; (**b**) H&E; (**c**–**i**) PAP

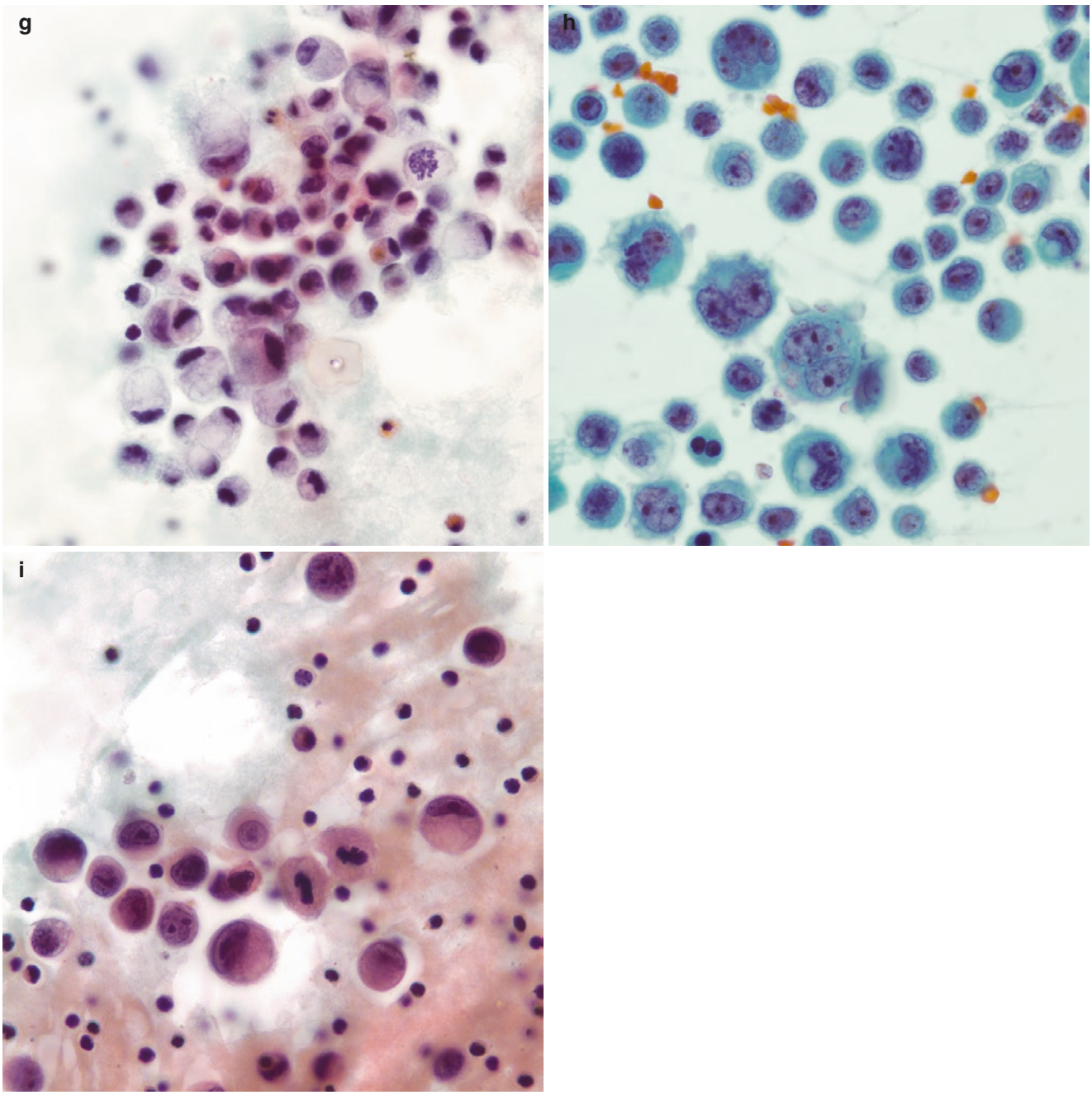


Fig. 7.1 (continued)

Colon Carcinoma, Tumors of the Appendix, and Pseudomyxoma Peritonei

Colorectal cancer (CRC), constituting for all practical purposes of adenocarcinomas, is the third most common malignancy in men worldwide, ranking second in women. It is the fourth and third most common cause of cancer-associated deaths in the two genders [1]. Unlike gastric and pancreatic cancer, effective screening available for this disease has led to reduced mortality. Metastatic disease in treated by chemotherapy, to which in recent years targeted therapy has been added, predominantly aimed at inhibition of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) [20].

Colon carcinoma may occasionally be found in effusion specimens, most frequently in the peritoneal cavity. Tumor cells are usually columnar and large, forming glandular, acinar, or papillary structures (Fig. 7.3a–d), but may be smaller and in more tightly arranged groups (Fig. 7.3e). Intracytoplasmic mucous vacuoles of various size may be evident (Fig. 7.3f–h). Nuclear palisading, nuclear membrane irregularities with indentations and lobulations, and apical cytoplasmic densities have been described as characteristic for adenocarcinomas of colonic origin [6, 21]. As in other

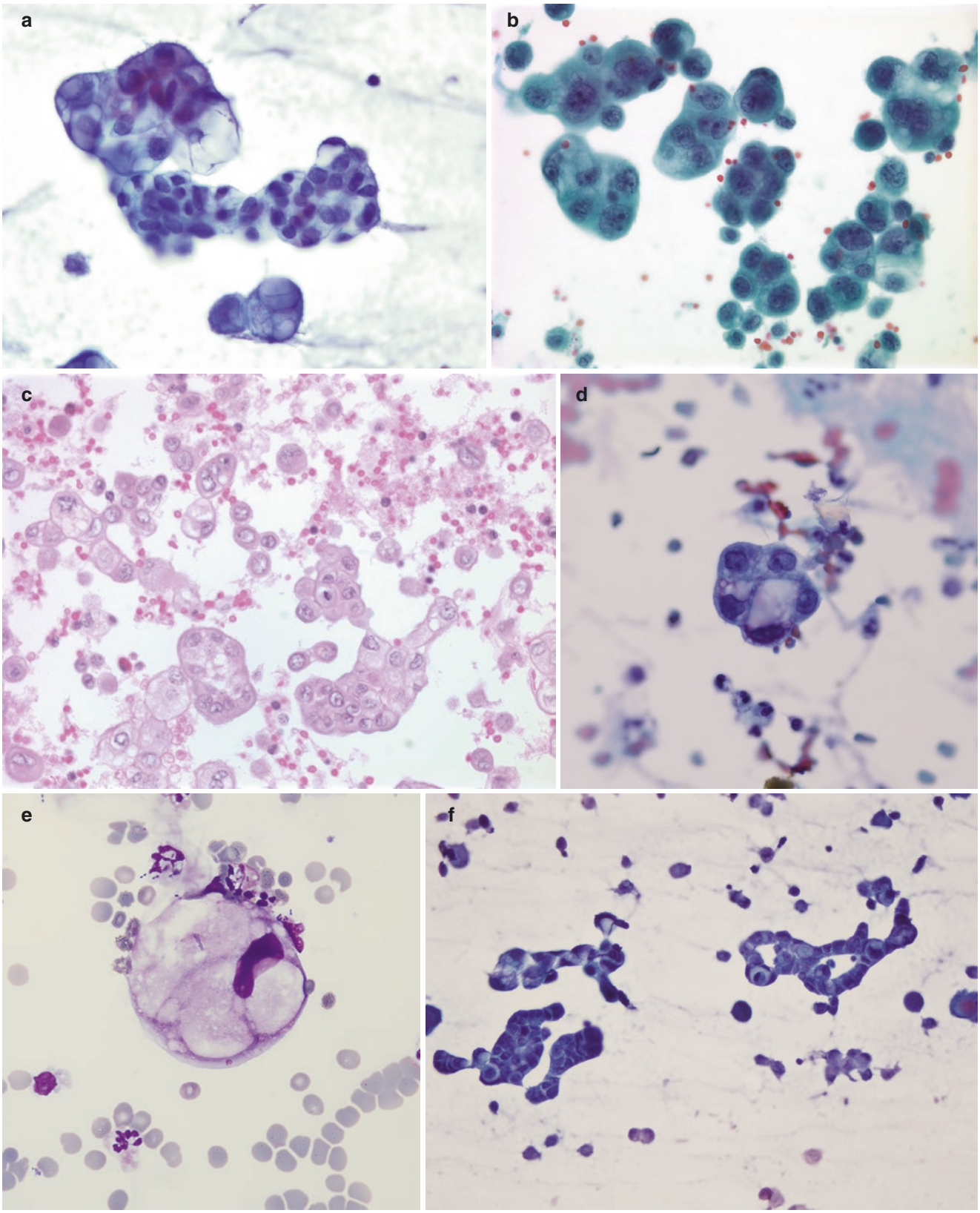
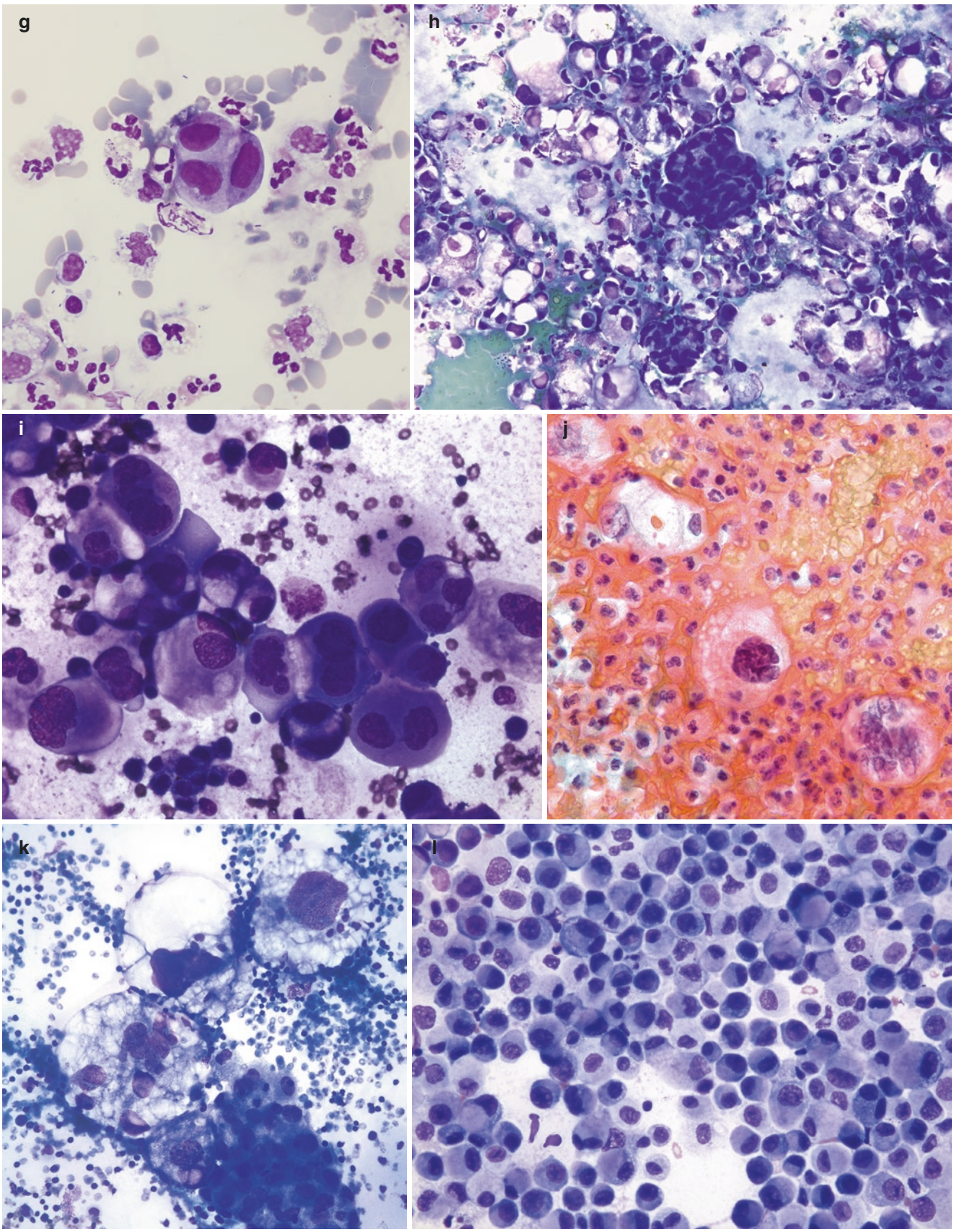


Fig. 7.2 Pancreatic carcinoma: (**a**–**c**) papillary groups; (**d**, **e**) vacuolated cells; (**f**) acinar groups; (**g**) small cohesive group; (**h**) tumor showing both dissociated cells and cohesive groups; (**i**) pronounced atypia; (**j**, **k**) pleomorphic cells; (**l**) dissociated poorly differentiated carcinoma. (**a**, **b**, **d**, **f**) PAP; (**c**, **j**) H&E; (**e**, **g**–**i**, **k**, **l**) MGG/Diff-Quik



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gastrointestinal tumors, pleomorphic cells, signet ring morphology, or dissociated poorly differentiated cells may be encountered in less differentiated tumors (Fig. 7.3f–j).

Pseudomyxoma peritonei (PMP) is characterized by the presence of mucinous ascites and diffuse peritoneal involvement in the form of mucin-containing nodules of variable size. While some foci may contain only mucin and host cells (fibroblasts, mesothelial cells, leukocytes), the majority contain neoplastic mucinous epithelium with a variable degree of atypia. The primary tumor is localized in the appendix in the majority of cases, although dissemination from other primary sites, mainly the ovary and colon, is occasionally seen. Ronnett et al. divided these cases into diffuse peritoneal adenomucinosis (DPAM) and peritoneal mucinous carcinomatosis (PMCA) based on the diagnosis of the primary appendiceal tumor (adenoma vs. carcinoma) and the abundance of epithelial elements, degree of atypia, and mitotic activity in the peritoneal lesions [22]. Differences in survival between these two groups were seen in this report, as well as in subsequent studies [22, 23]. New guidelines for classification and reporting of this tumor were recently published [24]. Among the changes in this document, low-grade and high-grade mucinous carcinoma peritonei were accepted as alternatives to the adenomucinosis and carcinomatosis terms, respectively, and PMP was defined as malignant disease [24].

In the largest study of cytological specimens to date, Jackson et al. reviewed 67 peritoneal washing specimens from PMP patients [25]. Epithelial elements were found in 63 specimens, whereas the remaining 4 contained only mucin. Good agreement was seen between the histological and cytological specimens in differentiating DPAM from PMCA.

In the Jackson series, tumor cells in DPAM cases were characterized by cohesive clusters or monolayered (honeycomb) sheets of cells with discrete cell borders; uniform small, round nuclei with smooth nuclear membranes and inconspicuous nucleoli; and absence of mitotic figures and single tumor cells. In PMCA specimens, tumor cells were found as single cells, small three-dimensional clusters, or irregular sheets. Cells were enlarged and had overlapping nuclei with irregular nuclear membranes, irregular chromatin, and variably sized nucleoli. Signet ring cells and mitotic figures were occasionally found [25].

In a recent report, tumor cells were found in cytological specimens from 18/21 patients, and the presence of higher cellularity was associated with more aggressive disease [26]. A PMP specimen from one of the authors' archive is shown in Fig. 7.3k.

A more rare diagnosis is the finding of a goblet cell carcinoid (adenocarcinoid) in effusion specimens. Only isolated reports of this entity have been published in the literature [27–31], and one of the authors diagnosed an additional specimen in a pleural effusion. These are aggressive tumors which combine the morphological features and immunohistochemical profile of carcinoid and mucinous carcinoma. Wojcik and Selvaggi observed clusters of uniform small cells containing nuclei with finely granular chromatin, small prominent nucleoli, and scant cytoplasm admixed with signet ring cells [27]. Others observed coarse hyperchromasia and nuclear overlap and molding [28] or the additional presence of larger cells with abundant granular cytoplasm, bean-shaped to round nuclei, and prominent eosinophilic nucleoli. Gland-like formations were found, some with eosinophilic material [29]. A tumor with predominant signet ring cell morphology and aggressive clinical behavior was recently described [31]. Our specimen consisted of cohesive groups of variable size, with cells that had vacuolated and eosinophilic cytoplasm, nuclei with relatively little atypia, but with rather conspicuous nucleoli (Fig. 7.3l, m).

Rare reports of dissemination from other non-pulmonary neuroendocrine tumors have been published, including metastasis from a thymic carcinoid in pleural effusion [32] and positive peritoneal cytology from two patients with non-functioning pancreatic endocrine tumors and one with ileal carcinoid [33]. In the latter paper, the cytological features were not described.

Hepatocellular Carcinoma (HCC)

HCC is the sixth most common and ranks third as cause of death worldwide, with more than 700,000 cases diagnosed in 2008. Considerable geographic variation exists, with the majority of cases diagnosed in Asia or in sub-Saharan Africa. Etiological factors include infection with hepatitis B and C viruses, alcoholism, and aflatoxin B1 exposure, as well as diabetes. HCC is a highly aggressive cancer developing most frequently in the context of pre-existing cirrhosis. Prognosis is extremely poor, especially in the presence of extrahepatic disease, and has not been significantly improved by chemotherapy. However, follow-up of individuals at risk by ultrasonography allows for diagnosis at earlier stages, in which surgery may be curative. Sorafenib, inhibitor of Raf kinase and receptor tyrosine kinases, has been shown to prolong survival in advanced disease [34].

The diagnostic yield of ascites from patients with liver disease was shown to be low.

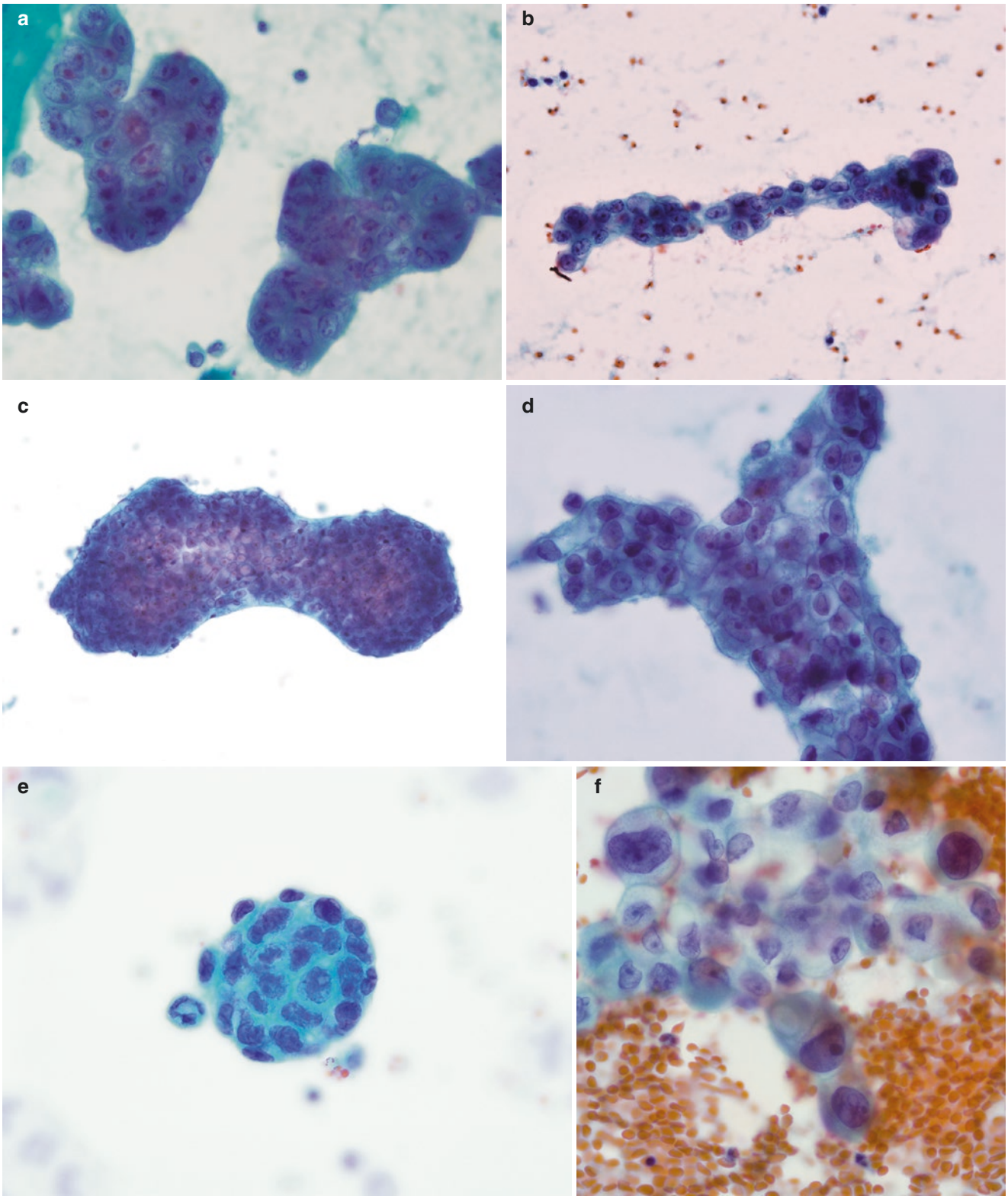
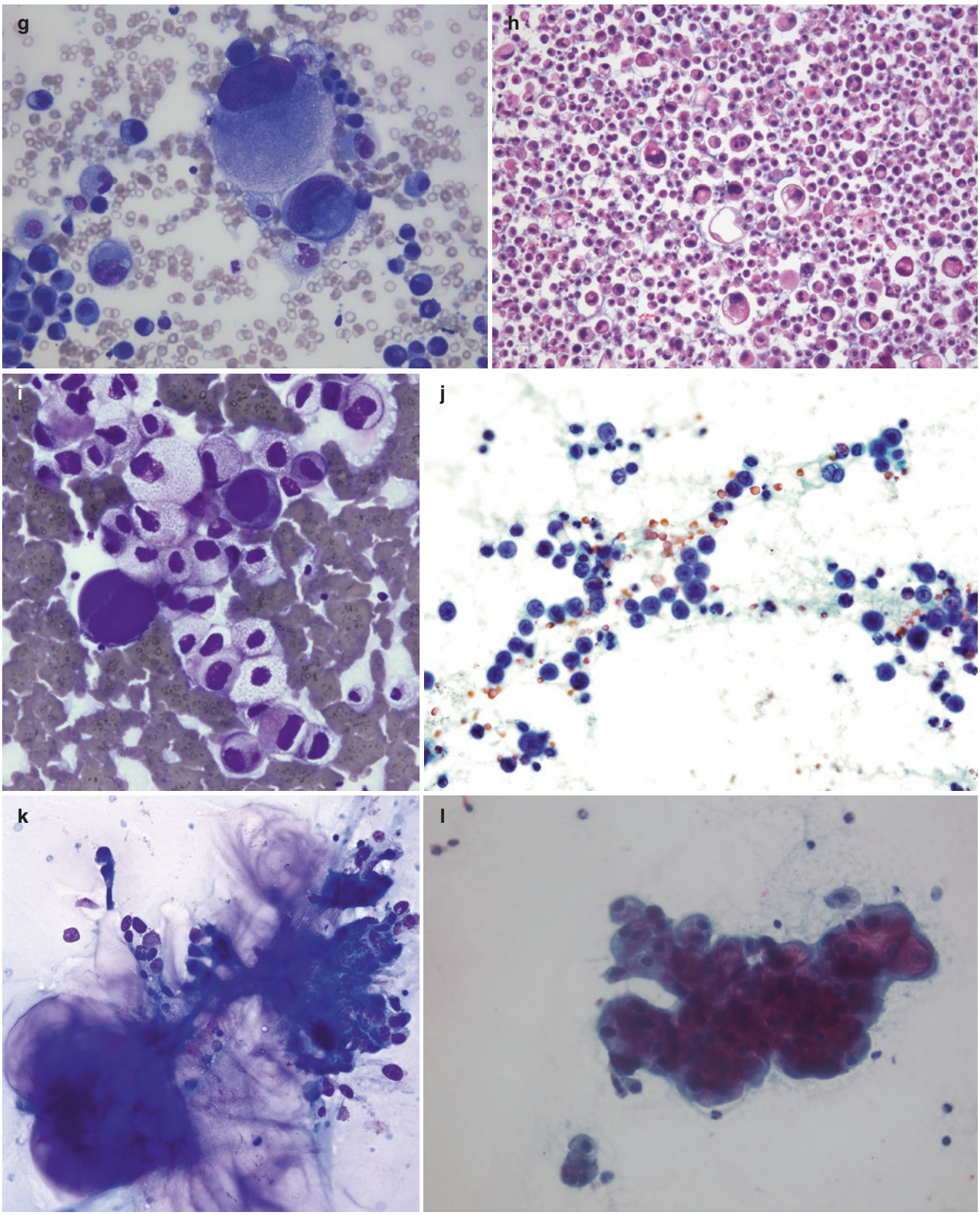


Fig. 7.3 Colon carcinoma: (**a**–**e**) glandular, acinar, papillary, or tight groups; (**f**–**h**) vacuolated cells; (**i**) pronounced atypia; (**j**) dissociated poorly differentiated carcinoma; (**k**) pseudomyxoma peritonei with copious mucin; (**l**, **m**) goblet cell carcinoid showing papillary group (**l**) and vacuolated cells with neuroendocrine features (**m**). (**a**–**f**, **j**, **l**) pap; (**g**, **i**, **k**) MGG/Diff-Quik; (**h**, **m**) H&E



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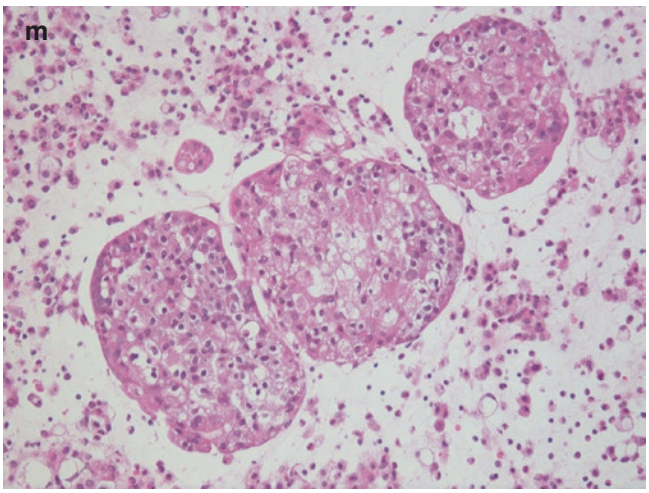

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Analysis of 167 specimens from 133 patients, including 17 with suspected HCC and 2 in which this diagnosis was previously made, resulted in no positive specimens [35].

Falconieri et al. reviewed smears from 106 patients with autopsy-proven HCC, of which 11 were positive. These had variable cellularity, with round or linear aggregates of polygonal cells with hyperchromatic or vesicular nuclei and inconspicuous nucleoli. Reactive changes were frequent [36]. Other authors noted a more frequent presence of neutrophils in the absence of superinfection in HCC ascites compared to specimens from patients with cirrhosis [37]. Two cases of sarcomatous HCC were reported [38]. Metastasis from a poorly differentiated HCC was diagnosed by one of the authors. In this effusion, the tumor consisted of large, highly atypical cells with irregular nuclear contours. Cells had variable n/c ratio, chromatin texture, and nucleolar size (Fig. 7.4a–d).

A case of cholangiocarcinoma effusion consisting of tumor cells with high n/c ratio, large nucleoli, and intracytoplasmic vacuoles, lying singly or in small groups, is shown in Fig. 7.4e, f. Another specimen, with immunostains, is shown in Fig. 7.4g–j.

A case of hepatoblastoma, the most common malignant liver tumor in children, was recently diagnosed by one of the authors. Tumor cells had epithelial morphology and nuclei with coarse chromatin and prominent nucleoli and was positive for Hep-Par1 (Fig. 7.4k–m).

Esophageal Carcinoma

Esophageal cancer, another highly aggressive gastrointestinal cancer, ranks as the ninth most common and sixth cause of death worldwide. Squamous cell carcinoma, which affects primarily the upper and middle two-thirds of the esophagus, is the most common histological type worldwide, whereas adenocarcinoma, which affects the middle and distal two-thirds of the organ, is the most common one in the USA and Europe. The proportion of the latter has been on the rise in recent years. Both entities are more common in men. Squamous cell carcinomas are strongly related to environmental factors, including smoking, alcohol consumption, exposure to very hot beverages, nitrosamines, and vitamin and mineral deficiency. Consumption of red meat increases disease risk, while fruit and vegetables have a protective effect. Adenocarcinomas are strongly related to gastroesophageal reflux and the presence of Barrett's esophagus, as well as to obesity, whereas consumption of fruit and vegetables and *Helicobacter pylori* infection are protective [39].

Malignant effusions due to metastatic esophageal carcinoma are infrequent. In a series of 85 patients with malignant pleural effusion, only 1 patient had a primary tumor of the esophagus [40].

Renshaw et al. reviewed 70 effusion specimens from 45 patients with biopsy-proven esophageal carcinoma [41]. Only 1 of 17 specimens from patients with squamous cell carcinoma contained tumor cells, compared to 21 of 53 effusions from adenocarcinoma cases. The latter were morphologically similar to adenocarcinomas of other origin, although some specimens were hypocellular, with few carcinoma cells.

The morphology of esophageal adenocarcinoma in effusions is as variable as it is in metastases from other organs. Cells may form cohesive groups with cells having irregular nuclei with vesicular chromatin and prominent nucleoli (Fig. 7.5a). Larger, more dissociated cells with mucin vacuoles of variable size may be seen (Fig. 7.5b), as well as areas with extracellular mucin (Fig. 7.5c). The primary tumor in this case was a well-differentiated adenocarcinoma (Fig. 7.5d). Other specimens consist of small cell groups or dissociated cells with high n/c ratio and very prominent nucleoli (Fig. 7.5e, f).

The squamous cell carcinoma case described by Renshaw had only three malignant cell groups, in which tumor cells had scant eosinophilic cytoplasm, high n/c ratio, and large hyperchromatic and irregular nuclei [41].

Differential Diagnosis

The majority of metastatic adenocarcinomas of gastrointestinal origin present with easily identifiable malignant cells, making the possibility of a reactive effusion improbable, whereas a minority contain fewer tumor cells. Notably, reactive mesothelial cells in several conditions related to gastrointestinal malignancy, such as cirrhosis, may be extremely atypical, as are mesothelial cells exposed to chemotherapy and radiation. The previously discussed guidelines related to

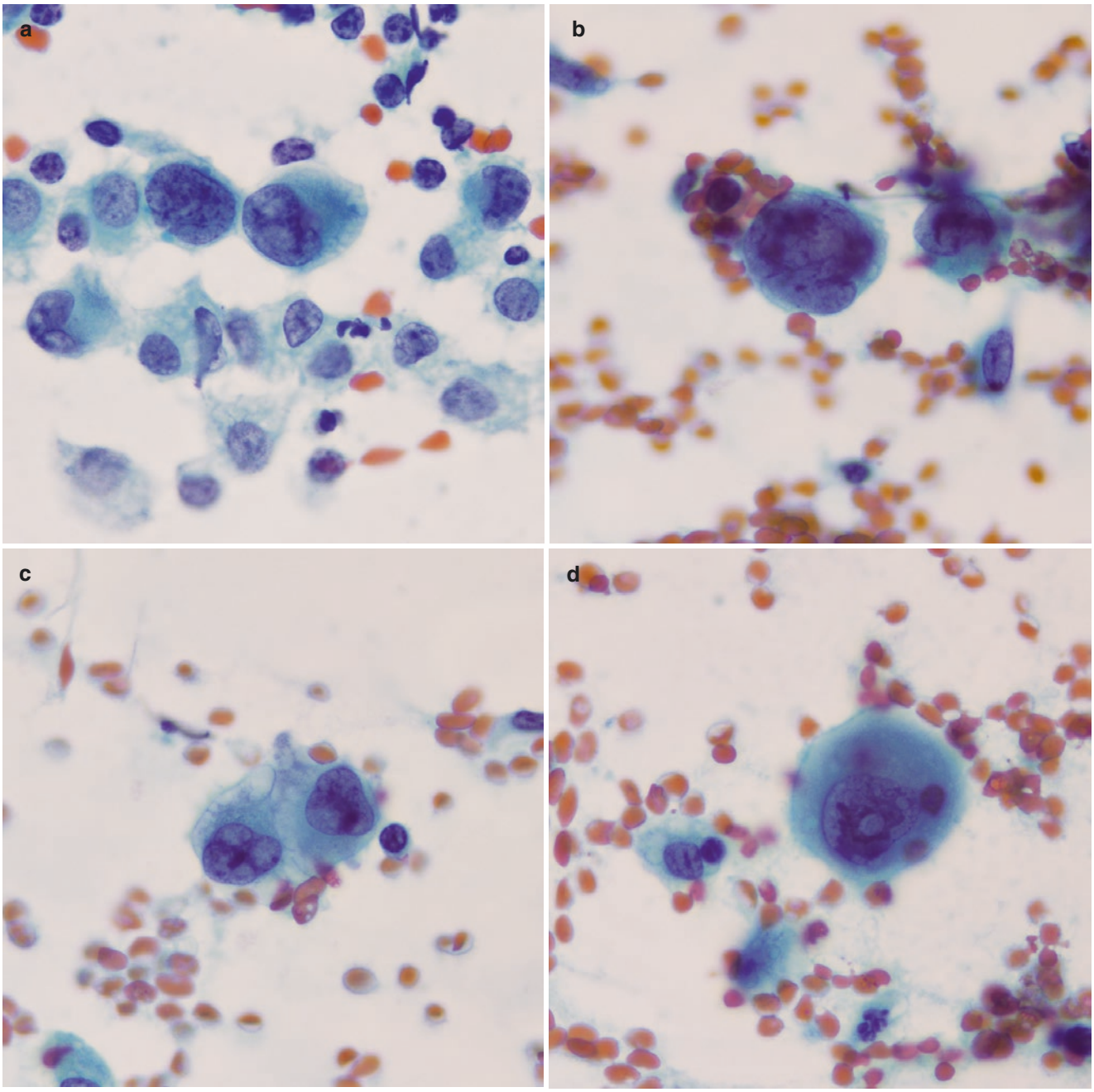
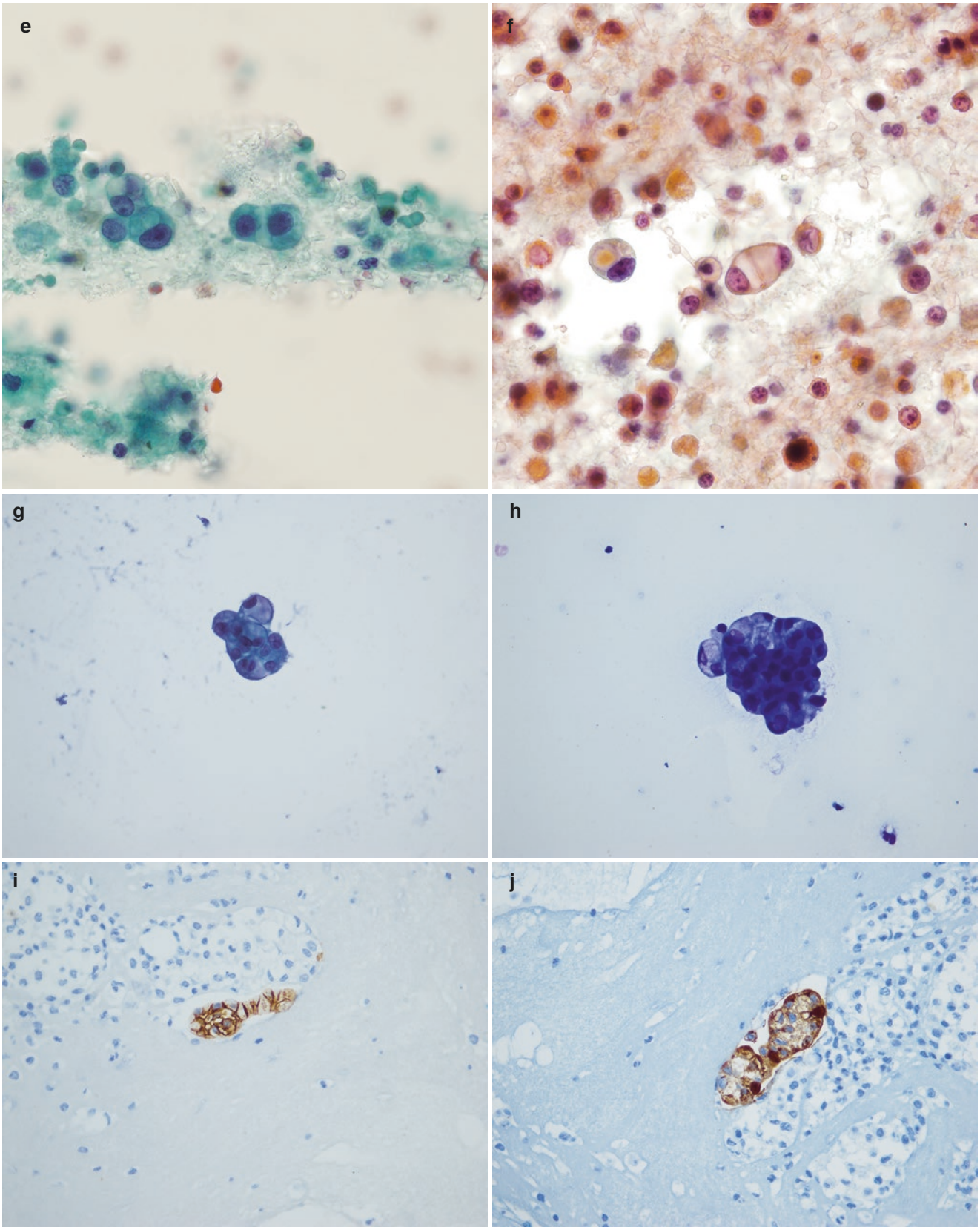


Fig. 7.4 Liver carcinoma: (**a**–**d**) *hepatocellular carcinoma*. Large and overtly atypical cells, lying singly or in small groups, with variable amount of lacy, occasionally vacuolated cytoplasm, some with very high n/c ratio. (**e**–**j**) *cholangiocarcinoma*, consisting of smaller cells with intracytoplasmic vacuoles pushing the nuclei. The latter are a clue for the true nature of the cells, despite the presence of doublets that may mimic mesothelial cells (**f**). (**a**–**g**) PAP; (**h**) MGG/Diff-Quik; (**i**) Ber-EP4; (**j**) B72.3. (**k**–**m**) *hepatoblastoma*. Tumor cells have epithelial morphology and nuclei with coarse chromatin and prominent nucleoli. (**k**) PAP; (**l**) H&E; (**m**) Hep-Par1



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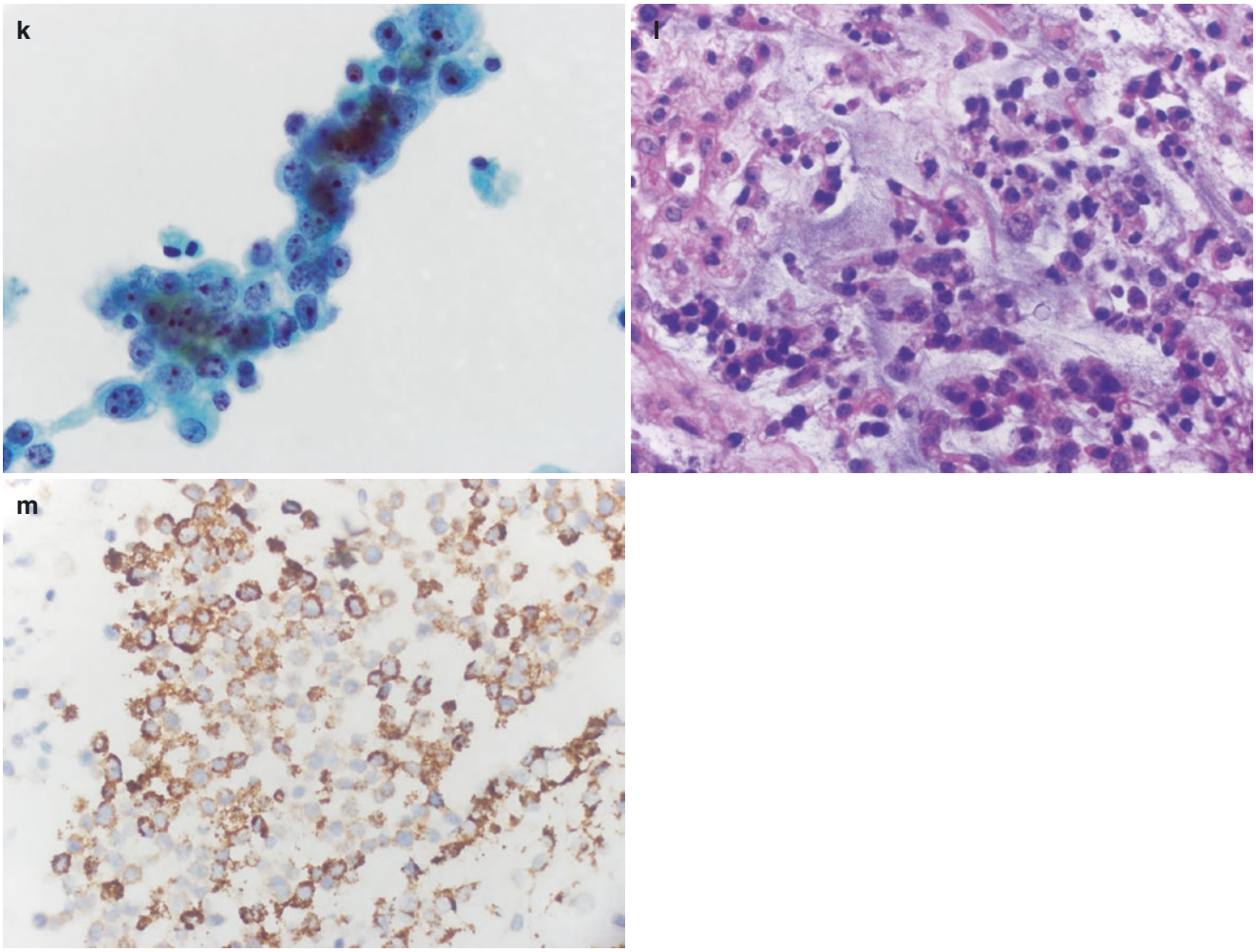


Fig. 7.4 (continued)

identification of foreign cell population and pattern recognition apply to the diagnosis of these tumors in the same manner they are relevant for the diagnosis of other metastases. The immunohistochemical panels used for diagnosing effusions as adenocarcinoma are presented in the **Appendix** of **Part I**. Mucin stains may also be helpful (Fig. 7.6a).

Well- and moderately differentiated tumors that are recognized as adenocarcinoma need to be differentiated from metastases from other organs, primarily from gastrointestinal tumors of other origin, as well as lung, breast, and ovarian carcinoma. Poorly differentiated tumors, especially with single-lying tumor cells, must be differentiated from any malignant tumor, including carcinoma, mesothelioma, hematological malignancies, germ cell or stromal sex-cord tumors of the ovary, sarcoma, and melanoma. The choice of immunohistochemical panel should be directly influenced by the likelihood that a given tumor is *not* an adenocarcinoma. Markers expressed by tumors of gastrointestinal origin are CDX-2, Villin, CEA, and mucins (Fig. 7.6b–e), as well as SATB2 in colon carcinoma. None of these is entirely specific, although strong expression of CDX-2 in the nuclei of all tumor cells is strongly suggestive of gastrointestinal origin. These markers are additionally poorly informative with respect to which organ along the gastrointestinal tract is the primary tumor site, as esophageal, gastric, pancreatic, and intestinal tumors have overlapping expression profiles. CK7/CK20 immunostaining may aid in localizing the primary tumor to the colon, as the majority of colonic adenocarcinomas are CK7-negative and CK20-positive (Fig. 7.6f). However, gastric, pancreatic, biliary, and esophageal carcinomas, as well as ovarian mucinous carcinomas, may have similar profile, with diffuse CK7 expression and focal or negative CK20 expression. HCC presents a distinct entity, as it expresses tumor markers shared by few other cancers, such as α-feto protein, glypican-3, Hep-Par1, and arginase-1 (see also Chap. 12). The above-discussed hepatoblastoma similarly expressed Hep-Par1 (Fig. 7.4m).

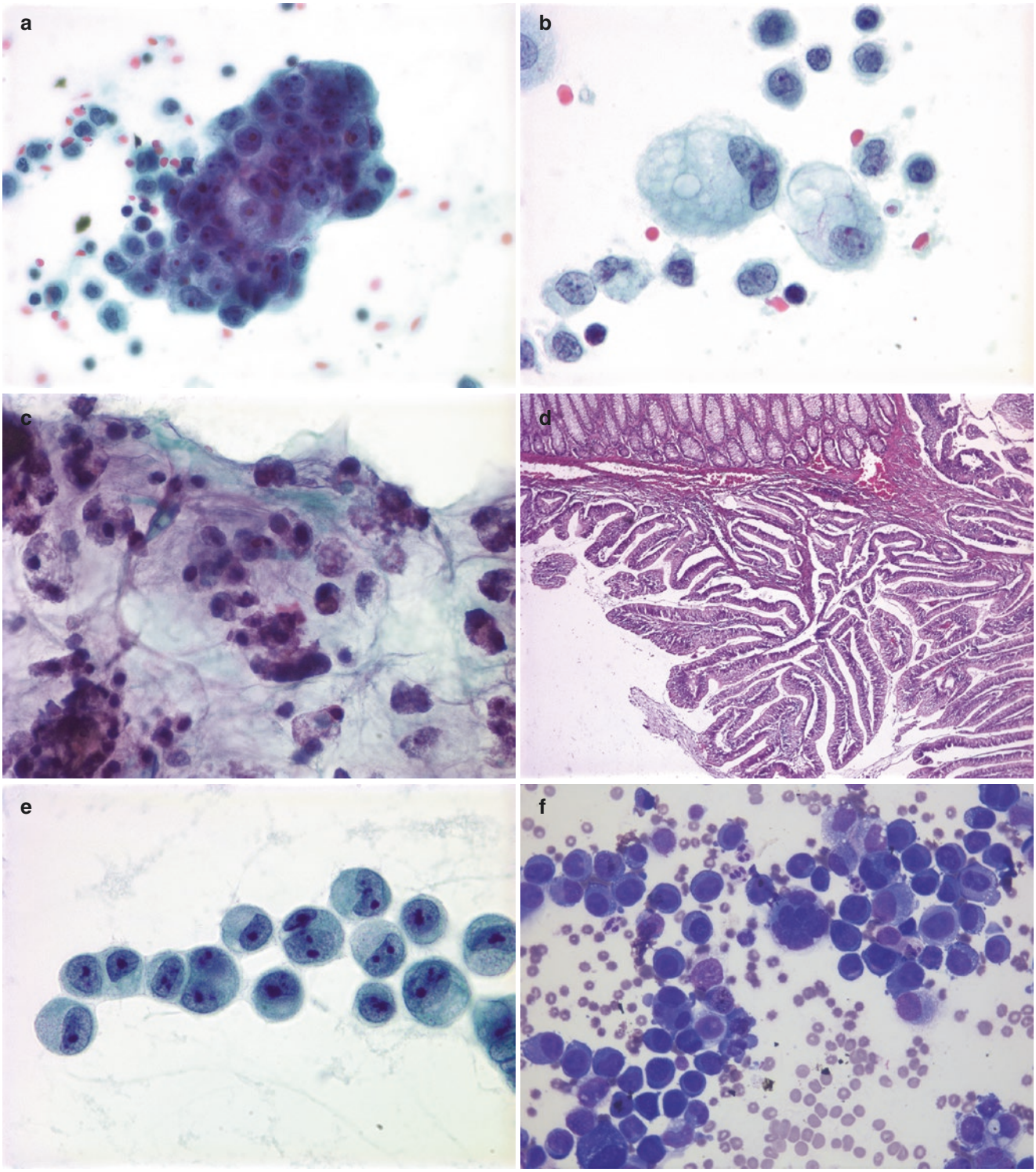


Fig. 7.5 Esophageal carcinoma: (**a**) cohesive group; (**b**) single cells of variable size, some vacuolated; (**c**) mucin with embedded tumor cells; (**d**) the primary well-differentiated esophageal adenocarcinoma; (**e**) carcinoma cells with pronounced atypia; (**f**) dissociated poorly differentiated carcinoma. (**a–c**, **e**) PAP; (**d**) H&E; (**f**) Diff-Quik

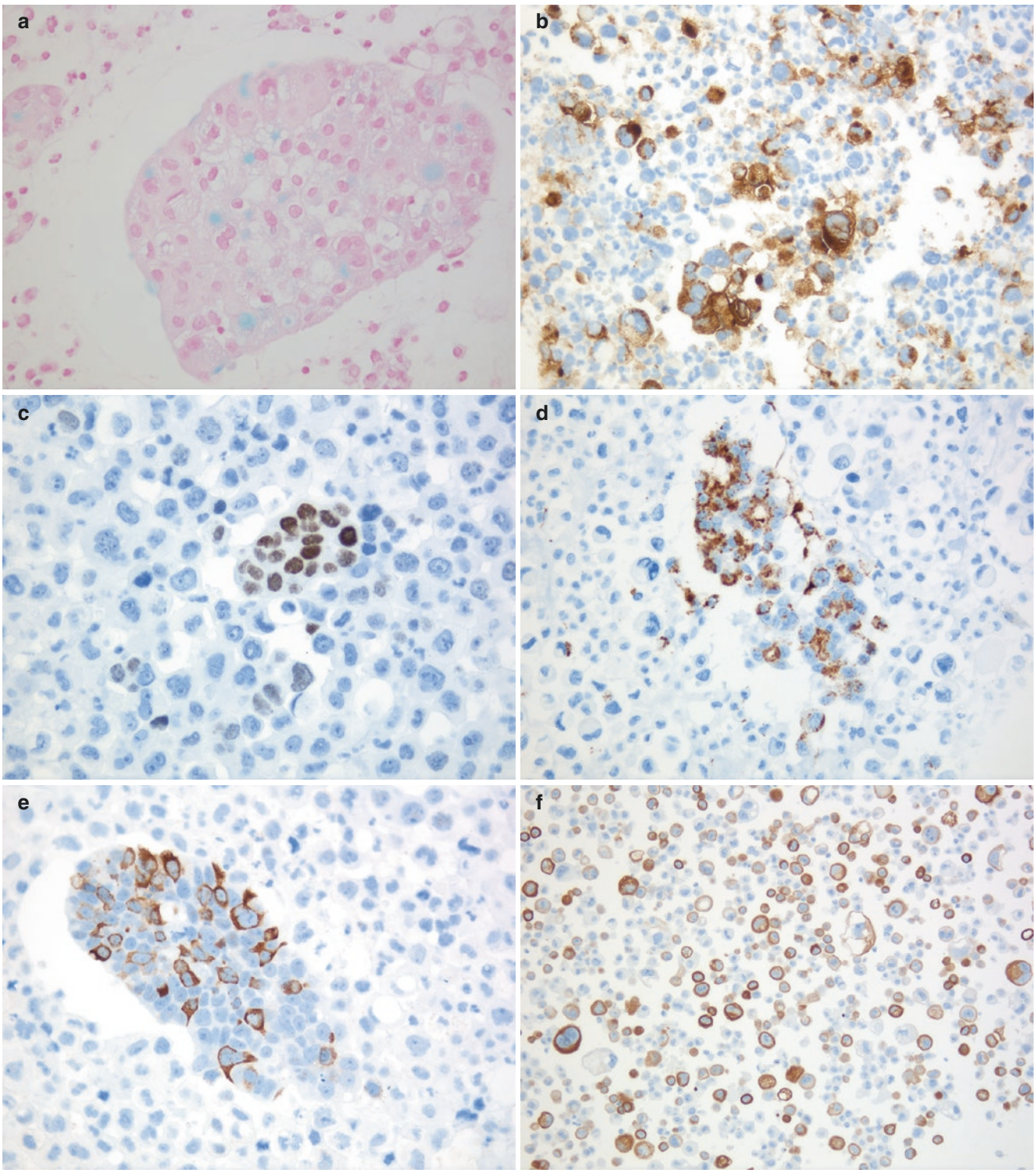


Fig. 7.6 Histochemistry and immunohistochemistry in gastrointestinal cancers: (**a**) alcian blue stain in goblet cell carcinoid; (**b**) CEA in gastric carcinoma; (**c**) CDX-2 in esophageal adenocarcinoma; (**d**) MUC5AC in gastric carcinoma; (**e**) MUC2 in esophageal carcinoma; (**f**) CK20 in colon carcinoma

Negative markers that may be helpful in excluding gastrointestinal origin are lung carcinoma markers, including TTF-1, surfactant, and Napsin A; breast carcinoma markers such as GATA3, AP-15 (GCDFP-15), and mammaglobin; female genital carcinoma markers, including PAX8, WT-1, and Napsin A; renal cell carcinoma markers such as PAX8, RCC, and CA IX; and urothelial carcinoma markers such as GATA3 and Uro-II (see other chapters and **Appendix** in this section). Staining for hormone receptors may be helpful but should be interpreted cautiously, as some non-gynecologic tumors may express estrogen or progesterone receptor.

The rare squamous cell carcinomas of esophageal origin in effusion need to be differentiated from the more common tumors of pulmonary origin and rare metastases from head and neck and uterine cervix carcinoma. Relevant clinical information is usually available in such cases.

Carcinomas of the Uterine Cervix and Corpus

Uterine cervix and uterine corpus cancer, consisting predominantly of carcinomas, are both common, ranking fourth and sixth in incidence in women worldwide. However, whereas cervical cancer is the fourth in causing cancer-related deaths, uterine corpus is not among the ten most common causes of cancer mortality globally and ranks tenth in developed countries [1]. This difference reflects both geographic variation and the biology and clinical behavior of these tumors. Cervical cancer is more common in developing countries, where both screening and treatment are sub-optimal, whereas uterine corpus cancer more often affects women in developing countries, where access to medical treatment is better [1]. Additionally, most uterine corpus carcinomas are diagnosed at earlier stage and consist of grade 1–2 endometrioid carcinomas, tumors that are less aggressive compared to carcinomas in other organs.

Metastatic spread from carcinoma of the uterine corpus or cervix to the serosal cavities is less common than in ovarian carcinoma, but is by no means a rare event, especially in the former cancer. Tumors of both origins are most frequently diagnosed in peritoneal effusions or washings, but dissemination to the pleural, and less frequently to the pericardial cavity, has been reported [42–51]. A case of metastatic cervical squamous cell carcinoma in a pericardial effusion was seen by one of the authors (Fig. 7.7a–c).

The vast majority of adenocarcinomas of the uterine corpus that are diagnosed in effusions originate from type II tumors, i.e., serous, clear cell, or poorly differentiated (grade 3) endometrioid carcinomas, although metastasis from type I carcinomas infrequently occurs. These tumors are morphologically impossible to differentiate from their counterparts of ovarian origin (see **Part I**, Chap. 3) (Fig. 7.7d-g).

Metastasis from cervical carcinoma more frequently originates from adenocarcinomas. The morphology of these tumors is usually nondescript and does not differ from that of other adenocarcinomas in effusions (Fig. 7.7h, i). Clinical data are therefore central to establishing the cervix as site of origin. Immunohistochemistry may be helpful, as discussed below.

Squamous cell carcinomas of cervical origin similarly resemble their counterparts in other organs (Fig. 7.7j–l). They may be of keratinizing or non-keratinizing type. Single cells or clusters of variable size are seen, as well as intercellular windows and cell-within-cell arrangement that may cause confusion with reactive mesothelial cells [42].

Rare reports describing the presence of other types of cervical carcinoma in effusions have been published. Metastasis from a mesonephric carcinoma in pleural effusion was reported [52]. Two cases of small cell neuroendocrine cervical carcinoma, of which one was in ascites and one in a pleural effusion, were described. The tumor presented with single cells with little molding, morphologically resembling lymphoma [53]. A primary cervical clear cell carcinoma with metastasis in ascites was reported [54], as well as recurrence of a primary cervical serous carcinoma in ascites [55]. One of the authors diagnosed a metastasis from a mucinous cervical carcinoma in a peritoneal effusion (Fig. 7.7m, n), as well as ascites with metastasis from a cervical adenocarcinoma with neuroendocrine differentiation (Fig. 7.7o, p).

Differential Diagnosis

The majority of grade 1–2 endometrioid adenocarcinomas of the uterine corpus stain immunohistochemically positive for hormone receptors, PAX8, and vimentin, stain in a patchy pattern for p16, have wild-type p53 staining pattern, and show loss of PTEN and occasionally of ARID1A. They may be positive for HNF1β. Grade 3 endometrioid adenocarcinomas more often have aberrant (strongly and diffusely positive or completely absent) p53 expression and stain diffusely and strongly for p16, as do serous carcinomas. Clear cell carcinomas express Napsin A and HNF1β and may have loss of ARID1A. They are usually negative for hormone receptors, with variable p16 and p53 pattern. None of these features is particularly helpful in differentiating these tumors from their counterparts in the ovary/tube/peritoneum, although WT1 tends to be less expressed in serous carcinomas of uterine corpus origin compared to their adnexal or peritoneal counterparts. These stains may nonetheless help in excluding adenocarcinomas of other origin.

Both squamous cell carcinoma and adenocarcinoma of the cervix are often positive for CEA, p16, and CK7, and squamous cell carcinomas additionally express CK5/6, p63, and p40, while adenocarcinomas are positive for CK8 and

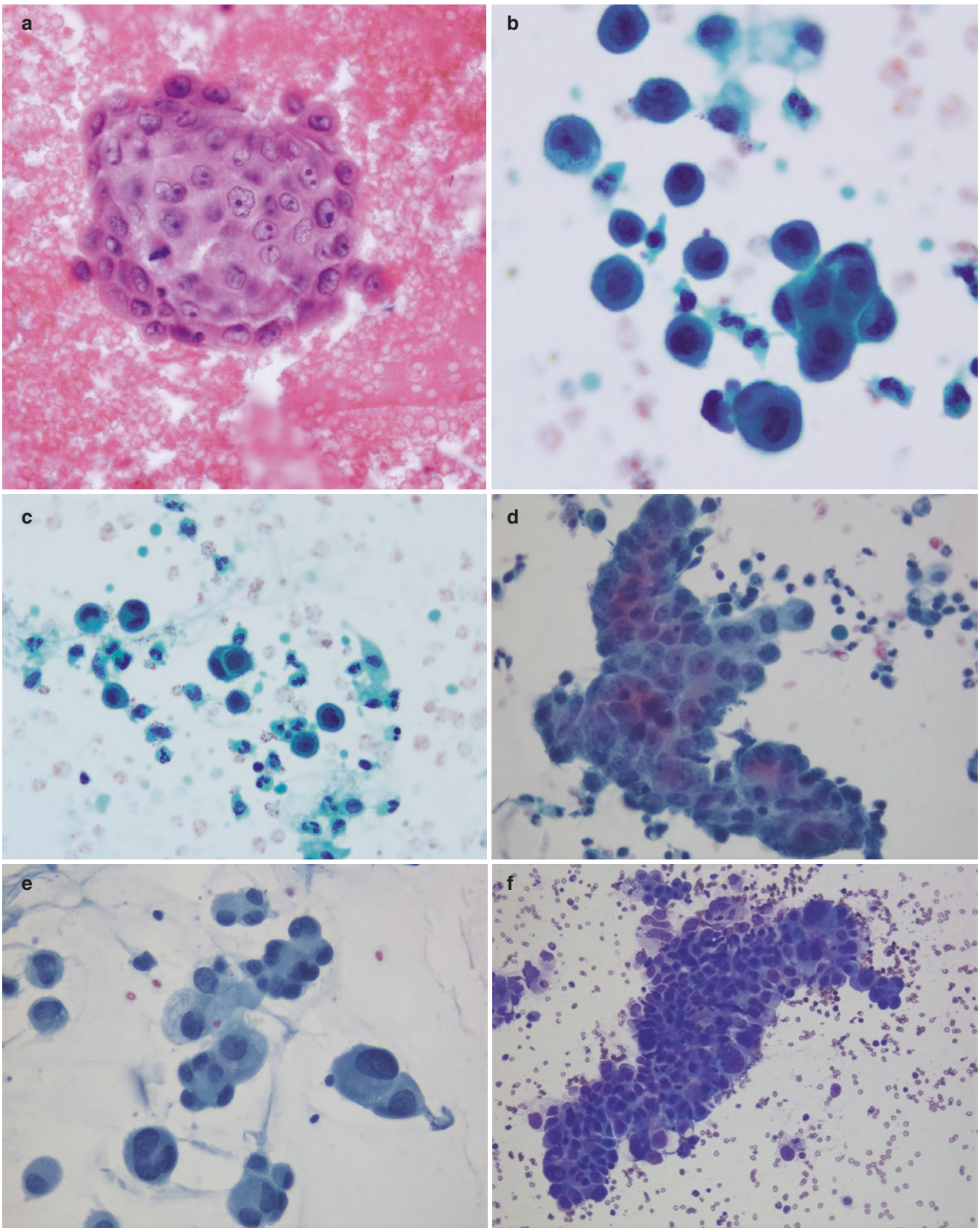
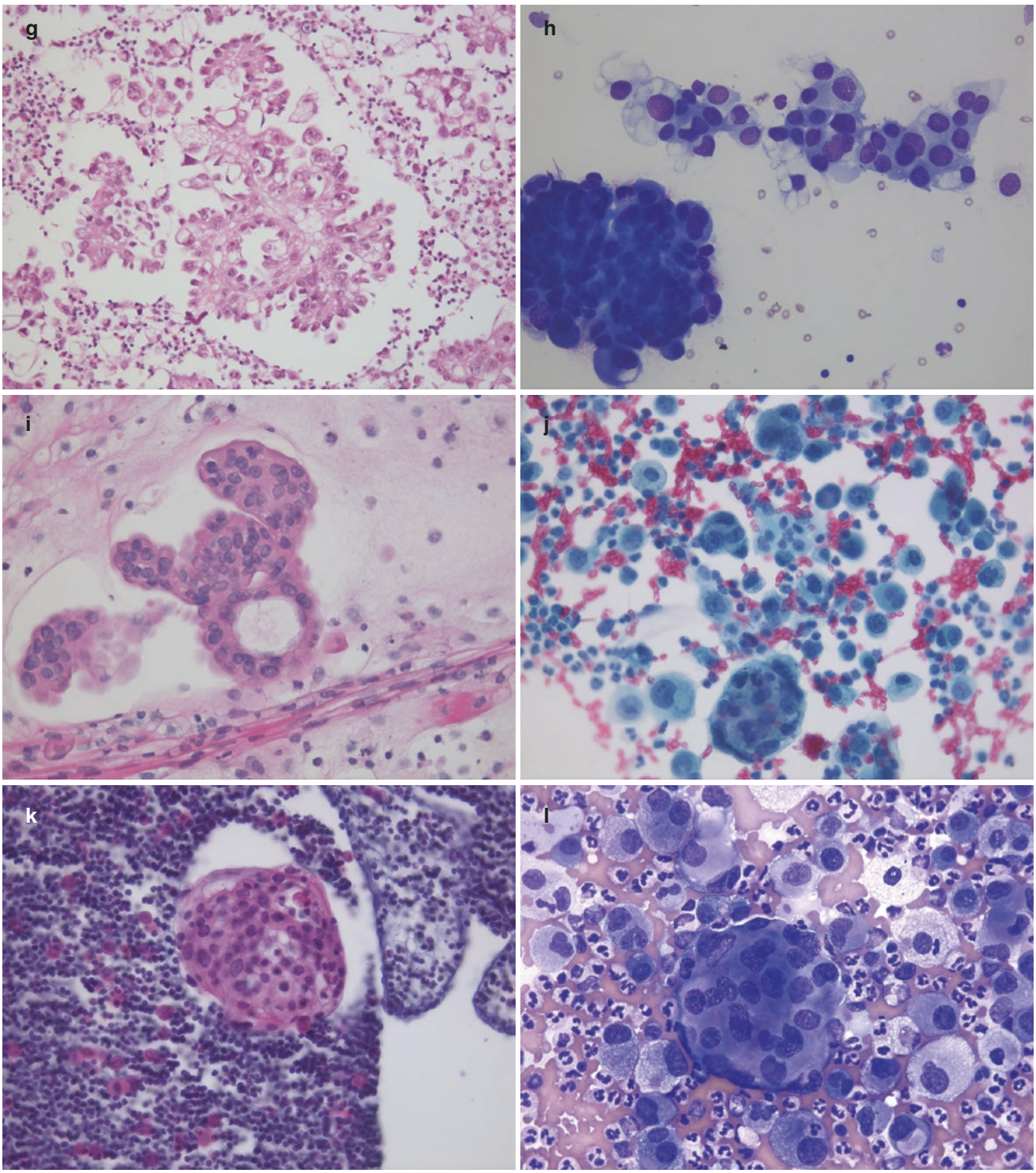


Fig. 7.7 Cervical and endometrial carcinoma: (**a**–**c**) cervix squamous cell carcinoma in pericardial effusion. Note cell-in-cell arrangement in **c**; (**d**) serous carcinoma of the endometrium; (**e**) clear cell carcinoma of the endometrium; (**f**, **g**) Endometrial carcinosarcoma metastasizing as serous adenocarcinoma; (**h**, **i**) cervical adenocarcinoma; (**j**–**l**) cervical squamous cell carcinoma in a peritoneal effusion; (**m**, **n**) cervical mucinous carcinoma; (**o**) cervical adenocarcinoma with neuroendocrine differentiation. (**a**, **g**, **i**, **k**, **n**, **o**) H&E; (**b**–**e**, **j**, **m**) PAP; (**f**, **h**, **l**) Diff-Quik. *Immunohistochemistry*: (**p**) synaptophysin in cervical adenocarcinoma with neuroendocrine differentiation; (**q**–**s**) cervical adenocarcinoma staining for Ber-EP4 (**q**), CEA (**r**), and p16 (**s**); (**t**) p63-positive in cervix squamous cell carcinoma in pericardial effusion



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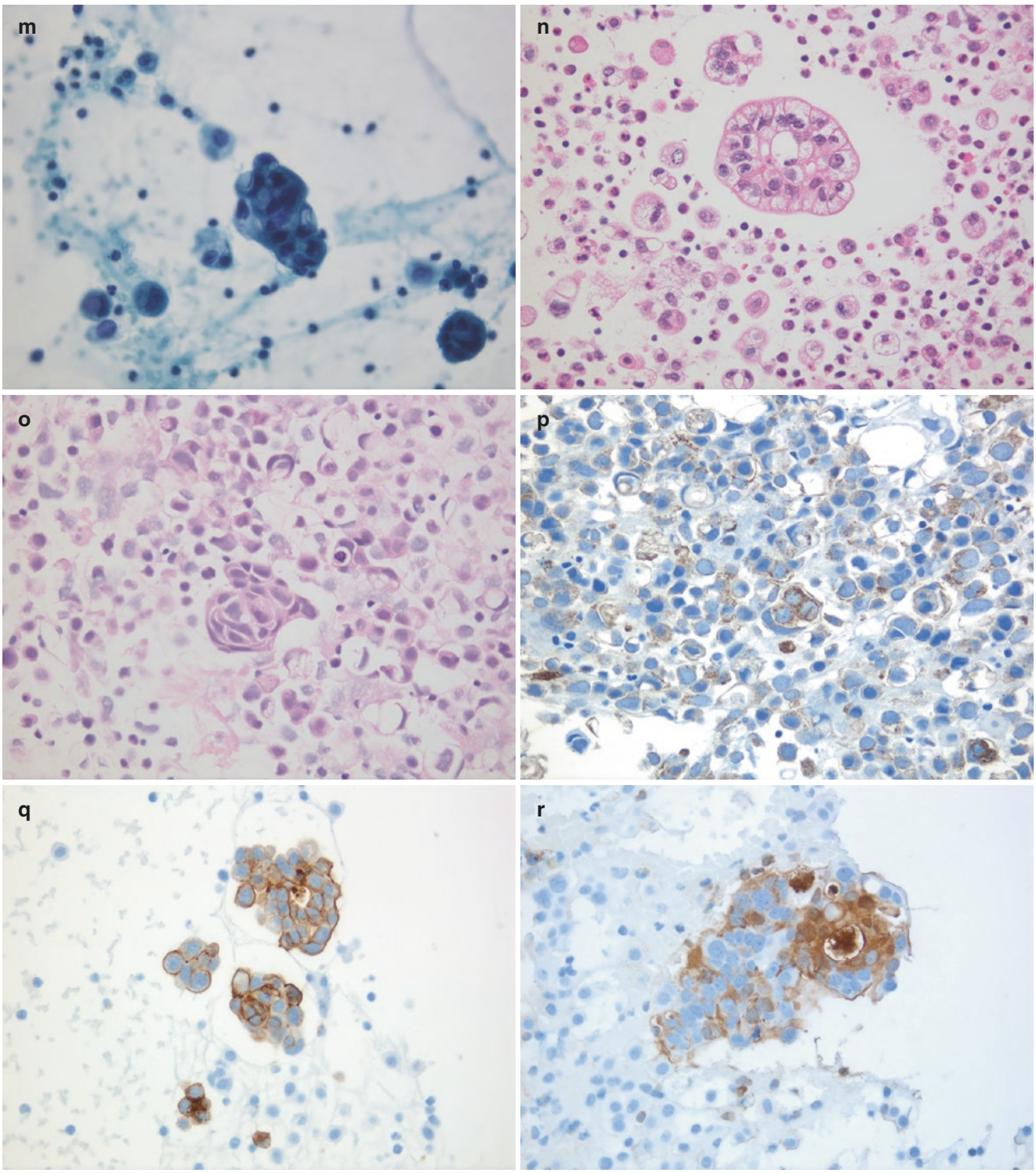

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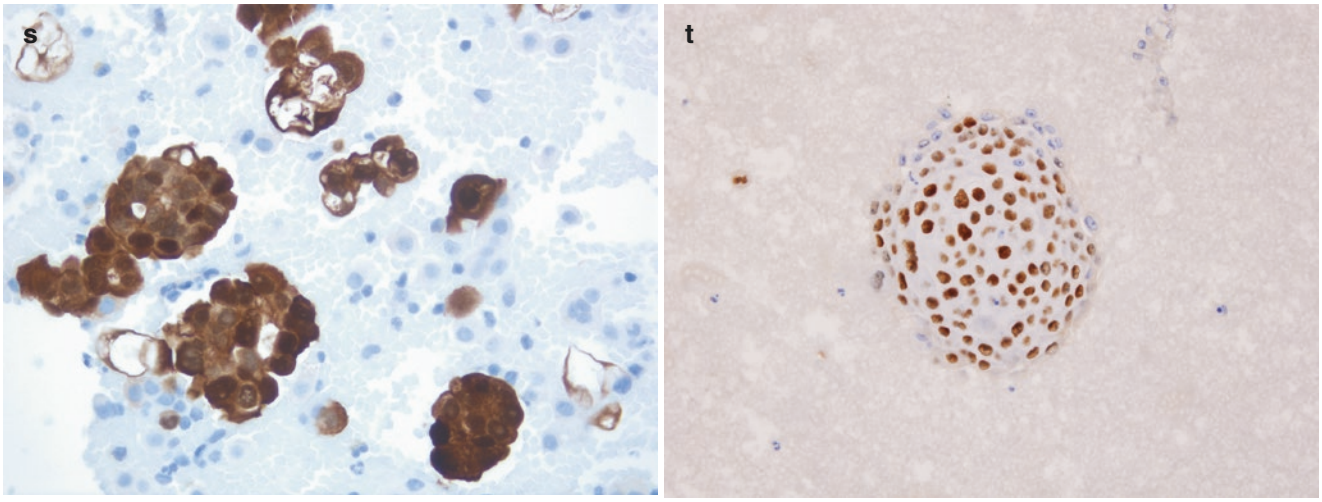

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Ber-EP4 (Fig. 7.7q–t). Overlaps in the staining pattern between these entities are not infrequent. Molecular genotyping for HPV may be of considerable help in establishing the cervical origin of a squamous cell carcinoma or adenocarcinoma.

Genitourinary Carcinomas

Involvement of the serosal cavities by metastatic carcinomas originating in the urinary tract is an infrequent but well-documented entity. In a series of 472 malignant pleural effusions, 6% of metastases in males were from genitourinary organs [56]. The primary tumor may involve any of the genitourinary tract organs, including the kidney, prostate, and urinary bladder. All three serosal cavities may be involved, with pericardial involvement being the least common.

Urinary Bladder Carcinoma

Tumors originating from the urinary bladder are usually transitional cell carcinomas [57–60], although two cases of signet ring cell carcinoma of bladder origin in ascites were described [61, 62], as well as metastasis from a transitional cell carcinoma of the renal pelvis [63].

Transitional cells carcinoma (TCC) may have variable morphologic features. Renshaw reviewed eight pleural effusions from five patients. Tumor cells had squamous or glandular morphology. Eosinophilic inclusions (Melamed-Wolinska bodies), which have been frequently observed in urine specimens and fine needle aspirates, were generally few, and their absence did not exclude the diagnosis of TCC [58]. McGrath et al. reported a case with numerous pleomorphic malignant cells, lying as single cells or in groups, in which numerous intracytoplasmic eosinophilic inclusions with clear halo were found. Few signet ring cells were additionally observed [57]. In the case reported by Fabozzi, tumor cells were found singly or in aggregates and had hyperchromatic nuclei of variable size with abundant cytoplasm. Only one cell had a large cytoplasmic vacuole [59]. Xiao found mostly dispersed tumor cells, as well as occasional small loose clusters, with moderate cellular pleomorphism, binucleation, and cell-in-cell arrangement. Cytoplasmic vacuoles and pseudo-windows were observed. Nuclei were centrally or paracentrally located and enlarged, with coarse chromatin, irregular nuclear membranes, and prominent eosinophilic nucleoli. Mitoses were rare [60].

A specimen with plasmacytoid morphology and another with pseudomesotheliomatous morphology were described [64, 65].

The largest series published to date, analyzed by one of the authors, included 25 specimens (15 pleural, 8 peritoneal, and 2 pericardial effusions) from 20 patients with urothelial carcinoma [66]. The predominant morphological pattern was of a single cell population with or without clusters or short cords, frequently with "cell wrapping." Nuclear enlargement with increased n/c ratio, irregular nuclear membranes, hyperchromatic coarse chromatin, and prominent nucleoli were observed, as were double or multinucleated cells, cells with vacuolated cytoplasm, or signet ring cells. These morphological characteristics were deemed non-specific, emphasizing the importance of patient history and ancillary techniques.

In selected specimens shown in this chapter, cells were predominantly found in clusters of variable size, including papillary structures and looser aggregates (Fig. 7.8a–c). Indian file-like arrangement was seen in one case

(Fig. 7.8d). Nuclei were enlarged, hyperchromatic, and overtly atypical. Nucleoli were prominent and mitoses were readily found (Fig. 7.8e). Distinct cell borders, cytoplasmic vacuolization, and a possible attempt to form eosinophilic vacuoles were additionally seen (Fig. 7.8f). Cell-in-cell arrangement was seen in another specimen (Fig. 7.8g). The degree of atypia appeared somewhat milder in the H&E-stained cell blocks in one case, but mitoses were evident there as well (Fig. 7.8h).

TCC express CK7, CK20, and CEA, as well as high-molecular-weight-keratin 34βE12 and more organ-specific markers such as GATA3, uroplakin II and III, and carbonic anhydrase IX. The combination of CK7, CK20, and CEA generally excludes many of the carcinomas that enter this differential diagnosis (e.g., breast, lung, and colon adenocarcinoma), although exceptions occur, but does not exclude adenocarcinomas of the upper gastrointestinal tract or ovarian mucinous carcinoma. Consequently, the more specific markers are often used to establish urothelial origin. The case shown in Fig. 7.8e, f, h expressed CK7, CK20, and high-molecular-weight keratin 34βE12 (Fig. 7.8i–k) but was negative for CEA and uroplakin III. A tumor with uroplakin II expression is shown in Fig. 7.8l.

Prostate Carcinoma

Prostate carcinoma metastases most frequently involve the pleural cavity [67, 68]. However, Saif reported a case in which malignant ascites was the only manifestation of metastatic disease [69], and a subsequent review of the literature in the years 1969–2005 revealed 12 patients with malignant ascites due to prostate carcinoma, either at diagnosis or at disease recurrence [70]. As with bladder carcinoma, an ascites specimen with signet ring cell morphology was reported [71].

Mai et al. reviewed 50 cytological specimens, including 6 pleural effusions. Tumor cells formed clusters with overlapping nuclei or sheets of cells. The cytoplasm varied from filmy to dense with indistinct cytoplasmic borders. Nuclei were usually round or oval, uniform, and hyperchromatic with a single nucleolus. Multinucleated tumor cells were not seen [67].

Renshaw reviewed 14 pleural effusions from ten patients. Specimens contained isolated tumor cells or small loosely cohesive groups. Cells had scant cytoplasm, round to oval nuclei, irregular nuclear borders, and prominent nucleoli. Three patients had small cell carcinoma, and these metastases were morphologically different [68]. Specimens seen by the authors had comparable morphology to that described in these two series (Fig. 7.9a–d), although mitoses, distinct cell borders, and cytoplasmic clearing were seen in one specimen (Fig. 7.9e). Another tumor had open acinar structures in addition to the more common solid groups (Fig. 7.9f).

Prostate carcinomas express prostate-specific antigen (PSA), p504s (AMACR), prostate-specific acid phosphatase (PAP), prostate-specific membrane antigen (PSMA), and p501S (prostein) [72]. However, negative staining for some of these markers can be seen in adenocarcinoma, particularly metastatic ones. It is therefore advisable to use several markers. One of the above-illustrated cases did express PSA, p504s, and PAP (Fig. 7.9g–i), while others were negative for one or two of these three markers.

Renal Carcinoma

The diagnosis of renal cell carcinoma (RCC) in serous effusions is a relatively rare one. In the series by Sears and Hajdu, 19/812 malignant pleural and 3/456 malignant peritoneal effusions originated from renal adenocarcinomas [73]. In the study by Spieler and Gloor, only 2/448 specimens were from patients with RCC [6].

Renshaw et al. studied eight RCC effusions, consisting of both clear cell and papillary carcinomas, and were able to differentiate these histological types in effusion only when well-defined papillae were present. Specimens had variable cellularity. Tumor cells were single or in clusters and had abundant clear to granular and vacuolated cytoplasm, large nuclei, vesicular or clumped chromatin, and large nucleoli [74]. Gupta et al. recently reported two cases, consisting of one clear cell and one papillary RCC, with emphasis on the occasionally bland morphology of this tumor which may be overlooked [75].

Specimens seen by two of the authors consisted of large cells with ample clear, foamy, or eosinophilic cytoplasm, vesicular nuclei with coarse chromatin, and large nucleoli, lying singly or in groups of variable size (Fig. 7.10a–h).

Several of the less common variants of renal carcinoma, including two cases of chromophobe RCC [76, 77], two cases of medullary carcinoma [78], and two cases of collecting duct carcinoma [79], have been diagnosed in effusions. Drut diagnosed a renal rhabdoid tumor in a 4-month-old patient who later developed malignant pleural effusion [80].

RCC expresses several immunohistochemical markers, including vimentin (Fig. 7.10i), EMA (Fig. 7.10j), PAX8 (Fig. 7.10k), CD10 (Fig. 7.10l), PAX2, and carbonic anhydrase IX (CA IX) (Fig. 7.10m). Chute and co-workers recently analyzed 11 RCC effusions, of which 6 were clear cell carcinomas, 3 papillary, and 2 RCC, not otherwise specified. CD10 and RCC antigen were expressed in 10/11 and 5/11 cases, respectively. PAX2 staining was negative or

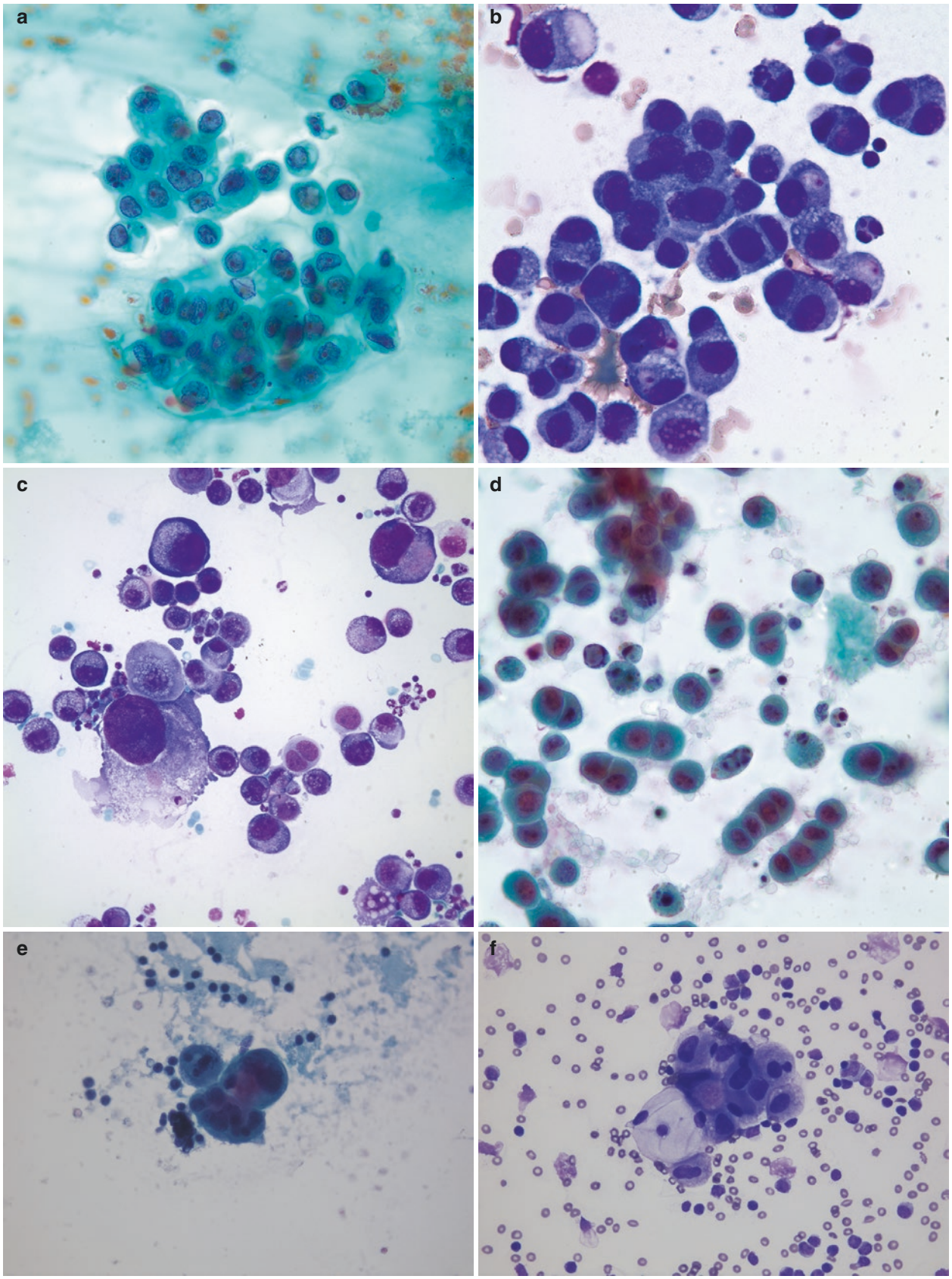
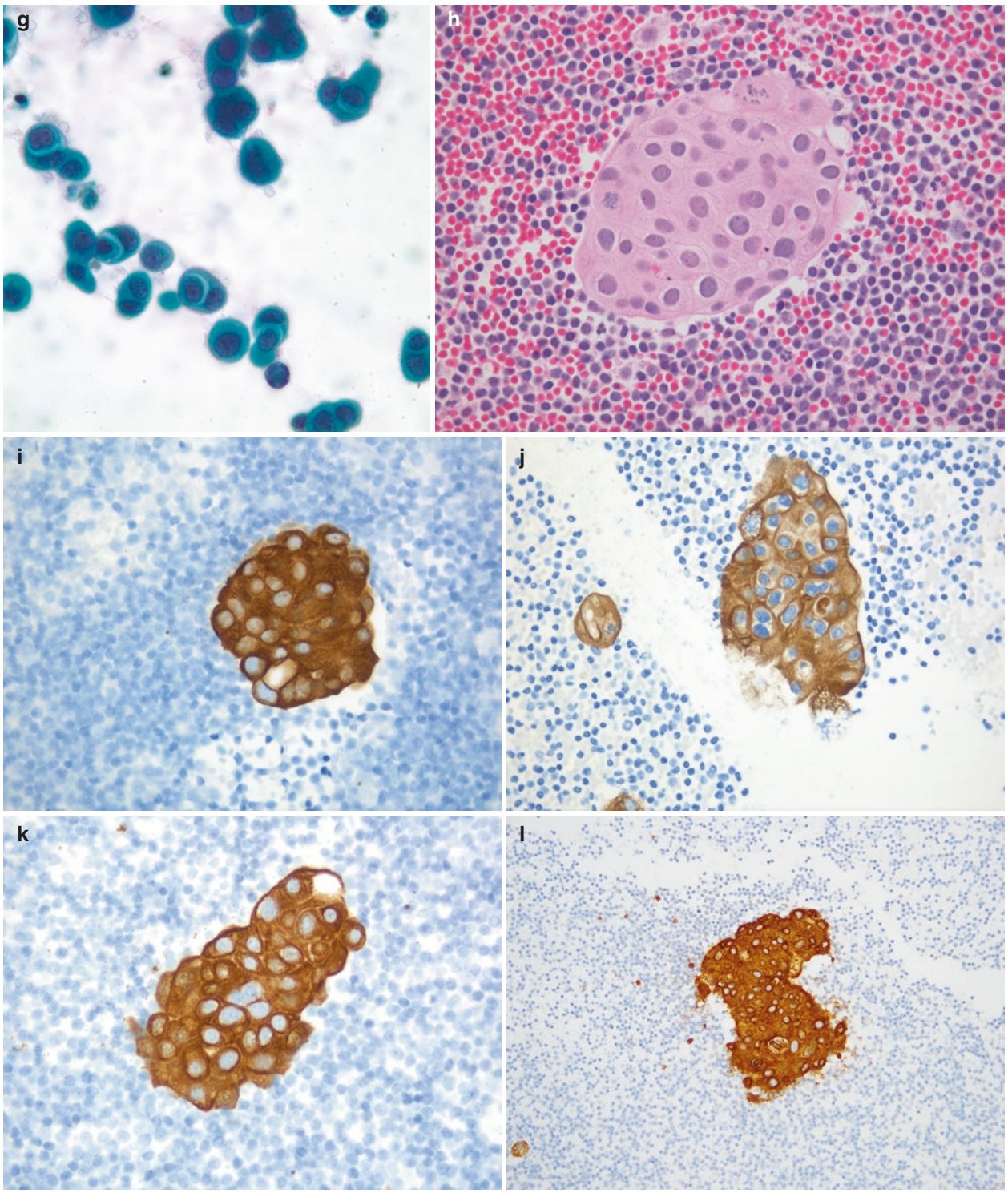


Fig. 7.8 Transitional cell carcinoma: (**a**, **b**) papillary groups; (**c**) vacuolated pleomorphic cells; (**d**–**f**) overtly atypical cells dissociated, in short cords and in small tight clusters. Note attempt to form eosinophilic core in **d**, **e**; (**g**) cell-in-cell arrangement; (**h**) two mitotic figures in a cell group with relatively mild atypia. (**a**, **d**, **e**, **g**) PAP; (**b**, **c**, **f**) MGG/Diff-Quik; (**h**) H&E. *Immunohistochemistry*: staining for CK7 (**i**), CK20 (**j**), and 34βE12 (**k**) in the case shown in **h**. Uroplakin II stain is shown in **l**



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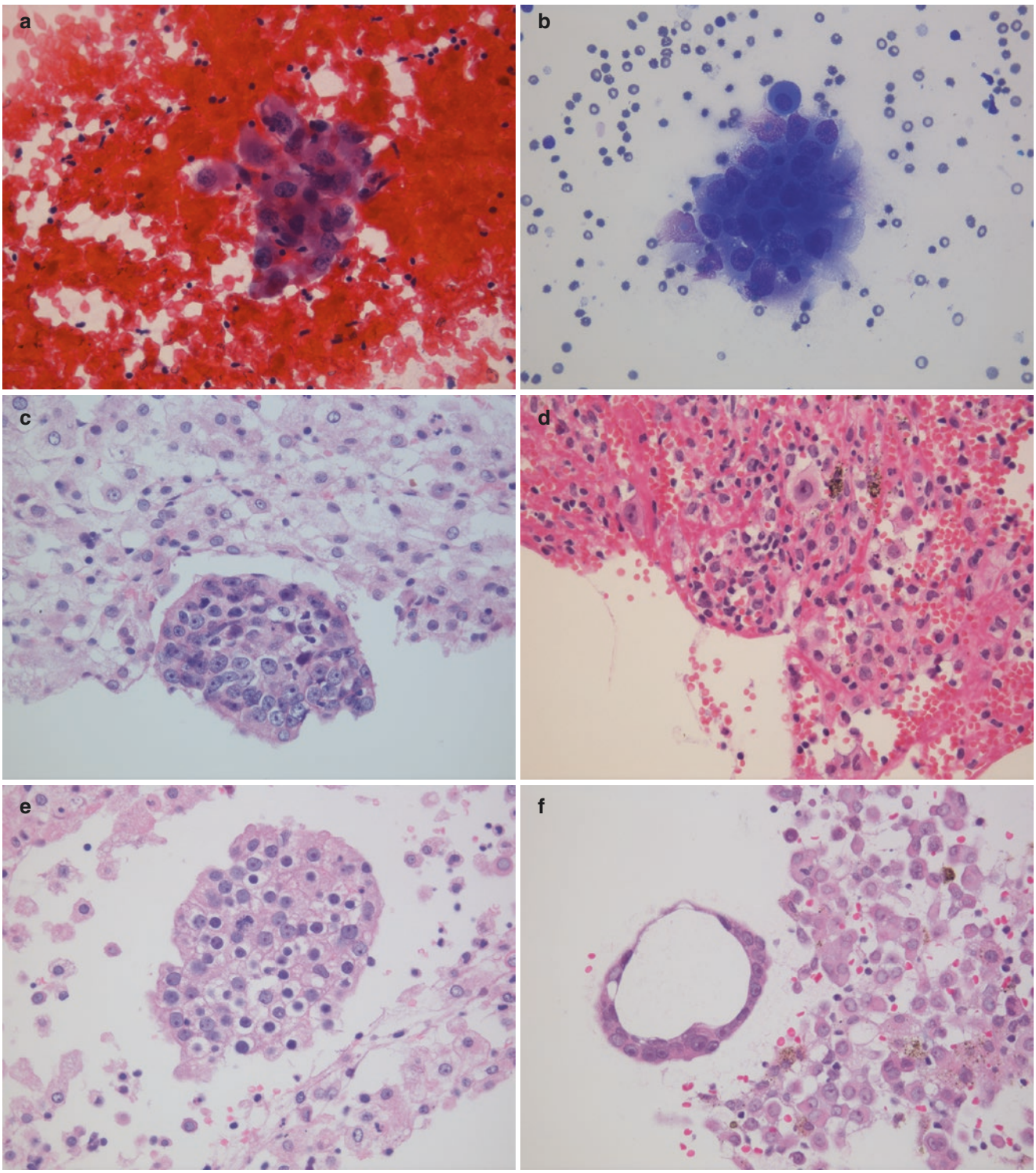


Fig. 7.9 Prostate carcinoma: (**a**–**c**) cohesive groups with atypical tumor cells having prominent nucleoli; (**d**) single-lying tumor cells; (**e**) mitosis; (**f**) open acinar form. (**a**) PAP; (**b**) Diff-Quik; (**c**–**f**) H&E. *Immunohistochemistry*: staining for PSA (**g**), p504s (**h**), and 34βE12 (**i**) in the case shown in **f**

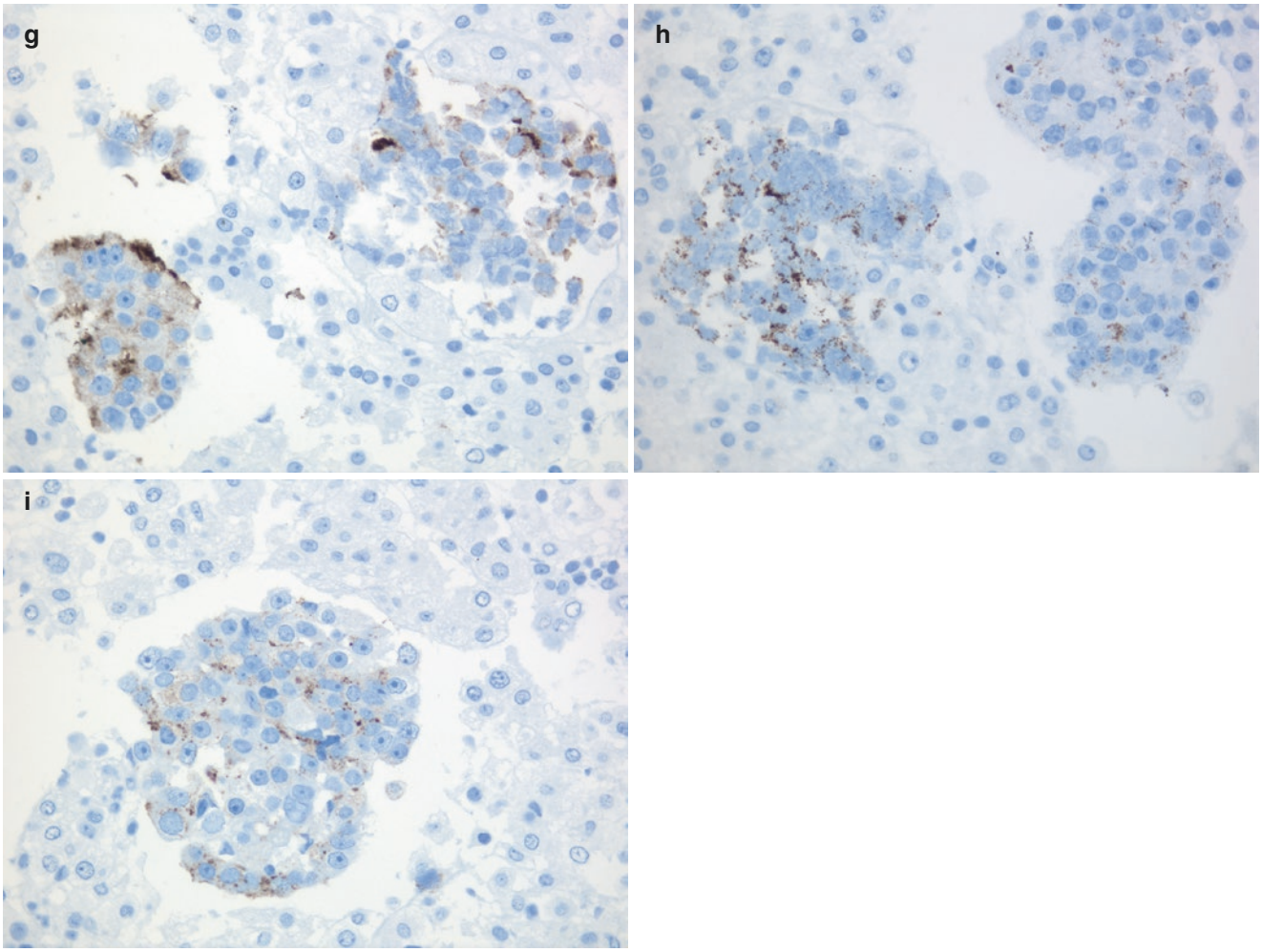


Fig. 7.9 (continued)

equivocal in RCC cells, whereas reactive mesothelial cells had strong cytoplasmic staining [81]. In contrast, in analysis of 24 cytological RCC specimens, including 4 effusions, both PAX2 and PAX8 were found to be sensitive markers, expressed in 83% and 88% of cases, respectively [82]. In the series of Waters et al., all tumors (eight and nine RCC effusions analyzed for PAX2 and PAX8 expression, respectively) were positive for both markers [83]. The single RCC in the series of Wiseman and co-workers expressed PAX8 and was negative for PAX2 [84], and the single RCC in the Tong series was similarly PAX8-positive [85].

Other Cancers

Germ Cell Tumors

Spreading of germ cell tumors to effusions is well-recognized and has been documented in both large series and case reports [86–96]. The majority of these tumors had their primary site in the ovary, although metastasis from other organs, mainly from the testis, has been reported. The series of Hajdu and Nolan included a total of 58 positive effusions from patients with germ cell tumors, including 26 pleural, 30 peri-

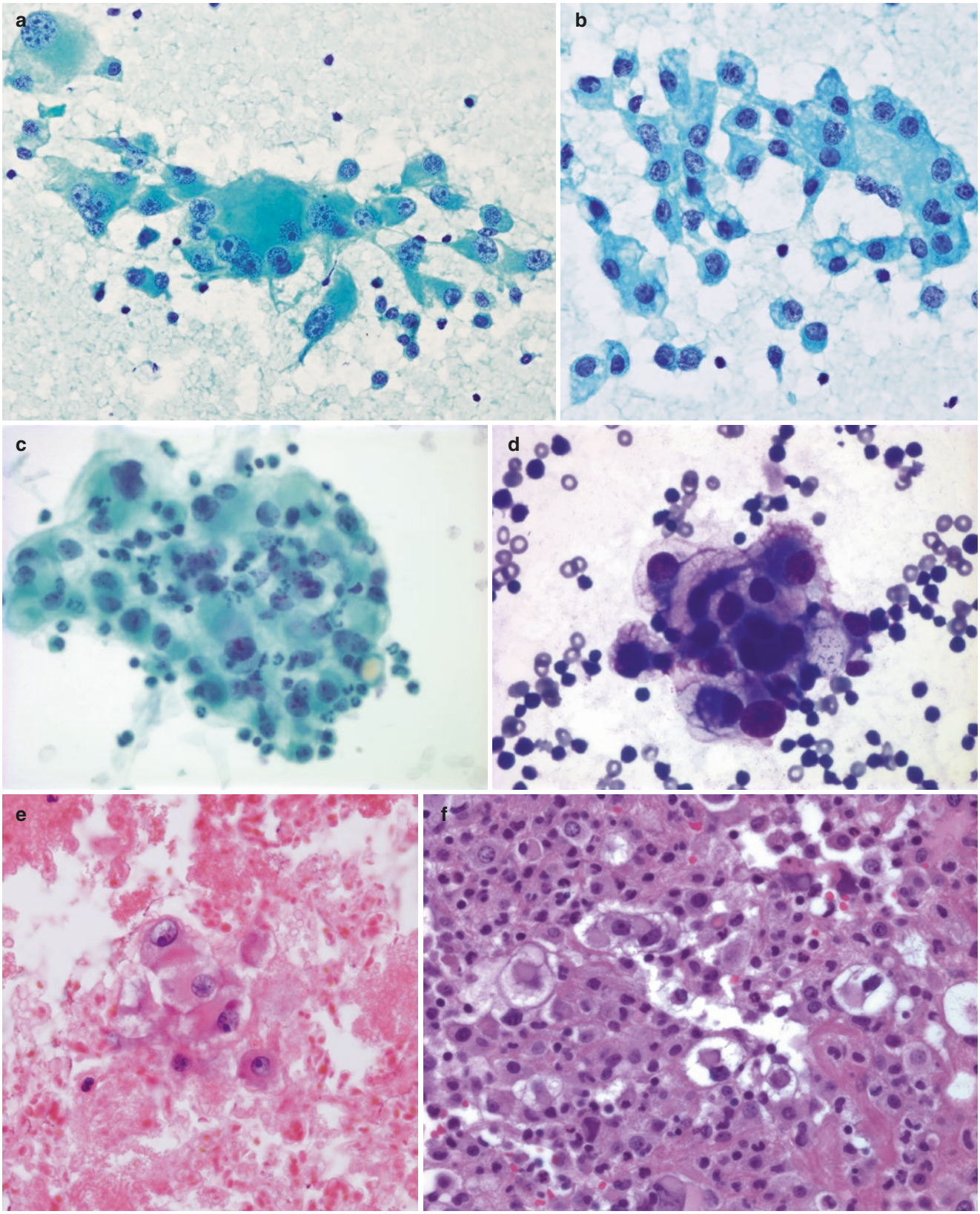
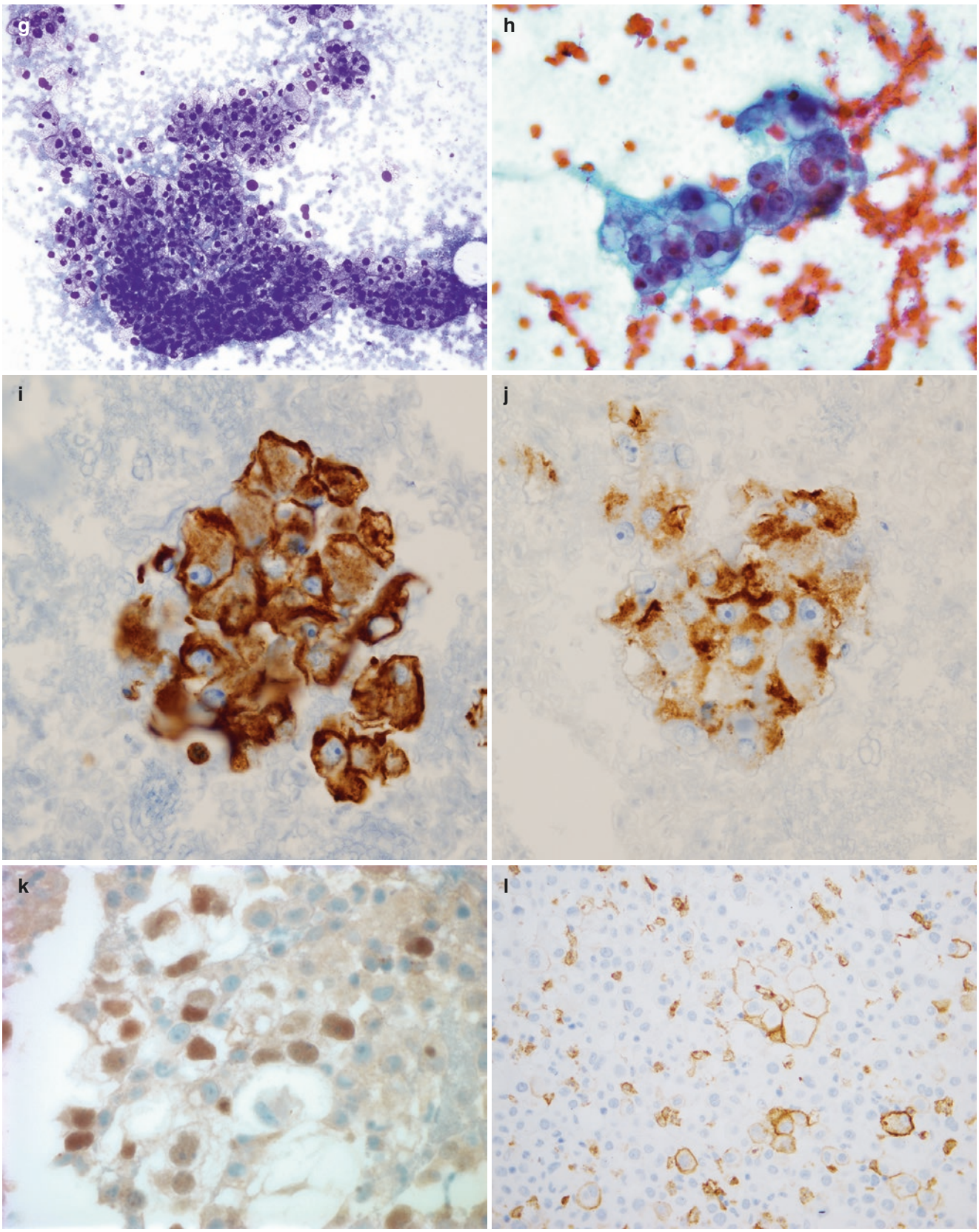


Fig. 7.10 Renal cell carcinoma: (**a**–**h**) atypical tumor cells with clear or eosinophilic cytoplasm in loose groups, doublets, or singly. (**a**–**c**, **h**) PAP; (**d**, **g**) Diff-Quik; (**e**, **f**) H&E. *Immunohistochemistry*: staining for vimentin (**i**), EMA (**j**), PAX8 (**k**), CD10 (**l**), and CA IX (**m**)



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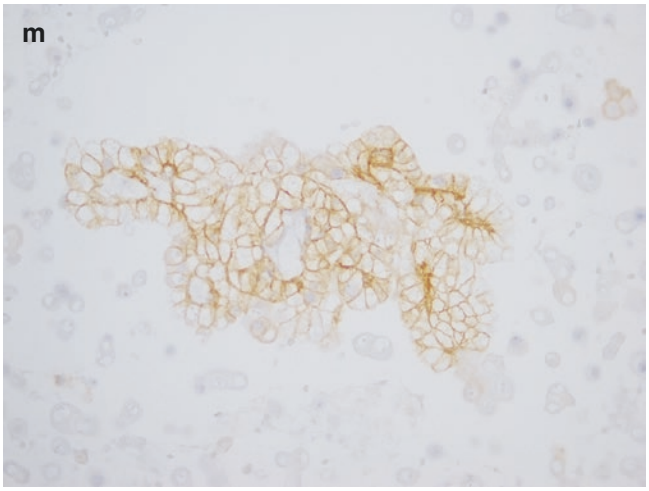


Fig. 7.10 (continued)

toneal, and 2 pericardial specimens [86]. Geisinger et al. reviewed 780 exfoliative cytology specimens from 144 patients younger than 17 years of age with nonlymphoreticular neoplasms. Among the 120 malignant pleural and peritoneal effusions reviewed, 12 were metastases from germ cell tumors [87]. Germ cell tumors constituted 8% of 88 malignant effusions in the series of Wong et al. [88].

Seminoma and dysgerminoma cells are uniform, with variable cytoplasm, and large oval or round centrally located nuclei with fine chromatin and prominent nucleoli. Cells are observed mostly as single-lying or in pairs [86, 87, 92]. Abe observed atypical cells with hyperchromatic nuclei and high nucleus/cytoplasm ratio in a metastatic testicular seminoma [94]. The dysgerminoma case seen by one of the authors similarly consisted of overtly atypical cells with high n/c ratio and large nucleoli, lying singly or in small groups (Fig. 7.11a, b).

Cells originating from Yolk sac tumors (endodermal sinus tumors) were described as small, dark, and cuboidal, lying in clusters [86]. Roncalli et al. observed loosely arranged irregular or papillary groups consisting of cells with ill-defined microvaculated cytoplasm, high n/c ratio, and prominent nucleoli. In cell block sections, tubular and microcystic structures were seen, as well PAS- and AFP-positive hyaline globules [90]. Comparable findings were described by Valente [92] and seen by one of the authors. In the latter case, the hyaline material was evident in the MGG-stained smears (Fig. 7.11c, d).

Embryonal carcinoma cells in effusions were described as relatively small pleomorphic cells with hyperchromatic nuclei and pale or poorly preserved cytoplasm. Cells were observed singly, in nondescript clusters or in glandular structures [87].

Rare reports of immature teratomas in effusion specimens have been published [87, 91, 93, 95]. Geisinger reported a case in an 11-year-old patient with a large grade III ovarian teratoma, in which the cells in pleural effusions resembled neuroblastoma [87]. Selvaggi reported two cases, of which one consisted of ependymal elements, and the second one of neuroepithelial elements [91, 93]. In the case reported by Ikeda, immature neuroepithelial cells forming rosette-like structures were admixed with keratinized squamous cells, squamoid metaplastic cells, and immature glial-appearing cells [95]. A specimen seen by one of the authors is shown in Fig. 7.11e–g.

The presence of choriocarcinoma in cytological specimens was reported [86] but is probably a very rare event. An effusion specimen with choriocarcinoma metastasis was seen by one of the authors (Fig. 7.11h).

The presence of mature teratoma elements, consisting of fat, keratin, and hair, in effusions does not constitute true metastasis and is observed in the event of spontaneous or iatrogenic spillage of mature teratoma elements (Fig. 7.11i, j). One should nevertheless be familiar with the morphological picture of this condition.

Germ cell tumors should be suspected when a malignant effusion is found in a child or young adult, although they may also occur later in life. The differential diagnosis of germ cell tumors in effusions depends on their type. Yolk sac tumors and embryonal carcinomas need to be differentiated from metastatic carcinomas. For the former tumor, this primarily includes clear cell carcinomas, as well as secretory endometrioid carcinomas and mucinous carcinomas.

Seminomas should be differentiated from carcinomas, as well as all other tumors that present with dissociated malignant cells. Germ cell tumors express to a varying degree embryonic markers such as SALL4, OCT4, SOX2, and Nanog. Yolk sac tumors additionally stain for AFP, whereas embryonal carcinomas are CD30-positive. Dysgerminomas stain for placental alkaline phosphatase (PLAP), c-Kit (CD117), and D2–40. Glypican-3 stains germ cell tumors, particularly yolk sac tumor, but is expressed in many carcinomas, and its presence should therefore be interpreted in the context of a broader panel of markers.

In young patients, the neuroepithelial cells in immature teratomas need to be differentiated from Wilms' tumor, neuroblastoma, embryonal rhabdomyosarcoma, Ewing sarcoma, and non-Hodgkin lymphoma [87, 39], which may be achieved based on morphology, immunohistochemistry, and for some of these entities, molecular analysis (see below).

Malignant Melanoma

The diagnosis of malignant melanoma in effusion specimens is an infrequent, though not a rare one, reflecting the ability of this tumor to metastasize to practically any organ. In the

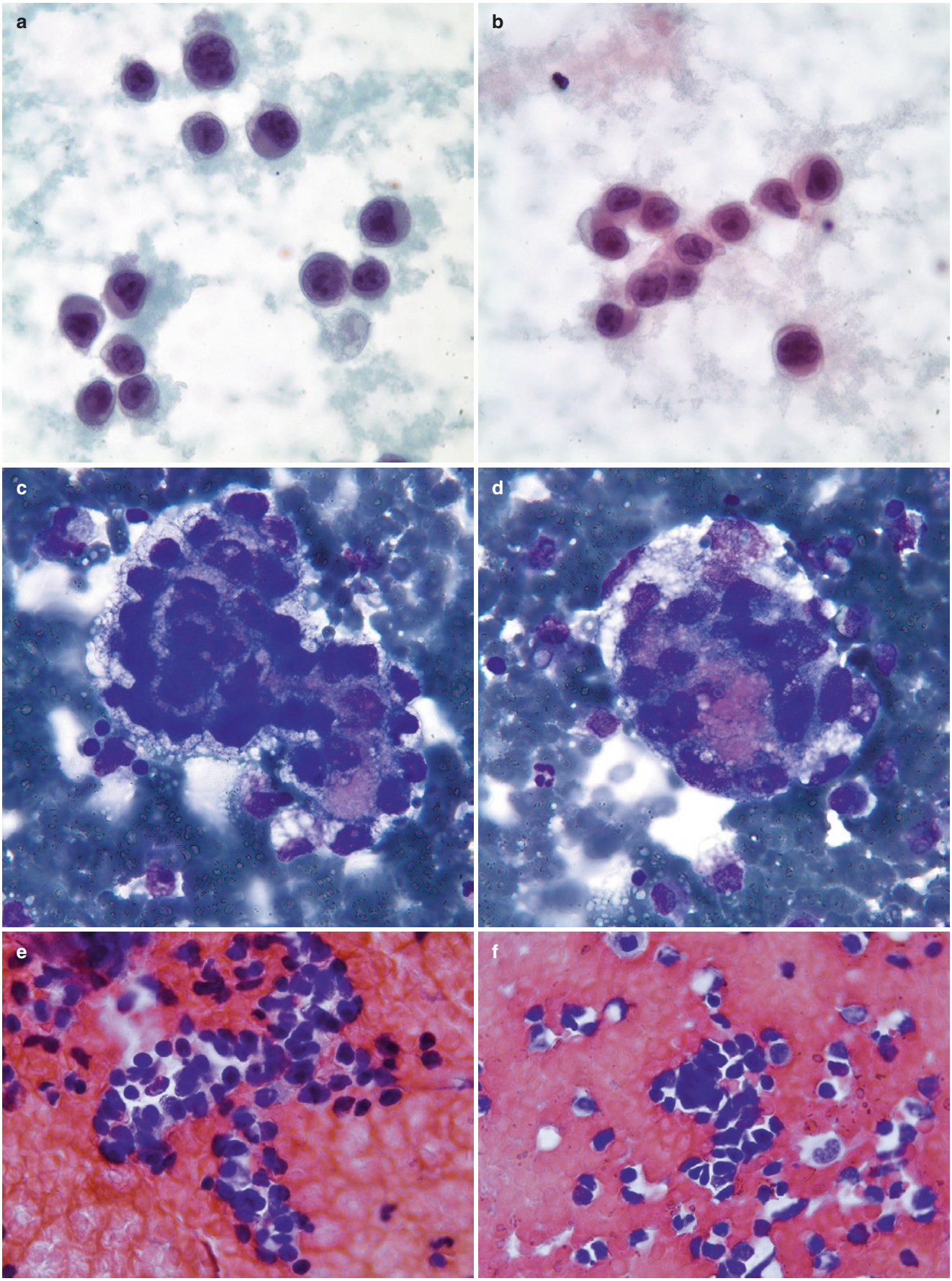


Fig. 7.11 Germ cell tumors: (**a**, **b**) dysgerminoma. Small cells with high n/c ratio, lying in short cords or singly. (**c**, **d**) Yolk sac tumor. Vacuolated cells and formation of metachromatic extracellular substance; (**e**–**g**) immature teratoma; (**h**) choriocarcinoma; (**i**, **j**) material from mature teratoma. (**a**, **b**, **j**) PAP; (**c**–**i**) MGG/Diff-Quik

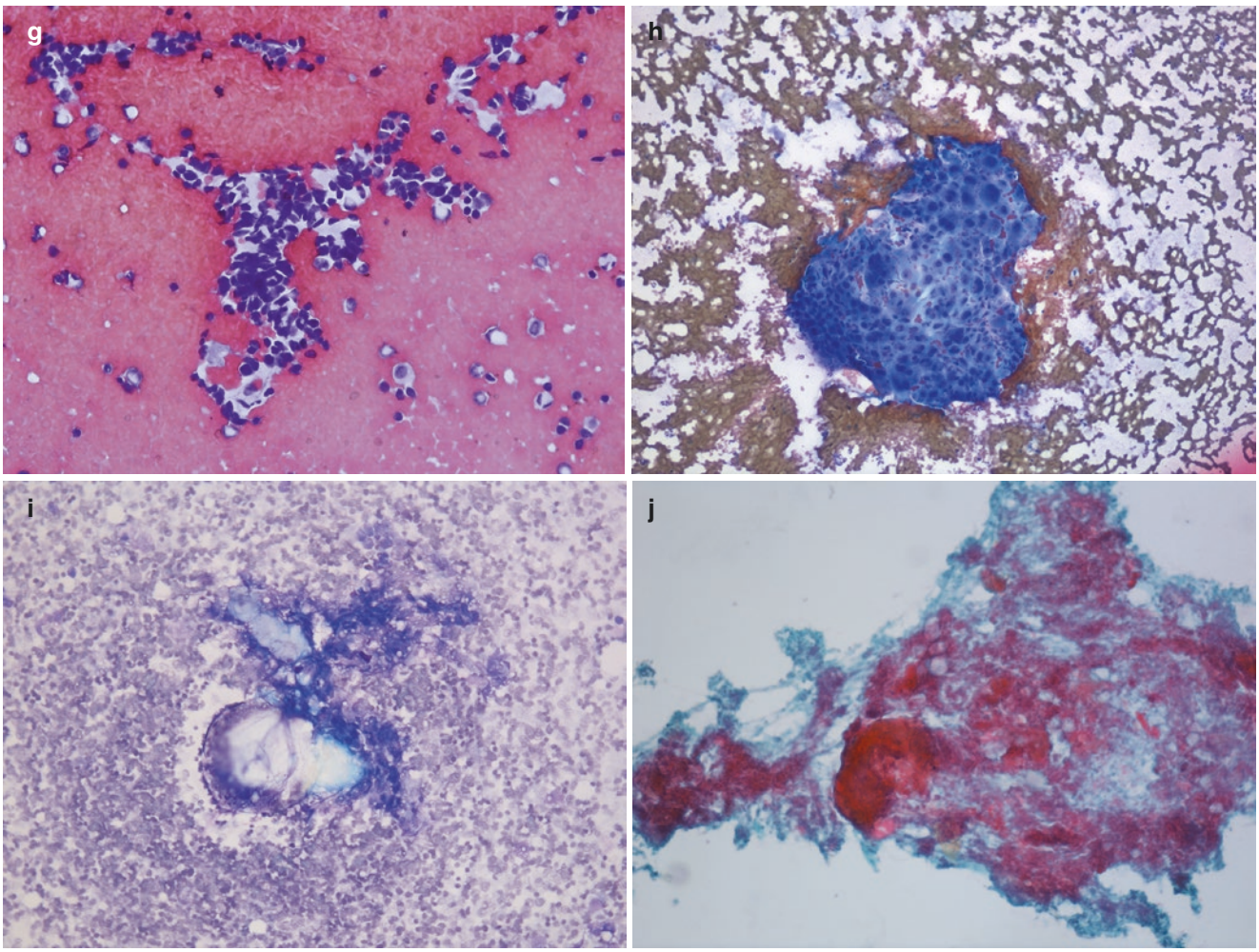


Fig. 7.11 (continued)

series by Johnston [56], malignant melanoma was the primary tumor in 10/472 patients with malignant pleural effusion, whereas Sears and Hajdu reported the presence of metastatic melanoma in 17/812 and 7/423 malignant pleural and peritoneal effusions, respectively [73].

The primary site is most frequently exposed skin, but metastasis from a primary tumor in the vulva was reported [97]. A primary pulmonary/pleural melanoma in a 13-year-old girl was recently described [98].

Melanoma metastases in effusions may be melanotic or amelanotic. Specimen cellularity is variable but may be very high (Fig. 7.12a, b). Cells may lie singly or in groups of variable size (Fig. 7.12a–d). The cytoplasm is generally abundant, with variable n/c ratio. Intracytoplasmic vacuoles are evident (Fig. 7.12a). Nuclei are large, overtly atypical, round or vesicular, and eccentrically placed, with coarse chromatin and one or multiple large nucleoli (Fig. 7.12e–h). The presence of pigment is strongly supportive of a melanoma diagnosis.

Longatto-Filho et al. reviewed 21 peritoneal and pleural melanoma effusions and found the majority to consist of single cells. Characteristic morphological features consisted of cytoplasmic pigment, perinuclear halos, cell cannibalism, and the presence of intranuclear inclusions, atypical mitoses, multinucleation, and prominent nucleoli [99]. Similar findings were reported in two other series [100, 101]. A case of melanoma with signet ring cells in a peritoneal effusion was reported [102].

The diagnosis of malignant melanoma in effusions is best supported by ancillary methods, especially when the primary site is unknown and/or the tumor is amelanotic. The Masson-Fontana silver stain detects melanin (Fig. 7.12i), but as in other areas of effusion cytology, immunohistochemistry is currently the most widely used method. In 1985, Pinto reported immunoreactivity of melanoma cells to S-100 in 4/7 melanomas [103]. Since then, several other markers, including HMB45, MART-1 (Melan-A), and SOX10, have been added to the panel

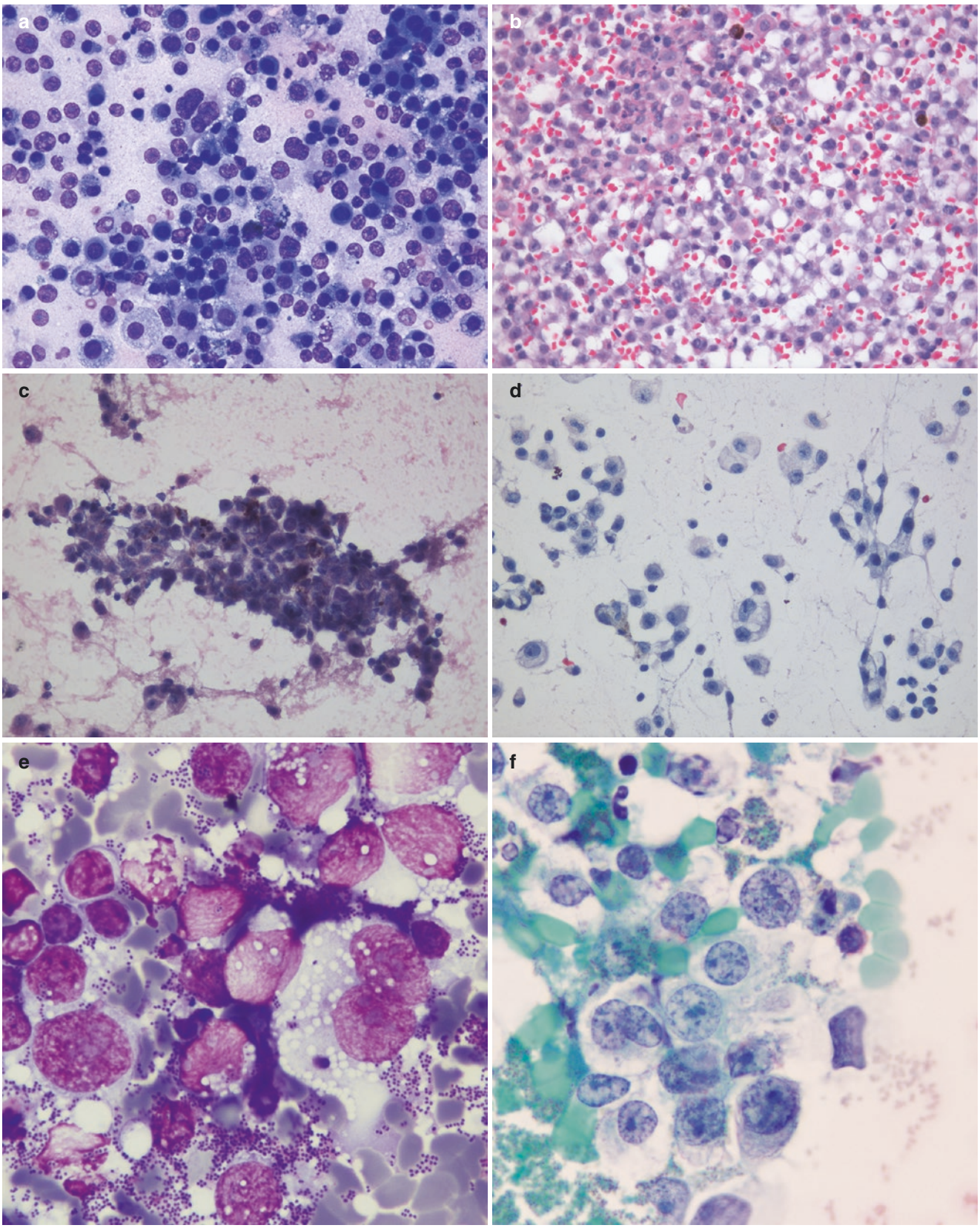
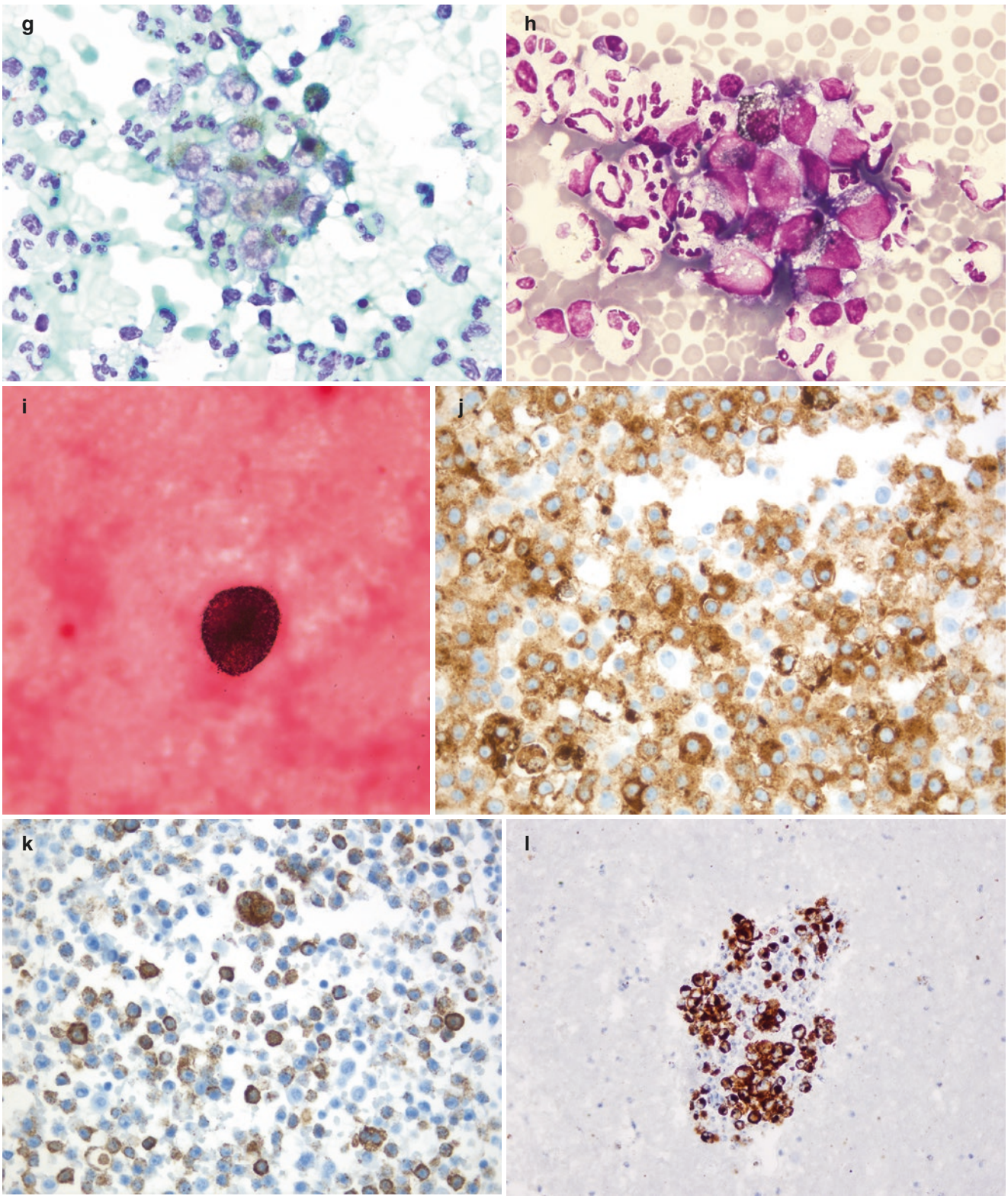


Fig. 7.12 Malignant melanoma: (**a**, **b**) numerous dissociated tumor cells; (**c**) cohesive group; (**d**) small loose groups and single cells. Melanin is seen in all four figures; (**e**–**h**) tumor cells with pronounced atypia. Note vacuolization and melanin granules in **e**. (**a**, **e**, **h**) MGG/Diff-Quik; (**c**, **d**, **f**, **g**) PAP; (**b**) H&E. *Histochemistry and immunohistochemistry*: (**i**) Masson-Fontana stain for melanin; (**j**) Melan-A (MART-1); (**k**, **l**) HMB-45; (**m**) vimentin



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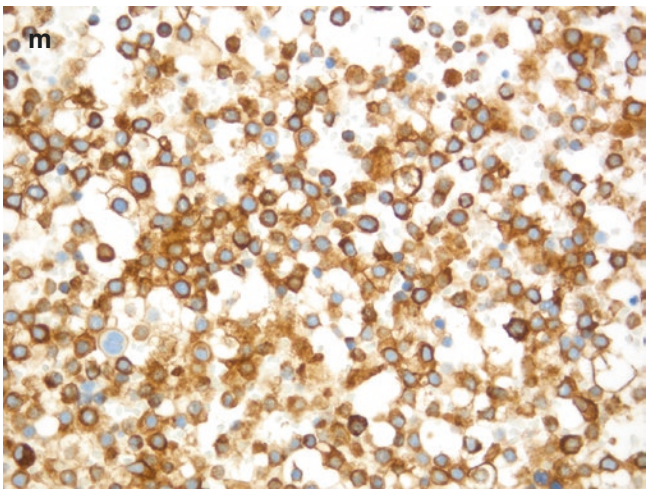

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of melanoma markers. HMB45 and Melan-A are often expressed in melanoma effusions (Fig. 7.12j–l), with sensitivity of 80% in the two largest series published to date [99, 100]. Vimentin is additionally expressed in this tumor (Fig. 7.12m) but is considerably less specific. The use of double-staining for WT1 and pan-cytokeratin AE1/AE3 was suggested to aid in the differential diagnosis between metastatic melanoma, metastatic carcinoma, and benign or malignant mesothelial cells in effusions, with melanomas (n = 17) usually displaying cytoplasmic WT1 expression and negative AE1/AE3 staining [104].

Merkel cell tumor, a skin tumor with neuroendocrine differentiation, may rarely affect the serosal cavities [105–107]. In the most recent report, tumor cells were seen singly, single-file or in clusters, and had round-to-oval nuclei, irregular nuclear borders, stippled chromatin, inconspicuous nucleoli, scant cytoplasm, and occasional nuclear molding [107].

Merkel cell tumor metastatic to effusion was recently seen by one of the authors. Tumor cells were immunhistochemically positive for CK20, synaptophysin, and chromogranin A, negative for TTF1 (Fig. 7.13a–e).

Sarcomas

Sarcoma metastasis to effusions is an infrequent event in adults but represents a considerable part of the diagnostic spectrum of malignant effusions in children and adolescents. Practically every type of sarcoma has been described at this anatomic site. Disease presentation as effusion is uncommon but has been described [108].

In the Geisinger series of pediatric patients, 43/80 malignant pleural effusions and 4/40 malignant peritoneal effusions were sarcomas [87], whereas Wong et al. reported that 7% of 88 malignant effusions were diagnosed as sarcoma [88]. A study of 24 sarcomas by Abadi and Zakowski included 8 malignant fibrous histiocytomas, 5 leiomyosarcomas, 3 rhabdomyosarcomas, 3 liposarcomas, 2 high-grade sarcomas, 1 osteogenic sarcoma, 1 synovial sarcoma, 1 one chondrosarcoma [109]. In another report, 28 of 154 effusions from sarcoma patients were positive and 6 were suspicious [110].

General characteristics of sarcomas in effusions described by Abadi included single cell arrangement, indistinct cell borders, nuclear pleomorphism, multinucleation, and the presence of a proteinaceous background with lysed blood [109].

In a recent series of 40 small round cell tumor effusions, including 14 Ewing sarcoma/primitive neuroectodermal tumor (PNET) specimens, 5 synovial sarcomas, and 6 rhabdomyosarcomas, no morphologic differentiators between these entities were observed [111]. In another series of 183 effusions from pediatric patients, 40 specimens were malignant, of which 9 were rhabdomyosarcomas, constituting the most common diagnostic entity [112].

Embryonal rhabdomyosarcomas consist of single-lying or loose groups of small cells with high n/c ratio. Nuclei have variable chromatin pattern and one or more conspicuous nucleoli (Fig. 7.14a–d). Geisinger described the presence of small notches in the nuclear membrane. Although the cytoplasm is scanty, as in all small round blue cell tumors, it was more voluminous than in neuroblastoma [87]. A specimen studied for DNA content using flow cytometry was shown to be aneuploid [113]. Metastasis from a testicular tumor with pleomorphic cells was described [114]. Uncommon primary sites for rhabdomyosarcomas which have been described are the ovary (two cases) [115], the prostate [116], and the breast [117]. A case of malignant pleural effusion from a rhabdomyosarcoma that developed in a mixed germ cell tumor of the testis was reported [118].

The diagnosis of rhabdomyosarcoma requires ancillary tests. Immunostaining for muscle markers, such as desmin and actin, and skeletal muscle markers such as myogenin (Fig. 7.14e) [119] and MYF-4 is helpful, as is electron microscopy showing muscle filaments. Embryonal rhabdo-

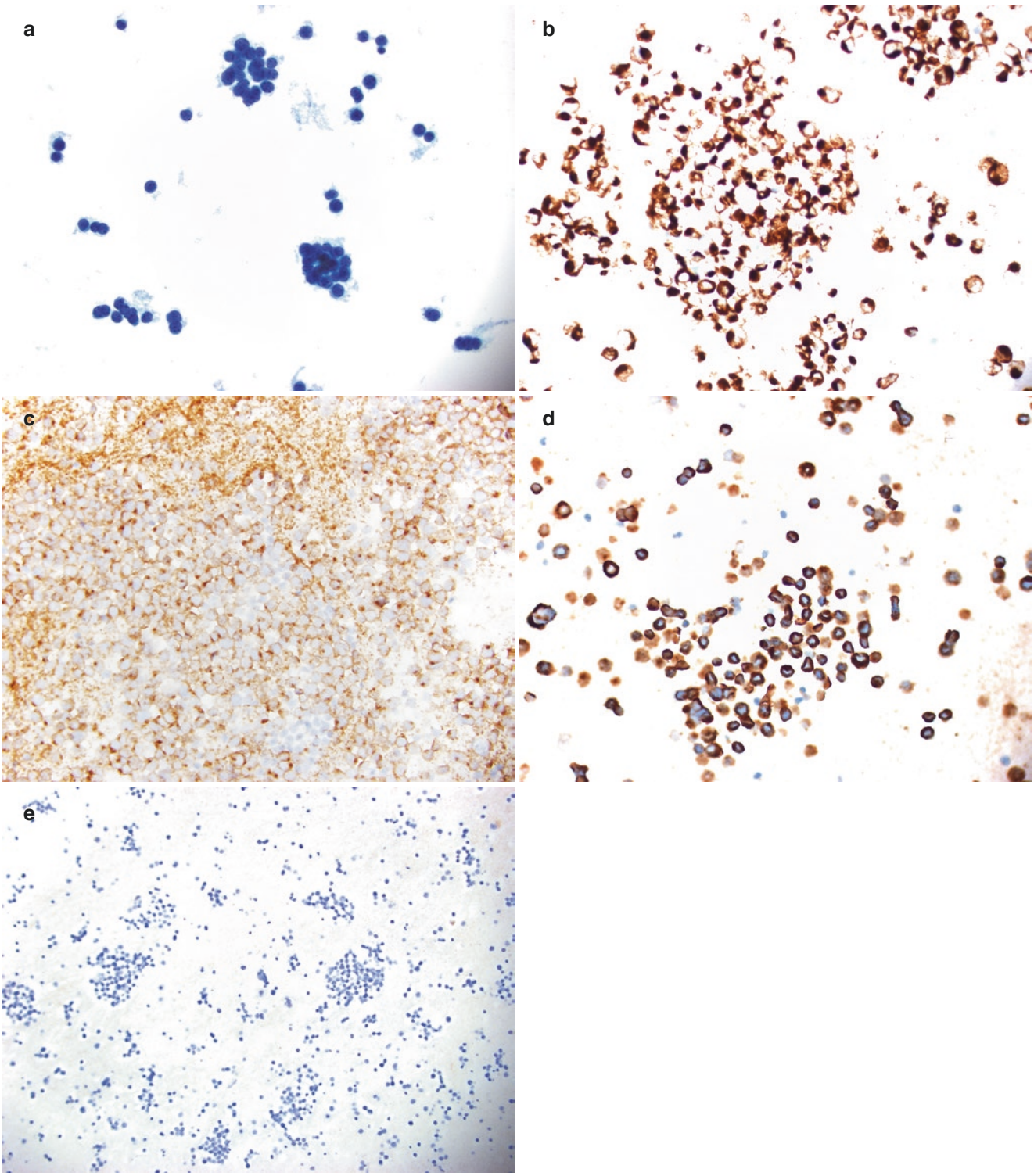


Fig. 7.13 Merkel cell tumor: (**a**) PAP stain showing tumor cells lying singly or in small groups. *Immunohistochemistry*: (**b**) CK20; (**c**) synaptophysin; (**d**) chromogranin A; (**e**) TTF1

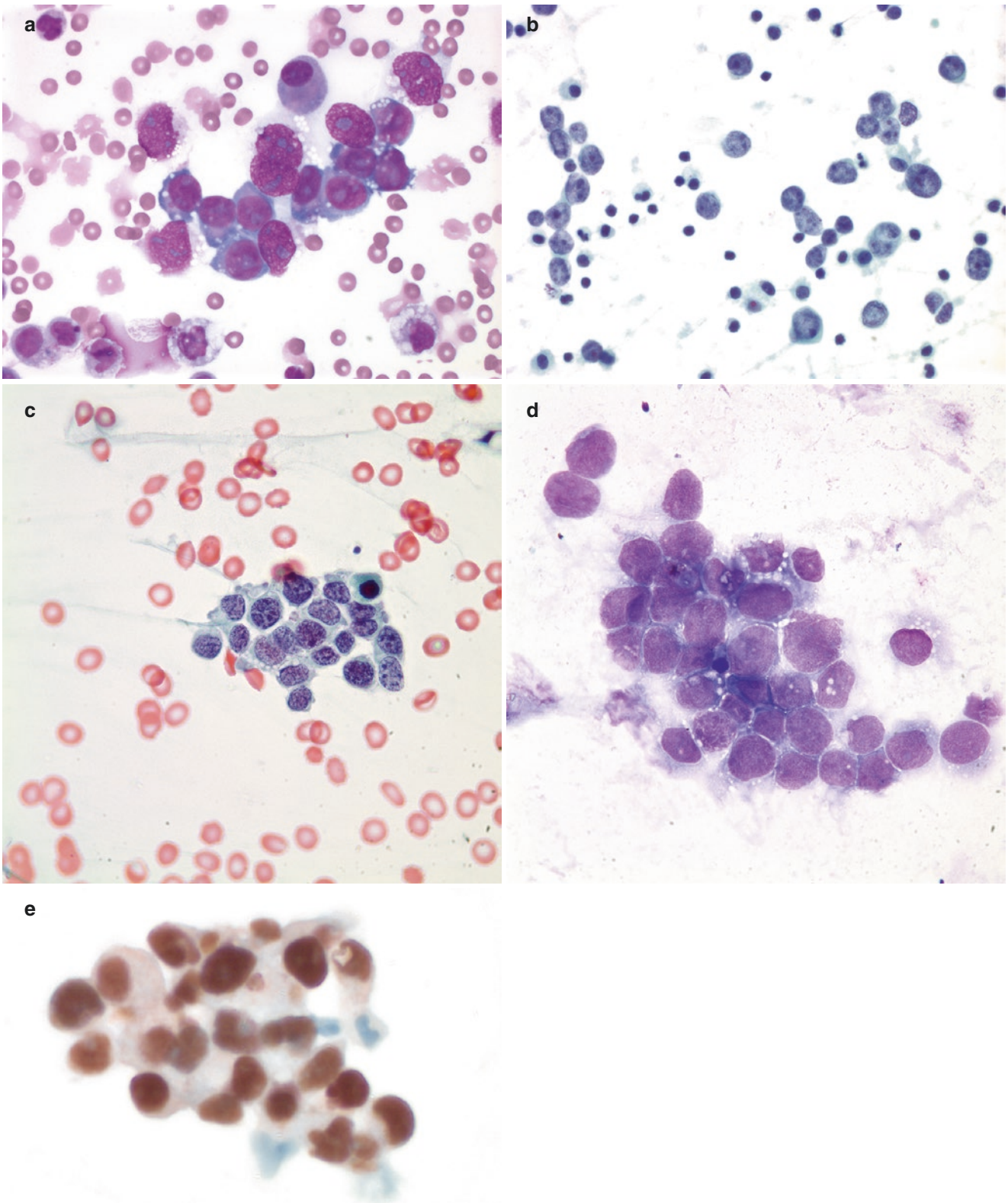


Fig. 7.14 Rhabdomyosarcoma: (**a**–**d**) small cells with high n/c ratio, dissociated or in small clusters; (**a**, **d**) MGG/Diff-Quik; (**b**, **c**) PAP. (**e**) immunostaining for myogenin in the specimen shown in **a**, **b**

myosarcomas have a specific translocation at t(2;13)(q35;q14) creating the PAX3-FKHR gene fusion that can be showed using FISH [120–122].

Ewing sarcoma is an obvious differential diagnosis to rhabdomyosarcoma. Geisinger studied nine pleural specimens and describes small malignant cells with very high n/c ratio, occasionally with no discernible cytoplasm, lying singly or in small loosely cohesive groups. Nuclei were irregular and jagged [87]. Similar morphological findings were observed in a case diagnosed by one of the authors (Fig. 7.15a, b).

In more recent studies, Ewing sarcoma cells in effusion were shown to have the characteristic t(11;22)(q24;q12) translocation creating the EWS/FLI1 fusion transcript, also shown in the case illustrated in this chapter, as well as additional aberrations (48, XY, i(1)(q11), +10), in one report [123, 124]. Ewing sarcoma cells are immunohistochemically positive for CD99 (Fig. 7.15c), vimentin, and neuron-specific antigen (NSE) [124].

Several cases of desmoplastic small round cell tumor in effusion have been reported [125–128]. In one of these studies, tumor cells expressed vimentin, desmin, cytokeratin, EMA, NSE, and CD57 (Leu-7) and exhibited the pathognomonic t(11;22)(p13;q12) translocation [126].

In a recently described case of a 30-year-old man, tumor cells in the pleural effusion had cell spheres without cores mimicking carcinoma or mesothelioma. The diagnosis was confirmed by immunohistochemistry and FISH, the latter showing *EWSR1* rearrangement [127]. In another report, cells in pleural effusion had a "floating island" pattern, characteristic of hepatocellular carcinoma, renal cell carcinoma, and adrenocortical carcinoma in effusions [128].

Several reports of angiosarcoma in effusions have been published [129–132]. Berry et al. studied three cases. Numerous single tumor cells and small loose clusters were seen. The malignant cells had delicate, finely vacuolated cytoplasm with distinct borders. Nuclei were irregular with indentations and had prominent nuclei and coarse chromatin.

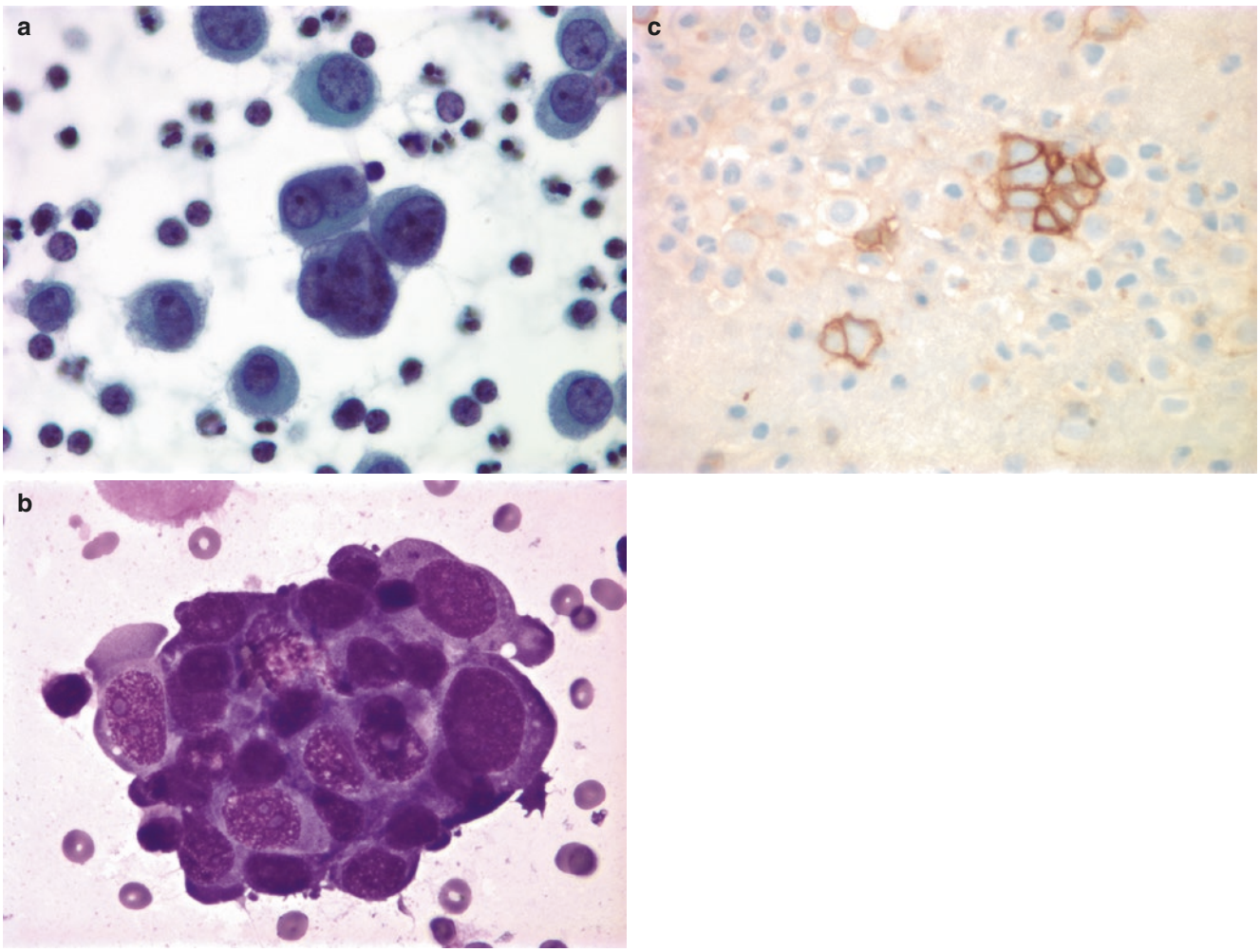


Fig. 7.15 Ewing sarcoma: (**a**, **b**), cell clusters of variable size with very high n/c ratio and large nucleoli; (**a**) PAP, (**b**) MGG/Diff-Quik. (**c**) immunostaining for CD99

Binucleate forms were occasionally seen [129]. An ovarian angiosarcoma metastasis in peritoneal effusion diagnosed by one of the authors consisted of cell groups of variable size, some with papillary architecture, with large poorly defined cells with overlapping nuclei, high n/c ratio, and large nucleoli, findings which may easily mimic adenocarcinoma (Fig. 7.16a–c) [131].

Alderman et al. had one angiosarcoma effusion in their series [119]. Angiosarcomas express vascular markers, including CD31, CD34 (Fig. 7.16d), and factor VIII.

Few cases of epithelioid hemangioendothelioma in pleural effusion have been described [133–136], in which tumor cells expressed vascular markers [133, 135, 136] or were shown to have Weibel-Palade bodies by electron microscopy [134]. A specimen diagnosed by one of the authors, positive for CD31, is shown in Fig. 7.16e–h.

Osteosarcoma was one of the commonly found tumors in the Geisinger series, with 22 positive specimens, of which 21 were pleural and 1 peritoneal. Cells were described as highly pleomorphic, with round, oval, or spindle-shaped form, relatively abundant eosinophilic cytoplasm, and nuclei which appeared to be pyknotic or were coarsely granular, with large nucleoli [87]. A case metastatic to ascites with poor outcome was described [137]. Two specimens seen by the authors consisted of highly atypical cells of variable form, with vacuolated cytoplasm, high-grade nuclei with large nucleoli and formation of osteoid (Fig. 7.17a–d).

A report of two pleomorphic liposarcomas that metastasized to pleural effusion was published, in which electron microscopy aided in establishing the diagnosis [138]. Abadi and Zakowski reported three specimens, in which cells had a pale and delicate cytoplasm and irregular nuclei with fine and even chromatin and small nucleoli [109]. A pleural effusion specimen with tumor cells in papillary structures mimicking carcinoma was described [139]. A specimen seen by one of

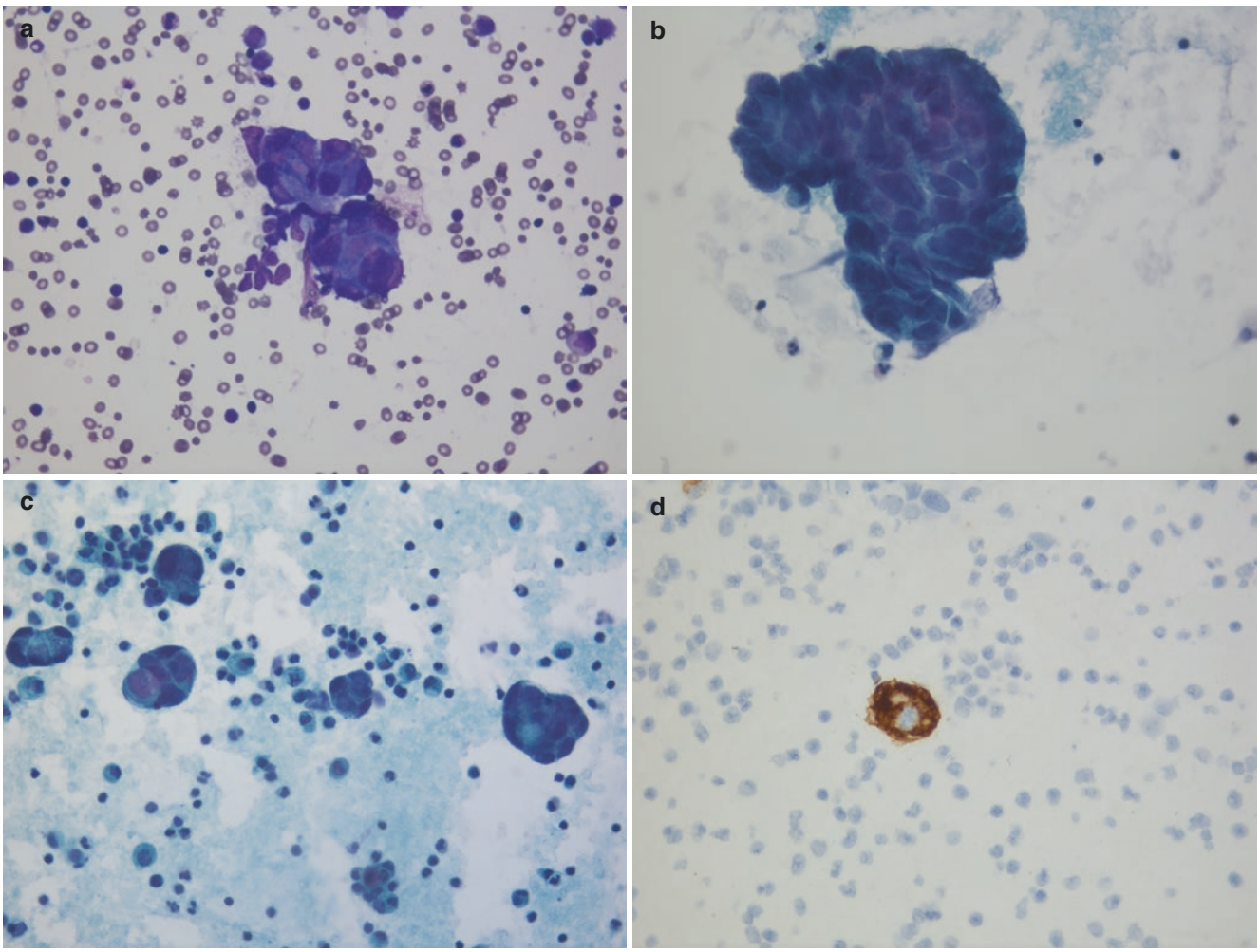


Fig. 7.16 Angiosarcoma: (**a**–**c**) tumor cell groups of variable size, some with papillary architecture which mimics adenocarcinoma. Cells are large and atypical; (**a**), MGG/Diff-Quik; (**b**, **c**) PAP. (**d**) CD34 immunostain. Hemangioendothelioma (**e**–**g**) tumor cells with epithelioid morphology. Cells have delicate chromatin and easily discernible nucleoli; (**e**, **f**) MGG/Diff-Quik; (**g**) PAP. (**h**) CD31 immunostain

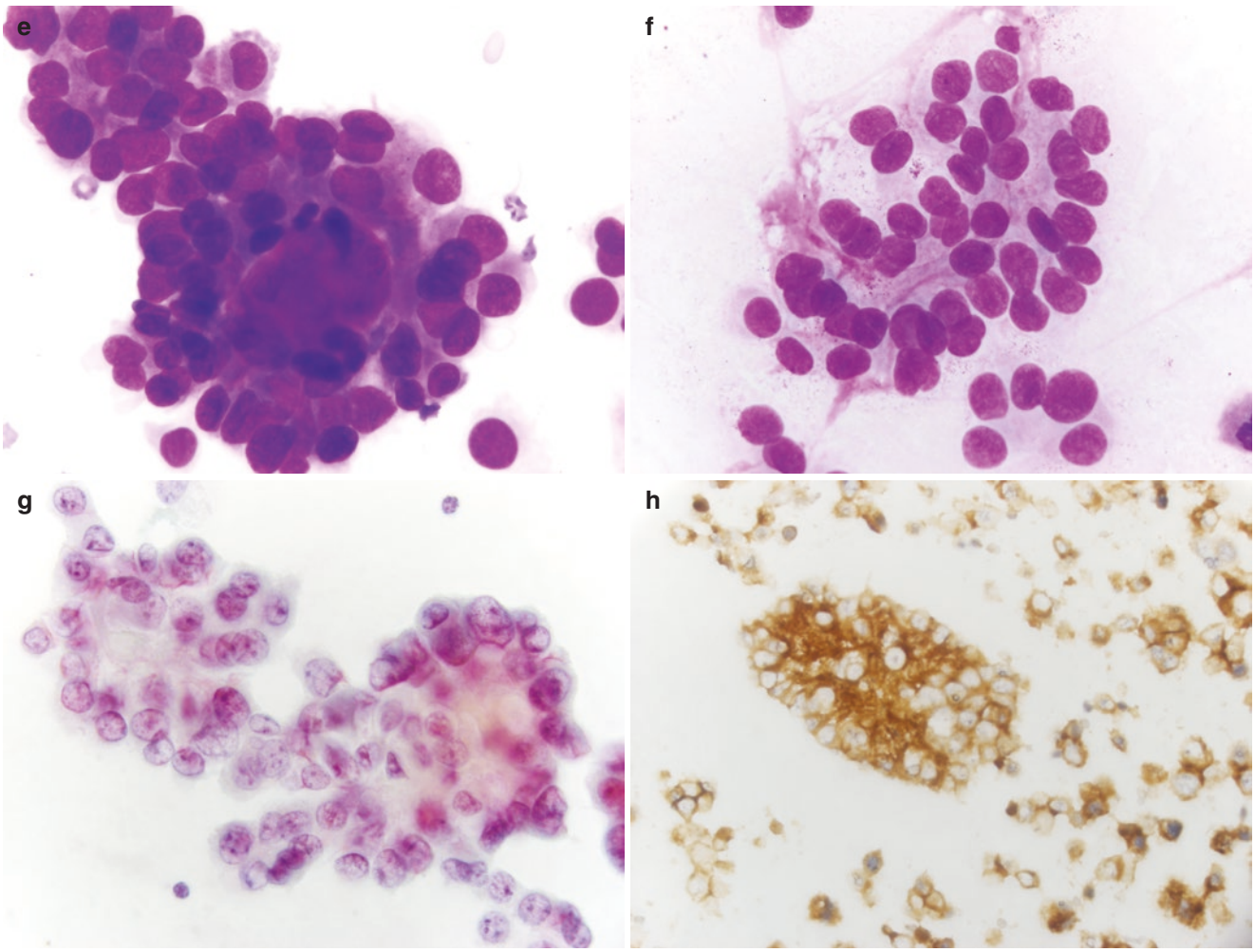


Fig. 7.16 (continued)

the authors consisted of large lipoblasts with vesicular nuclei containing one or two large nucleoli. Tumor cells stained for vimentin and MDM-2 (Fig. 7.18a–c).

Metastases from a dedifferentiated chondrosarcoma of the femur and from a primary chondrosarcoma of the urinary bladder were described [140, 141]. A myxoid chondrosarcoma in pleural effusion was described, consisting of cells that had exclusively epithelioid morphology, with a potential to be misdiagnosed as carcinoma [142]. A case of myxoid chondrosarcoma seen by one of the authors consisted of spindle cells with cartilaginous material in the background (Fig. 7.19a–c).

Metastasis from a sclerosing fibrosarcoma of the buttock in a pleural effusion was reported [143], in which tumor cells were arranged in medium-sized epithelioid clusters. Tumor cells had pleomorphic nuclei with occasional multinucleation, with fine chromatin and small nucleoli. Recently, positive pleural effusion in a 63-year-old female patient diagnosed with cardiac myxofibrosarcoma was reported [144]. Tumor cells were medium to large in size, occasionally multinucleated, and had round nuclei with fine chromatin and prominent nucleoli, and pale and lace-like cytoplasm. A case seen by one of the authors consisted of more monomorphic spindle cells (Fig. 7.19d).

The presence of synovial sarcoma in serous effusions was reported in several studies [87, 109, 111, 145, 146], of which the former three displayed a biphasic pattern and the fourth was monophasic, with a spindle cell component. Expression of cytokeratins, vimentin, and EMA, as well as the pathognomonic t(X;18)(p11;q11) translocation, was seen in one of the specimens, which was characterized as a newly established cell line [146].

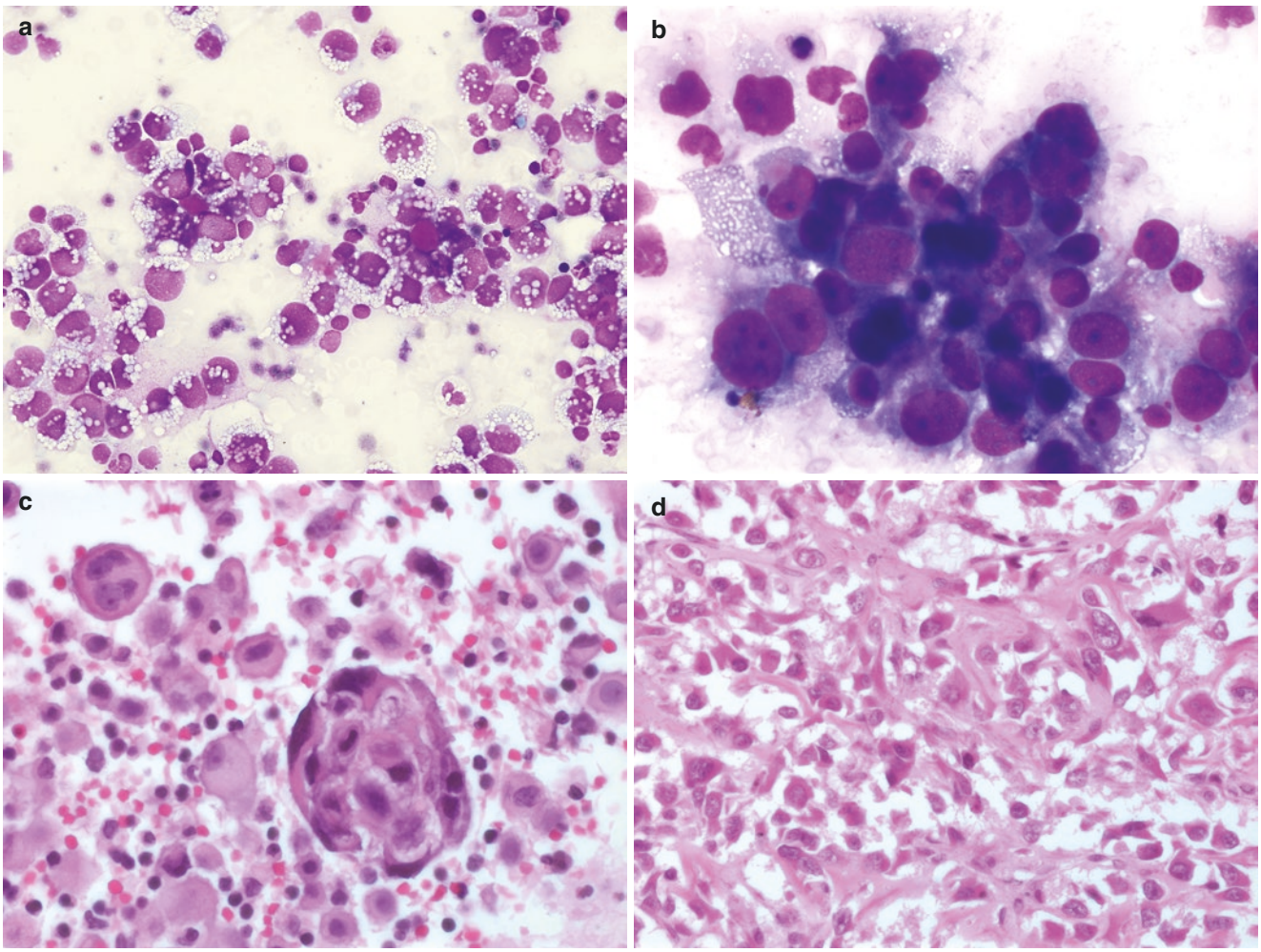


Fig. 7.17 Osteosarcoma: (**a**–**d**) large and highly atypical tumor cells in groups of variable size and form, some dissociated. Extracellular osteoid is evident. (**a**, **b**) MGG/Diff-Quik; (**c**, **d**) H&E

Eight malignant fibrous histiocytomas, five leiomyosarcomas, and two high-grade sarcomas were characterized in the Abadi series [109]. These had single-lying pleomorphic cells, in agreement with their histological properties. A case of myxoid leiomyosarcoma in a peritoneal washing specimen was reported, in which cells had epithelioid and spindle cell morphology [147]. A case of inflammatory malignant fibrous histiocytoma was recently described [148]. A high-grade leiomyosarcoma was seen by one of the authors (Fig. 7.20a, b).

Other sarcomas or other soft tissue tumors diagnosed in effusions are uterine sarcoma with rhabdoid features [149], ovarian adenosarcoma [150], clear cell sarcoma (malignant melanoma of soft parts) [151], and melanotic schwannoma [152].

A series of six cytological specimens, including three effusions, from five patients diagnosed with the new entity epithelioid inflammatory myofibroblastic sarcoma was recently published [153].

Tumor cells in effusion specimens were fewer than in FNA specimens, and consisted of large degenerated epithelioid cells with eccentrically located nuclei. Tumors were ALK-positive by immunohistochemistry and had *ALK* rearrangement by FISH.

While not a true sarcoma, the possibility of a carcinosarcoma metastasizing in the form of sarcomatous elements should be kept in mind, although this is a very rare event [154].

Small round blue cell tumors other than the ones discussed above, including neuroblastoma and Wilms' tumor, are an important differential diagnosis in effusion cytology in the pediatric or young adult population.

The series of Farr and Hajdu consisted of 51 malignant effusions from patients with neuroblastoma, including 48 pleural and 3 peritoneal specimens. Effusions were moderately cellular, with small, round, or polygonal cells with

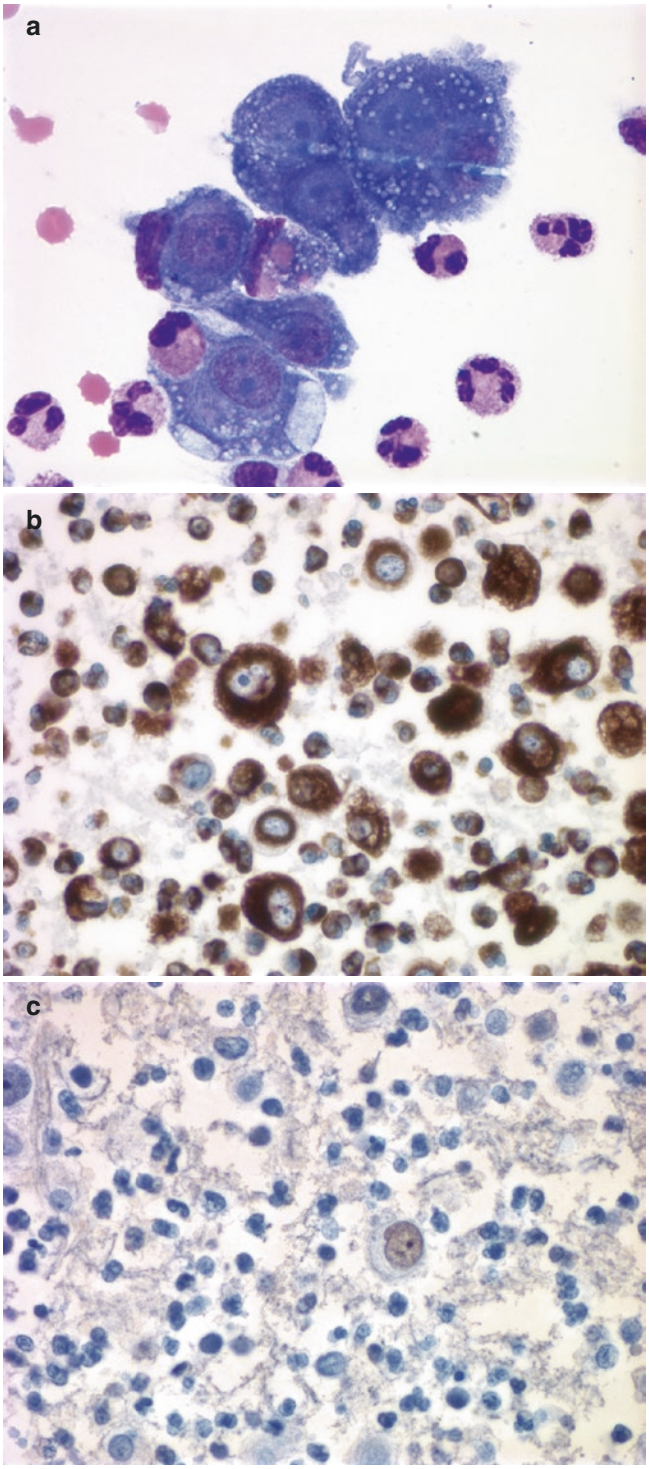


Fig. 7.18 Liposarcoma: (**a**) large atypical lipoblasts, MGG/Diff-Quik; (**b**, **c**) immunostaining for vimentin (**b**) and MDM-2 (**c**)

round or oval hyperchromatic nuclei, one or two round nucleoli, and scant cytoplasm. Rosette formation was seen in the majority of specimens [155]. Geisinger described the presence of large flat plaques, short chains with molding, and rosettes in 23 studied specimens. Rare specimens from patients with medulloblastoma, pinealoblastoma, and retinoblastoma were morphologically indistinguishable from neuroblastomas [87].

Cells in Wilms' tumor lie singly or in pairs and organoid structures are rarely found. A biphasic cell population consisting of round or polygonal cells and plump spindle cells was described, both with hyperchromatic nuclei, even chromatin distribution, prominent nucleoli, and sparse cytoplasm [87]. The role of effusion cytology in correctly staging these patients was emphasized in a case report by Baliga et al. [156].

Examples of neuroblastoma, Wilms' tumor, and PNET effusions are shown in Fig. 7.21a–f.

Head and Neck Cancers

Metastasis from a primary tumor at this anatomic region is uncommon in effusion cytology but has been reported. Spreading from nasopharyngeal carcinoma has been reported in two series [73, 87]. Metastasis from a squamous cell carcinoma, e.g., from laryngeal carcinoma (Fig. 7.22a, b), may be observed and needs to be differentiated from a primary tumor of the lung or other origin.

Thyroid carcinoma of various histological type, including papillary carcinoma (Fig. 7.22c–h) [157–159] and its follicular variant [160], Hürthle cell carcinoma [161] and medullary carcinoma [162] (Fig. 7.22i, j) may be detected in serous effusions. A case of malignant pleural effusion as the site of recurrence for a sclerosing mucoepidermoid carcinoma of the thyroid with eosinophilia was additionally reported [163].

Three relatively large series of this rare entity were published in recent years [164–166]. Olson et al. found in their archives six metastatic thyroid carcinomas in effusions, all in the pleural cavity, in a period of 26 years, including four papillary carcinomas and two anaplastic carcinomas. Four specimens available for morphological assessment had variable degrees of cellularity, lymphocytic infiltration, nuclear features of papillary carcinoma, single tumor cells, and fragments [164]. Lew and co-workers published a series of five cases of metastatic papillary thyroid carcinoma, all within the pleural cavity. Tumor cells had characteristic nuclear features of this entity, as well as cytoplasmic vacuolization [165]. The series of Vyas and Harigopal similarly included five pleural effusions with metastatic papillary thyroid carcinoma [166].

The diagnosis of thyroid carcinoma is supported by positive immunostaining for thyroglobulin (Fig. 7.22k), PAX8, and TTF-1, although the latter two markers are far more commonly observed in gynecological and lung adenocarcinoma effusions, respectively, in everyday practice.

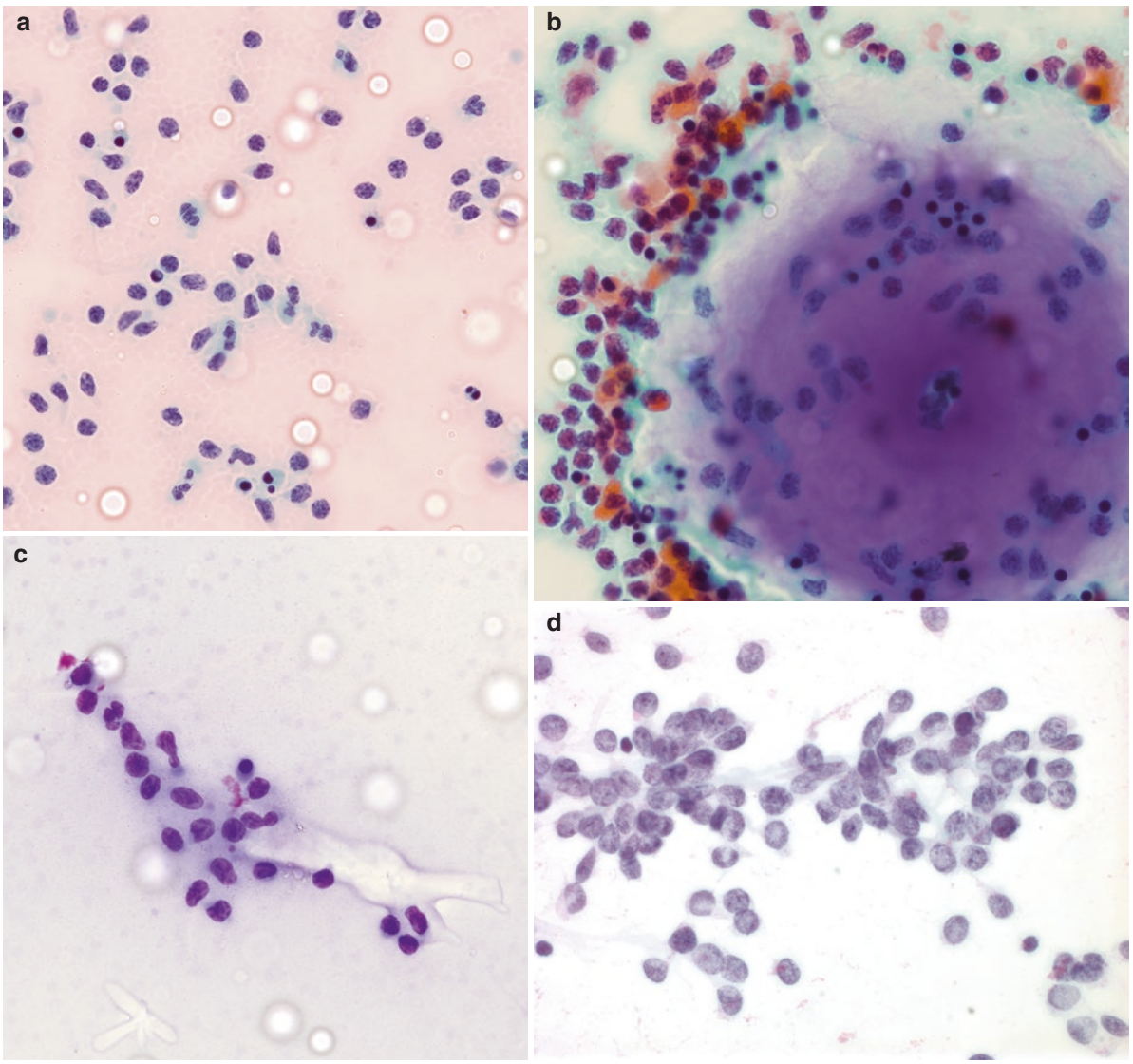


Fig. 7.19 Chondrosarcoma: (**a**–**c**), relatively small spindle-shaped tumor cells lying singly or in loose branching groups. Note cartilaginous material in **b**. (**a**, **b**) PAP; (**c**) MGG. Fibrosarcoma (**d**) relatively small spindle-shaped tumor cells lying singly or in loose branching groups. PAP

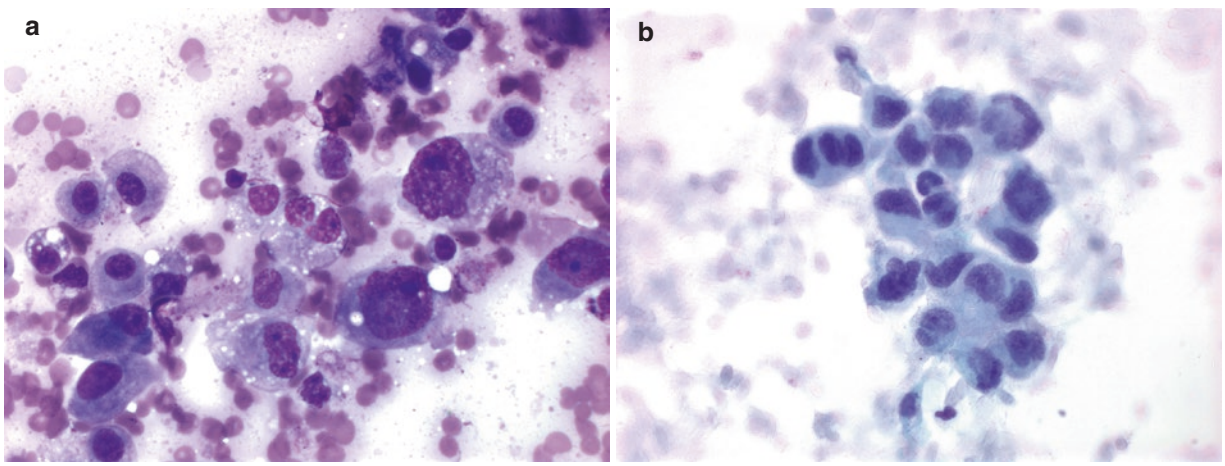


Fig. 7.20 Leiomyosarcoma: High-grade tumor with markedly atypical cells. (**a**) Diff-Quik; (**b**) PAP

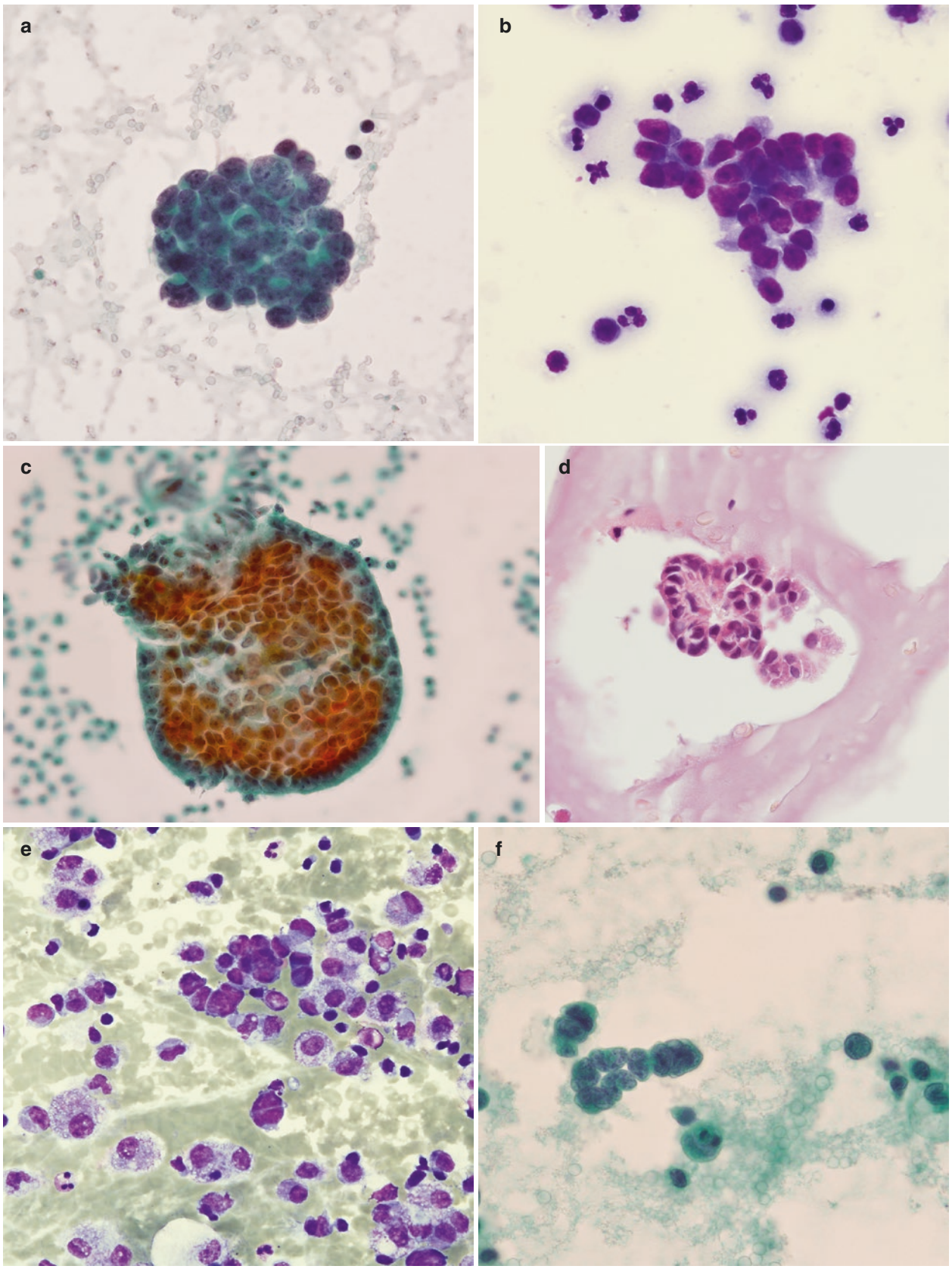


Fig. 7.21 Primitive neuroectodermal and small round blue cell tumors: (**a**) *neuroblastoma*. Tight cluster of atypical cells with high n/c ratio, coarse chromatin, and distinct nucleoli; (**b–d**) *Wilms' tumor*. Small tumor cells with moderate atypia and distinct nucleoli forming primitive structures. (**e**, **f**) *PNET*. Tumor cells with high n/c ratio, some poorly preserved, with molding and cytoplasmic vacuolization (**e**) or chain formation (**f**). (**a**, **c**, **f**) PAP; (**b**, **e**) MGG; (**d**) H&E

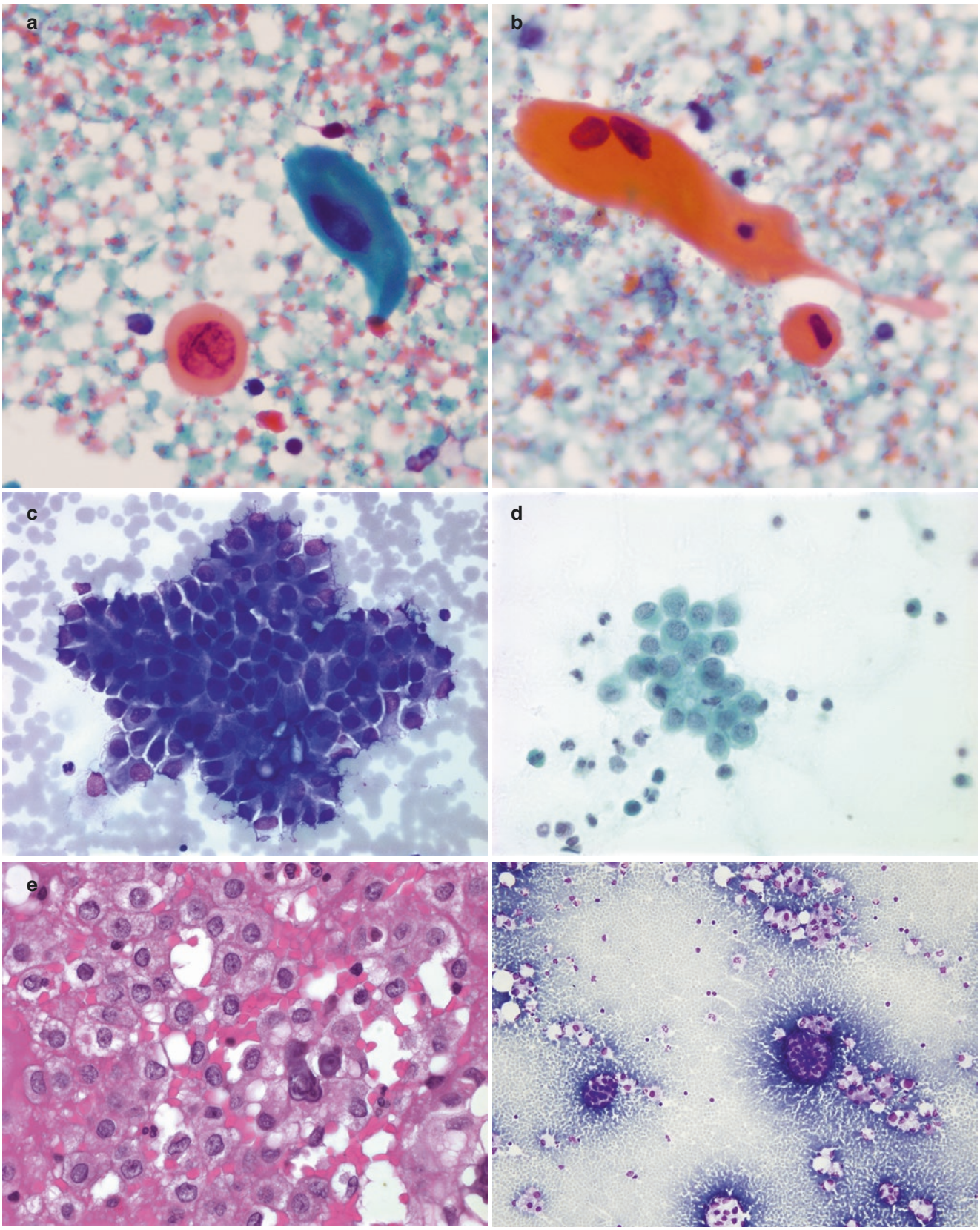
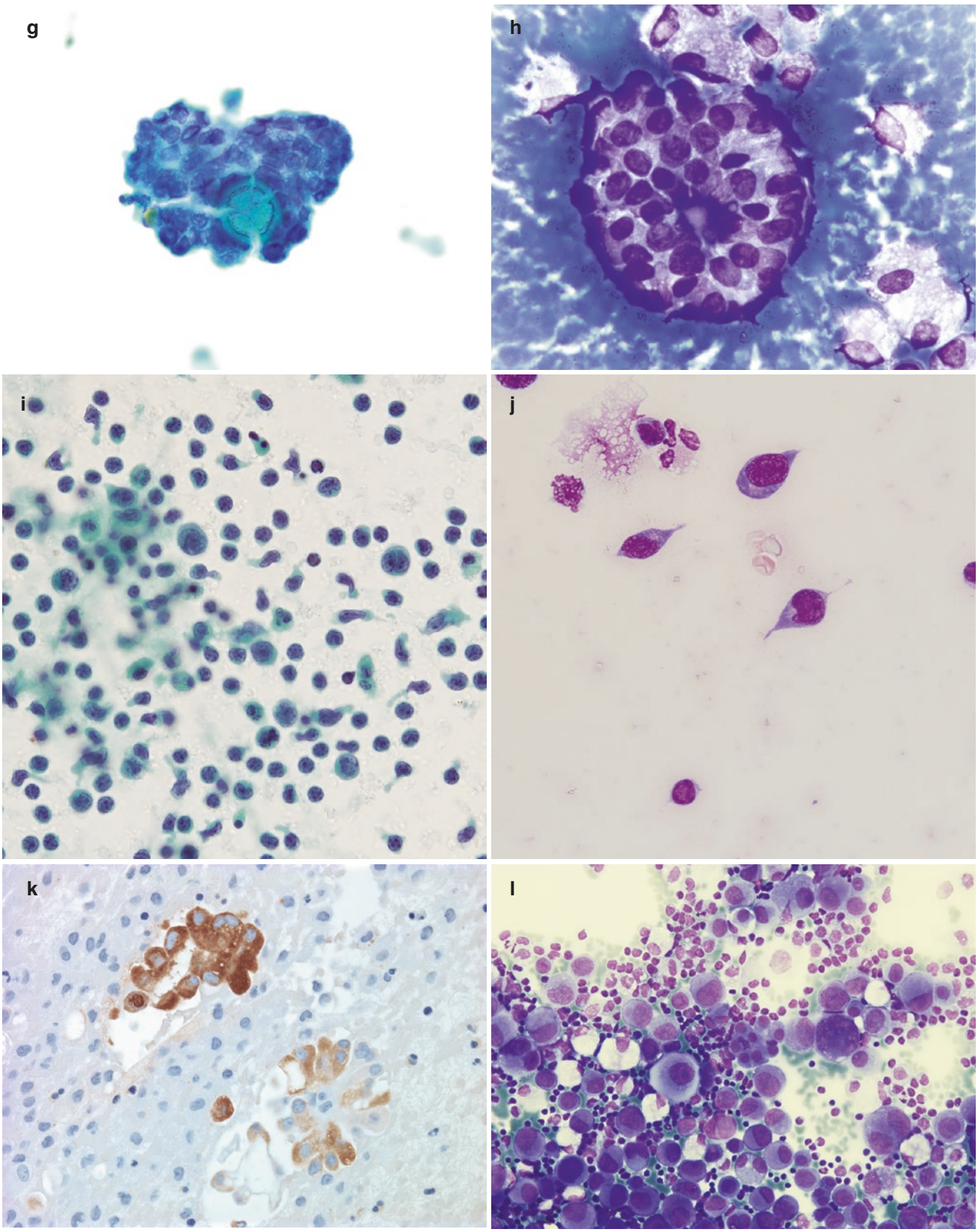


Fig. 7.22 Head and neck tumors. *Larynx*: (**a**, **b**) squamous cell carcinoma of the larynx. *Thyroid*: (**c**–**h**) two papillary thyroid carcinomas. Calcifications are evident in both cases. (**i**, **j**) medullary carcinoma of the thyroid. Dissociated cells of variable size, some spindle-shaped. (**a**, **b**, **d**, **g**, **i**) PAP; (**c**, **f**, **h**, **j**) MGG/Diff-Quik; (**e**) H&E. (**k**) thyroglobulin immunostaining in the specimen seen in **c** to **e**; *Parotid*: (**l**–**n**) metastatic carcinoma of parotid gland origin. Dissociated tumor cells are seen in **l**, **m**, MGG/Diff-Quik; (**n**) androgen receptor immunostaining



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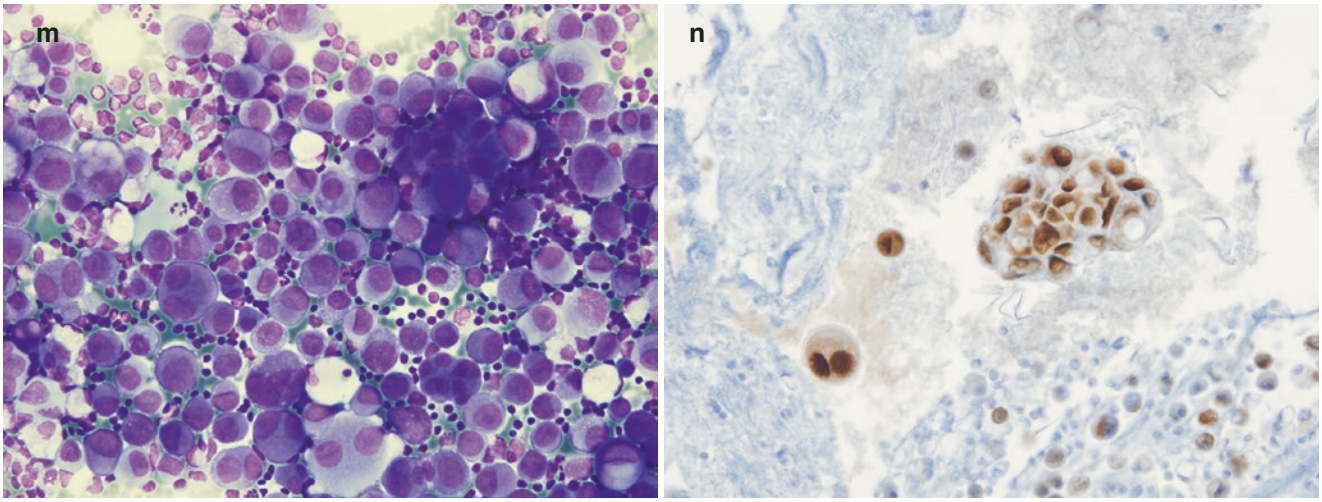

Fig. 7.22 (continued)

Rare reports of malignant effusions with non-thyroidal head and neck tumors have been published, including metastasis from a lymphoepithelial carcinoma in the pleural cavity [167] and metastasis from an adenoid cystic carcinoma [168]. Metastasis from the latter entity was also described from a primary cutaneous tumor [169].

Metastatic carcinoma of parotid gland origin was diagnosed by one of the authors. Tumor cells expressed androgen receptor (Fig. 7.22l–n).

Concluding Remarks

The breadth of differential diagnosis of cancer in serous effusions is evident from the above-discussed entities, as well as from the other chapters in this section. As is true for all pathology specimens, clinical data may resolve much of the difficulty. Their absence requires careful prioritizing of the most plausible differential diagnoses based on the morphological findings and patient age and gender. This may aid in directing the ancillary tests in a cost-effective direction. Nevertheless, some undifferentiated tumors require inclusion of all major cancer types in the differential diagnosis. In these cases, the use of selected antibodies that identify carcinoma, melanoma, sarcoma, and hematological tumors is mandated, followed by a second panel which should be more focused on the tentative diagnosis. Our suggestions for antibody panels that are relevant in the diagnostic algorithm for effusion work-up, with focus on epithelial and mesothelial cells, are presented in the **Appendix** of this section. Molecular testing is rapidly becoming central in classifying some of the malignancies affecting the serosal cavities, including in soft tissue and bone tumors, pediatric cancers, and hematological malignancies, but as carcinomas outnumber all other cancers, the majority of cases can still be resolved using immunohistochemistry. High-throughput technology, particularly next-generation sequencing, is likely to play a growing role in the setting of targeted therapy for these tumors in coming years.

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