Body Cavity Fluids

5

Introduction

The body cavities, including pleural, pericardial, and peritoneal cavities, lie within a double-layered serous membrane lined by flat mesothelial cells. The inner layer invests the organs and is called the visceral layer, and the outer is called the parietal layer. A potential space separates the two layers. Under normal conditions the cavities contain only minimal amount fluid which lubricates the two adjacent layers as they move. Larger amount of fluid, an effusion, accumulates during disease states.

Two types of effusions are recognized, transudate and exudate.

- *Transudate* results from imbalance of hydrostatic and oncotic pressures. Hydrostatic pressure is increased and oncotic pressure is reduced in congestive heart failure, cirrhosis, peritoneal dialysis, and nephrotic syndrome. Transudate may be straw-colored, clear or opalescent, and watery, with a low protein content of <3 g/dL, low lactate dehydrogenase (LDH), and specific gravity of less than or equal to 1.015 with low cellularity.
- *Exudate* results from increased capillary permeability due to injury to mesothelium as in malignancy, inflammatory conditions, connective tissue diseases, pulmonary infarction, drug sensitivity, or trauma. Exudates have relatively high total protein content of >3 g/dL, high LDH, and a specific gravity of more than 1.015 with high cellularity.

The distinction between transudate and exudate is made by measurement of protein concentration and specific gravity. This distinction is important because cytological examination of a transudate is generally not needed, whereas an exudate may result from malignant tumors or infectious processes and requires cytological assessment.

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Body Cavity Fluid Preparations

TP and SP have been utilized for non-gynecologic (non-gyn) specimens since 1991 and 1999, respectively. Since then, the use of LBP has become widespread. Several laboratories have now substituted traditional preparations (i.e., smears, filters, cytocentrifuges, and cell block) with LBP or now use LBP in addition to the classical methods. LBP perform as well, and sometimes better than, traditional preparations.

Types of Body Cavity Fluid

The body cavity fluid specimens pose a daily challenge in current cytopathology practice, especially with regard to distinguishing malignancies from reactive mesothelial cells. Specimen types include pleural, peritoneal (ascites), and pericardial effusions, cerebrospinal fluid, and pelvic washings (PW). Neoplastic entities can be:

1. *Pleural and peritoneal effusions*
   - *Primary*
     - Mesothelioma
     - Papillary serous carcinoma (peritoneal effusion)
   - *Secondary* (*metastatic*)
     - Epithelial
       - Adenocarcinoma of the lung, breast, GIT, and gynecological origin
       - Squamous cell carcinoma
       - Small cell carcinoma
     - Non-epithelial
       - Hematopoietic and lymphoid malignancies
       - Melanoma
       - Sarcoma
2. *Pelvic washings*
   - Same as the above

Immunocytochemistry

Immunocytochemistry is useful in distinguishing reactive mesothelial cells from malignant cells, evaluation of unknown primary sites of origin, and confirming a known malignancy involving body cavity fluids. For immunostaining, cell block sections are recommended, but immunostains can also be performed on additional LBP made from residual specimens.

Cytology of Body Cavity Fluids on LBP

The cytological criteria of malignancy include high specimen cellularity with two distinct cell populations. In a CAP interlaboratory comparison program TP performed slightly better than classical preparations in diagnosing adenocarcinoma in body cavity fluid cytology. In this regard, some caveats follow:

- With malignant effusions, typically there is a history of malignancy.
- An effusion as primary presentation of malignancy is rare.
- Bloody effusions are more likely to be associated with malignancy (blood does not obscure cells in LBP).
- Malignant effusions show high cellularity and cellular discohesion.
- Pleural effusions, processed as TP, do not appear to provide additional diagnostic value when compared to cytospin DQ-stained preparations for distinguishing mesothelioma from adenocarcinoma, since the key distinguishing cytological features of mesothelioma and adenocarcinoma can be observed in both preparations [1].
- Malignant cells in body cavity fluids differ from those in exfoliative, brushing, and FNA specimens.
- Cells "round up" in effusions, and this feature is more prominent in LBP.

Diagnostic Categories for Body Cavity Fluid Cytology

Usually four diagnostic categories are used including negative, atypical, suspicious, and positive for malignancy.

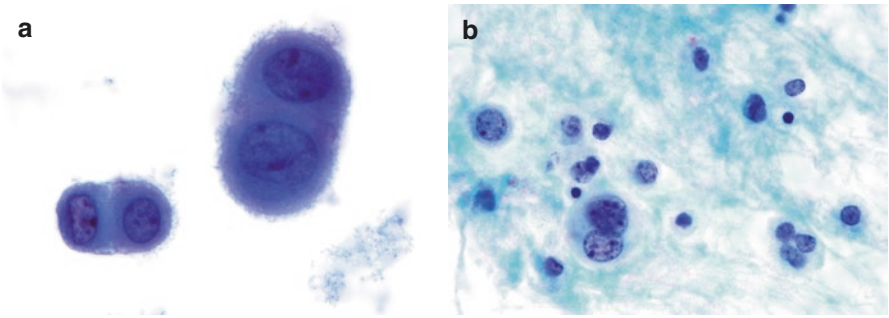

Fig. 5.1 Benign pleural effusion. (**a**) Mesothelial cells are the most common type of cells in effusions. Mesothelial cells are larger than other cells typically seen in effusions (i.e., lymphocytes and histiocytes) and contain abundant amphophilic cytoplasm. There is peripheral paler staining of cytoplasm (cytoplasmic "skirt"). Mesothelial cells may appear singly or in clusters. When two mesothelial cells lie together, they often form a "window" between the cells due to long microvilli. Epithelioid features in mesothelial cells can be mistaken for metastatic adenocarcinoma, especially when reactive changes are present (TP). (**b**) The larger cells with coarser chromatin, one binucleated, are mesothelial cells; other cells present are lymphocytes and histiocytes. While LBP typically shows a clean background, some granular material may be evident, representing degenerated blood cells and fibrin (TP)

Fig. 5.2 Benign peritoneal washing. Compared to effusions, washing specimens have a tendency to disrupt the mesothelial lining. Here, a monolayered sheet of benign mesothelial cells can be seen with an organized honeycomb appearance. The chromatin is bland. Also present are single mesothelial cells, inflammatory cells, and histiocytes. Mesothelioma should be excluded when sheets of mesothelial cells are seen in effusions (TP)

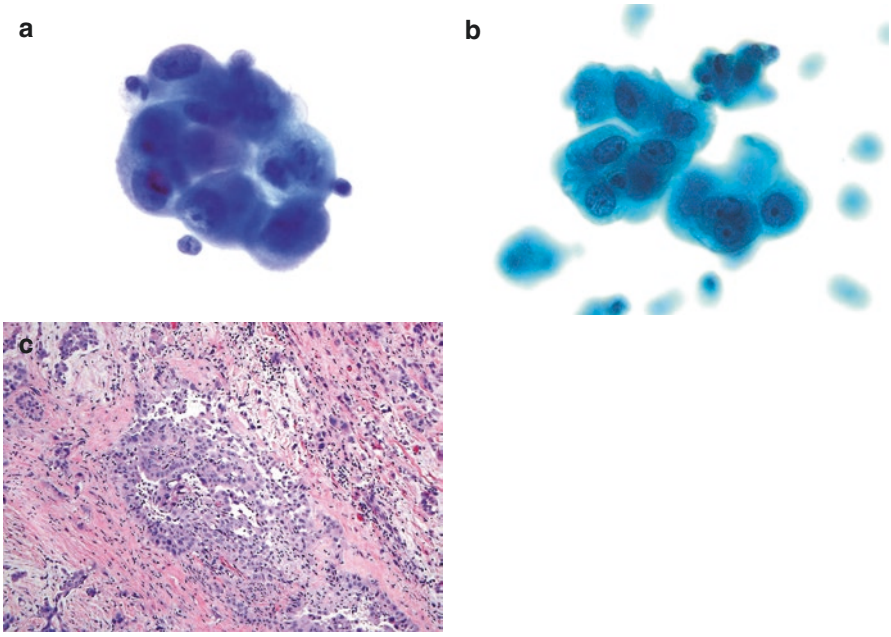

Fig. 5.3 Mesothelioma. (**a**) Compared to sheets of mesothelial cells seen in previous figures, mesothelioma cell nuclei are enlarged and overlap. Note parachromatin clearing around macronucleoli and nuclear hyperchromasia. The "hobnail" appearance is more suggestive of mesothelial origin than adenocarcinoma. Clinical history of asbestos exposure and smoking and radiological evidence of pleural or peritoneal plaques or nodularity are helpful (TP). (**b**) Mesothelioma in SP specimen. Note similarity in cytological appearance with TP in (**a**) with "hobnail" appearance, prominent nucleoli, parachromatin clearing, and "windows" between cells (SP). Mesothelioma can have different morphologies [2]. (**c**) Histologically, the mesothelial cells are epithelioid and infiltrate pleura (H&E). The images depicted are from a pleural effusion from an 80-year-old shipyard worker. Immunostains can help exclude metastatic adenocarcinoma, a malignancy which is more common in effusions than mesothelioma. Mesothelioma (and reactive mesothelial cells) is positive for calretinin and WT1, while adenocarcinoma is positive for epithelial markers such as BerEP4 and MOC31

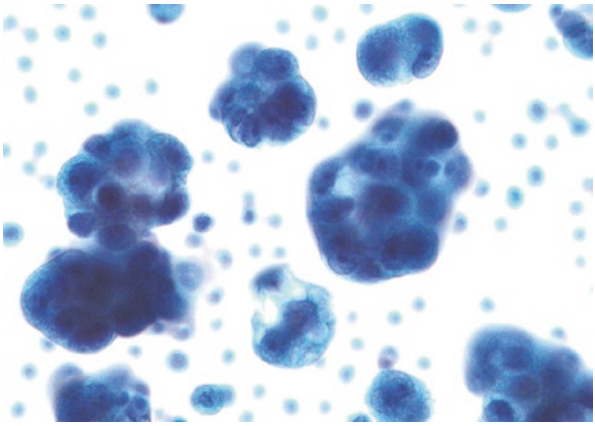

Fig. 5.4 Metastatic ovarian adenocarcinoma. The specimen is hypercellular, with clusters of malignant cells that have prominent nucleoli and high nuclear-to-cytoplasmic ratio. The carcinoma cells are large and their three-dimensional quality is maintained on SP. Some cells show mucinous vacuoles which indent nuclei. Note smooth edges ("community" border) of cell clusters. The background cells are out of focus being in a different plane of focus (SP). Reactive mesothelial cells can also have vacuolization that may be mistaken for mucin [3]; however, benign vacuoles in mesothelial cells do not indent nuclei

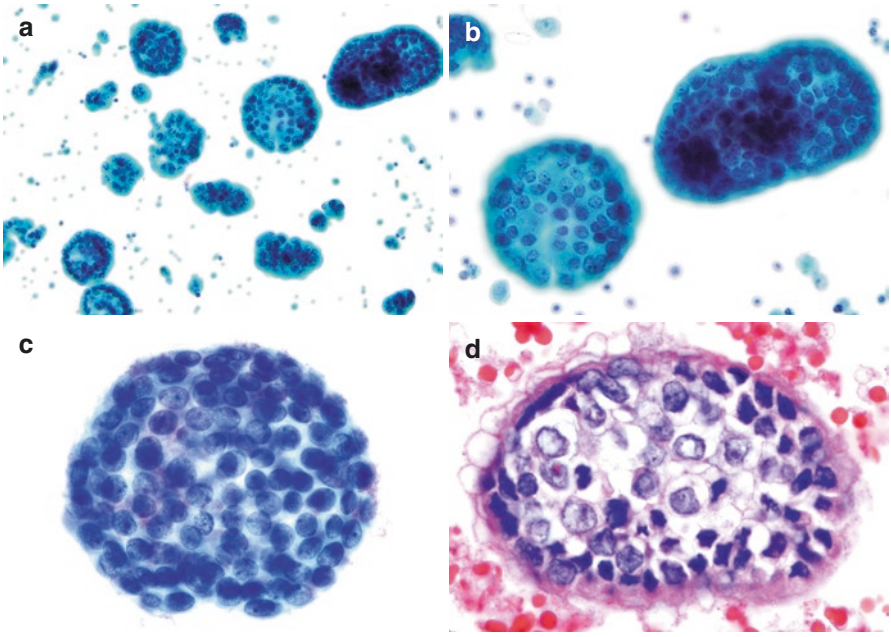

Fig. 5.5 Metastatic ductal carcinoma of the breast. (**a**, **b**) Metastatic ductal carcinoma of the breast showing high cellularity. Note three-dimensional clusters of cells with smooth borders, known as proliferation spheres or "morulas," a characteristic feature of metastatic breast carcinoma. Compare this to the scalloped border of mesothelioma in Fig. 5.3a, b. Single malignant cells are present. Nuclei are moderately enlarged, somewhat hyperchromatic with nucleoli and parachromatin clearing, and cytoplasm is denser (**a**, SP; **b**, SP). (**c**) The morula as seen on TP has similar cytomorphology to SP. However, cytoplasm is less dense than SP (TP). Most effusions are evaluated for metastatic malignancies and usually show two-cell population of benign mesothelial cells and malignant cells. **(d)** The corresponding correlate of morula on cell block (H&E)

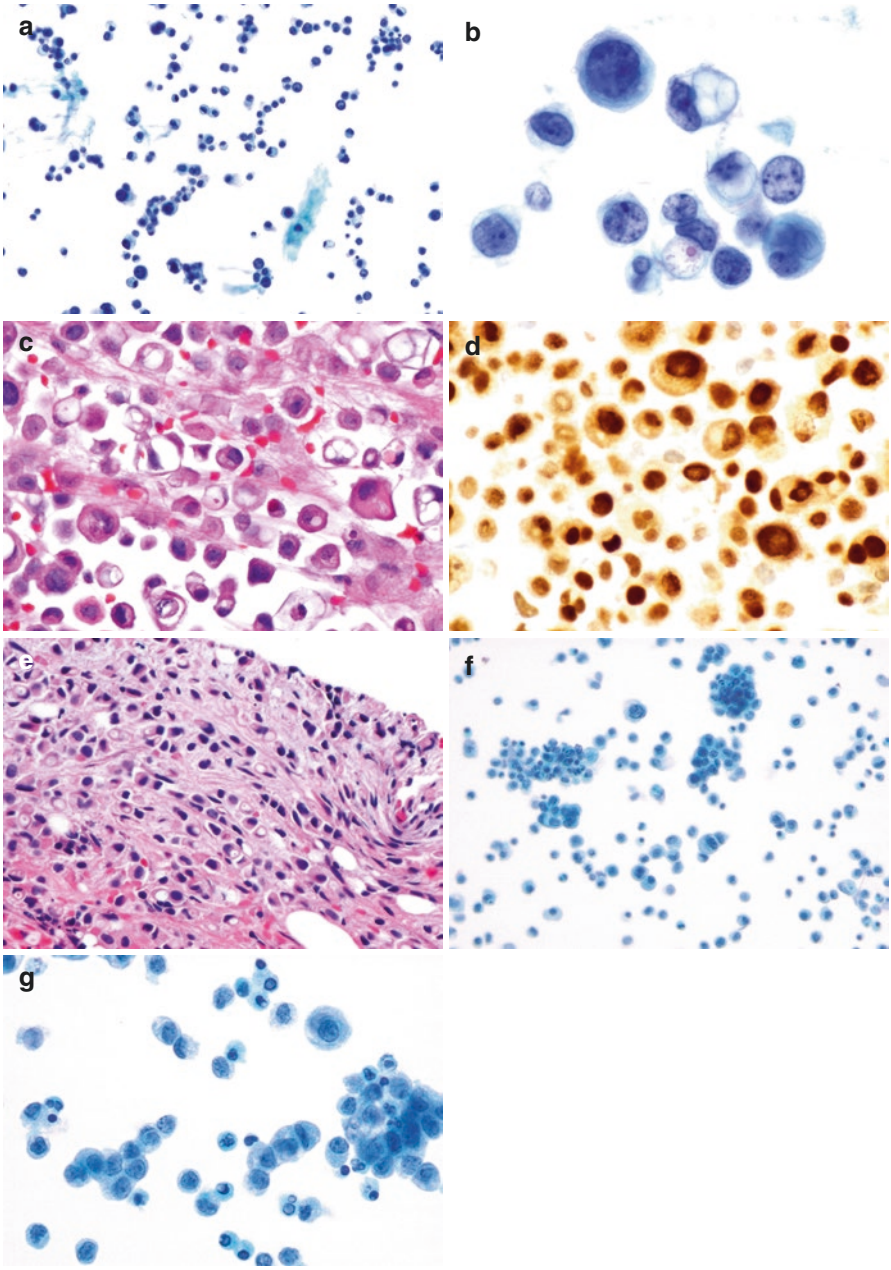
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Fig. 5.6 Metastatic lobular carcinoma of the breast. (**a**) A highly cellular specimen, but in contrast to previous figure of ductal breast carcinoma. Lobular carcinoma cells are more discohesive and are more difficult to distinguish from background mesothelial cells. Some cells appear to form distinct linear arrangements ("Indian-file" pattern). Note small cell size and eccentrically located nuclei (TP). (**b**) Closer inspection reveals the neoplastic cells vary in size and shape (pleomorphic). Nuclei are eccentric with irregular, thick membranes, vesicular chromatin, and small nucleoli. The cytoplasm is vacuolated. Note characteristic signet ring cell with cytoplasmic vacuole and pink-staining mucinous condensation. Such cells are pathognomonic for lobular carcinoma of the breast (TP). (**c**) Cytomorphology seen on cell block is comparable to TP. A few cells show mucinous condensation, which would be highlighted by a mucicarmine stain (H&E). (**d**) An immunohistochemical study for GATA-3 on the cell block section shows strong nuclear positivity, confirming breast origin (GATA-3 IHC). One study has shown that immunostains perform equally well on TP as on cell block sections. The latter preparations are superior for nuclear markers such as p53 [4]. (**e**) Core biopsy of primary lobular carcinoma shows similar cytological features as TP and cell block, with infiltrating single cells (H&E). (**f**, **g**) Metastatic lobular carcinoma of the breast in a pleural effusion processed as SP. Cytomorphology is similar to that described for TP in figures (**a** and **b**) (SP)

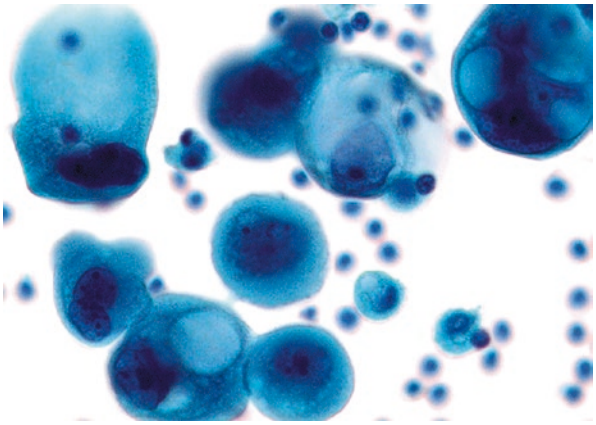

Fig. 5.7 Metastatic adenocarcinoma of the lung. This is one of the most common malignancies to involve pleural cavity. Malignant cells are greatly enlarged and show enlarged, irregular, hyperchromatic nuclei with prominent nucleoli and large cytoplasmic vacuoles, some multiple. Mucinous condensation is not seen. In a patient with a history of lung adenocarcinoma and absence of any other malignancy, the cytomorphology alone is enough for a diagnosis without confirmatory IHC. Molecular assessment, if requested by clinicians, can be performed on cell block preparations (SP)

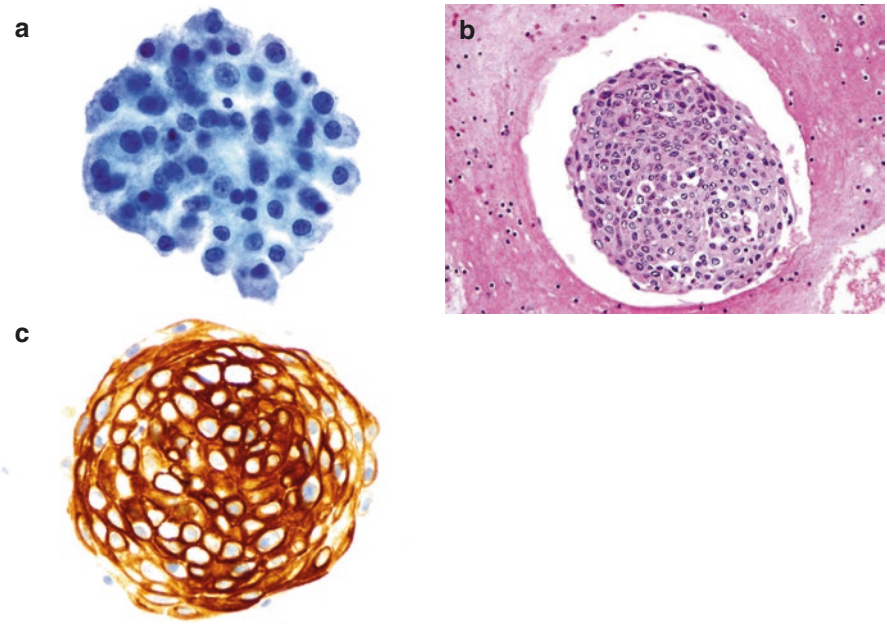

Fig. 5.8 Metastatic squamous cell carcinoma of the lung. (**a**) This was a challenging case as malignant cytology on TP was not clearly evident. The cell block preparation was instrumental in rendering an accurate diagnosis. Squamous cell carcinoma uncommonly involves pleural effusions; the cells here have centrally placed nuclei and appear to have spaces between the cytoplasmic borders. This feature may mimic "windows" seen between cells of mesothelial origin and suggest mesothelioma. The cytoplasm does appear somewhat dense, and the cell border appears smooth [5] (TP). (**b**) The cell block material shows a rounded cluster of tumor cells within a distinct lacunar space, often formed artifactually around metastatic carcinomas on cell block preparations. Even at low-power microscopy, cytology appears similar to TP (H&E); (**c**) immunostain for cytokeratin 5/6, performed on cell block sections, shows strong cytoplasmic positivity (CK5/6 IHC). Other squamous cell carcinoma markers such as p40 and p63 (nuclear stains) were also immunoreactive in this case

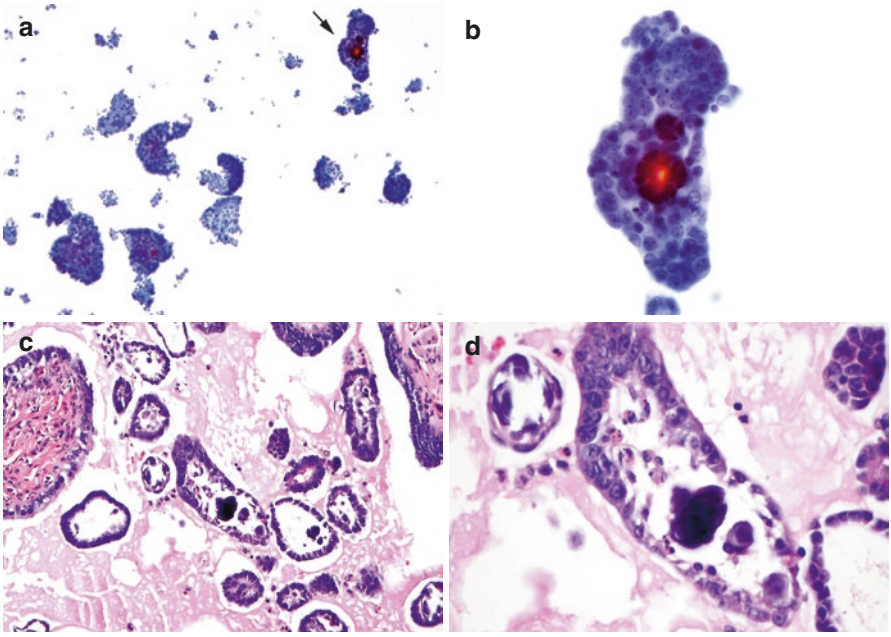

Fig. 5.9 Borderline serous tumor of the ovary. (**a**) The specimen has high cellularity with large hyperchromatic, papillary three-dimensional structures, smaller groups, and single cells. Note intact psammoma body in a group at 2 o'clock position (TP). **(b)** At closer examination, the three-dimensional group of tumor cells contain psammoma bodies. Note smooth "community" border, overlapping tumor cells with subtle cytological atypia. Peritoneal effusions may contain psammoma bodies in the absence of malignancy when mesothelial hyperplasia is present. Nuclear atypia is absent in benign mesothelial cells [6] (TP). (**c**, **d**) Histological section shows borderline tumor of the ovary. (**c**, H&E; **d**, H&E)

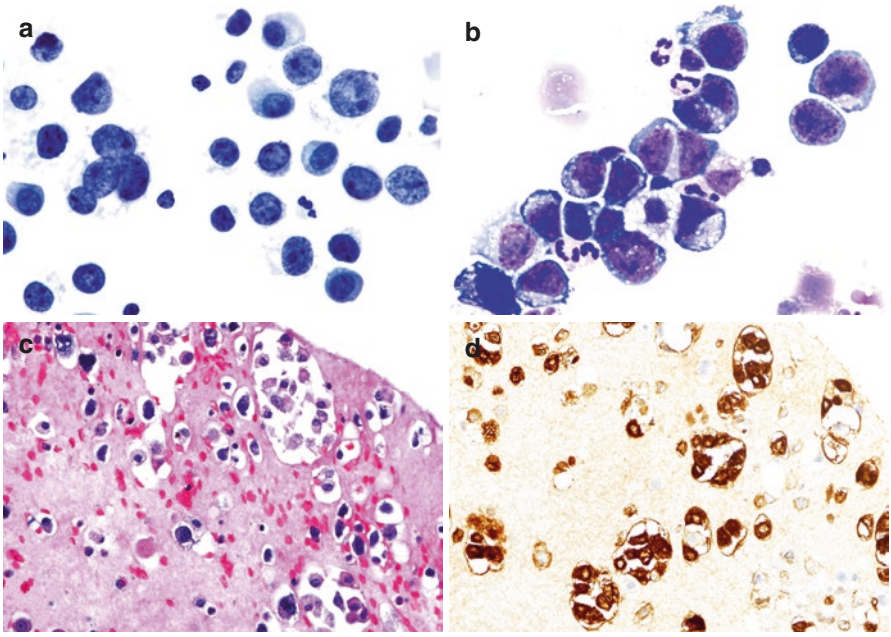

Fig. 5.10 Acute myeloblastic leukemia (AML). (**a**) Hematolymphoid processes can involve effusions and may blend with inflammatory cells. In this case, the patient has a history of AML which involved the pleural cavity. The cells are mostly singly dispersed, are large (compared to neutrophils), have delicate cytoplasm and enlarged nuclei with coarse chromatin on TP, and may be difficult to distinguish from mesothelial cells and other malignancies. Differential diagnosis with single malignant cell includes poorly differentiated carcinoma and melanoma (TP). (**b**) A Giemsa-based stain allows myeloid features of the malignant cells to be better recognized. The characterization of acute leukemias is based on a multiparametric analysis including clinical features, cell morphology, cytogenetics, and flow cytometry. The latter is important in identification of lineage. Additional material needs to be submitted for special studies (Giemsa-stained TP). (**c**) AML on cell block shows individual atypical cells, some binucleated, in lacunar spaces (H&E); (**d**) immunostain for CD163 was positive

Suggested Reading

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