8 Mediastinum and Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

Henryk A. Domanski, Nastaran Monsef, Anna M. Domanski, and Włodzimierz Olszewski

Mediastinum

Introduction

Due to the complex anatomy of the mediastinum and its proximity to a number of organs, a variety of neoplastic and nonneoplastic lesions may occur in the mediastinum (see Table 8.1). The majority of these are accessible via fine-needle aspiration cytology (FNAC) [1–6]. The main indication for FNA in the mediastinum is to distinguish between neoplasm and nonneoplastic conditions and between benign and malignant neoplasm. FNA of the mediastinum has been successfully used for the confirmation of metastasis from different origins. Since the introduction of FNA guided by endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS), its use has rapidly increased in staging of lung carcinoma and in establishing the mediastinal lymph node status in other malignancies. In addition, FNA of the mediastinum has been increasingly accepted as a diagnostic modality in the investigation of primary mediastinal neoplasm. As in other locations, rapid on-site evaluation (ROSE) of the FNA aspirate increases diagnostic yield and possibility to receive material for ancillary techniques [7].

H. A. Domanski (✉) · A. M. Domanski
Department of Pathology, Skåne University Hospital, Lund, Sweden
e-mail: henryk.domanski@med.lu.se; anna.domanski@skane.se

N. Monsef
Department of Pathology and Genetics, University Hospital, Linköping, Sweden
e-mail: nastaran.monsef@regionostergotland.se

W. Olszewski
Department of Pathology, The Maria Sklodowska-Curie Cancer Center and Institute of Oncology, Warsaw, Poland
e-mail: wtolszewski@coi.waw.pl

Diagnostic Accuracy of FNA

Powers et al. [3] reported in a multi-institutional analysis of 189 cases of percutaneous mediastinal FNA a diagnostic sensitivity and specificity of 87–88% for the detection of neoplasm and 82–83% for distinguishing benign from malignant disease. In this study of FNAC of mediastinal lesions in adults, the most common primary neoplasm was malignant lymphoma and thymoma. In a study by Shabb et al. [8], FNA yielded the correct diagnosis in 86% of cases. Malignant lymphomas followed by neurogenic neoplasm, germ cell neoplasm, and sarcomas are the most common mediastinal neoplasms in pediatric population [9]. A high rate of correct diagnosis in FNAC of mediastinal lesions in children has been also reported [10].

With respect to transbronchial and transesophageal sampling of mediastinal neoplasm, accuracy of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for staging of lung carcinoma shows sensitivity of up to 98.7% and specificity of 100% [11–13].

Table 8.1 The most common mediastinal targets of FNA correlated to anatomical compartment

Region of mediastinum	Type of neoplasm/lesion
Superior	Thymoma/thymic lesions
	Retrosternal goiter
	Lymphoma
	Metastatic carcinoma
Anterior	Lymphoma
	Thymoma/thymic lesions
	Germ cell tumors and teratomas
	Metastatic carcinoma
	Endocrine tumors
	Soft tissue neoplasms
Middle	Lymphoma
	Sarcoidosis
	Metastatic carcinoma
	Cysts (bronchogenic, pericardial)
Posterior	Neural neoplasms
	Neuroblastoma and ganglioneuroma
	Lymphoma

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Nonneoplastic Lesions

Cysts

Mediastinal cysts of different types are occasional targets of FNA. The precise diagnosis of a benign cyst in the mediastinum may be difficult to render from aspiration smears, as many aspirates yield only watery or mucoid fluid with scattered histiocytes and inflammatory cells (see Fig. 8.1). In such cases, the results of cytological examination correlated with imaging studies and clinical data may indicate benign cyst. In some aspirates from mediastinal cysts, smears contain some of the lining cells, which may help to pinpoint a specific diagnosis. Distinguishing thymic cysts from cystic thymoma may be impossible, however, as aspirates from both entities may contain thymic elements. Some other mediastinal neoplasms such as teratoma, seminoma, thymic carcinoma, and neuroendocrine carcinoma may all undergo cystic changes (see Fig. 8.2), and guiding FNA sampling from solid areas of the lesion is necessary to obtain diagnostic smears.

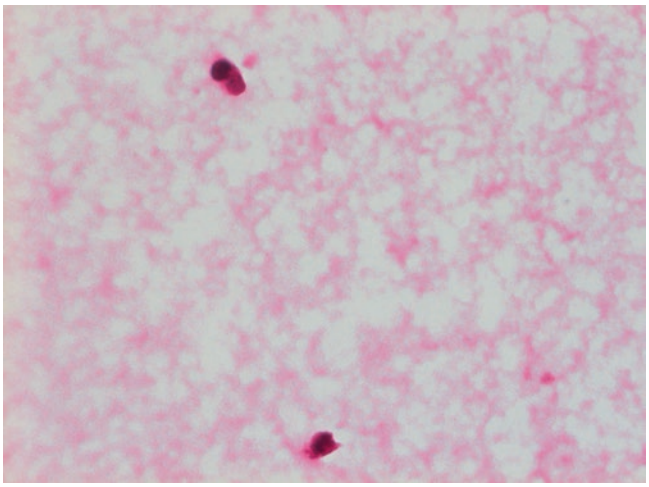

Fig. 8.1 Mediastinal cyst. Smear shows nonspecific picture of watery fluid with scattered histiocytes (hematoxylin and eosin [H&E])

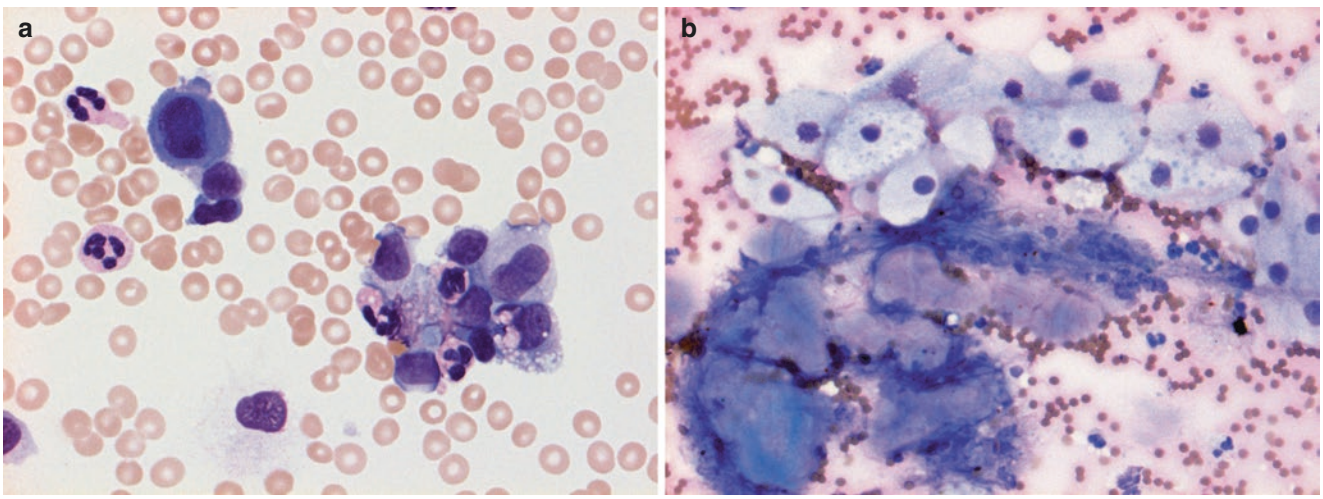

Fig. 8.2 Mediastinal cyst. (**a**) A poorly cellular smear with scattered columnar cells without any specific diagnostic features. (**b**) Mature squamous cells indicative for mature cystic teratoma (May–Grünwald–Giemsa [MGG])

Inflammatory and Reactive Lesions

Enlarged mediastinal lymph nodes and masses suspected as being malignant may show an inflammatory picture. Granulomatous processes may be representative for tuberculosis [14] and other inflammations such as sarcoidosis (see Fig. 8.3) [15] but also for reactive components of neoplastic processes (see Fig. 8.4). Etiologic factors such as bacterial and fungal infections as well as autoimmune disease can lead to the development of chronic (sclerosing) mediastinitis.

Goiter may be present as a mediastinal mass. Aspiration smears from such lesions display the same cytological features as goiter presenting in the neck (see Fig. 8.5).

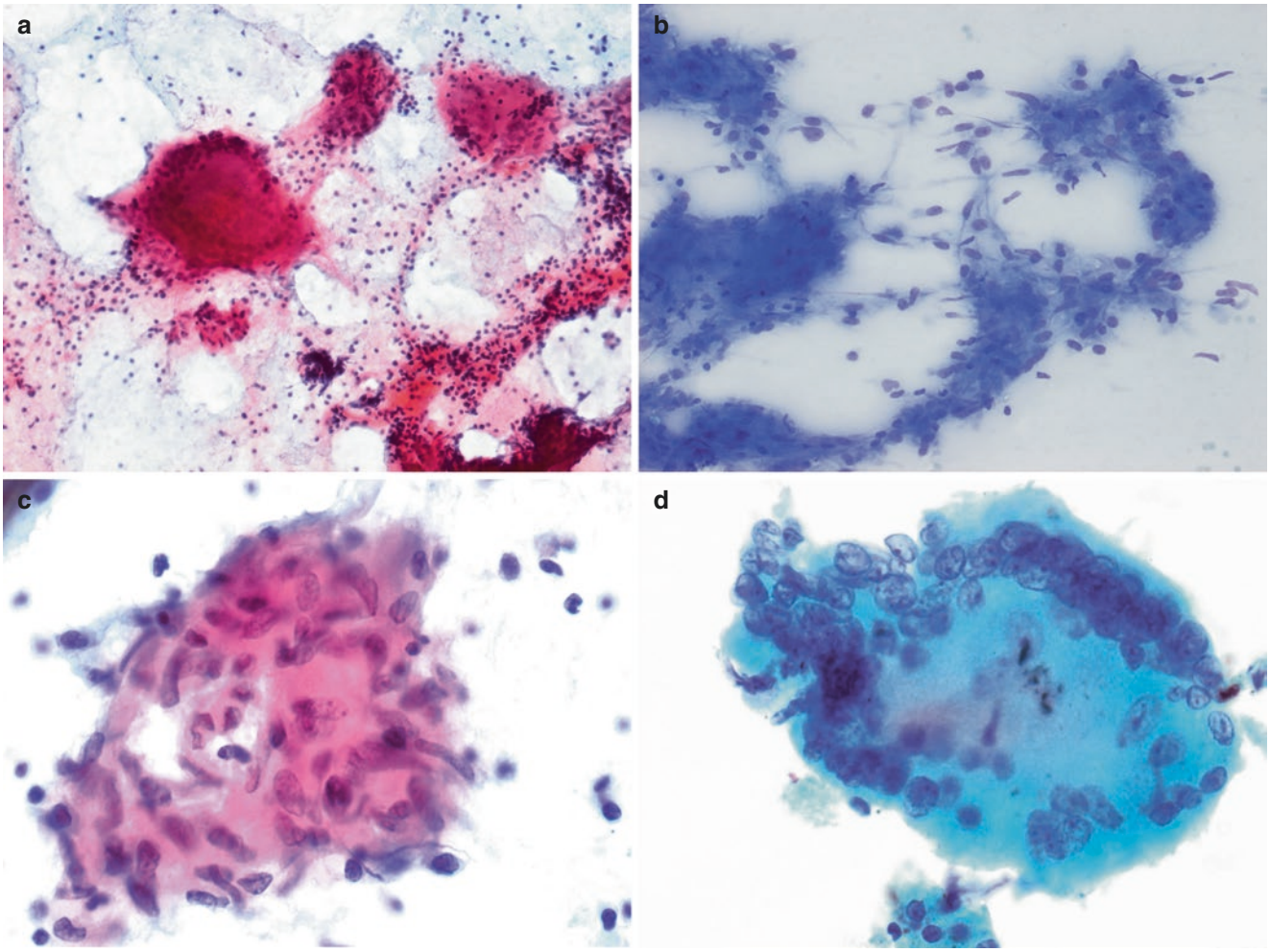

Fig. 8.3 Epithelioid granuloma. (**a**–**c**) Non-necrotizing epithelioid cell granulomas in sarcoidosis (H&E; MGG). (**a**, **d**) Note multinucleated giant cells (H&E; Papanicolaou [Pap] stain)

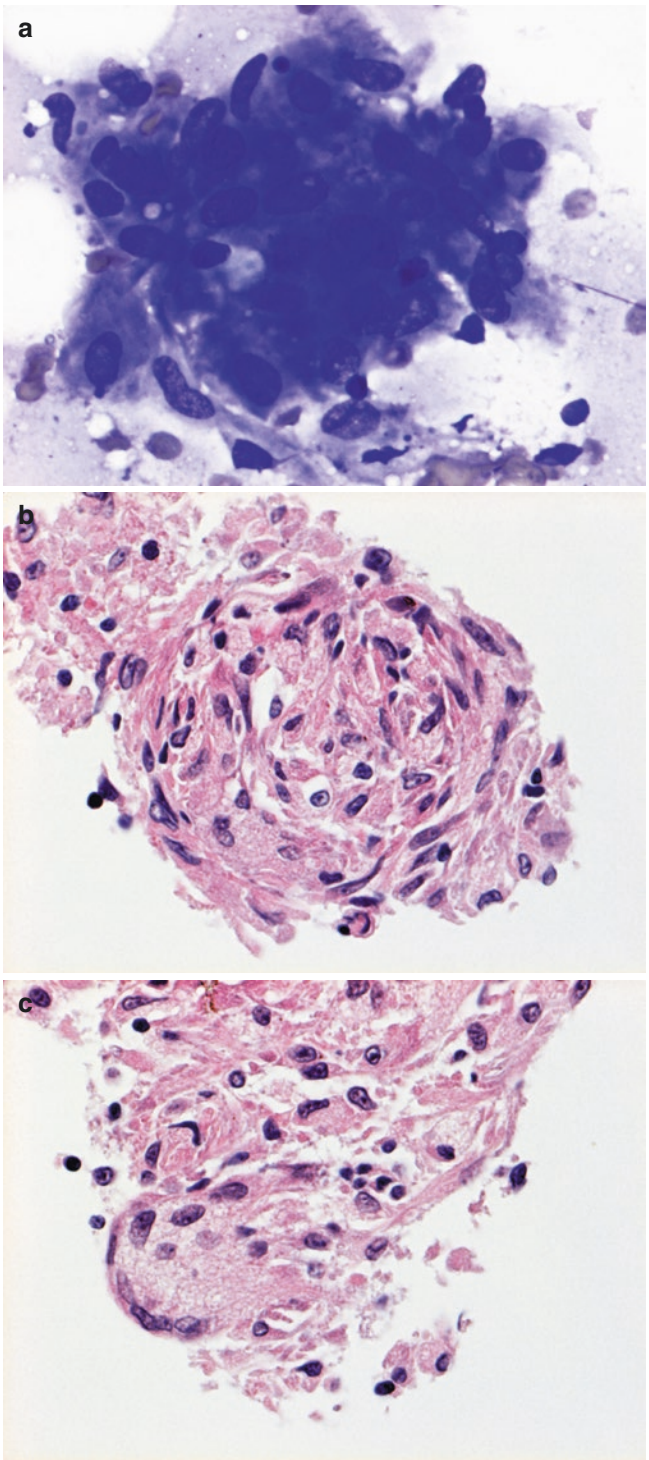

Fig. 8.4 Epithelioid granuloma. Non-necrotizing epithelioid cell granulomas in FNA from the mediastinal lymph node in a patient with metastasizing squamous cell carcinoma. (**a**) Diff-Quik-stained FNA smears. (**b**, **c**) Cell block sections with well-preserved architectural pattern of granuloma and adjacent giant cell (cell block, Cellient; Hologic; Bedford, MA, USA)

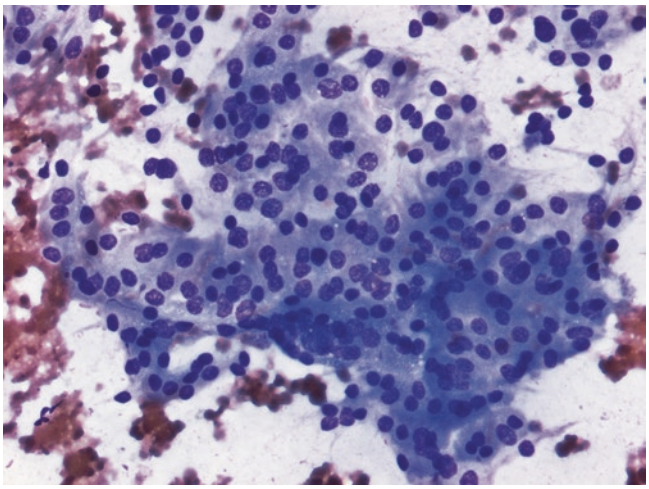

Fig. 8.5 Mediastinal goiter. FNA smears from a mass in superior mediastinal compartment display cytological features of goiter (MGG)

Thymoma

According to the earlier 1999 World Health Organization (WHO), classification of thymomas, types A and AB, was considered to be noncancerous (benign). Types B1 to B3 were classed as low-grade (slow growing), between benign and malignant. Type B2, cortical thymoma, is most commonly associated with myasthenia gravis. Type C was definitely cancer. It is important to realize that this classification was not of great clinical value. The histopathological classification of thymomas has been the subject for long-standing debate, and variable results have been present regarding the reproducibility of the earlier WHO classification. The 1999 WHO histologic classification was revised in 2004 and later 2015 [16]. The currently most widely used histologic classification of thymomas is that of the WHO 2015. The 2015 WHO histologic classification system added additional histologic and immunohistochemical criteria in the different subtypes of thymic neoplasms, and a new atypical type A thymoma variant [16]. The clinical significance of the WHO classification system is still debatable [17, 18]. Along with current concepts of thymomas classification, it can be difficult to distinguish thymomas as to whether they are benign and malignant, as all major thymoma variants can recur and/or metastasize irrespective of tumor stage. The new proposed more clinically relevant TNM system [19, 20] includes parts of the WHO histologic classification and the most commonly used Masaoka-Koga staging system based on the local micro- and/or macroscopic invasion of the tumor and the presence of lymphogenous or hematogenous metastasis. These new histologic classification and staging systems are useful to standardize histopathology reports and as a prognostic indicator for thymic malignancy and tumor recurrence. Classification of thymic neoplasm is even more difficult to apply to FNA samples, as smears of thymomas display variable morphology, depending not only on the specific subtype of tumor but also on heterogeneity of tumor tissue in different areas of the same neoplasm. Reliable cytological criteria for the diagnosis of all subtypes of thymoma defined by the WHO have not yet been established. Primary FNA diagnosis and attempt to classify thymoma in FNA smears in relatively limited material according to the WHO classification have showed high accuracy in some reports [21, 22].

Cytological features helping to render a diagnosis of thymoma from smears include a biphasic pattern of epithelial and lymphocytic components. There are, however, cases with predominantly lymphocytic (smears from WHO type B lymphocyte-rich thymoma) or epithelial components (predominant cell type in smears from WHO type A thymoma) (see Fig. 8.6). FNA smears composed of largely cohesive sheets and clusters of bland-looking polygonal, oval, or occasionally spindle cells with moderate to abundant cytoplasm and well-defined cytoplasmic borders probably represent benign thymomas.

Thymic carcinomas—"high-grade malignant epithelial tumors of the thymus" (C thymomas in the WHO classification)—are carcinomas with several distinct variants and a morphologic appearance similar to squamous carcinoma (see Figs. 8.7 and 8.8), clear cell carcinoma, mucinous carcinoma, anaplastic carcinoma, sarcomatoid carcinoma, and neuroendocrine carcinoma. Correct subtyping of thymus neoplasm according to the WHO and other classifications is thus challenging in FNA smears alone, but separation of thymic neoplasms into low-grade and malignant categories can be done. Similarly, as a cytologic diagnosis of carcinoma can be rendered from FNA smears [23], a specific diagnosis of thymic malignancy may be difficult and requires close correlation with clinical and radiographic findings [22].

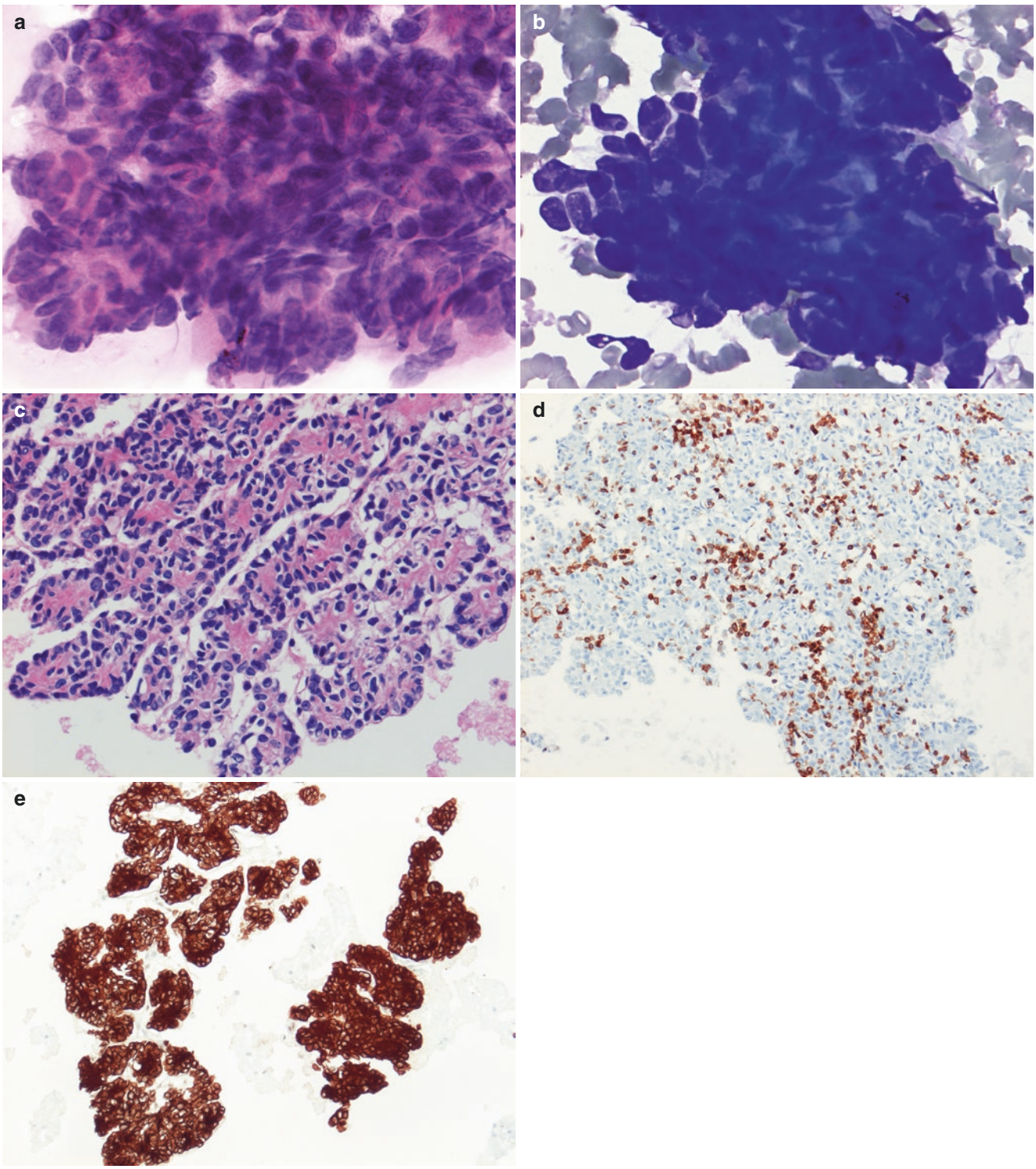

Fig. 8.6 Thymoma type A. (**a**, **b**) FNA smears from superior mediastinal compartment composed of largely cohesive clusters of polygonal and oval cells with slight acinar formations (H&E; MGG). (**c**) Cell block sections showing glandular structures and rosettes without a lumen. (**d**, **e**) Immunostains showing scattered CD3-positive lymphocytes and keratin-positive epithelial component (cell block)

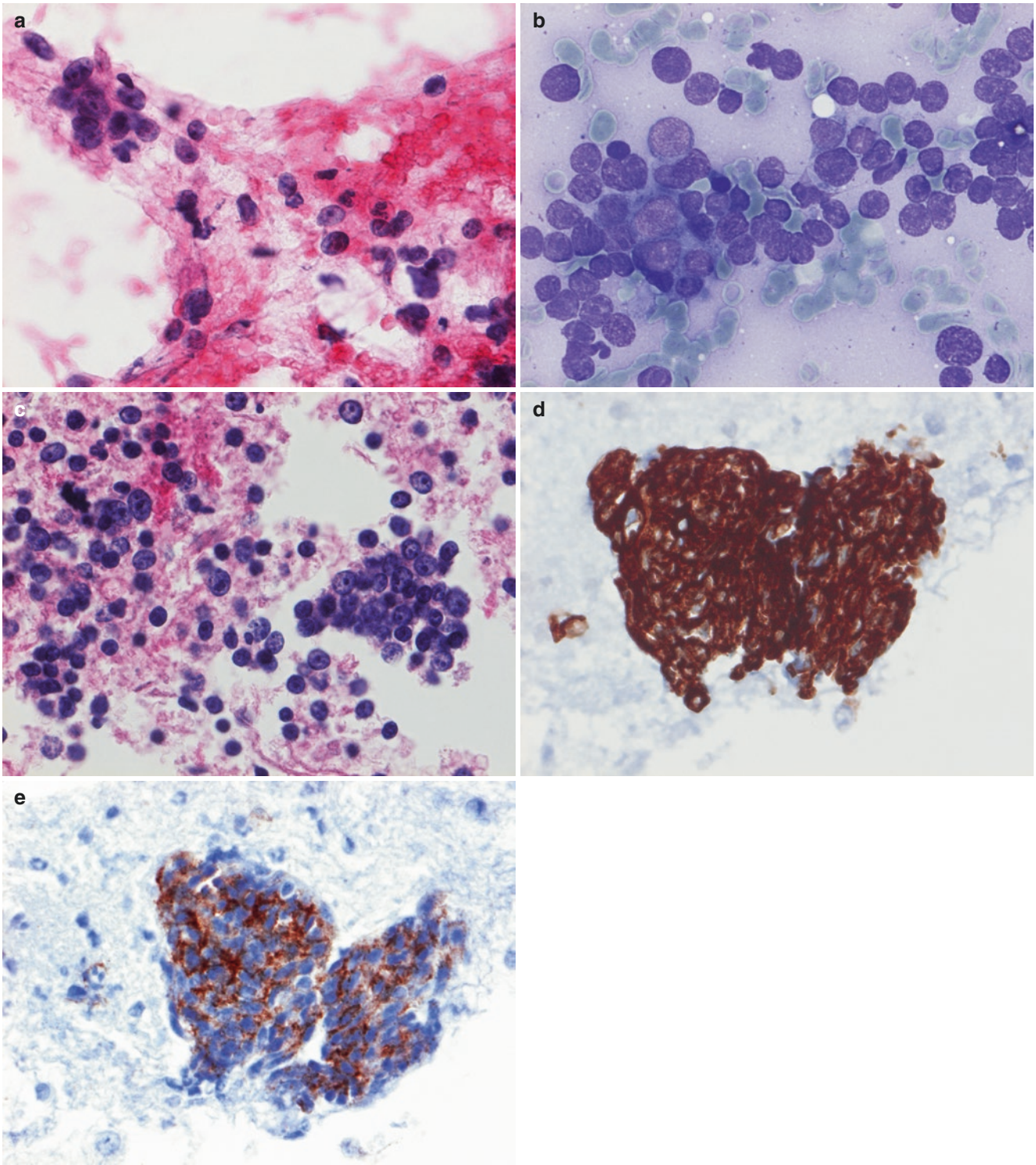

Fig. 8.7 Thymoma type C (thymic carcinoma). (**a**, **b**) FNA smears dispersed single cells or small groups of cells with poorly preserved cytoplasm and bare nuclei with occasional molding (H&E; MGG). (**c**) Cell block section (H&E). (**d**, **e**) Tumor cells are strongly positive for CK5 and weekly positive for CD117 (cell block). The final diagnosis was poorly differentiated squamous cell carcinoma

Metastatic Neoplasm

Metastases are much more common in the mediastinum than are primary tumors. The mediastinum can harbor metastases from almost any primary tumor. Most metastases are from lung carcinoma, followed by breast carcinoma, thyroid, and prostate (see Fig. 8.8) [3, 24]. Mediastinal lymph nodes may also be the site of metastatic sarcomas [5]. In rare circumstances, the mediastinum is a primary site for sarcomas. Metastatic malignant melanoma is not uncommon in mediastinal location.

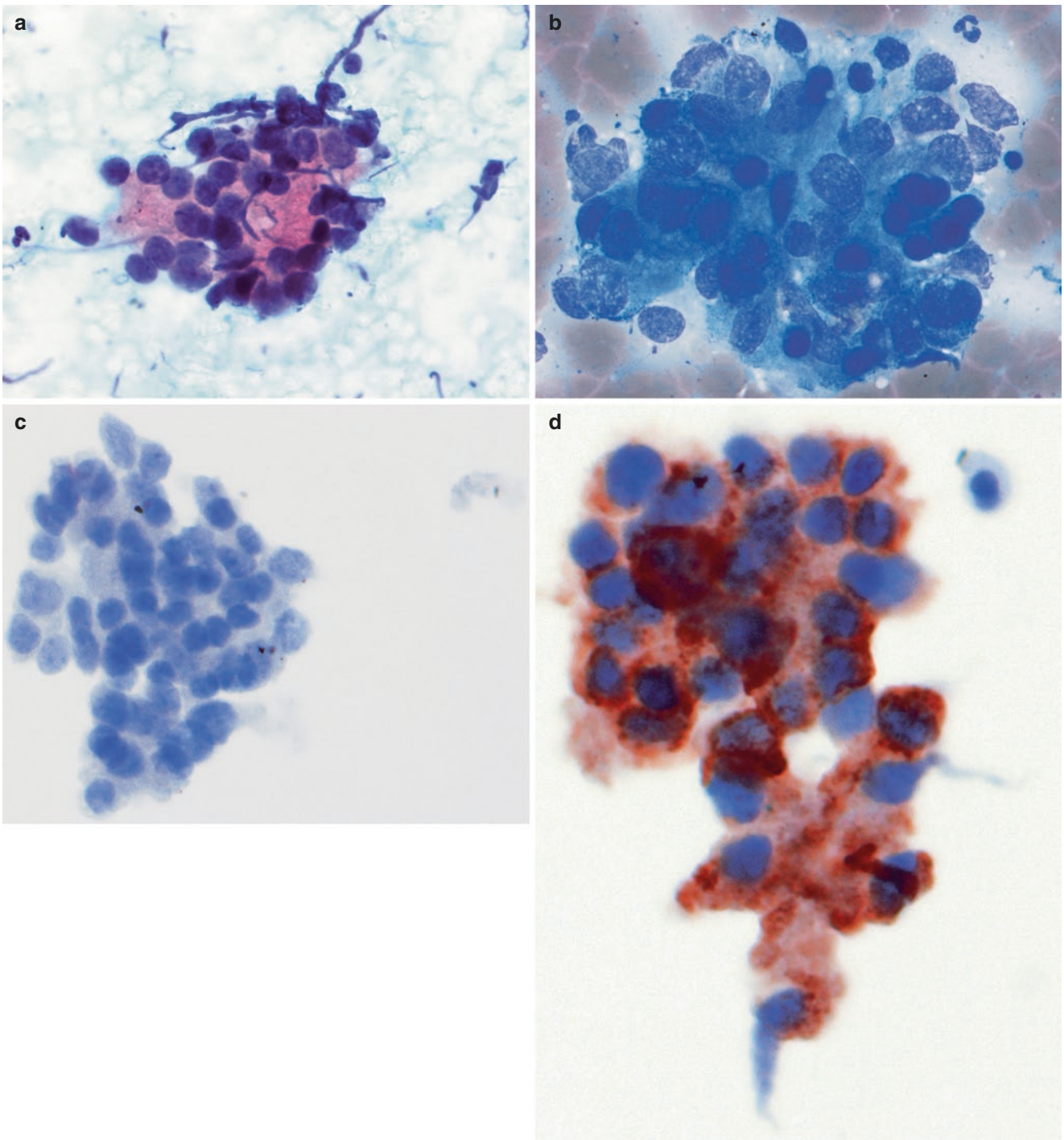

Fig. 8.8 Metastatic prostatic adenocarcinoma. EBUS-TBNA of mediastinal lymph nodes. (**a**, **b**) Clusters of epithelial cells arranged in acinar/alveolar formations (Pap stain; MGG). (**c**, **d**) Immunostainings with results negative for TTF-1 and positive for prostate-specific antigen (PSA) confirm prostate origin

Germ Cell Neoplasm

Germ cell tumors comprise approximately 15% of mediastinal neoplasm in adults and 25% in children. Similar to gonadal sites, germ cell neoplasm may be divided into seminomas and nonseminomatous tumor such as embryonal carcinoma, endodermal sinus tumor (yolk sac tumor), choriocarcinoma, mixed germ cell tumors, and teratomas. Immature teratomas occur almost exclusively in males, whereas mature cystic teratomas occur in both males and females with slight female preponderance. Most germ cell tumors arise within or adjacent to thymus. Morphology and immunophenotype of mediastinal germ tumors are similar to those in a gonadal location (see Fig. 8.9) [5, 25], and clinical correlation and imaging constitute an important part of cytological evaluation of mediastinal lesions (see Fig. 8.10) [26].

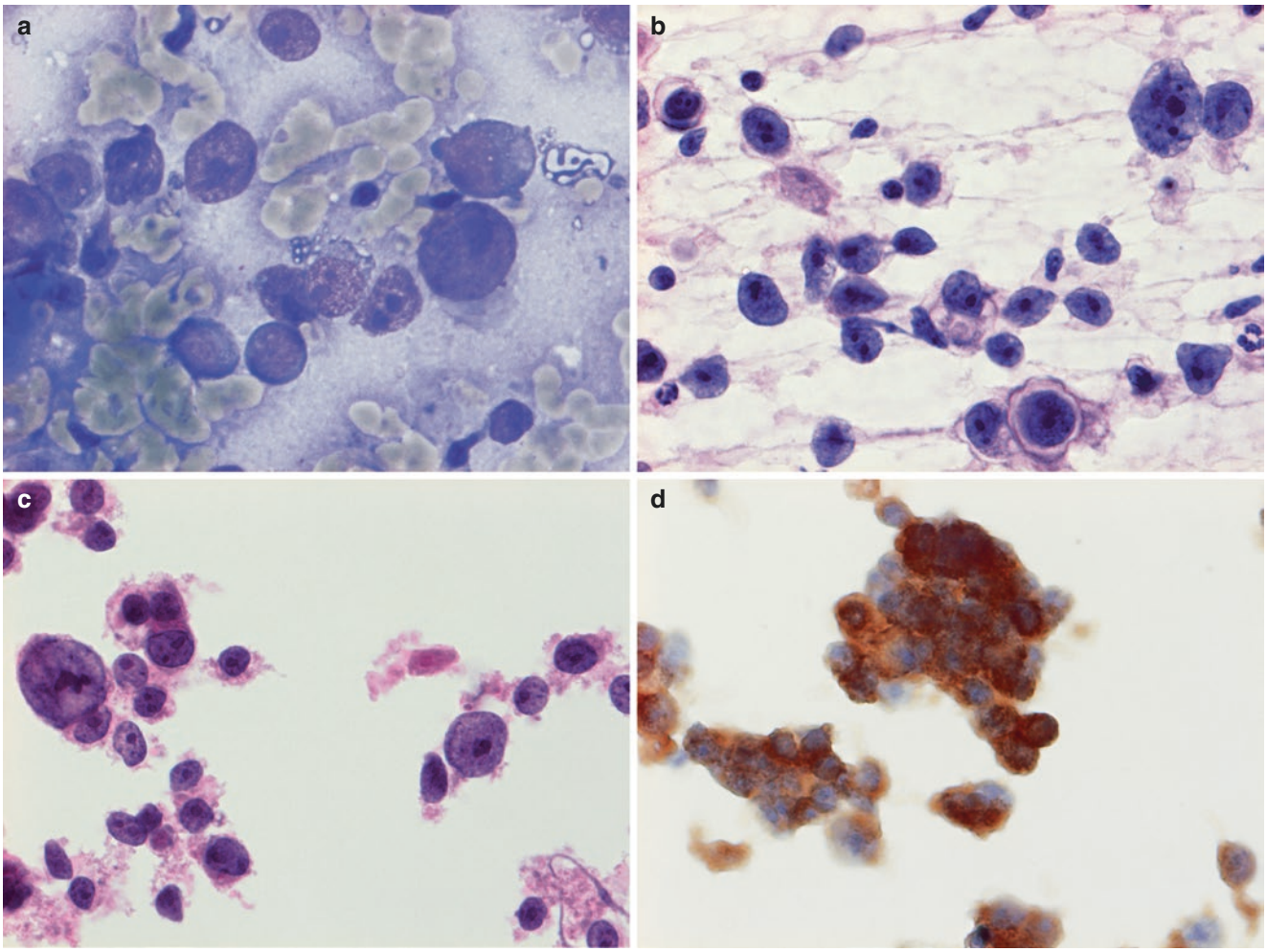

Fig. 8.9 Seminoma. (**a**–**c**) Large, dispersed, round-to-oval, epithelioid cells with prominent nucleoli (**a** and **b**, MGG, H&E; **c**; ThinPrep). (**d**) Tumor cells are positive for placental alkaline phosphatase (PLAP) (ThinPrep)

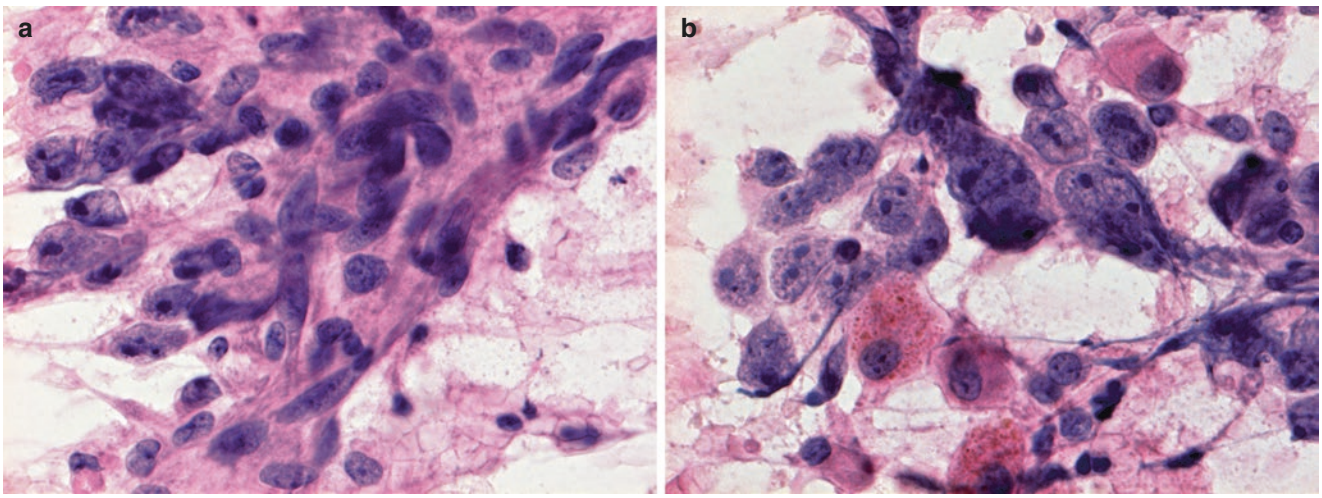

Fig. 8.10 Metastatic malignant teratoma. (**a**, **b**) Clusters of oval, polygonal, and spindle cells with irregular nuclei showing coarse chromatin and large nucleoli (H&E)

Lymphoproliferative Neoplasm

Most types of lymphoma may involve mediastinal lymph nodes, either as primary site or manifestation of systemic lymphoma. Primary lymphoma is the most common mediastinal neoplasia examined by FNAC [3]. The mediastinum is a common site of Hodgkin's lymphoma of nodular sclerosis type (see Fig. 8.11) and anaplastic large-cell lymphoma. Other lymphoma subtypes may also be present in mediastinal FNA smears (see Fig. 8.12) [27]. The cytology of lymphoproliferative neoplasm is described in Chap. 9.

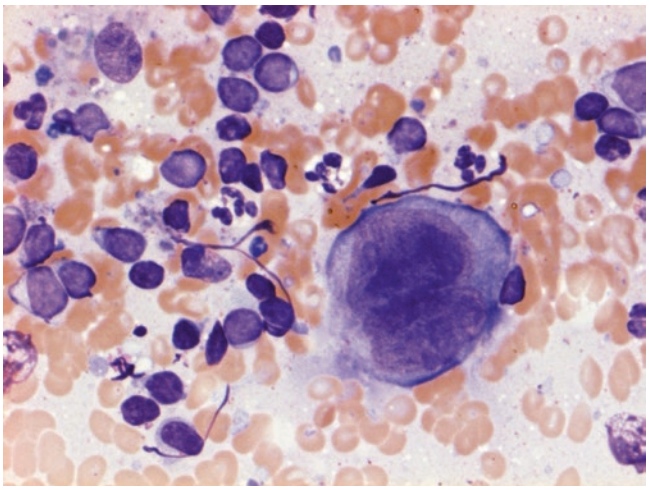

Fig. 8.11 Primary mediastinal Hodgkin's lymphoma. Characteristic binuclear Reed–Sternberg cell (MGG)

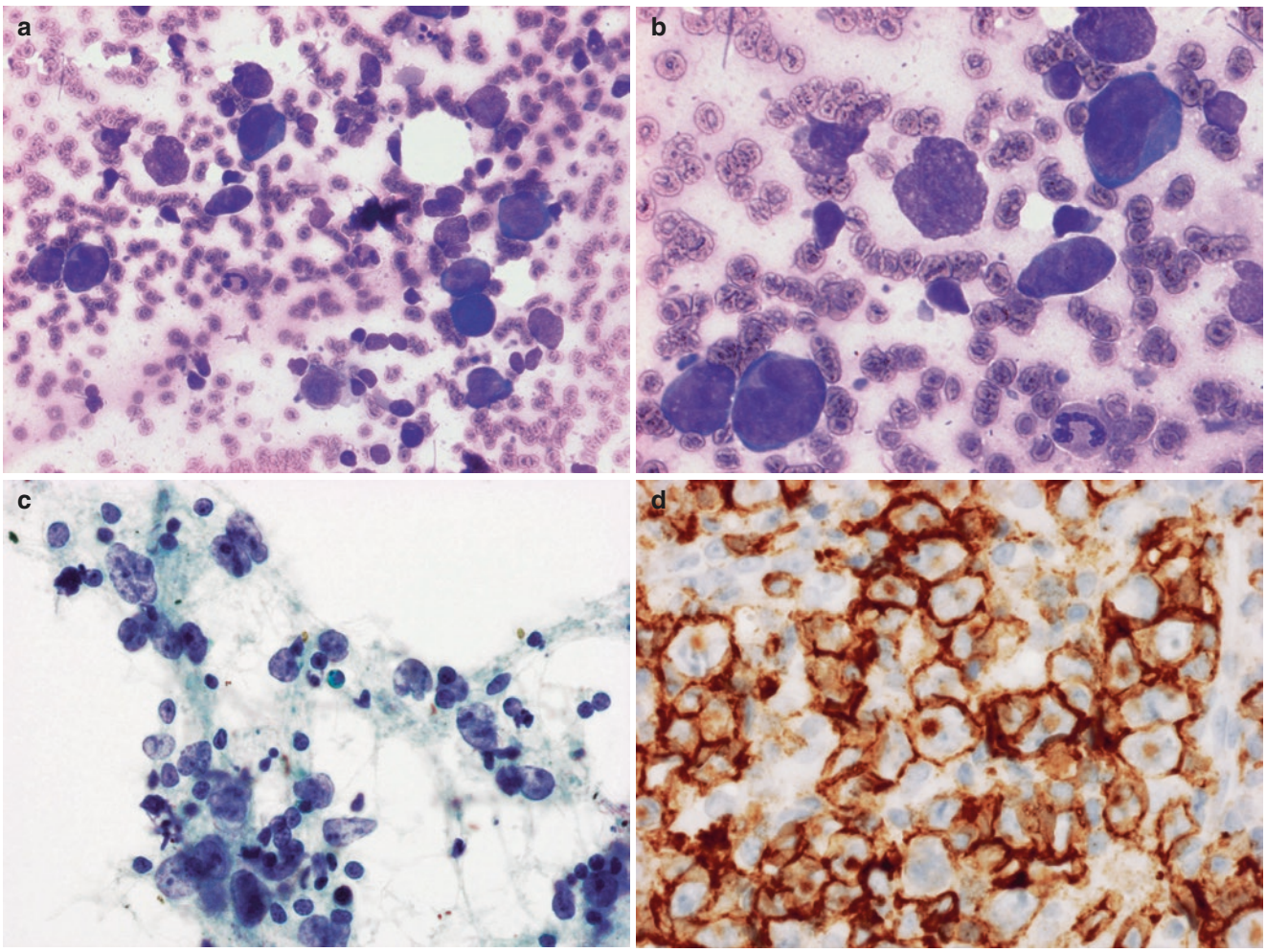

Fig. 8.12 Primary mediastinal non-Hodgkin's lymphoma. (**a**–**c**) Scattered pleomorphic cells with irregular nuclei and scant basophilic cytoplasm (MGG; Pap stain). (**d**) Immunostains show CD20-positive cells (ThinPrep). Flow cytometry confirmed diagnosis of large-cell diffuse B-cell lymphoma

Neuroendocrine Tumors

Neuroendocrine neoplasms in the mediastinum arise usually in the thymus [8] and constitute a group of tumors labeled as neuroendocrine carcinomas. Well-differentiated neuroendocrine carcinomas comprise typical and atypical carcinoid (see Fig. 8.13) and poorly differentiated neuroendocrine carcinomas of small-cell and large-cell neuroendocrine carcinoma. It has to be pointed out that neoplasms corresponding to well-differentiated neuroendocrine carcinoma display a biologically aggressive course compared to typical lung carcinoid. Criteria for cytologic diagnosis are similar to those in other sites (see Chap. 7).

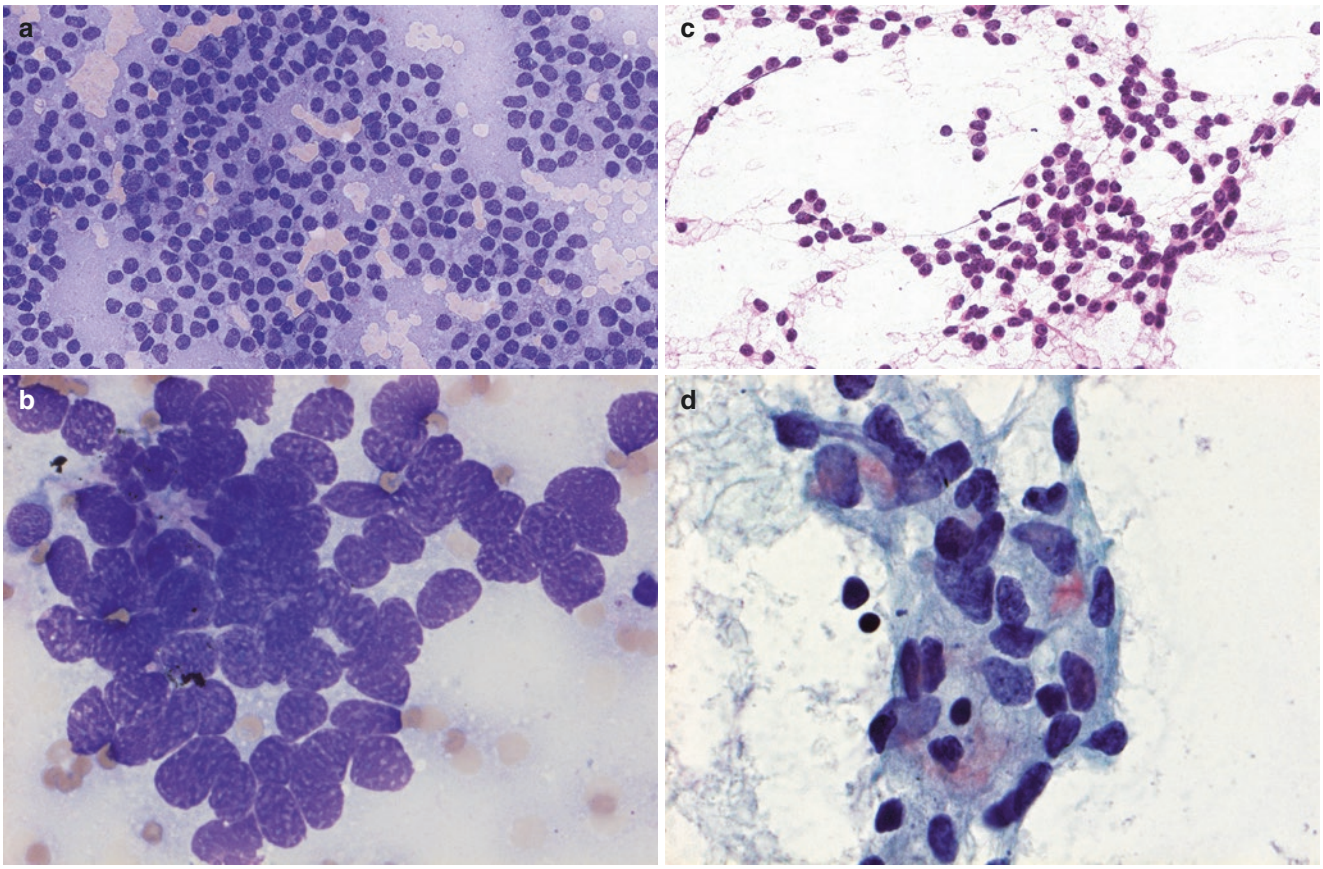

Fig. 8.13 Atypical carcinoid. (**a, b**) Poorly preserved cells; bare nuclei without distinct nuclear details (MGG). (**c, d**) Tumor cells with irregular nuclei and granular chromatin pattern, better appreciated in alcohol-fixed smears. (**d**) Spindle-shaped nuclei can be confused with spindle cell thymoma, and immunostains with neuroendocrine markers are necessary to make correct diagnosis (H&E and Pap stain)

Neural Neoplasm

Neural neoplasm commonly arises in the posterior mediastinum. Both mediastinal nerve sheath neoplasm (see Fig. 8.14) [2, 28–31] and neuroectodermal tumors [32–35] may be diagnosed by FNAC [36]. Detailed cytomorphology of nerve sheath neoplasm is described in Chap. 13 and neuroectodermal neoplasm in Chap. 16.

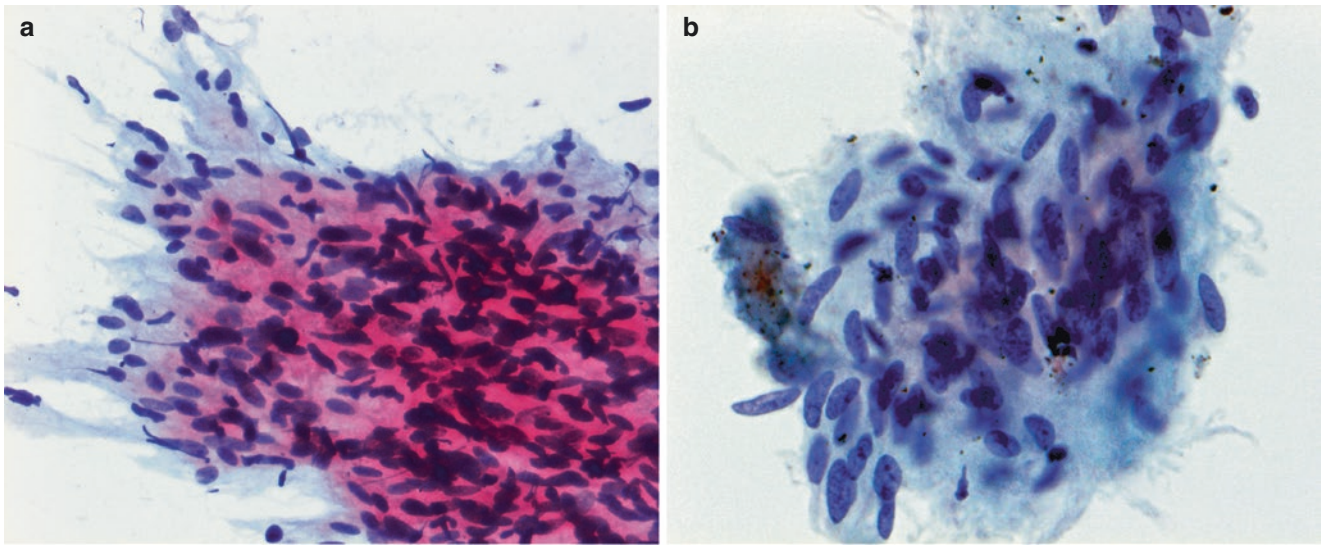

Fig. 8.14 Schwannoma. (**a**, **b**) FNA of mass in posterior mediastinum showing clusters of relatively uniform spindle cells embedded in the fibrillar matrix. Note some cells with tapered, coma-like nuclei (Pap stain)

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA)

Introduction

Lung cancer treatment is dependent upon the stage and histological type of the tumor. Lung cancer staging describes the extent of disease and is determined by a diagnostic workup. The tumor staging for patients with non-small-cell lung carcinoma (NSCLC) is based on a staging system, accepted in 2010 by the International Union Against Cancer [37]. In patients diagnosed with lung carcinoma, the imaging studies such as chest radiograph, computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, and positron-emission tomography (PET) are used to search for metastases. In the early 1990s, endoscopic ultrasonography (EUS) was already used for evaluation of gastrointestinal malignancies, and EBUS was developed as a new tool for the examination of airways, structures around the central airways, and the mediastinum. Although CT imaging has been useful in the evaluation of mediastinal structures, the new technology of EBUS was meant to compensate for the inability of CT to differentiate between different layers of the bronchial wall. The probe of EBUS was able to pass a stenosis and examine distal lesions. In addition, it could visualize the depth of mucosal invasion for staging of early lung cancer and could be used to guide endobronchial therapy. The method was soon applied to the evaluation of benign and malignant mediastinal lesions and mediastinal vessels [38, 39] and the reliable diagnosis of infectious diseases and granulomatous inflammation such as sarcoidosis [39–41]. EBUS-guided FNA is currently widely used in the evaluation of mediastinal, hilar, and lung parenchymal lesions [12, 42–44]. In addition EBUS-guided FNA of the mediastinal lymph nodes offers a less-invasive alternative to lymph node staging compared to mediastinoscopy [13, 45–48], which requires general anesthesia with increased morbidity and mortality risks [49]. The complications associated with EBUS are nausea, pericarditis, mediastinal infections, and pneumothorax, but no mortality has been reported to date [47, 50, 51].

Technical Considerations

Mediastinoscopy provides limited access to many lymph node stations such as the subcarinal station 7. The posterior and inferior mediastinum is more accessible by transesophageal ultrasound-guided fine-needle aspiration biopsy (EUS-FNA) [52]. EBUS, on the other hand, is more useful in the evaluation of anterior and superior mediastinal lymph nodes. These two methods can be combined in the staging of lung tumors. It has been shown that the combination of these methods [53–57] with PET/CT imaging and surgical staging increases the overall sensitivity [58–61].

Two different imaging modalities for the EBUS technique have been introduced. The radial probe, an ultrasound miniature probe inserted through the instrument channel of a standard bronchoscope, provides a 360° image (see Fig. 8.15) [62]. This probe does not allow simultaneous tissue sampling because the probe must be removed before sampling tools may be inserted. It is usually used for the evaluation of depth of tumor invasion and biopsies of peripheral lung lesions. The second imaging technique involves the curvilinear (or linear) probe (see Fig. 8.16) [63, 64], which provides a 60° image and a real-time view of the sampling needle of the bronchoscope. The linear imaging increases the chance of adequate and representative sampling and is used for assessment of mediastinal and hilar lymph nodes [65].

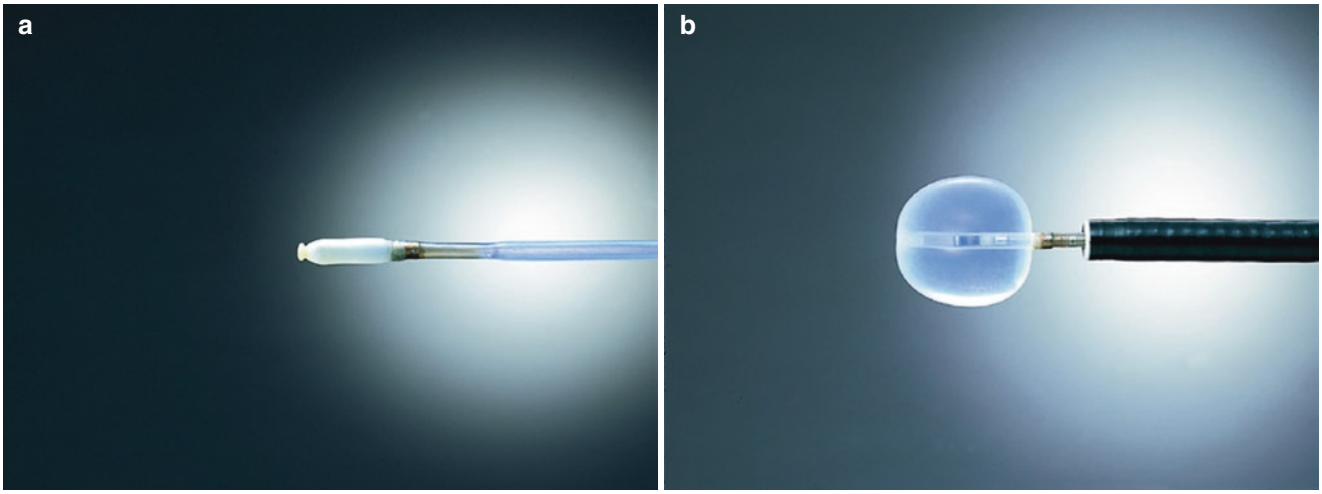

Fig. 8.15 (**a**) Radial ultrasound probe (UM-BS20-26R; Olympus Inc. Germany) equipped with a balloon sheath (**b**) that fits through the working channel of a standard therapeutic bronchoscope. (With permission of Olympus Sverige AB. Box 1816, SE-171 23 Solna, Sweden)

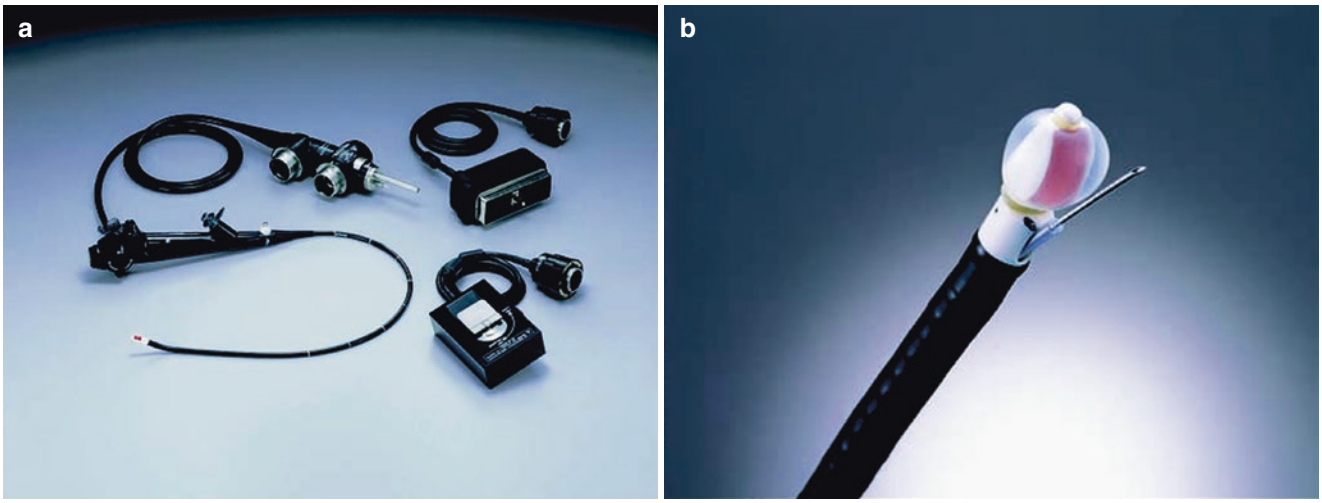

Fig. 8.16 (**a**) The linear scanning ultrasonic bronchovideoscope (BF-UC180F, Olympus Inc., Germany) for real-time EBUS-TBNA with linear probe (**b**). (With permission of Olympus Sverige AB. Box 1816, SE-171 23 Solna, Sweden)

Handling of the Specimen

In evaluation of EBUS FNA, the background of the smears should consist of cells from a lymph node to guarantee correct sampling, especially if no tumor cells are found on the slide (see Fig. 8.17). The samples usually yield excellent materials for immunochemistry to classify neoplasms by their specific profile [66], which is a crucial question in cases in which mediastinal FNA reveals metastasis of primary lung carcinoma or a metastasis of unknown origin (see Figs. 8.18, 8.19 and 8.20). Cytology specimens from EBUS samples can also be used for the genetic testing with additional immunochemistry for detecting EGFR (see Fig. 7.1) [67], ERBB2, BRAF, and KRAS mutations as well as ALK, RET, and ROS1 translocations. PD-1/PDL-1 status of tumor cells on cytology specimens can be used to identify patients which might have benefit of PD-1/PDL-1 checkpoint inhibitor.

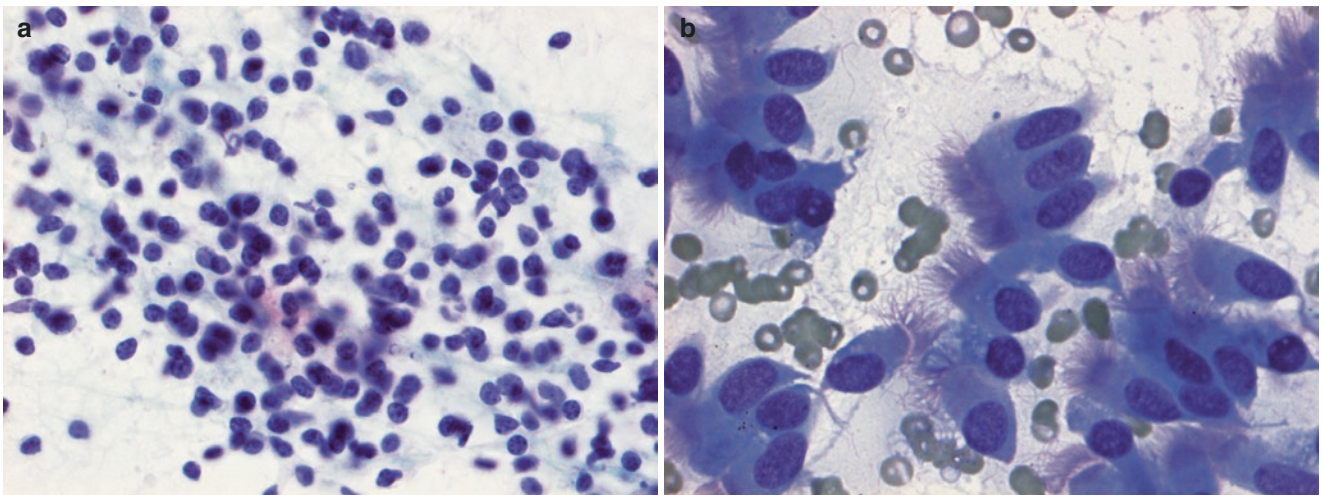

Fig. 8.17 EBUS-TBNA. (**a**) Presence of lymphocytes in the background of the smears guaranteed representative sampling. (**b**) Respiratory cylinder epithelial cells without lymphocytes means not representative sampling (MGG)

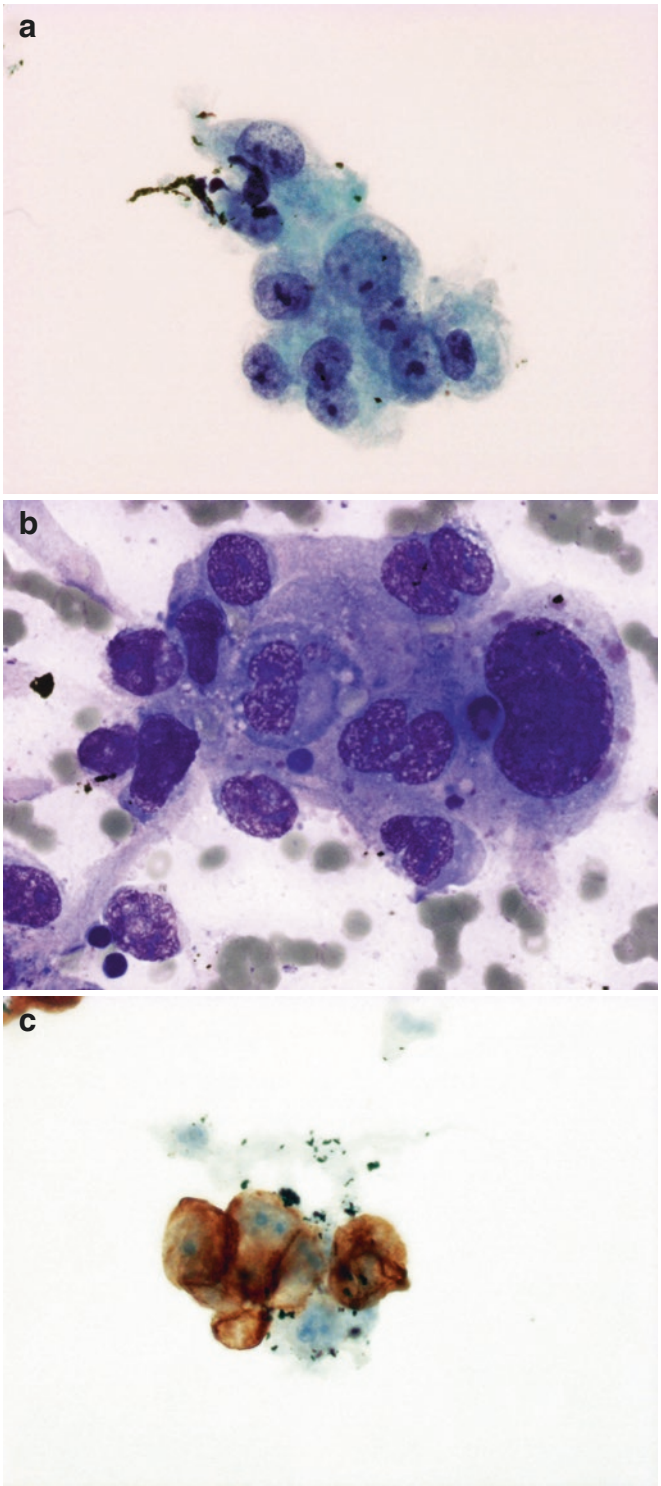

Fig. 8.18 EBUS-TBNA. (**a**, **b**) Poorly differentiated adenocarcinoma of the lung metastasizing to the mediastinal lymph nodes (Pap stain; MGG). (**c**) Tumor cells stains positive with cytokeratin CK7

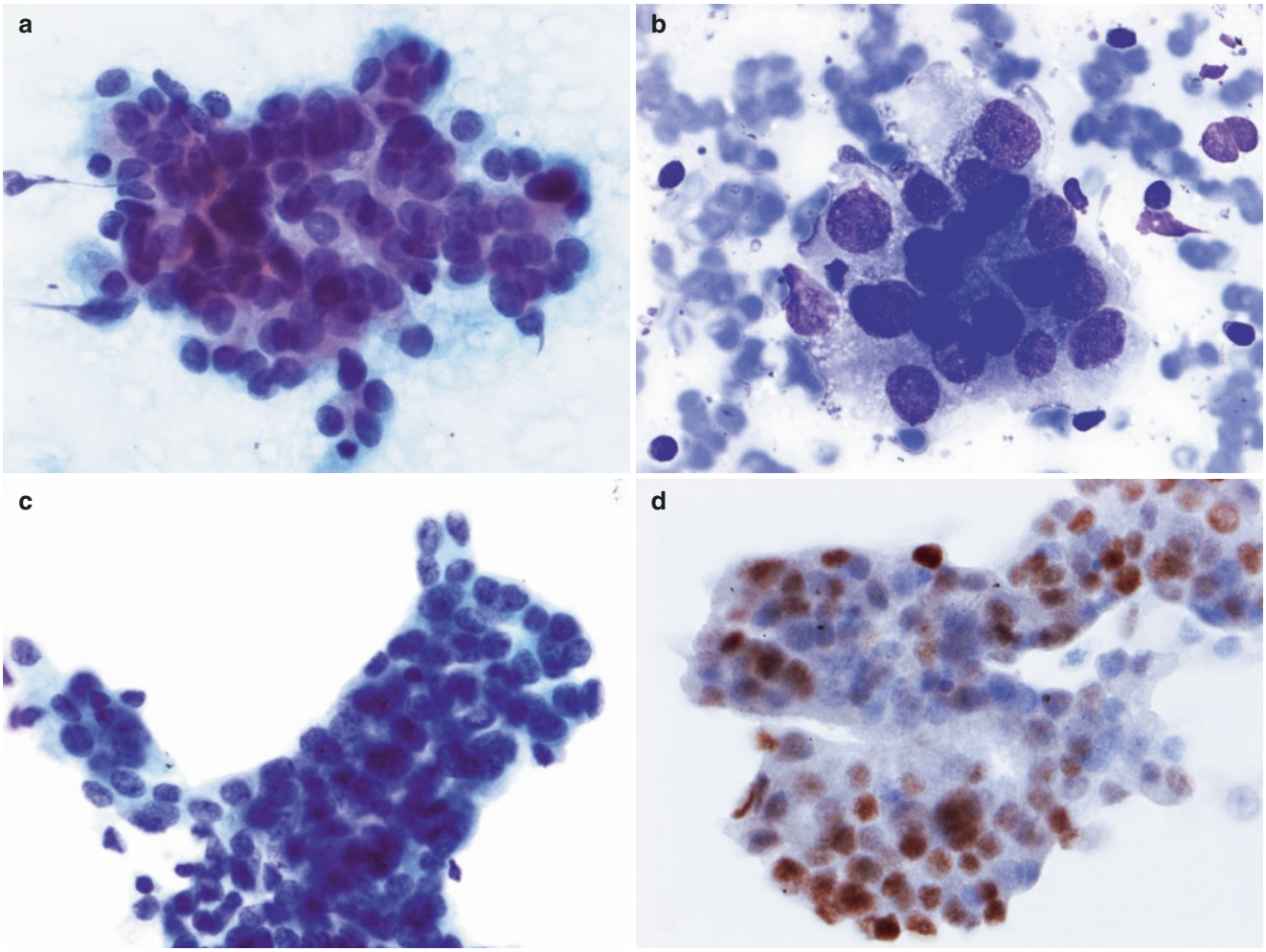

Fig. 8.19 EBUS-TBNA. (**a**, **b**) Breast carcinoma metastasizing to the mediastinal lymph nodes (Pap stain; MGG). (**c**) Liquid-based preparation with a cluster of malignant cells (Pap stain). (**d**) Tumor cells stain positive with estrogen

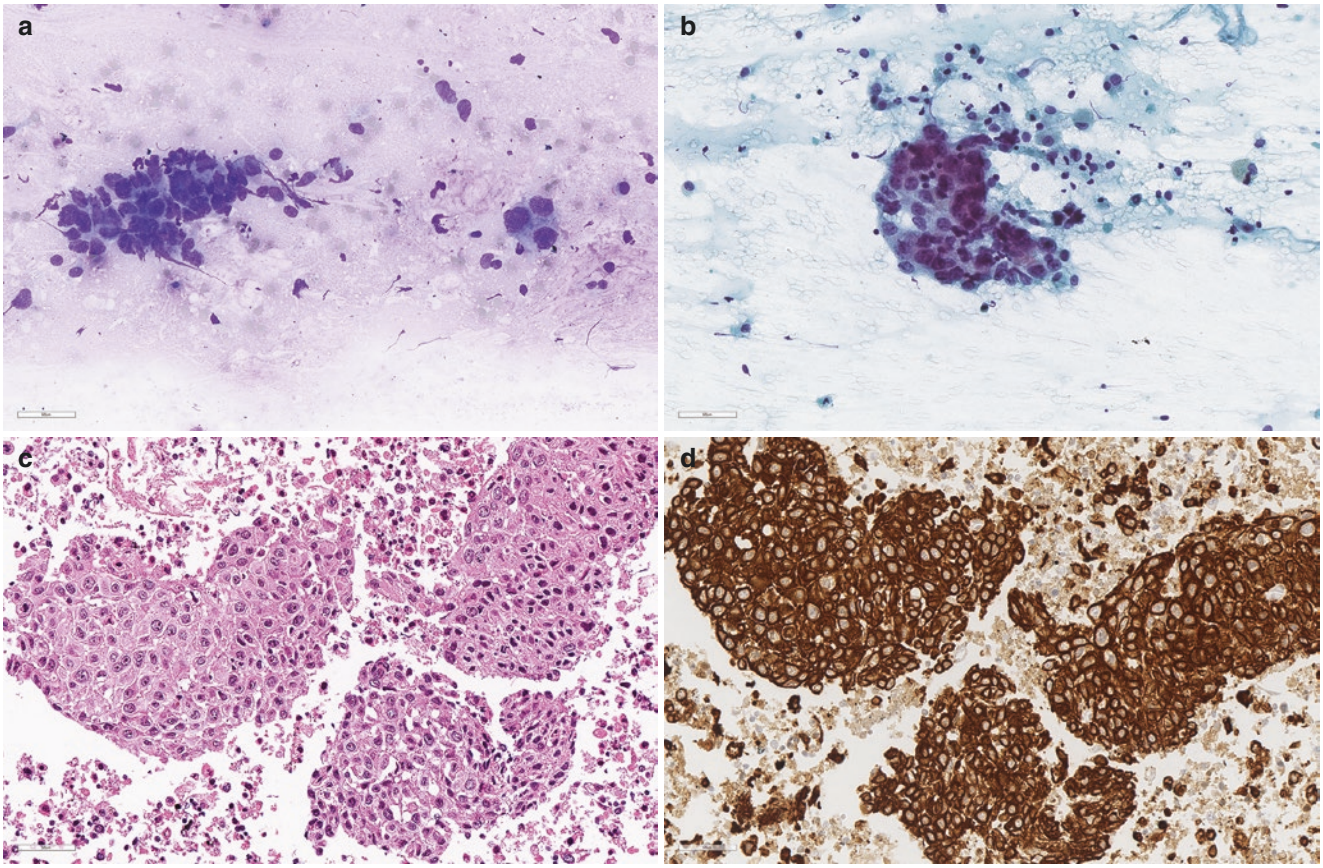

Fig. 8.20 EBUS-TBNA. (**a**, **b**) Squamous cell carcinoma of the lung metastasizing to the mediastinal lymph nodes. Clusters of pleomorphic tumor cells, dispersed tumor cells, and naked nuclei (MGG; Pap stain). (**c**) Cell block section shows large sheets of tumor cells consisted with squamous cell carcinoma (cell block; H&E). (**d**) Tumor cells show distinctive keratin (CK5) positivity

Diagnostic Accuracy

EBUS drawbacks include the need of considerable training, the relatively high cost compared to conventional transbronchial needle aspiration (TBNA), and the inability to image and access the subaortic and paraesophageal lymph nodes. In addition, to improve diagnostic accuracy, this procedure requires the presence of a cytopathologist or cytotechnologists for on-site evaluation of smears. Although the overall sensitivity of EBUS is approximately 93% [11, 59, 68–70], the high rate of false-negative findings (up to 20% reported by some studies) makes this diagnostic tool inferior to mediastinoscopy with its low false-negative findings of 11% [58]. The study, which reports the sensitivity of the EBUS as high as 99% [12], indicates however that the reliability of this technique may depend on the experience level of the bronchoscopist and cytologist. Pulmonology training programs more focused on TBNA performed with EBUS rather than conventional TBNA have been shown to increase specimen adequacy and correct diagnoses [71].

The new technology of EBUS, together with various ancillary methods (e.g., immunocytochemistry and molecular genetic studies on cytological material), has provided new opportunities for faster, safer, and more adequate diagnosis. The lung tumors can be diagnosed and staged by one procedure in an outpatient setting. For some malignancies, such as lymphomas, EBUS technology is usually insufficient for final diagnosis and classification of the lymphoma but may lead the workup in the right direction. In the future, development of more easily used instruments may improve the sensitivity and accuracy of EBUS and may open doors to new diagnostic areas [72].

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