Lung and Mediastinum

6

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6.1 Introduction

Exfoliative cytology and fine needle aspiration (FNA) are valuable tools for the evaluation of pulmonary lesions. In the pediatric population, the most common cytologic specimens from the respiratory tract are bronchoscopy-acquired specimens, including bronchoalveolar lavages (BALs) and bronchial brushings/washings. Sputum specimens are infrequently seen as it is difficult or impossible to obtain an adequate sample representative of a deep cough from children. Bronchial brushings are usually performed if there is a visible, discrete lesion on bronchoscopy, whereas a washing is typically done if there is no discrete endobronchial lesion. BAL specimens are obtained by infusion and re-aspiration of sterile saline into distal areas of the lung. These specimens are typically utilized in the evaluation of suspected infection in both immunocompetent and immunocompromised patients, and for routine follow-up of lung transplant recipients to exclude unsuspected infection. Of note, up to 25 % of stem cell transplant recipients have pulmonary complications and will require evaluation to exclude a pulmonary infection [1]. In addition, BALs can be therapeutic in the setting of pulmonary alveolar proteinosis, cystic fibrosis, and asthma, to provide symptomatic relief to patients. In the setting of infection, BALs have a sensitivity of approximately 82 % and a specificity of 53 %. Although malignancy is rare in children, a variety of different conditions can lead to atypia that mimics malignancy, including reactive bronchial cells and pneumocytes in the setting of inflammation, infection, diffuse alveolar damage, bone marrow transplantation, and chemotherapy. When there is a neoplasm, a metastatic neoplasm should be considered before diagnosing a primary lung neoplasm. One study revealed that 81 % of lung neoplasms in the pediatric population are due to metastatic lesions with nephroblastoma (Wilms tumor) being the most common, followed by osteosarcoma [2]. Overall, benign and reactive changes, in addition to metastatic tumors, should strongly be considered before making a diagnosis of a primary lung malignancy in a child or adolescent. Whereas CT-guided FNA or endobronchial ultrasound (EBUS) guided transbronchial needle aspiration (TBNA) is routinely used to evaluate pulmonary and mediastinal masses in adults, aspirates from these sites are infrequently

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Table 6.1 Pediatric pulmonary lesions encountered in exfoliative cytology and/or FNAs

Non-neoplastic pediatric lung lesions	Neoplastic pediatric lung lesions
Reactive or prior treatment-related changes	Clear cell (sugar) tumor
Infection	Epithelioid hemangioendothelioma
Aspiration or Trauma/Fat emboli (with positive Oil Red O staining)	Inflammatory myofibroblastic tumor
Pulmonary alveolar proteinosis	Juvenile squamous papilloma
Bronchogenic cysts	Metastatic tumors
Hamartomas	Pleuropulmonary blastoma
	Salivary gland-type tumors (Mucoepidermoid carcinoma, adenoid cystic carcinoma)
	Carcinoid
	Primary adenocarcinoma

Table 6.2 Summary of pediatric mediastinal lesions by compartment

Anterior/superior mediastinum (5 Ts)
• Thymic lesions • Thyroid lesions • Teratoma or germ cell tumors • Terrible lymphoma • Terribly common metastatic neoplasms • Vascular tumors • Hernia
Posterior mediastinum
• Neurogenic and neuroblastic tumors • Bronchogenic and congenital cysts • Hernia • Paraspinal abscess • Vertebral lesions
Middle mediastinum
• Lymphoma • Bronchogenic cysts

encountered in the pediatric population, in part due to the low incidence of lung cancer in children and adolescents. However, fine needle aspiration biopsy and/or core needle biopsy may be of use in cases where the clinical and radiologic picture cannot differentiate between neoplastic and infectious lesions. Some of the common, as well as uncommon, lesions encountered in cytologic specimens from the lung and mediastinum in the pediatric population are summarized in Tables 6.1 and 6.2, respectively.

6.2 Cytology of Normal and Benign Elements in the Lung

- Benign respiratory epithelial cells are columnar with basally oriented nuclei, terminal bars, and cilia.
- Creola bodies are hyperplastic or papillary clusters of bronchial cells with occasional vacuolization and small nucleoli that can be seen with asthma or bronchiectasis.
- Reactive atypia (mild nuclear enlargement and prominent nucleoli) can be seen with radiation, chemotherapy, or severe inflammation (Fig. 6.1).
- Reserve cell hyperplasia or proliferation is more common when there is lung injury and shedding of the normal respiratory tract epithelium. These cells appear in tightly packed clusters with small nuclei and scant cytoplasm.
- Macrophages have abundant foamy to vacuolated cytoplasm, oval to round nuclei, and occasional prominent nucleoli. The vacuolated cytoplasm may have debris or other ingested material, such as hemosiderin or anthracotic pigment. The presence of macrophages is used to confirm the adequacy of sputum samples and BALs (Fig. 6.2).
- Lipid-laden macrophages can be highlighted with an Oil Red O stain, and these cells can be elevated in patients with lipoid pneumonia, fat embolism syndrome, pulmonary aspiration, or amiodarone toxicity (Fig. 6.3).
- Curschmann spirals are coiled strands or helical casts of inspissated mucus that appears darkly stained. These are a non-specific finding, seen with excess mucus production (e.g., asthma) (Fig. 6.4).
- Charcot-Leyden crystals are small, eosinophilic to orangeophilic, rhomboid-shaped crystals that are derived from the granules of degranulated/degenerating eosinophils, usually in the setting of asthma and other causes of eosinophilia. These can be seen in allergic

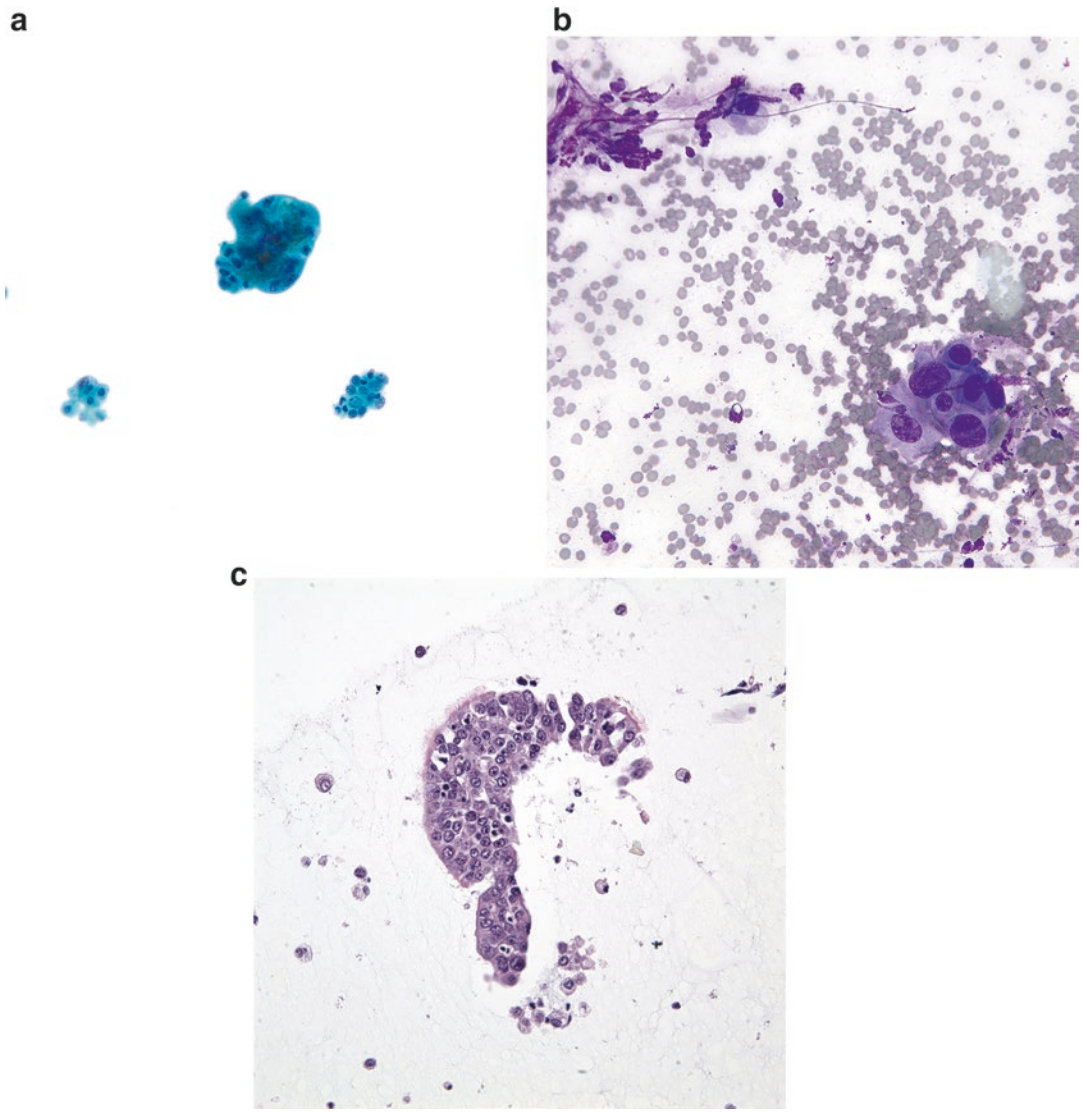

Fig. 6.1 Reactive epithelial atypia in BAL (**a**. Papanicolaou stain, high power; **b**. Diff-Quik stain, high power; **c**. H&E stain, high power). Lung specimens from patients status post chemotherapy showing reactive pneumocytes and reactive bronchial epithelial cells. These cells have mild nuclear enlargement without irregularities, and are seen in association with benign cells, including ciliated bronchial cells on the cell block (**c**).

bronchopulmonary aspergillosis with numerous eosinophils and fungal hyphae (Fig. 6.5).

- Ciliocytophthoria appears as detached ciliary tufts, and is associated with viral infection (e.g., adenovirus) but can also be a non-specific finding (Fig. 6.6).
- In systemic disease (autoimmune, cystic fibrosis, asthma), the lung can show a variety of reactive changes. In asthma, increased eosinophils are often present within mucus. Cystic fibrosis is characterized by thick mucus plugs, often with abundant mixed inflammation. Most pulmonary specimens from these patients are obtained to evaluate for infection. Two particular infections, *Burkholderia cepacia* and *Pseudomonas aeruginosa*, are relatively common in cystic fibrosis patients and can have implications for disease progression.

- Pollen or starch granules: Starch granules appear as clear and refractile cubes with a Maltese cross appearance under polarized light. Pollen appears as spherical structures that are colorful, have a thickened wall, and may have small internal bodies or a spiked border, and can mimic large yeast forms or other infectious organisms, in addition to other contaminants.
- Drug particles: Dark black carbonaceous material can appear within histiocytes in drug users, particularly crack/cocaine smokers. Rhomboid crystals can appear with aspiration of barium sulfate.

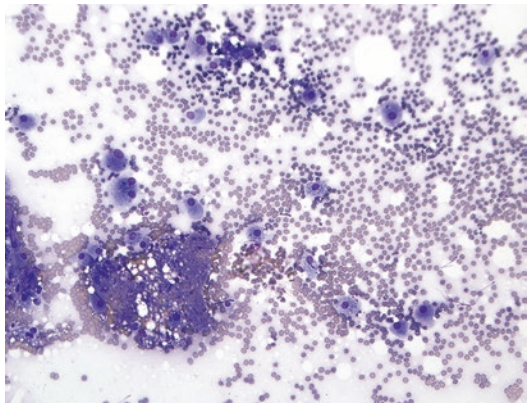

Fig. 6.2 Non-diagnostic lung FNA in a pediatric patient showing benign macrophages (Diff-Quik stain, medium power). The aspirates show benign macrophages in a bloody background and do not characterize a mass lesion in the lung. Thus, these findings are non-diagnostic.

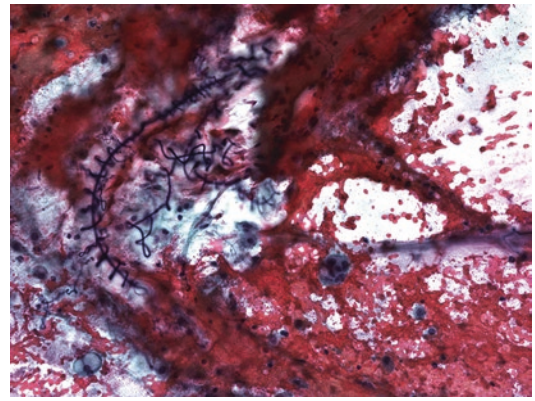

Fig. 6.4 Curschmann spirals in a bronchial specimen (Papanicolaou stain, medium power). These darkly stained spiral shaped structures represent thick, inspissated mucus.

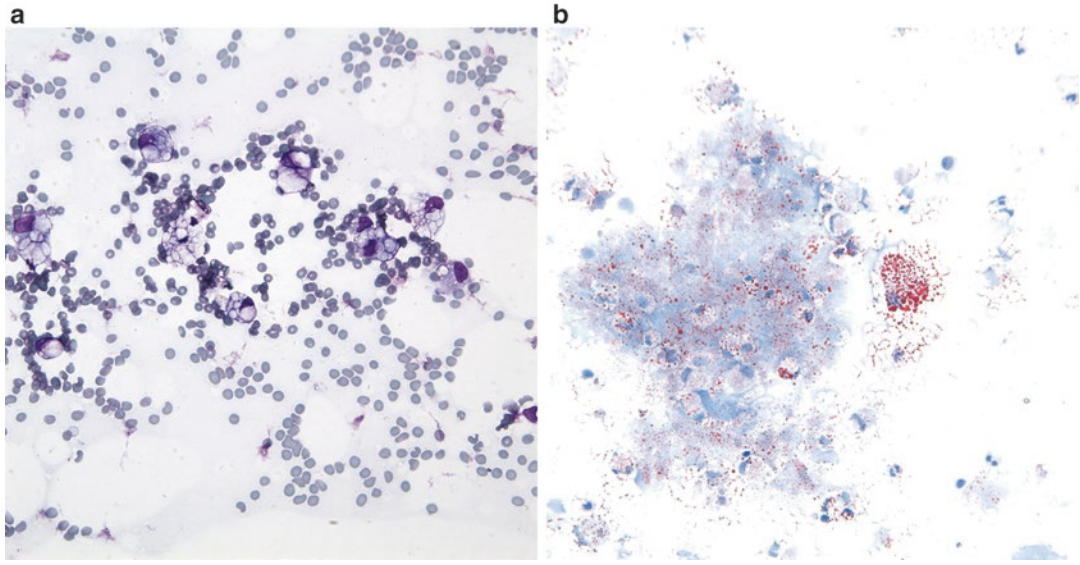

Fig. 6.3 Lipid laden macrophages (**a**. Diff-Quik stain, high power, **b**. Oil red O stain, high power). Lipid laden macrophages are frequently a sign of aspiration, along with other etiologies, in children. Thus, identification of them is important and an Oil Red O stain can help prove their presence (**b**).

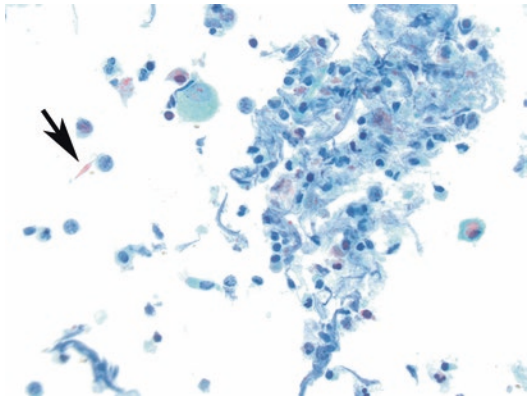

Fig. 6.5 Charcot-Leyden crystals (Papanicolaou stain, high power). Eosinophilic rhomboidal crystals (*arrow*) are frequently seen with eosinophilic-rich infiltrates. They can be an important clue that the inflammatory cells are predominantly eosinophils given that the eosinophilic granules are hard to identify on a Papanicolaou stain.

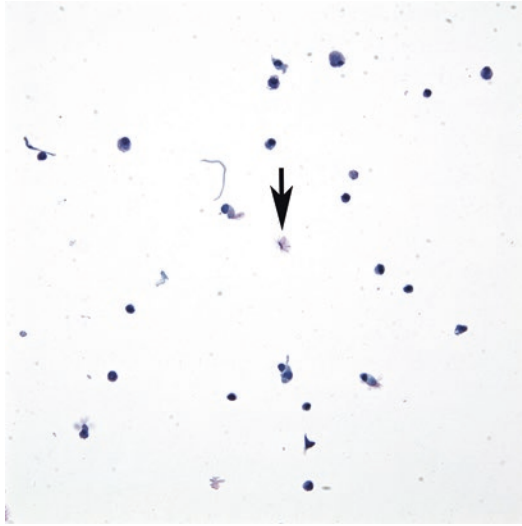

Fig. 6.6 Ciliocytophthoria (Papanicolaou stain, medium power). Detached ciliary tufts (ciliocytophthoria) can be seen in BALs of patients with adenovirus infection and should not be confused with organisms or contaminants (*arrow*).

6.3 Bronchogenic Cysts

Clinical Features

These developmental cysts arising from the foregut appear most frequently as a posterior mediastinal cyst, but can also be intrapulmonary.

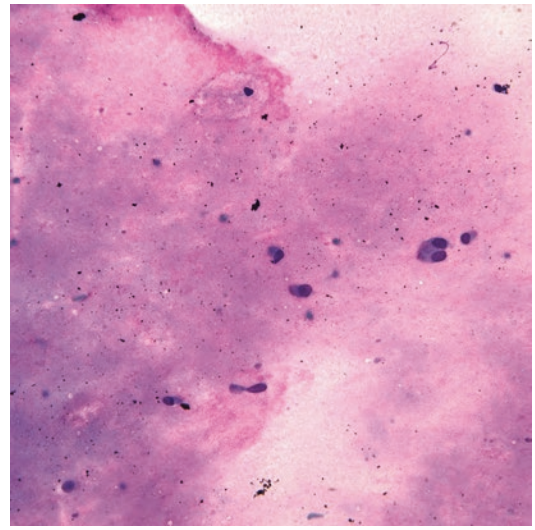

Fig. 6.7 Bronchogenic cyst (Diff-Quik stain, low power). This bronchogenic cyst shows thickened proteinaceous fluid with a few ciliated cells.

These are rare lesions, but can compress the airway if large.

Cytological Features

Aspirates yield thick proteinaceous to mucoid fluid with variable types of lining cells, including ciliated, squamous, or simple columnar epithelium (Fig. 6.7). Liquid-based cytology can be helpful for demonstrating the cyst lining cells and excluding thymic or neoplastic cysts (e.g., germ cell tumors with cystic change).

Differential Diagnosis

A cystic lesion in the mediastinum or lung of a child raises the differential diagnosis of thymic cyst, mediastinal goiter, lymphangioma, cystic pulmonary airway malformation (CPAM; formerly congenital cystic adenomatoid malformation), mesenchymal cystic hamartoma, and neoplastic cysts (e.g., cystic teratoma or other germ cell tumor with cystic change). In contrast to bronchogenic cysts, most of the congenital malformations and hamartomas in this age group are within the lung and are multicystic lesions with small cysts.

Pearls

If small lymphocytes are identified from a cystic lesion in the mediastinum in the pediatric population, the possibility of a thymic cyst should be considered. Flow cytometry and/or immunoperoxidase stains can be used to support thymic origin by identifying immature and maturing T-cells that are positive for TdT, CD1a, and CD3.

6.4 Infectious Disease

Clinical Features

Fine needle aspiration biopsy has not been routinely used for the diagnosis of infectious disease in the lung. Thus, there are few studies evaluating its effectiveness. One paper in the adult literature reported a range of sensitivity of 21–47 % for FNA and 52–94 % for core needle biopsy [3]. One study in the pediatric population reported a sensitivity of 88 %, but did not separate FNA from core needle biopsy [4]. Another noted that CT-guided biopsy had a high diagnostic yield of 60 %, but only yielded organisms already isolated from peripheral blood [1]. Occasionally, FNA performed for infectious disease of the lung may reveal an undiagnosed tumor of the chest wall or mediastinum.

Cytological Features

Infections that present as discrete masses in the lung frequently show either abscess formation, granulomatous inflammation, or a cystic fungal ball. Aspirates show abundant histiocytes with a variable numbers of small lymphocytes and neutrophils in the background (Figs. 6.8 and 6.9). Stains for fungal elements and/or acid fast bacteria can be performed on aspirate smears and may be useful; however, if there are only rare yeast or fungal elements, the possibility of specimen contamination with *Alternaria* or other fungi or oropharyngeal contamination from Candida should be considered [5] (Fig. 6.10). Well-formed granulomas with clusters of epithelioid histiocytes are suggestive of fungal or mycobacterial infection (Fig. 6.11). Fungal balls typically show abundant granular debris with fungal hyphae present. BAL is commonly used for the cytologic evaluation of suspected infection but, in the setting of a mass lesion, may not yield representative material. Depending on the etiologic agent, BALs can show neutrophils, lymphocytes, and/or histiocytes, necroinflammatory debris and reactive epithelial cells. Gram, methenamine silver, AFB and Fite stains can be helpful for identifying microorganisms on cytospins, liquid-based preparations or cell blocks from BALs. Viral infections, such as cytomegalovirus and herpes virus, can also be seen in BAL specimens (Fig. 6.12).

Triage

Material should be submitted from the FNA or BAL for microbial cultures and special stains. When handling the specimen, care should be taken to avoid contamination. Since complications such as pneumothorax are common in lung FNA, few passes may be performed, and each pass should be triaged carefully. If the needle tip is not touched to the slide when the first drop(s) are taken for smears, the remaining specimen may be rinsed into sterile saline for microbiologic studies. If the smears show anything other than an infectious process, this rinse can be used for other ancillary studies (flow cytometry, cell block, etc.). In addition, if there is abundant hemodilution on subsequent passes, unstained smears could be prepared from the best pass and sent for special stains [5].

Differential Diagnosis

Neoplastic disease, metastatic or primary, may mimic an infectious lung mass radiologically. Although atypical bronchial cells and/or pneumocytes can be present in the setting of infection, cytologic features of malignancy, such as increased nuclear to cytoplasmic ratios, nuclear pleomorphism, nuclear membrane irregularity, and hyperchromasia are absent. Lymphocytic infiltrates associated with infectious processes are polyclonal, in contrast to the monoclonal proliferations associated with non-Hodgkin lymphomas.

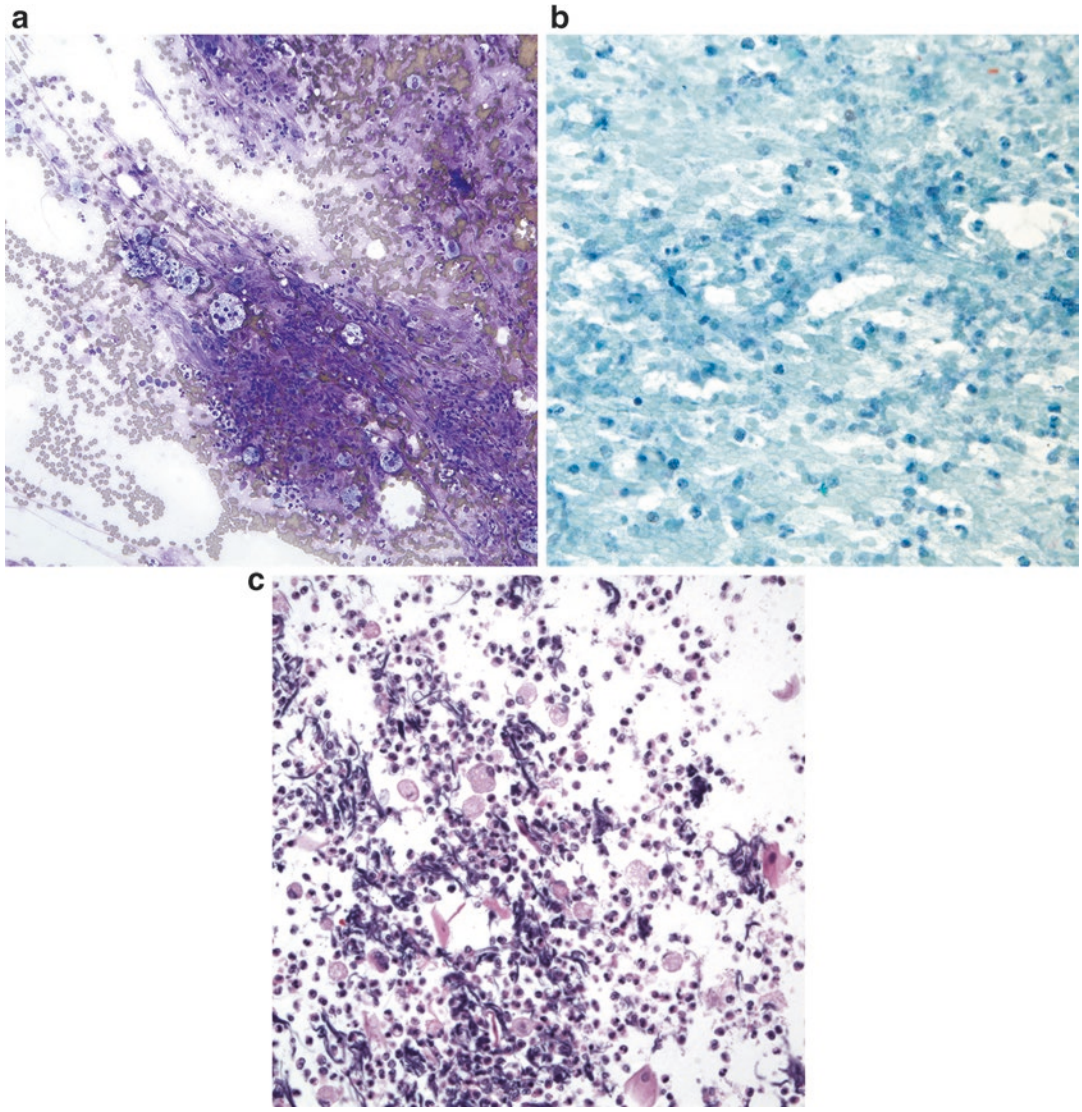

Fig. 6.8 Lung abscess (**a**. Diff-Quik stain, medium power; **b**. Papanicolaou stain, medium power; **c**. H&E stain, high power). The aspirates show abundant neutrophils and granular debris in this FNA from a lung mass.

Pearls

Primary lung carcinomas are exceedingly rare in the pediatric population. When atypical squamous or glandular cells are identified in an FNA or exfoliative specimen from the lung of a child or adolescent with a mass lesion, reactive atypia in metaplastic squamous cells, bronchial cells or pneumocytes secondary to infection should be excluded before considering malignancy.

6.5 Alveolar Proteinosis

Clinical Features

Pulmonary alveolar proteinosis (PAP) is a rare disorder associated with impaired or dysfunctional surfactant clearance. Some cases are congenital, due to mutations in surfactant protein-B, *ABCA3* or GM-CSF receptor genes. This is in

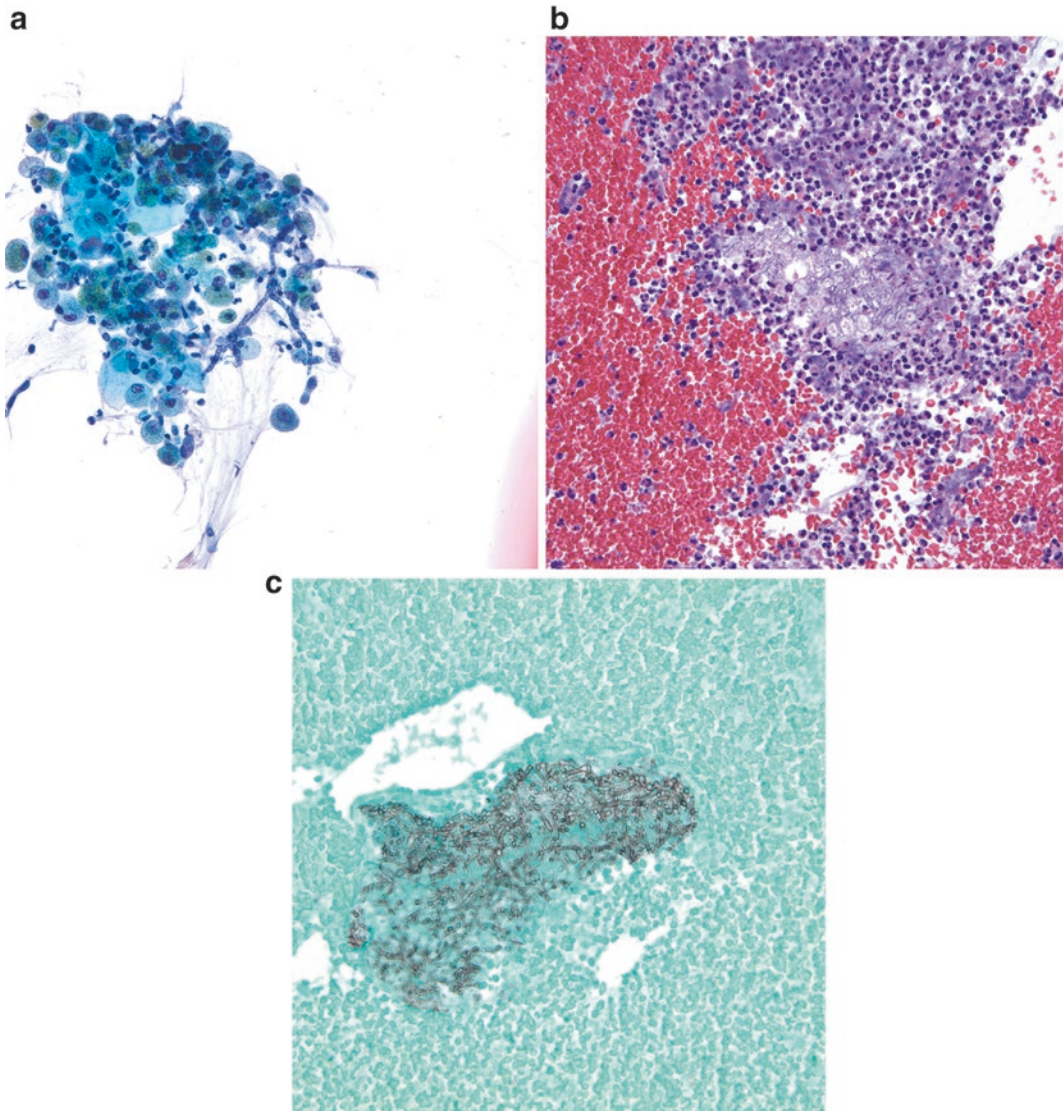

Fig. 6.9 Fungal infection creating mass lung lesion in a young patient (**a**. Papanicolaou stain, high power; **b**. H&E stain, high power; **c**. Grocott stain, high power). The aspirates show branching fungal hyphae within a background of acute inflammation, debris, and reactive changes. The Grocott stain shows branching fungal hyphae, compatible with Aspergillus (**c**).

contrast to adults, in which most cases are acquired and due to autoantibodies to GM-CSF. Most other pediatric cases are secondary to infection, drugs, foreign material, treatment for malignancy, or idiopathic causes. PAP is characterized by accumulation of lipid-rich proteinaceous material in alveolar spaces leading to respiratory distress or failure. On imaging, patients have diffuse, bilateral, pulmonary infiltrates or opacities, without features of fibrosis or chronic lung disease. BALs can be performed in these patients for diagnosis and therapeutic purposes.

Cytological Features

The BALs from patients with PAP have abundant, acellular, PAS-positive diastase-resistant, lipid-rich proteinaceous material, often in large globules, and pulmonary macrophages containing similar

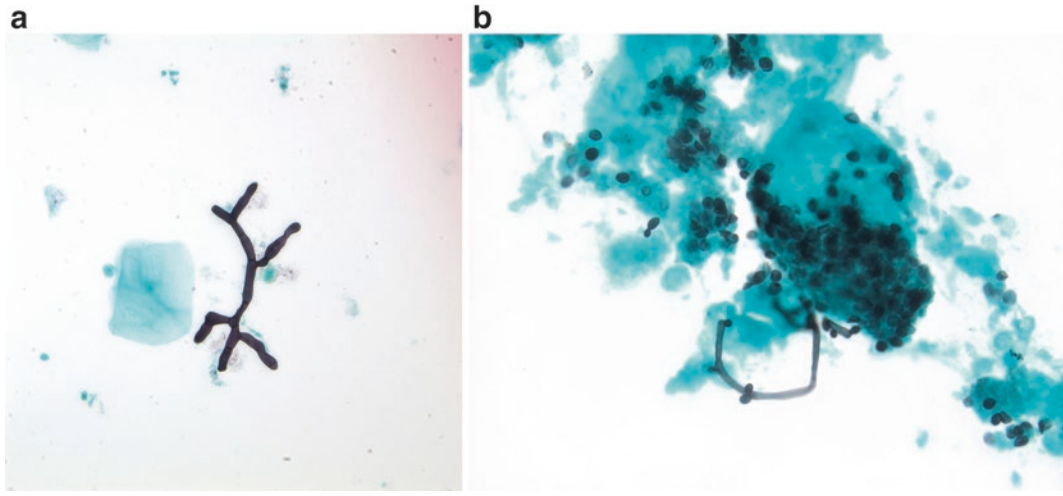

Fig. 6.10 Other fungal organisms in children (**a**, **b**. Grocott stain, high power). *Fusarium* identified in this pediatric lung specimen was morphologically similar to Aspergillus (**a**). Candida can also be identified in BAL specimens in children and may represent contamination from the oropharynx (**b**).

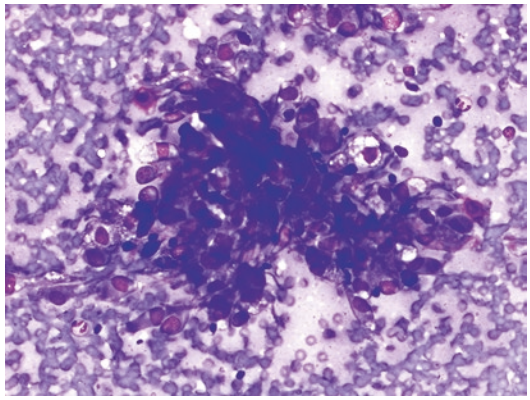

Fig. 6.11 Granulomatous inflammation in the lung (Diff-Quik stain, high power). There are clusters of epithelioid histiocytes and scattered small lymphocytes, compatible with epithelioid granulomas.

material. Degenerating macrophages, lamellar bodies, cholesterol crystals, and reactive pneumocytes can also be present, but inflammation is usually absent (Fig. 6.13). PAS and PAS-D stains can be performed on additional cytospins, liquid-based preparations or sections from a cell block to support the diagnosis.

Differential Diagnosis

The other possibilities to consider are mucus plugs or alveolar casts from *Pneumocystis jirovecii* infection. Mucus plugs lack the intense PAS-positivity seen in PAP but stain with mucicarmine or Alcian blue, while methenamine silver stains can help to exclude *Pneumocystis jirovecii* infection.

Pearls

Electron microscopy shows that the lamellar bodies are proteinaceous surfactant material.

6.6 Primary Lung Neoplasms

Primary lung neoplasms are so rare in the pediatric population that they are frequently not included in the differential diagnosis of mass lesions. Over two-thirds of cases are malignant, the majority of which are bronchogenic in origin. Carcinoid tumor is the most common pediatric lung malignancy accounting for 33 % of malignant cases, followed by bronchogenic carcinoma (28 %), mucoepidermoid carcinoma

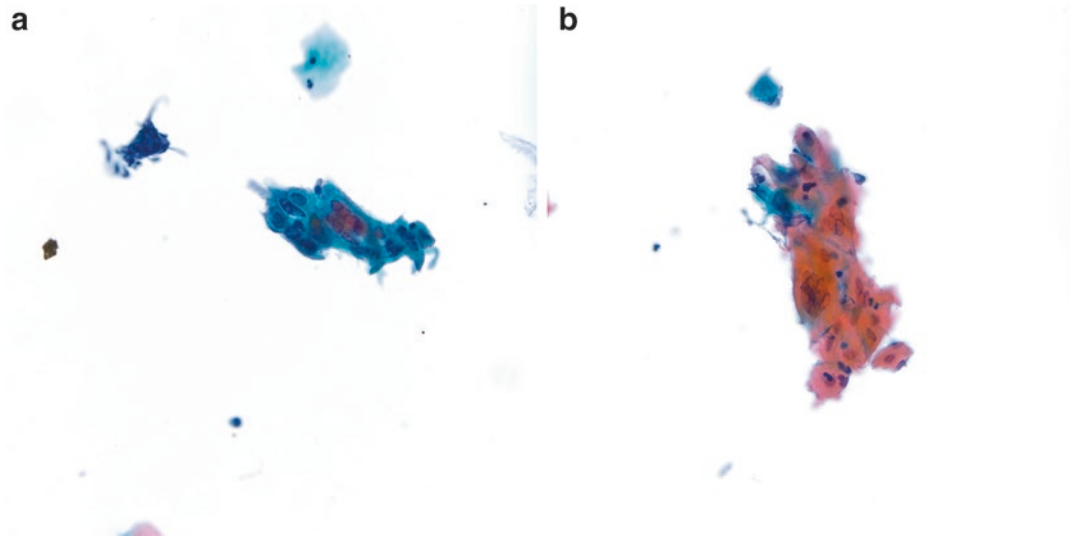

Fig. 6.12 BAL specimen showing HSV infection in an immunocompromised child (**a**, **b**. Thin Prep, Papanicolaou stain, high power). The squamous cells in this specimen show prominent nuclear enlargement, margination of the chromatin, and multinucleation, which are clues of an HSV infection.

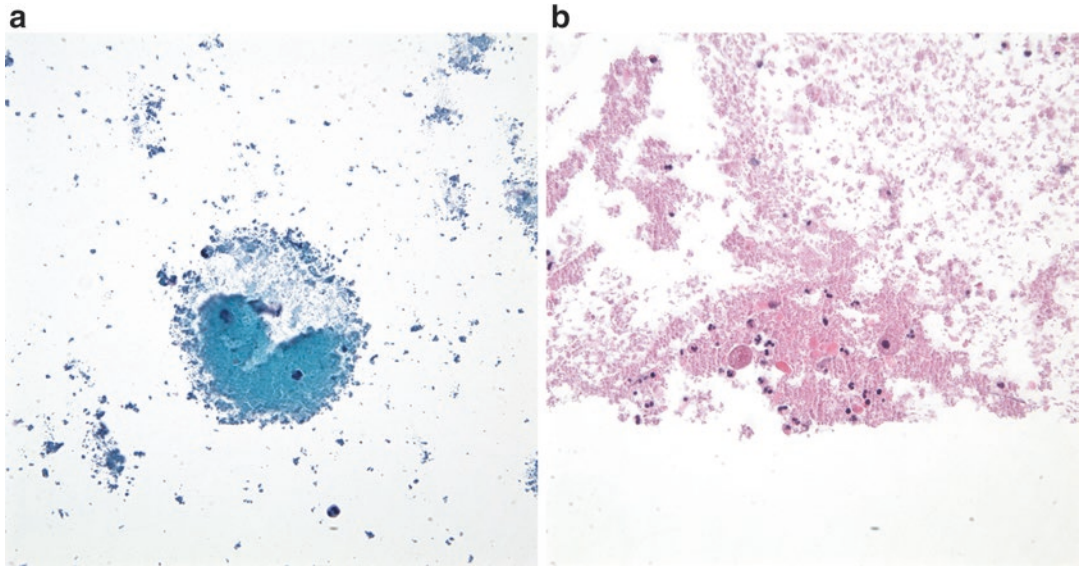

Fig. 6.13 Pulmonary alveolar proteinosis (**a**. Papanicolaou stain, high power; **b**. H&E stain, high power). This BAL from a patient with longstanding pulmonary alveolar proteinosis shows proteinaceous acellular material forming large globules and prominent background debris.

(9 %), and pleuropulmonary blastoma (8 %). Benign tumors are more frequently located in the parenchyma with inflammatory myofibroblastic tumor accounting for 70 % of benign cases, followed by hamartoma (12 %) [6, 7]. Bronchial tumors may be amenable to transbronchial biopsy; however, this technique is rarely used in the pediatric population. Although FNA can be used in children and adolescents, the tumors seen in these patients are often difficult or impossible to diagnose with confidence given the limited cells aspirated in these cases

and the need for architectural evaluation (e.g., hamartoma or inflammatory myofibroblastic tumor).

6.6.1 Inflammatory Myofibroblastic Tumor

Clinical Features

Inflammatory myofibroblastic tumors (IMTs) are the most common lung tumors in patients under 15 years of age, and are usually found incidentally on imaging. These tumors typically present as a solitary, peripheral mass lesion and behave in a benign fashion in the majority of cases.

Cytological Features

The aspirates yield relatively bland, plump spindle cells arranged in sheets, clusters and singly with a background of lymphocytes, plasma cells, and myxoid matrix. Scattered lesional cells with a ganglion-like appearance and foamy xanthomatous cells can also be seen. A collagenous or hyalinized stroma can be seen on cell block or core biopsy as well. Preparation of a cell block for immunoperoxidase stains is important to confirm the myofibroblastic nature of the tumor cells (positive for smooth muscle actin, negative for S100, cytokeratin, and desmin), and to assess for the presence of ALK-1 or ROS positivity. Rearrangement of *ALK, ROS1,* and genes of other actionable kinases is present in approximately 90 % of IMTs in the pediatric population and can be assessed by FISH or other molecular techniques [8].

Differential Diagnosis

The differential diagnosis includes organizing pneumonia and other spindle cell neoplasms, such as solitary fibrous tumor.

Pearls

Immunoperoxidase staining for ALK-1 and ROS, and FISH or other molecular studies to demonstrate *ALK* or more recently described *ROS1* rearrangements in these tumors can be of therapeutic importance. Although IMT is currently classified as a tumor of intermediate malignant potential unlikely to metastasize, it can be locally aggressive and encroach on vital structures. Some of these tumors have been shown to be responsive to crizotinib.

6.6.2 Clear Cell (Sugar) Tumor of the Lung

Clinical Features

These tumors are part of the PEComa family of neoplasms, and although they are more likely to occur in adults, they are important to recognize in pediatric patients. These typically present as a solitary, well-circumscribed lesion in the periphery of the lung.

Cytological Features

These tumors yield cellular aspirates composed of large epithelioid and spindle cells with clear to eosinophilic or granular cytoplasm. The cytoplasm typically contains PAS-positive diastase-digestible glycogen granules. A cell block is necessary to confirm that the clear cells are positive for HMB45 and MelanA, and negative for cytokeratins and CD1a. Focal staining with S100 can be seen, but staining with macrophage markers (CD68) should be negative. A PAS stain should highlight the cytoplasmic granules. TFE3 immunostaining has been described in some PEComas [9].

Differential Diagnosis

The main diagnoses to consider are Langerhans cell histiocytosis (LCH), non-Langerhans histiocytosis, and vacuolated histiocytes from a reactive process (e.g., lipoid pneumonia or drug treatment). Unlike LCH, clear cell tumors are CD1a negative and do not stain with macrophage markers. Also, LCH involving the lungs is more likely to occur in adult smokers than in children. In adults, the differential diagnosis includes metastatic renal cell carcinoma (RCC). However, unless there is a history of clear cell or translocation RCC, this is not typically a consideration in the pediatric population.

Pearls

TFE3 immunoreactivity and gene fusions have been reported in a subset of PEComas, outside of the lung, in a small series of cases [9]. This is important to recognize given that clear cell tumors of the lung can mimic a metastatic translocation-associated renal cell carcinoma, which is also positive for TFE3.

6.6.3 Mucoepidermoid Carcinoma

Clinical Features

Mucoepidermoid carcinoma is a salivary gland-type malignancy that can arise from submucosal glands of the bronchus and is usually centrally located. Tumors are typically considered low-grade with good prognosis if excised, and although they can recur, rarely manifest in a high-grade, aggressive form.

Cytological Features

Aspirates from these tumors can yield a variety of cell types, including squamous cells, intermediate cells, and mucus-secreting cells. The malignant cells can be deceptively bland and the proportion of each cell type varies considerably with the degree of differentiation of the tumor. A mucin stain performed on a cell block or smear can be used to demonstrate the presence of cytoplasmic mucin. In addition, FISH studies are increasingly important as the majority of these tumors show a *MAML2* gene rearrangement due to t(11;19), and can help distinguish mucoepidermoid carcinoma from other neoplasms in the differential diagnosis [10].

Differential Diagnosis

The main entities to consider are adenosquamous carcinoma, adenocarcinoma, pleomorphic adenoma, and benign goblet cell metaplasia.

Pearls

Although uncommon, salivary gland-type tumors can occur in the lung in the pediatric population. Morphologic distinction between primary pulmonary and metastatic salivary gland-type carcinomas is not possible, and therefore clinical correlation is essential.

6.6.4 Juvenile Squamous Papillomas

Squamous papillomas of the lower bronchial tree are rare but can occur in children and adolescents and are HPV-positive. They appear as pedunculated lesions on bronchoscopy and consist of fibrovascular stalks covered by squamous epithelium. In some cases, atypical squamous cells with nuclear enlargement, nuclear irregularities, and features suggestive of HPV infection can also be seen in cytologic specimens (Fig. 6.14). Given the rarity of squamous cell carcinoma in pediatric patients, a papilloma should be considered before making a diagnosis of squamous cell carcinoma in this age group. Squamous papillomas can also break off and seed the lower airway or lung parenchyma, where they can attach and grow independently, resulting in more numerous lesions.

6.6.5 Epithelioid Hemangioendothelioma (EHE)

These are rare tumors that can occur in other locations outside of the lung, including liver, head and neck, and soft tissue/bone. EHEs typically have an indolent course. On cytology, the key feature is the presence of bland, vacuolated, epithelioid endothelial cells with intracytoplasmic lumina containing red blood cells. Immunohistochemical stains performed on a cell block demonstrate that the cells are positive for ERG, FLI-1, CD31, and CD34. TFE3 is also frequently positive. FISH studies in these tumors have shown a t(1;3) translocation of *WWTR1-CAMTA1*.

6.7 Metastatic Neoplasms to the Lung

Clinical Features

Many metastatic lesions can be confidently diagnosed based on the clinical history and radiographic features. For certain primary malignancies, including osteosarcoma, adrenal cortical carcinoma

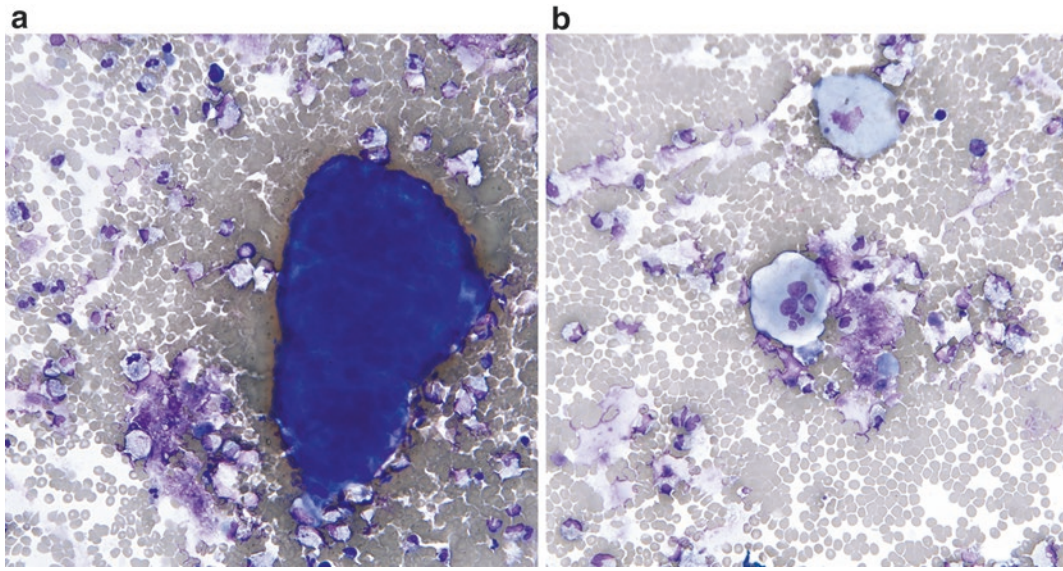

Fig. 6.14 Juvenile papilloma of the bronchus (**a**, **b**. Diff-Quik stain, high power). Juvenile papillomas of the respiratory tract can show papillary fragments and scattered atypical squamous cells with features of HPV infection.

and hepatoblastoma, resection of the lesions remaining after chemotherapy confers a definitive survival benefit and is becoming standard of care [11]. Aspiration biopsy is only occasionally performed to confirm metastasis or resolve a question of infection vs. metastasis. Patients present with nodules detected on imaging workup. One study showed that the most significant predictors of malignancy were: (1) peripheral location, (2) lesions measuring between 5 and 10 mm, (3) lesions in the right lower lobe, and (4) a primary diagnosis of osteosarcoma, Ewing sarcoma or hepatocellular carcinoma [12].

Cytological Features

With the exception of osteosarcoma, most lesions that metastasize to the lung release cells easily and are amenable to FNA biopsy. However, cellular yield will depend on the technique of the practitioner. The larger gauge needles needed to reach the nodules also tend to give more bloody specimens. Cellular smears show cytologic features similar to those seen in the primary neoplasms, which are addressed in more detail in other chapters. Given that many of the pediatric malignancies are small round blue cell tumors, many of these neoplasms have similar morphology and need to be distinguished from lymphoid cells as well as each other (Figs. 6.15, 6.16, and 6.17). A cell block is essential to confirm that the tumor cells are morphologically and immunophenotypically similar to the patient's previously diagnosed tumor. On-site evaluation is also critical given that the differential diagnosis often includes infection; thus, immediate evaluation can exclude infection and maximize cell block material.

Differential Diagnosis

Differential diagnostic considerations depend on the type of tumor and are included in discussions of the primary tumors in other chapters. Histiocytes can appear as large cells with folded nuclei that may be concerning for malignancy. However, regularity of the nuclear membranes, even chromatin, and a uniform spectrum of cells without pleomorphism are clues to the correct identity of these cells.

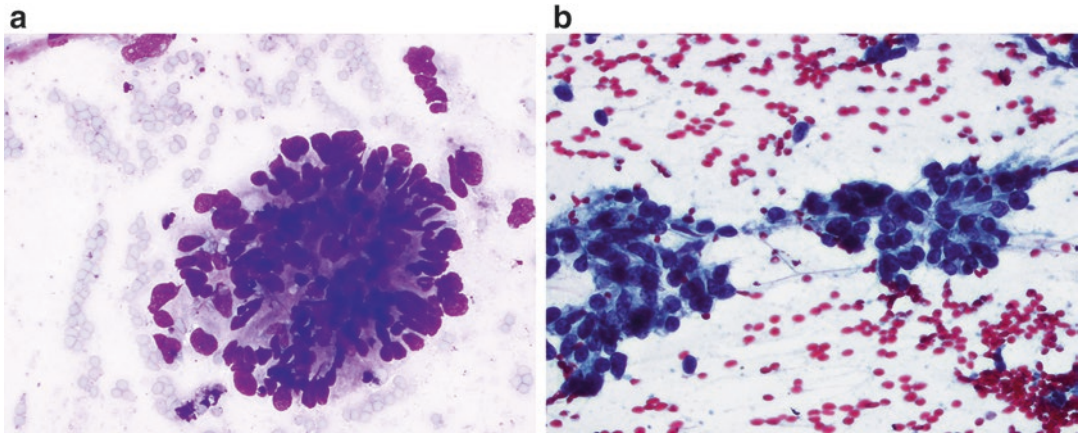

Fig. 6.15 Wilms tumor metastatic to lung (**a**. Diff-Quik stain, high power; **b**. Papanicolaou stain, high power). This is a metastasis in a patient with a known history of Wilms tumor showing pseudorosettes of cells with large pleomorphic nuclei and prominent molding. The Papanicolaou stain highlights the irregular chromatin and small nucleoli.

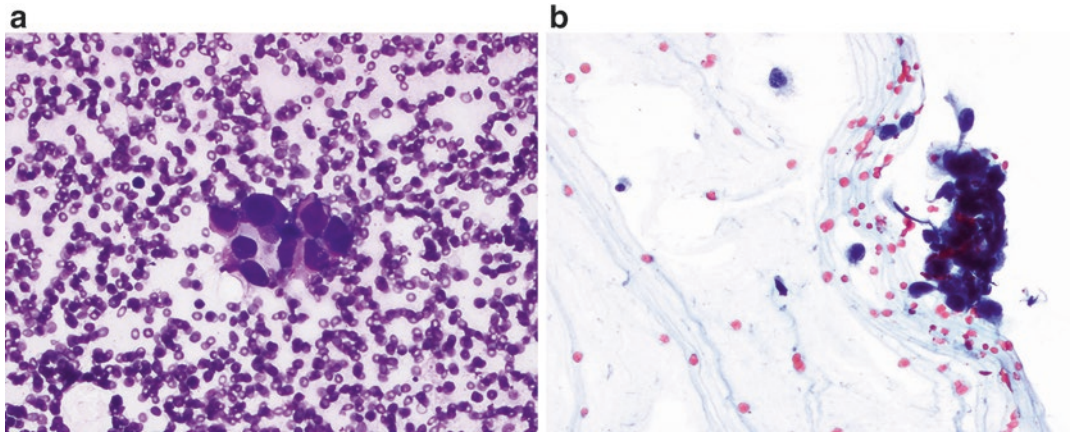

Fig. 6.16 Osteosarcoma metastatic to lung (**a**. Diff-Quik stain, medium power; **b**. Papanicolaou stain, high power). Large pleomorphic cells with irregular nuclear membranes and moderate amounts of cytoplasm are seen. Occasional multinucleated cells may be present.

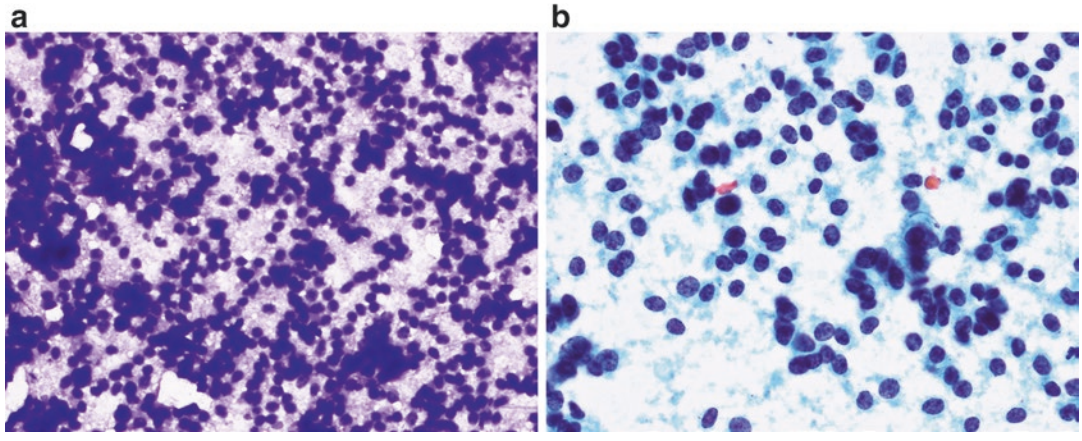

Fig. 6.17 Ewing Sarcoma metastatic to lung (**a**. Diff-Quik stain, high power; **b**. Papanicolaou stain, high power). Dyscohesive small round blue cells with round nuclei and granular chromatin are present. The background material has a somewhat reticulated or tigroid-like appearance due to the glycogen within the tumor cells (**a**).

Pearls

Correlation of the cytologic features of a presumed metastatic lesion with the histologic appearance of the patient's known primary tumor is often helpful and may obviate the need for ancillary studies.

6.8 Mediastinum

The mediastinum consists of the tissues in the central thorax. Its boundaries are defined by the thoracic inlet superiorly, the parietal pleura bilaterally, the sternum anteriorly, the spine and ribs posteriorly, and the diaphragm inferiorly. The mediastinum is usually divided into three main compartments: anterior/superior, middle and posterior. There is a high prevalence of malignancy in pediatric mediastinal masses (37–61 %) and a large number of tumors are hematolymphoid in origin [13, 14]. Given the need for ancillary studies such as cytogenetics and flow cytometry, tissue biopsy is often necessary to obtain enough tissue for diagnosis. However, fine needle aspiration biopsy can be a useful tool at the time of surgery to localize viable lesional tissue prior to core needle biopsy and direct the distribution of material for ancillary studies. Aspirates rinsed in saline or RPMI can be sent for cytogenetics and flow cytometry and air dried smears can provide cellular monolayers for FISH studies, reducing the amount of tissue cores that need to be diverted from histology. The majority of masses that present in the anterior mediastinum are lymphomas (2/3 non-Hodgkin lymphoma, 1/3 Hodgkin lymphoma), followed by germ cell tumors. Approximately three quarters of germ cell tumors in the mediastinum are benign teratomas followed by yolk sac tumors. In the posterior mediastinum, the most common lesions are neurogenic including neuroblastoma, ganglioneuroblastoma, and ganglioneuroma [23]. A summary of pediatric mediastinal lesions is seen in Table 6.2.

6.8.1 Anterior/Superior Compartment

The anterior compartment of the mediastinum encompasses the area from the sternum to the anterior pericardial sac. The superior portion of the mediastinum, including tissues above the great vessels of the heart, is usually considered part of the anterior mediastinum. Tissues in the anterior compartment include the thymus, scattered lymph nodes, and loose connective tissue. Tumors of the anterior mediastinum include lymphoma, thymoma, germ cell tumors, thyroid lesions, metastases, and vascular lesions. One way to summarize the lesions of the anterior mediastinum is to use the 5 T's, which represent: thymic lesions, thyroid lesions, teratoma and other germ cells tumors, terrible lymphoma, and terribly common metastatic tumors (Table 6.2).

6.8.1.1 Lymphoma

Clinical Features

Lymphoma is the most common malignancy in the mediastinum accounting for about half of all mediastinal malignancies. Two-thirds of lymphomas are non-Hodgkin lymphomas (e.g., lymphoblastic and large cell) and one third are Hodgkin lymphomas [13]. Most lymphomas present in multiple sites, many of which are more amenable to biopsy than the mediastinum (e.g., cervical lymph nodes, bone marrow). Also, due to the need for multiple ancillary studies, open biopsy is often a preferred method of obtaining tissue. However, FNA and small core biopsies are increasingly being used for primary diagnosis or in the setting of recurrence, given that, for many lymphomas, diagnosis is based on cytogenetic and immunophenotypic findings, rather than architecture. Patients present with symptoms of airway compression, including cough, stridor, and respiratory distress. Occasionally there are symptoms of superior vena cava obstruction and markedly elevated lactate dehydrogenase (LDH) levels. Patients with Hodgkin lymphoma also may present with B-symptoms of weight loss, night sweats and malaise.

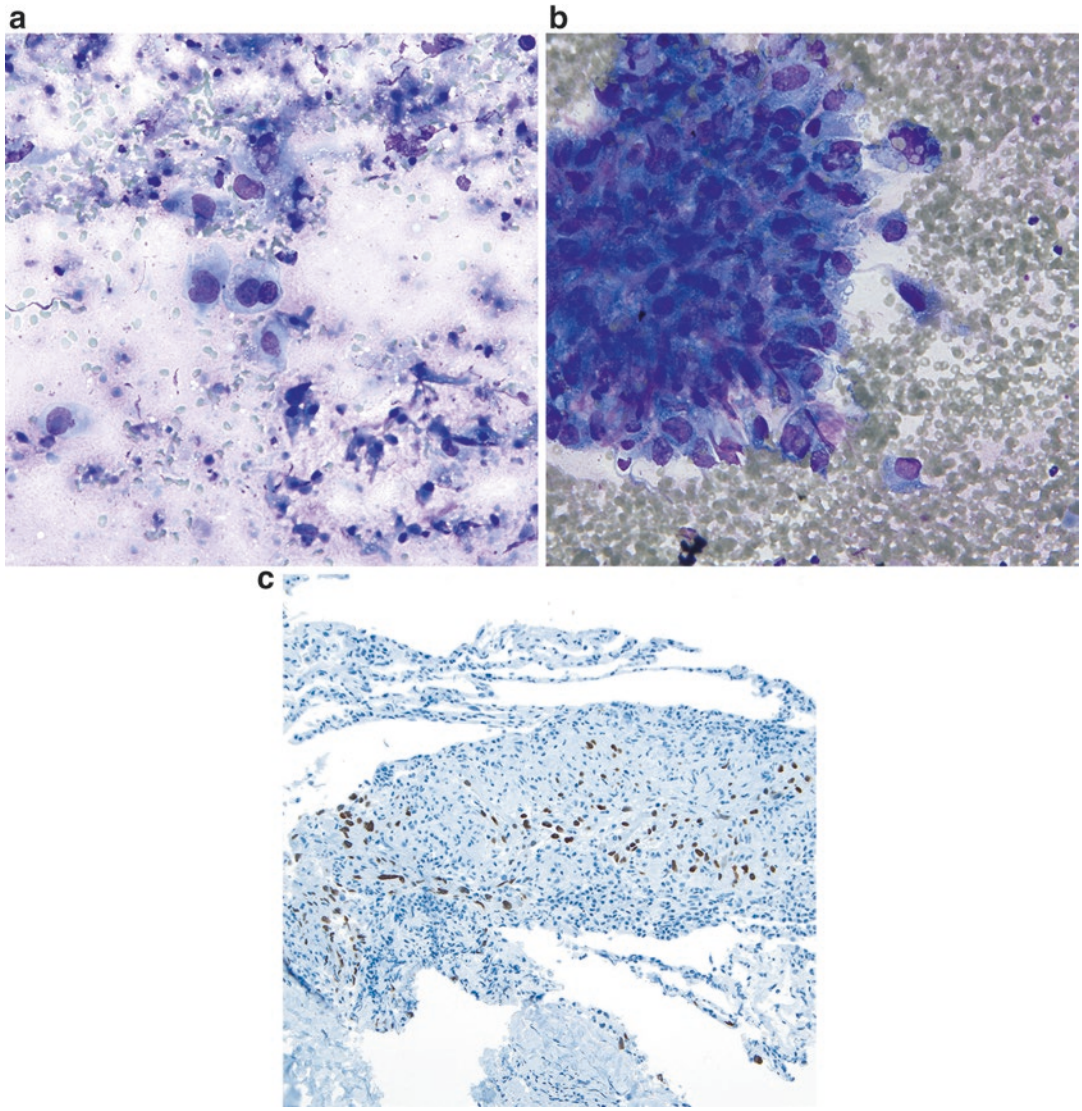

Fig. 6.18 Metastatic yolk sac tumor to the lung (**a**, **b**. Diff-Quik stain, high power; **c**. SALL4 immunostain). This is a metastasis in a young patient with a known yolk sac tumor that metastasized to the lung, which shows loosely cohesive pleomorphic tumor cells, which are positive for SALL4 immunostaining.

Cytological Features

The cytomorphology will depend on the type of lymphoma, as discussed below and in greater detail in Chap. 3.

- *Lymphoblastic Lymphoma*: Smears show a dyscohesive population of monotonous small lymphocytes. The lymphocytes have a high nuclear to cytoplasmic ratio and may show atypical nuclear features such as nuclear folds or membrane irregularities. The nuclear chromatin is usually fine and powdery without a conspicuous nucleolus (Fig. 6.19). The key to diagnosis is lack of variation in size and cell type. A lesser population of tingible body macrophages may be present. Subclassification of lymphoma requires flow cytometry and/or immunohistochemistry.
- *Large Cell Lymphoma*: Smears usually show large atypical cells with variable amounts of

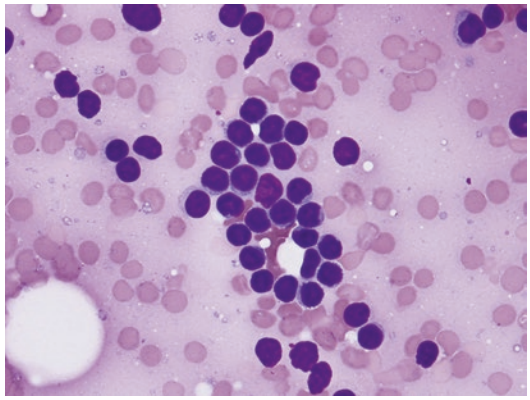

Fig. 6.19 Lymphoblastic lymphoma (Diff-Quik stain, high power). Small to intermediate sized lymphoid cells with immature chromatin are seen in this patient with a T-lymphoblastic lymphoma/leukemia of the anterior mediastinum.

cytoplasm and large nuclei with irregular membranes. The neoplastic cells should have a nuclear size greater than that of a histiocytic nucleus (Fig. 6.20). Large cell lymphomas may present in cohesive clusters mimicking a solid neoplasm.

- *Hodgkin Lymphoma*: Smears show variable numbers of Reed–Sternberg (RS) cells and Reed–Sternberg variants in a background of mixed lymphoid cells. In the pediatric population, Hodgkin lymphomas tend to have more abundant RS cells making the diagnosis

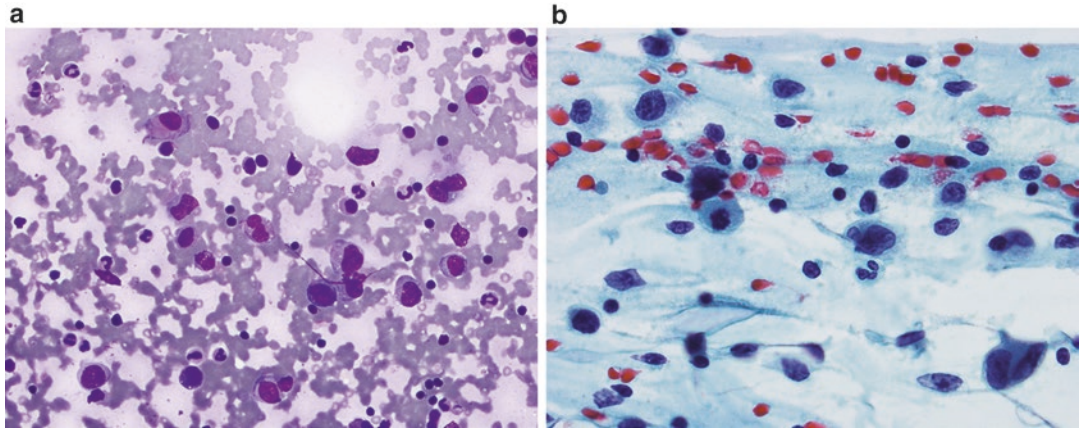

Fig. 6.20 Anaplastic large cell lymphoma (**a**. Diff-Quik stain, high power; **b**. Papanicolaou stain, high power). These aspirates show a predominance of highly atypical large lymphoid cells with occasional boomerang or horseshoe shaped nuclei, compatible with a large cell lymphoma such as anaplastic large cell lymphoma.

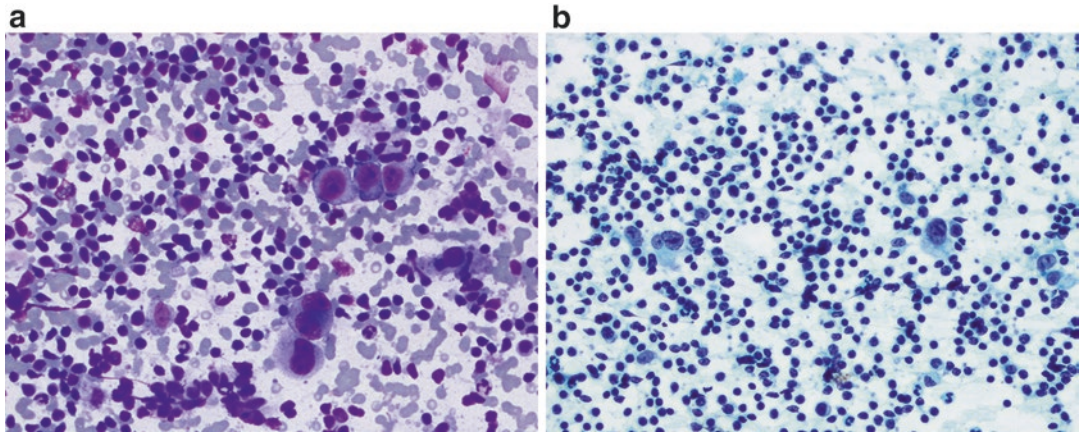

Fig. 6.21 Classical Hodgkin Lymphoma of the mediastinum (**a**. Diff-Quik stain, high power; **b**. Papanicolaou stain, high power). The large lymphoid cells are seen in a background of small lymphocytes, and show some binucleated large cells with prominent nucleoli (Reed–Sternberg cells).

possible on FNA alone. RS cells show abundant cytoplasm and large round to oval nuclei with prominent nucleoli. The background lymphoid cells usually show intermixed eosinophils (Fig. 6.21).

On-site evaluation is usually helpful in cases of lymphoma. Flow cytometry shows a reactive pattern in classical Hodgkin lymphoma, and thus, if RS cells are seen at on-site evaluation, material may be better allocated for cell block for immunoperoxidase stains than for flow cytometry. In contrast, if a lymphoblastic or large cell lymphoma is suspected, then flow cytometry and cell block material are typically needed for a definitive diagnosis.

Differential Diagnosis

Malignant germ cell tumors are the second most common anterior mediastinal mass in children and can also show large atypical, dyscohesive cells within a background of smaller lymphocytes, which can mimic a large cell lymphoma. Germ cell tumors show more cohesive clusters and tend to have more abundant cytoplasm and prominent nucleoli, without conspicuous lymphoglandular bodies. Myeloid sarcoma can also mimic large cell lymphomas morphologically but can be distinguished by flow cytometry and immunoperoxidase stains. The differential diagnosis for lymphoblastic lymphomas includes reactive lymphoid tissue and small round blue cell tumors. Classical Hodgkin lymphomas, particularly those with a paucity of RS cells, can be difficult to distinguish from reactive lymphadenopathy, whereas those with abundant RS cells may mimic a large cell lymphoma, germ cell tumor, or malignant melanoma.

Pearls

Myeloid cells can mimic lymphomas or atypical histiocytes, and myeloid sarcoma should be considered when evaluating a cellular hematolymphoid proliferation in the mediastinum. Myeloid sarcoma is negative for lymphoid markers but positive for CD33 by flow cytometry, and MPO and CKIT on immunoperoxidase stains (Fig. 6.22).

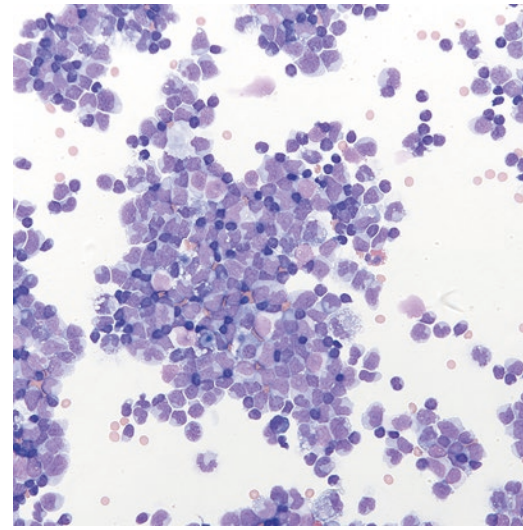

Fig. 6.22 Myeloid sarcoma presenting as a pleural/soft tissue mass (Diff-Quik stain, high power). Immature appearing myeloid cells with powdery chromatin and irregular nuclei are present in this cellular aspirate from a soft tissue mass in a patient with a known history of acute myeloid leukemia.

6.8.1.2 Germ Cell Tumors

Clinical Features

Germ cell tumors develop from cells in the primordial germ cell crest that fail to properly migrate to the urogenital ridge. Approximately 4–18 % of germ cell tumors arise in the mediastinum which is the fourth most common site after the ovary, sacrococcygeal region, and testis [13, 15, 16]. Most mediastinal germ cell tumors are in the anterior mediastinum/thymus, although rare tumors have been reported in the pericardium/heart and posterior mediastinum [15, 16]. Benign teratomas comprise up to 70–85 % of mediastinal germ cell tumors [15, 16]. While seminoma is the most common malignant germ cell tumor in the adult population, yolk sac tumor is more common in pediatrics [17, 18]. Most patients present with respiratory symptoms, such as shortness of breath and cough; some patients additionally show weakness, loss of appetite, and/or chest pain. Benign teratoma can frequently be diagnosed by imaging and malignant components may be indicated by

serum markers (e.g., serum alpha-fetoprotein, beta-human chorionic gonadotropin). Complete surgical resection is the mainstay of treatment so patients with low stage disease are frequently taken directly to surgery; however, FNA may be used in cases that are indeterminate by imaging or that appear cystic. Patients with extensive disease and/or potential airway compromise may present for biopsy (with or without FNA) prior to neoadjuvant chemotherapy.

Cytological Findings

The morphology depends on the predominant type of germ cell tumor seen in the lesion, as described below:

- *Teratoma*: Cystic teratomas may show predominantly cyst contents—anucleate squamous debris or mucin—with scant fragments of glandular or squamous epithelium. Neural tissues and stromal tissues are usually more cohesive and less likely to release cells on FNA. The nuclear features are usually bland, consistent with the mature nature of the tissues.
- *Yolk Sac Tumor*: Cytological findings vary corresponding to the histologic heterogeneity of yolk sac tumors. Tumors with well-formed Schiller–Duvall bodies may yield papillary fragments on FNA. Intracytoplasmic and extracytoplasmic hyaline globules may be present and can be an important clue to the diagnosis. Irrespective of histologic type, aspirates should contain cells with malignant features including increased nuclear to cytoplasmic ratios and nuclear pleomorphism, hyperchromasia, and membrane irregularities (Fig. 6.23).
- *Seminoma*: Smears show a biphasic population of large polygonal tumor cells intermixed with small lymphocytes and granulomas. The tumor cells show abundant cytoplasm with clear borders and large round nuclei with prominent nucleoli. A tigroid background can be seen in many cases on Diff-Quik-stained slides due to the presence of glycogen (Fig. 6.24).

Differential Diagnosis

When cystic, the differential diagnosis includes foregut duplication cysts or bronchogenic cysts, mediastinal goiter, and thymic cysts, but these lesions tend to be very hypocellular. Non-cystic germ cell tumors can mimic large cell lymphomas, lymphoblastic lymphomas, or other high-grade large cell malignancies.

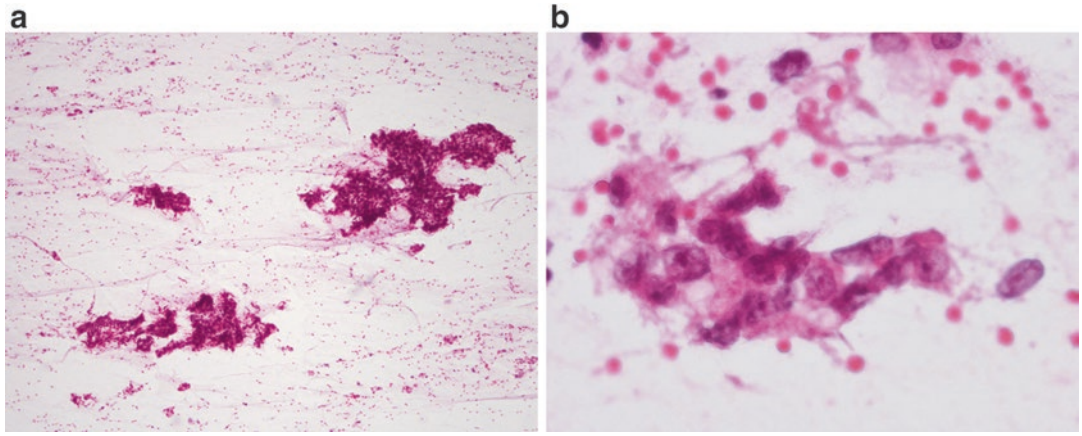

Fig. 6.23 Mediastinal germ cell tumor with yolk sac component (**a**. H&E stain, low power, **b**. H&E stain, high power). The aspirates from this yolk sac tumor show papillary-type groups of tumor cells with cytoplasmic vacuolization, prominent nucleoli, and cytoplasmic hyaline globules.

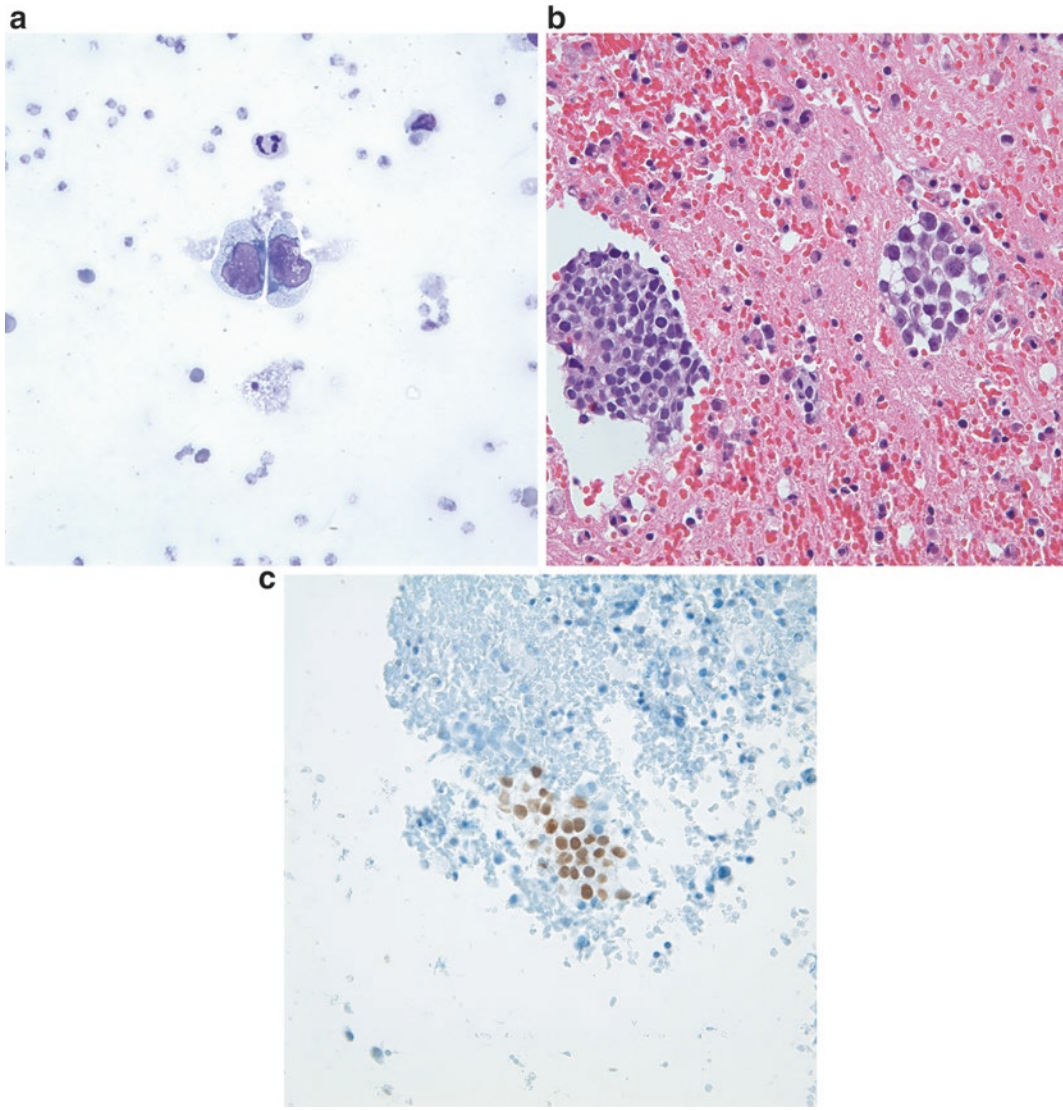

Fig. 6.24 Metastatic seminoma involving the pleural fluid (**a**. Diff-Quik stain, high power; **b**. H&E stain, high power; **c**. OCT3/4 stain, high power). Dyscohesive large cells with centrally located nuclei, prominent nucleoli, and moderate amounts of clear cytoplasm are identified. The OCT3/4 stain shows strong nuclear staining, confirming the presence of a germ cell tumor.

6.8.1.3 Thymus

Lesions in the thymus include cysts, hyperplasia, and tumors. Cysts and hyperplastic lesions usually are diagnosed radiologically and do not require FNA. Solid tumors arising in and around the thymus include lymphomas, thymomas, thymic carcinomas, neuroendocrine tumors, and germ cell tumors, and these are typically amenable to biopsy for planning of further management.

Thymoma

Clinical Features

Thymomas are rare in pediatrics accounting for 1–4 % of pediatric mediastinal masses [14, 19]. However, it is the fourth most common tumor after lymphoma, germ cell tumors, and neurogenic tumors [17]. Thymomas rarely present for FNA diagnosis even in the adult population,

given that the lobulated nature and presence of fat are radiological clues to the diagnosis. Patients usually present with respiratory complaints, including cough and shortness of breath. Myasthenia gravis, which is associated with thymoma in 30 % of cases in the adult, is only associated with thymoma in 5 % of pediatric cases [17].

Cytological Features

Aspirates of thymoma vary depending on the histology of the lesion. Lymphocytic thymomas (type B) are the most common and are the only type reported in pediatrics [20]. On histology, these lesions show varying amounts of epithelial clusters in a background of small lymphocytes. Concordantly, aspirates show abundant small lymphocytes with a variable population of epithelial cells. The recognition of the latter is necessary to distinguish thymoma from reactive lymphoid tissue. These epithelial cells usually present in tightly clustered fragments of bland cells with round to oval nuclei and finely granular chromatin [21]. Flow cytometry and/or immunoperoxidase stains on a cell block can be helpful to confirm the presence of thymic T-lymphocytes, which are positive for CD3, TdT, and CD1a. In addition, thymic epithelium can be confirmed with p63 and cytokeratin, and a thymic carcinoma can be excluded with a CD5 immunostain given that thymic carcinomas are CD5-positive.

Differential Diagnosis

The differential diagnosis includes small cell lymphoma, classical Hodgkin lymphoma with a paucity of RS cells, and small round blue cell tumors.

Pearls

Newer immunoperoxidase stains can also help mark thymic epithelium, including CKIT and PAX8. PAX8 can be particularly helpful given that it is a nuclear stain, and typically only stains thyroid, renal, Müllerian, and thymic lesions.

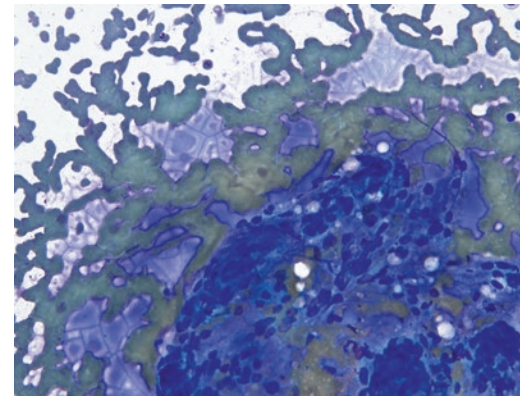

Fig. 6.25 Mediastinal goiter (Diff-Quik stain, medium power). Mediastinal thyroid tissue can show features of a benign colloid nodule, and an important clue is the cracking of the watery colloid in the background.

6.8.1.4 Vascular Malformations

Vascular malformations, including lymphangiomas/cystic hygromas and hemangiomas, account for 3–6 % of mediastinal tumors in children [13]. These are usually easily diagnosed by radiology and are generally not amenable to FNA. Rarely lesions with thrombosis may mimic a solid neoplasm. Cytology shows old blood, fibrin and hemosiderin laden macrophages.

6.8.1.5 Mediastinal Goiter or Thyroid Tissue

Thyroid tissue can also extend into the anterior mediastinum and show the spectrum of changes seen in the normal thyroid, ranging from benign colloid nodules to malignant papillary thyroid carcinoma. Mediastinal goiters usually present as large cystic masses that can radiologically mimic bronchogenic cysts. A combination of colloid and follicular epithelial cells are important for the diagnosis (Fig. 6.25). If cystic, liquid-based cytology can be helpful to identify the thyroid follicular cells, which will also stain positive for TTF1 and thyroglobulin. PAX8 is not as helpful given that thymic epithelium will also be PAX8 positive and is in the differential diagnosis of a cystic anterior mediastinal mass.

6.8.2 Posterior Compartment

The posterior compartment consists of the tissues between the posterior pericardial sac and the spine/chest wall. This includes the descending aorta, esophagus, sympathetic chain of the nervous system, trachea, and lymph nodes. A summary of posterior mediastinal lesions is seen in Table 6.2.

6.8.2.1 Congenital Cysts

Congenital cysts include bronchogenic cysts, esophageal duplication cysts, and enteric cysts which are malformations/remnants of the embryonic foregut. These are usually diagnosed radiographically and are not subject to FNA. If aspirated, liquid-based cytology and immunoperoxidase stains can be helpful to try to identify and characterize the cyst lining cells. Unfortunately, some cases just show cystic fluid or histiocytes and cannot be definitively diagnosed.

6.8.2.2 Lymph Nodes

Most lymph nodes in the mediastinum are located along the trachea and great vessels of the heart. These are frequently involved and enlarged in systemic diseases, including infections, lymphoma, and widely metastatic neoplasms. In the adult population, endoscopic ultrasound guided biopsy of lymph nodes may be performed via the trachea or the esophagus. This has also been performed successfully in the pediatric population [22]; however, most children present with widespread disease that has other lymph nodes/sites that are more readily accessible.

6.8.2.3 Neuroblastoma Spectrum

Clinical Features

Tumors of the neuroblastoma spectrum (neuroblastoma, ganglioneuroblastoma, ganglioneuroma) are the most common tumors in the posterior mediastinum and the most common mediastinal tumor in children under 2 years old [23]. Only 11–26 % of pediatric neuroblastoma cases present in the thoracic cavity. These tumors tend to have a better prognosis, although the reasons are not fully understood. Thoracic neuroblastoma frequently presents with localized disease (66 % stage I and II vs 45 % in other sites) and is less frequently *MYCN* positive [23]. Of the patients who present with opsoclonus-myoclonus, up to 50 % have been found to have a slowly growing chest tumor [24]. Patients frequently present with a mass discovered on an X-ray performed to evaluate upper respiratory symptoms. Younger patients with aggressive tumors may have symptoms of chest pain, paraplegia, and Horner's syndrome. Adolescent patients occasionally have incidental findings on routine X-rays. As with lymphoma, patients with meta-

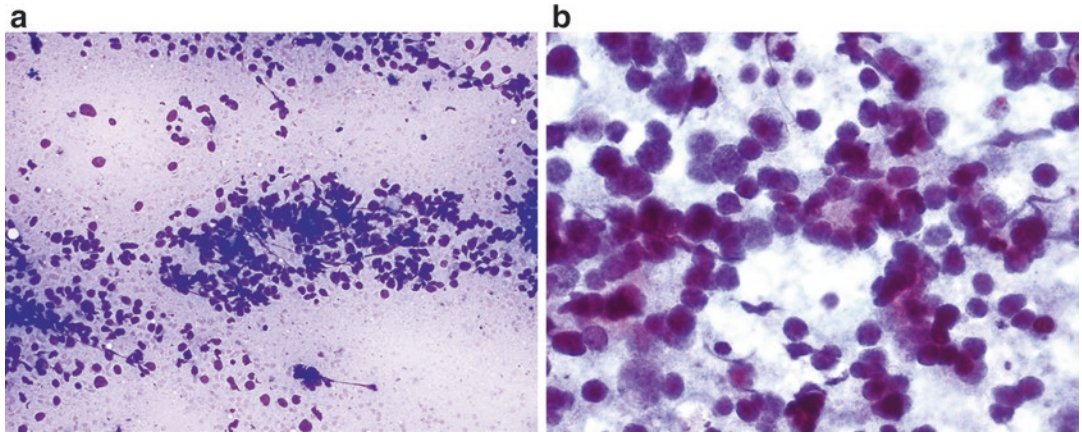

Fig. 6.26 Neuroblastoma in the posterior mediastinum (**a**. Diff-Quik stain, high power; **b**. Papanicolaou stain, high power). The aspirates are cellular and reveal a small round blue cell tumor with immature granular chromatin, nuclear molding, and rosette formation.

static neuroblastoma may have more accessible lymph nodes for biopsy in the cervical region.

Cytological Features

Smears from neuroblastoma show abundant small round blue cells with prominent nuclear molding. Occasional Homer Wright rosettes or balls of cells may be present. Fibrillary neuropil may be present, but can be difficult to identify. On Papanicolaou stain, the neuroblastic nuclei show fine granular chromatin without prominent nucleoli (Fig. 6.26). Occasional maturing ganglion cells may be seen. Ganglioneuromas are less amenable to FNA as they are less cellular and less prone to release cells, but will show large epithelioid ganglion cells with prominent nucleoli, abundant cytoplasm, and Nissl substance within a background of bland comma-shaped spindled Schwann cells. Biopsies from ganglioneuroblastoma show variable findings depending on the area sampled; however, even without a neuroblastic component identified on FNA, these tumors are typically excised to completely exclude a component of neuroblastoma. A cell block or core biopsy can be helpful for performing immunoperoxidase stains to confirm neuroblastic, Schwannian, or gangliocytic origin of cells. While FNA biopsy may be diagnostic of neuroblastoma, the mitotic karyorrhectic index (MKI) cannot be calculated on aspirate smears. If a minimally invasive procedure is planned, every effort should be made to obtain at least one tissue core for complete staging.

Differential Diagnosis

The differential diagnosis depends on the predominant cell type. For cases with abundant spindle cells, mesenchymal tumors are in the differential diagnosis. For tumors with a more prominent gangliocytic component, epithelioid tumors, large cell lymphomas, melanoma, and germ cell tumors enter the differential diagnosis. If there is a prominent neuroblastic component, then other small round blue cell tumors, including lymphoblastic lymphoma, Ewing sarcoma, and rhabdomyosarcoma enter the differential diagnosis.

6.9 Conclusions

The mediastinum and lung contain a wide spectrum of entities to consider when a mediastinal or thoracic lesion is identified on imaging. Given the variety of ancillary studies required for a definitive and accurate diagnosis, FNA and small biopsies can play a powerful role in triage and management by helping to confirm which lesions require surgery (e.g., primary lung neoplasm) and which can be better managed in non-surgical ways (e.g., lymphoma, infection, metastatic tumor).

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