Category IV: Neoplasm—Undetermined Malignant Potential

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Background

The category of "neoplasms of low malignant potential" was created in order to aid in clinical decision-making and treatment. These neoplasms do not fit into the more traditional cytological diagnostic categories of "negative, atypical, suspicious, and positive." The difference between a "benign neoplasm" and a tumor of low malignant potential "borderline neoplasm" is very subtle. Although most of the neoplasms in this group behave in a benign fashion, that is, cured after complete excision, many "borderline" neoplasms have a tendency for local recurrences and occasional metastatic potential after excision. Neoplasms of low malignant potential often present as incidental findings on imaging studies for unrelated reasons. Neoplasms of low malignant potential are often described radiographically as circumscribed nodules or "coin-like lesions." These tumors rarely produce symptoms; however, if present, cough, hemoptysis, and recurrent pneumonia are the most commonly encountered symptoms due to mass-forming effect in the tracheobronchial tree. Neoplasms of low malignant potential often present as solitary nodules, and the radiographic appearance is not enough to exclude the possibility of a malignant neoplasm; therefore, intervention more often in the form of a fine-needle aspiration (FNA) biopsy for further characterization is necessary [1]. Exfoliative cytology such as bronchial brushing or lavage has low diagnostic yields because of the low growth rate of these tumors which often have intact overlaying bronchial mucosa, when protruding into the bronchial tree.

Therefore, cytopathologists and technologists need to be familiar with their cytological features for accurate classification. Most of these entities are rare, produce

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cellular smears, and have overlapping features with a malignant counterpart, thus increasing the difficulty in reaching an accurate diagnosis.

Definition

The "neoplasm of low malignant potential" category is defined as neoplastic lesions whose cytomorphological/histological features cannot predict clinical behavior.

Epithelioid Hemangioendothelioma

Epithelioid hemangioendotheliomas (EHEs) are vascular tumors of low to intermediate grade with metastatic potential. Although rare, these tumors are seen predominantly in women of childbearing age (approximately 80% of the cases). EHEs typically present as multiple bilateral pulmonary nodules, synchronous hepatic nodules are often seen, and therefore, the initial presentation mimics metastatic disease or a multifocal infectious process. Single pulmonary nodules may also be seen. Most patients are asymptomatic, but if symptoms are present, cough and pleuritic chest pain are the most common. Histologically this tumor is characterized by the presence of bland cells arranged in nests or cords within a hyaline myxoid stroma. A useful diagnostic feature is the presence of intracytoplasmic vacuoles, some of which may contain red blood cells. Tumor nodules may also fill alveolar spaces resembling a polypoid growth pattern [2–6].

Tumor cells are positive for vascular markers such as CD 31, CD 34, ERG, and factory VIII. Cytokeratin expression is present in 25–30% of cases, which represents a diagnostic pitfall. EHEs have a characteristic translocation t(1;3)(p36.3;q25) involving the WWTR1 and CAMTA1 genes [3].

The 5-year survival rate for patients with EHE ranges from 40% to 70% (average 60% survival rate) for patients with multifocal disease. For tumors presenting as a single nodule, metastasis are a late event. EHE can present with pleural involvement mimicking clinically and radiographically malignant mesothelioma. Involvement of the pleura is a poor prognostic indicator. The diagnosis of pleural malignant mesothelioma in a woman of childbearing age without significant history of asbestos exposure should be rendered with caution, and EHE should be excluded. Other poor prognostic findings include extensive intrapulmonary and pleural spread, weight loss, anemia, and hemorrhagic pleural effusions [2–4, 7].

Cytological Criteria: Epithelioid Hemangioendothelioma

Cytological Criteria [2, 4–7]: Epithelioid Hemangioendothelioma (Figs. 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, and 6.7)

- Low to moderate cellularity
- Cells with eccentric, signet-ring, or "rhabdoid"-appearing nuclei
- Cells contain eosinophilic cytoplasm, which may be scant to abundant

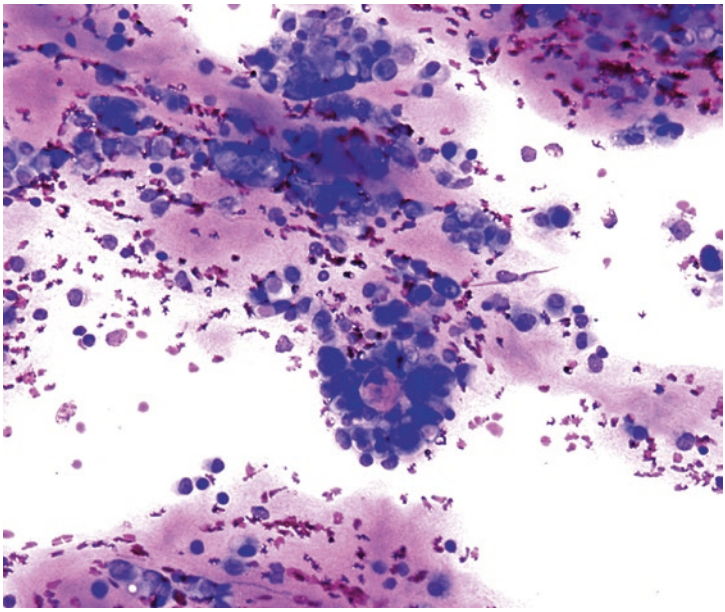

Fig. 6.1 Epithelioid hemangioendothelioma. Tumor cells may appear singly or loosely attached to a metachromatic central core. Individual cells are eccentric with mild to moderate nuclear atypia and small nucleoli. Intracytoplasmic vacuoles can be seen, representing vascular lumina. Background metachromatic or myxoid matrix should prompt consideration of mesenchymal tumor (direct smear, Diff-Quik). We acknowledge Dr. Saqi from Columbia University NY for providing the image

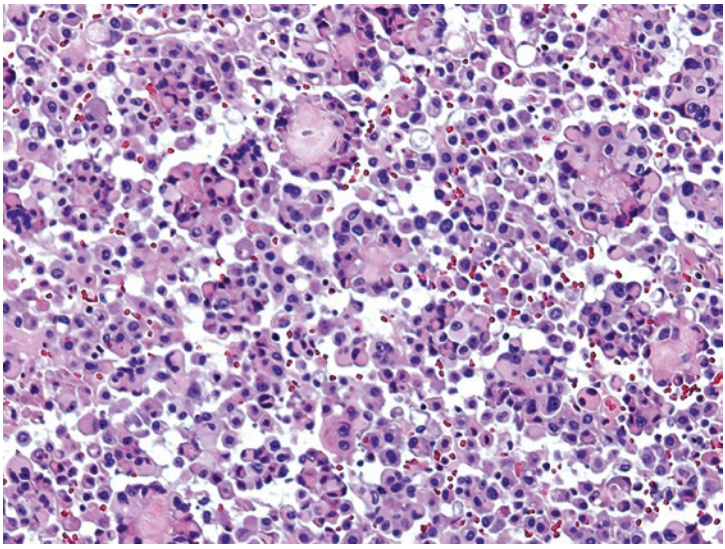

Fig. 6.2 Epithelioid hemangioendothelioma. Tumor cells in cell block display similar findings with acellular central core and loosely cohesive cells around the perimeter with occasional hobnail appearance. Intracellular lumina can be seen more easily, representing blood vessels (cell block, hematoxylin and eosin). We acknowledge Dr. Saqi from Columbia University NY for providing the image

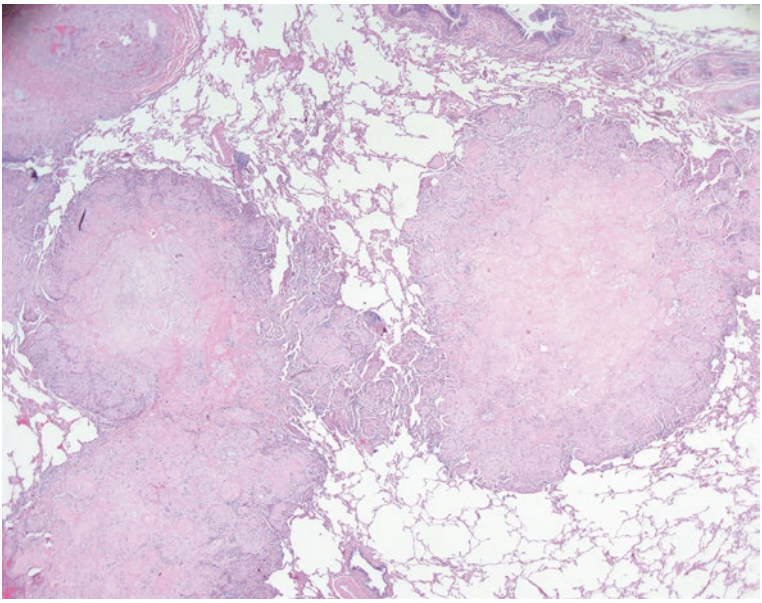

Fig. 6.3 Epithelioid hemangioendothelioma. On histology, EHEs demonstrate multiple nodules with pushing borders (hematoxylin and eosin). Note hyalinized matrix

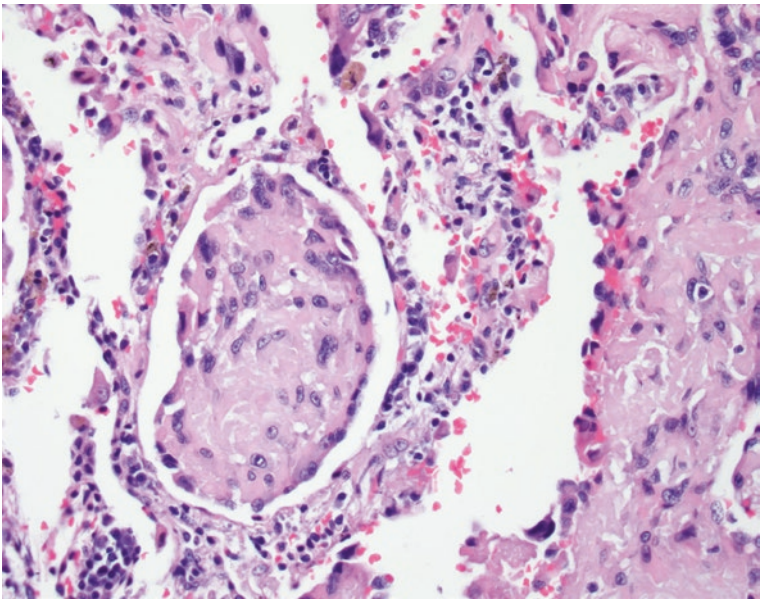

Fig. 6.4 Epithelioid hemangioendothelioma. Polypoid growth pattern within the alveoli. The bland tumor cells forming the nodules are small and round to oval (hematoxylin and eosin)

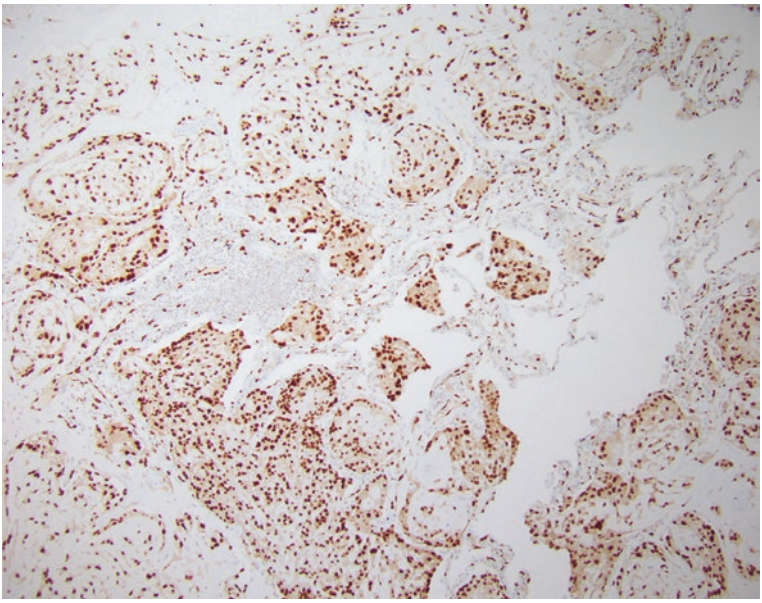

Fig. 6.5 Epithelioid hemangioendothelioma. Tumor cells express ERG

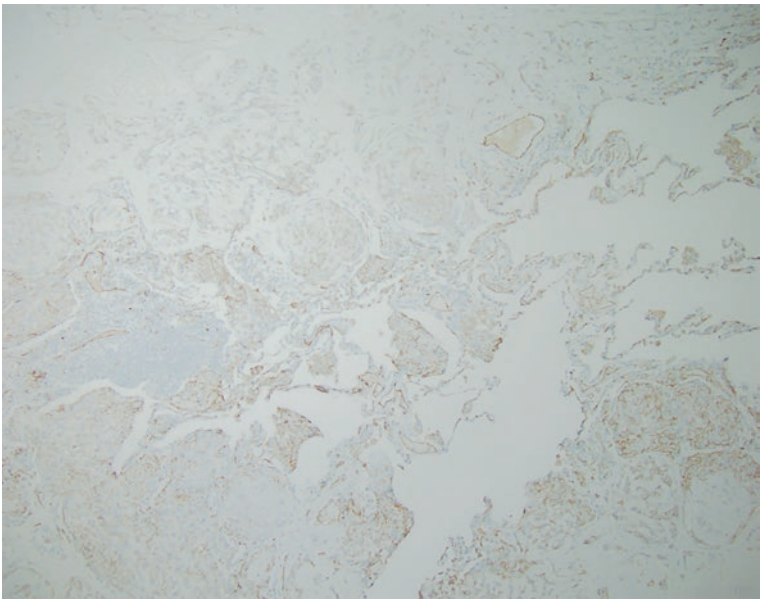

Fig. 6.6 Epithelioid hemangioendothelioma. Tumor cells express CD31

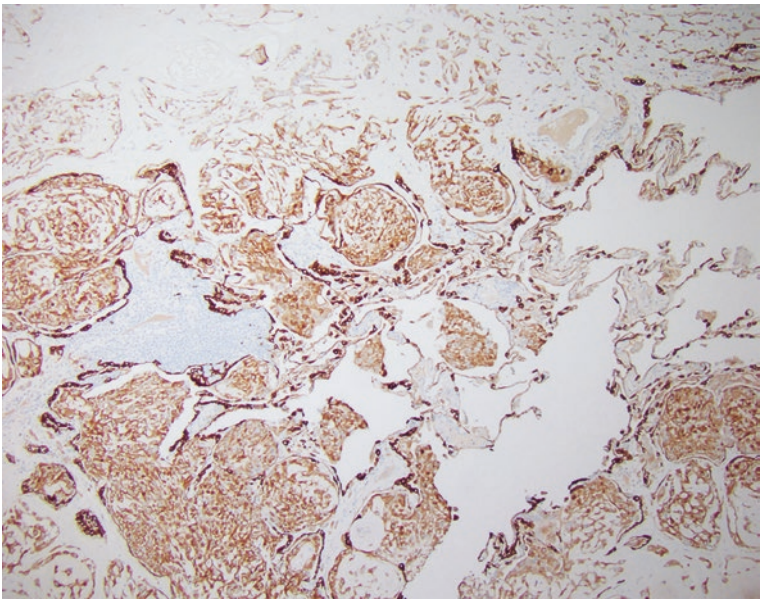

Fig. 6.7 Epithelioid hemangioendothelioma. Tumor cells express CAM5.2, thus mimicking an epithelial tumor

- Cytoplasmic vacuoles representing vascular lumina, which may contain red blood cells
- Cells may surround central amorphous metachromatic core
- Mitotic rate is low or absent
- Nuclei are round to oval with multiple nucleoli
- Mild to moderate nuclear atypia may be present

Explanatory Notes

The differential diagnosis of EHE includes angiosarcoma, sclerosing pneumocytoma (sclerosing hemangioma), malignant mesothelioma, adenocarcinoma, metastatic carcinomas/sarcomas, and pulmonary amyloidoma. Immunohistochemical stains and cytomorphological features are always helpful in pointing out the correct diagnosis.

Angiosarcoma is a high-grade sarcoma with high mitotic rate and nuclear atypia. Although angiosarcoma is also positive for the same vascular markers as EHE, the former lacks the typical WWTR1 and CAMTA1 translocation seen in EHE [7].

Malignant mesothelioma cells are positive for calretinin, D2-40, and WT-1, which are not expressed in EHE.

Although EHE can express keratin, this tumor lacks expression of tissue-specific markers such as TTF-1, NAPSIN-A, and PAX-8, among others. Sclerosing pneumocytoma cells are positive for TTF-1. The myxoid stroma of EHE does not show birefringent deposit such as seen in amyloidoma. Foreign body giant cells that are seen in amyloidoma are not present in EHE.

Management

The best therapy for EHE is surgical resection of the nodule if possible. Systemic chemotherapy can be used in cases of disseminated disease and/or pleural involvement [8].

Clear Cell Tumor of the Lung (Sugar Tumor)

Clear cell tumor of the lung, also known as "sugar tumor," is a rare pulmonary neoplasm that belongs to the perivascular epithelioid cell tumor (PEComa) family. Although rare, the tumor is more common in adults. Clear cell tumors are circumscribed but not encapsulated and can have significant size variations. They are often identified as a mass (more than 3 centimeters) and due to their slow growth pattern often present as an incidental finding. The tumor is frequently vascular with sinusoidal-type thin-walled blood vessels. Tumor cells are round to oval with distinct cytoplasmic borders and fine nuclear chromatin. Tumor cells are rich in glycogen (PAS-positive and diastase-sensitive) [9] which results in a granular and eosinophilic clear cytoplasm. Anisonucleosis and nuclear inclusions can be present. Clear cell tumors lack significant atypia, mitotic figures, or necrosis [3, 10, 11]. In smears, the cells are organized in cohesive, often papillary clusters. Naked nuclei are often seen [11].

Similar to PEComas from other sites, the tumor cells are positive for vimentin and HMB-45 and show variable positivity for S-100, smooth muscle actin, and CD34 [3, 9, 12, 13]. Clear cell tumors are consistently negative for keratins [9, 11–14].

Cytological Criteria: Clear Cell Tumor of the Lung

Cytological Criteria [3, 14]: Clear Cell Tumor of the Lung (Figs. 6.8, 6.9, 6.10, 6.11, 6.12, 6.13, and 6.14)

- Moderate cellularity
- Cohesive clusters of tumor cells
- Rounded, oval, or spindled cells with distinct cell borders and abundant clear or eosinophilic vacuolated cytoplasm [11]
- Nuclear size shows mild variation
- Nucleoli may be prominent
- Mitotic figures and necrosis are rare to absent
- Thin-walled sinusoidal vessels
- Strong diastase-sensitive PAS positivity
- Proteinaceous background

Explanatory Note

Clear cell tumors (sugar tumor) are part of the PEComatous tumor group that can arise at several sites throughout the body. PEComas are thought to originate from the perivascular epithelioid cells. In the lungs, PEComas can be classified as

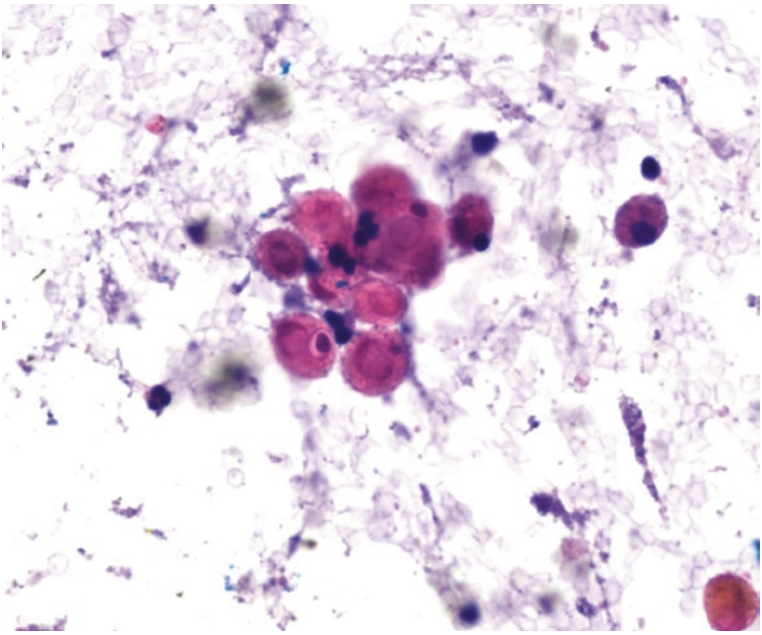

Fig. 6.8 Clear cell tumor of lung. Rounded cells with distinct cell borders and abundant clear or eosinophilic vacuolated cytoplasm seen on touch prep. Note numerous naked nuclei in a proteinaceous background. We acknowledge Dr. Esther Adler from NYU Langone for providing the image

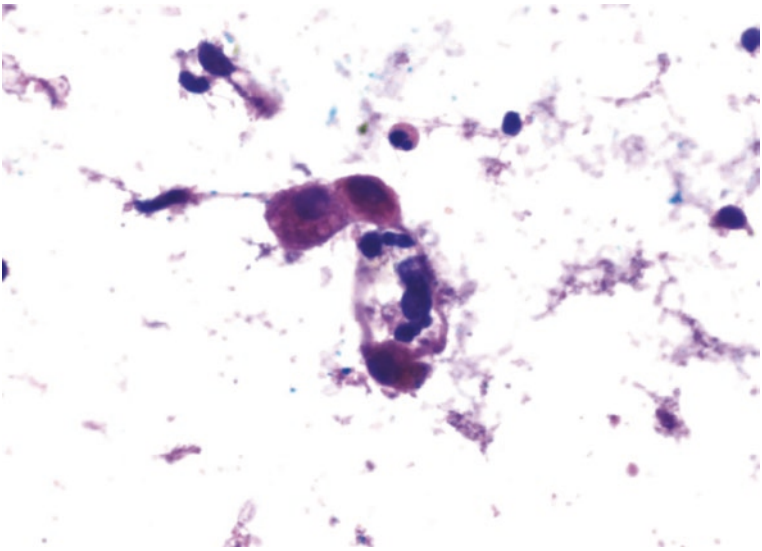

Fig. 6.9 Clear cell tumor of lung. Polygonal or spindled bland cell. Cells have distinct cell borders and abundant clear or eosinophilic vacuolated cytoplasm seen on touch prep. We acknowledge Dr. Esther Adler from NYU Langone for providing the image

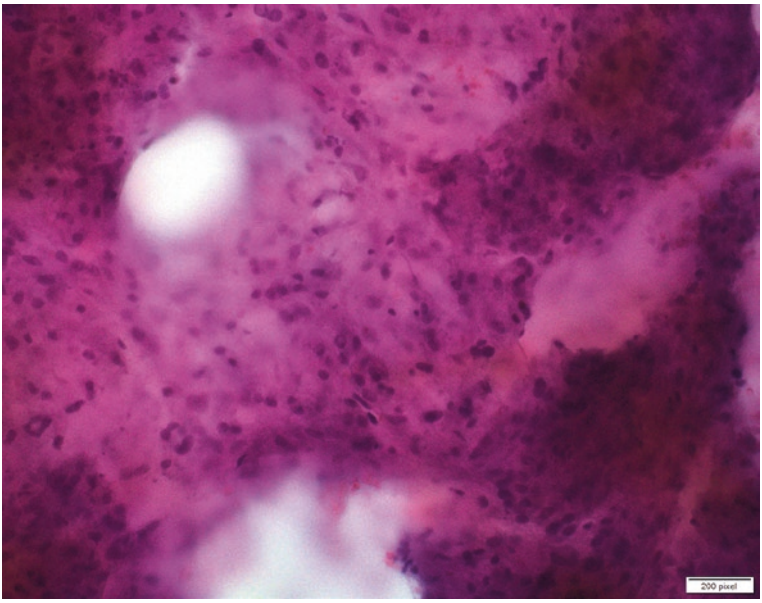

Fig. 6.10 Clear cell tumor. Cohesive tridimensional tight clusters. Note bland nuclear features with mild nuclear pleomorphism. Nuclear inclusions can be seen. Touch prep

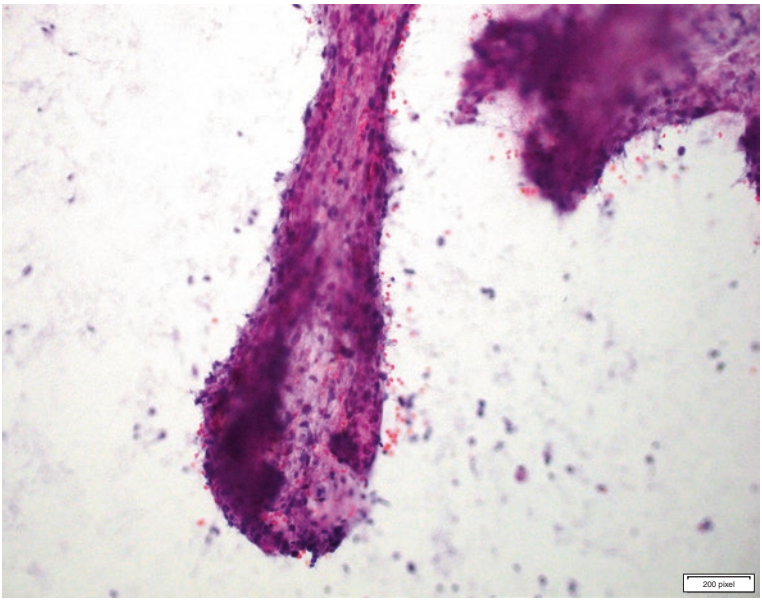

Fig. 6.11 Clear cell tumor. Sinusoidal pattern seen in a touch prep. Note flat endothelial cells surrounding a cluster of bland clear cells. Note numerous naked nuclei in the background

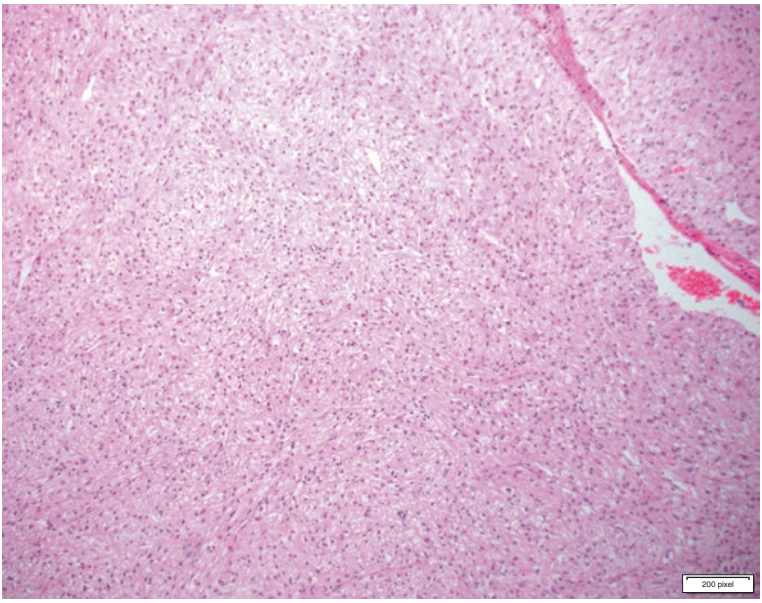

Fig. 6.12 Clear cell tumor of the lung. Histologically this tumor demonstrates bland cells with eosinophilic to clear cytoplasm with thin-walled vessels. Cells have minimal cytological atypia. No necrosis is identified

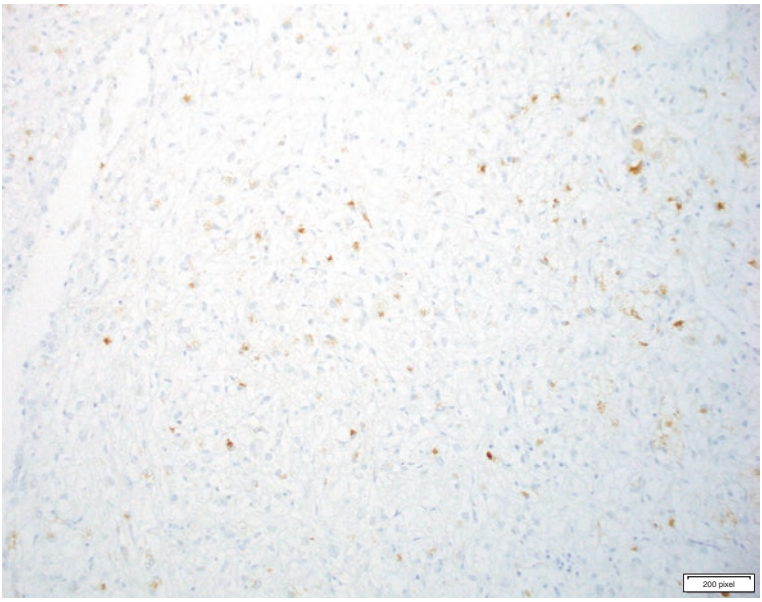

Fig. 6.13 Clear cell tumor of lung. Tumor cells demonstrate HMB45 positivity that can be focal. Tumor cells are negative for keratin (not shown)

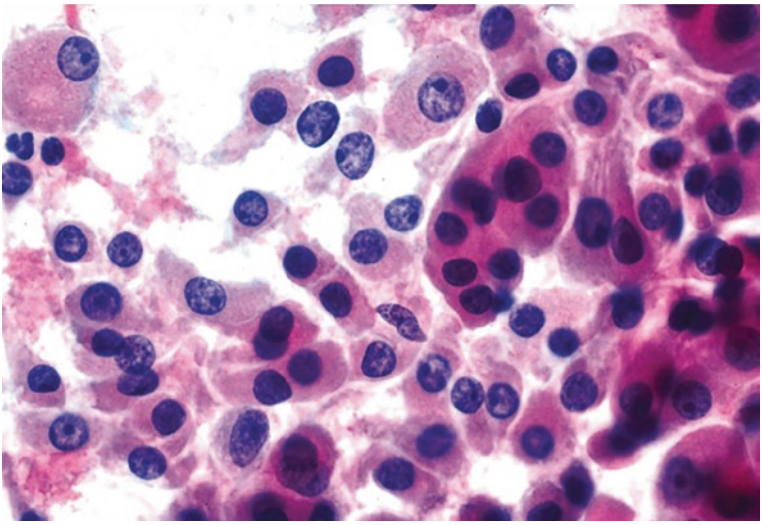

Fig. 6.14 Clear cell renal cell carcinoma. Smears show sheets of cells with foamy, granular cytoplasm, with round to ovoid nuclei and conspicuous nucleoli. Note the similarities of cytological features with pulmonary clear cell tumor. It is very difficult to distinguish these two entities on cytological features only. Metastatic renal cell carcinomas are much more common than pulmonary clear cell tumors. Clinical history and immunohistochemical and cytochemical stains (PAS) are necessary to reach the correct diagnosis. We acknowledge Dr. Wei Sun from NYU Langone for providing the image

borderline/benign tumors, such as "clear cell tumor, sugar tumor," or malignant PEComas. Interestingly lymphangiomatosis (LAM) is also considered a low-grade neoplasm in the PEComa category of tumors; however, LAM do not form masses and rather manifest as cystic lesions in the lung. The main differential diagnosis of clear cell tumor is metastatic renal cell carcinoma, clear cell type. Renal cell carcinoma shares similar cytomorphology with clear cell tumors of the lung with cellular smears containing papillary clusters with clear tumor cells lining the "papillae." Both tumors are vascular and therefore show the papillary appearance in smears. Contrary to clear cell tumors of the lung, metastatic renal cell carcinomas are positive for keratin, PAX-8, and other specific markers [3, 9].

Metastatic melanoma and clear cell sarcoma also enter the differential diagnosis. Both tumors share positivity for HMB-45 with clear cell tumors of the lung, but in contrast, mitotic figures and cytological atypia are common findings. Granular cell tumor of the lung is also a rare neoplasm that shares histology and immunohistochemical similarities to clear cell tumor; however, the former lacks diastase-sensitive PAS positivity seen in clear cell tumor. In granular cell tumor, PAS positivity is diastase-resistant.

Therefore, the cytological diagnosis of clear cell tumors of the lung should be made only after careful evaluation of special stains and immunohistochemical studies. The most important task for the cytopathologists when dealing with a clear cell tumor in the lung is to rule out metastatic renal cell carcinoma [9].

Management

Conservative surgical resection is considered curative.

Sclerosing Pneumocytoma

Sclerosing pneumocytoma, previously called sclerosing hemangioma, is a tumor derived from primitive respiratory epithelial cells and is composed of a dual population of surface cells resembling type II pneumocytes and round cells (so-called stromal cells). Both cell types are positive for TTF-1 by immunohistochemical stain. The distinct characteristic of this tumor is keratin expression. The superficial cells express pan-keratin markers, including keratin 7, whereas the "stromal cells" are positive only for EMA and negative for other keratins.

Sclerosing pneumocytomas are often discovered incidentally, due to its slow growth pattern; the tumors can be large, frequently larger than 3 cm. The tumor occurs predominantly in women (80% of cases). Most patients are asymptomatic [3, 15].

Sclerosing pneumocytomas are heterogeneous tumors histologically and may have solid, papillary, sclerosing, and hemorrhagic patterns, thus mimicking pulmonary adenocarcinomas, which is the main differential diagnosis, therefore. The diagnosis of sclerosing pneumocytomas in frozen section, small biopsies, and cytology can be very difficult [9].

In cytologic smears and cell block preparations, this lesion recapitulates the classic histologic patterns. The cells are typically bland and can present in papillary clusters or flat sheets. The two cell populations are not easily identifiable in cytological preparations. Bland cells with fine chromatin and intranuclear inclusions are the most common finding, thus mimicking a well-differentiated pulmonary adenocarcinoma. Mild cytologic atypia, prominent nucleoli, and mitotic figures can be seen in both tumors. However, marked atypia, significant pleomorphism, and necrosis are not characteristic of pneumocytoma. The diagnosis of pneumocytoma on FNA or small biopsy requires recognition of two distinctive cell types that can be confirmed by immunohistochemical stains [9, 15, 16].

Cytological Criteria: Sclerosing Pneumocytoma

Cytological Criteria [9, 15, 16]: Sclerosing Pneumocytoma (Figs. 6.15, 6.16, 6.17, 6.18, 6.19, 6.20, and 6.21)

- Solid, papillary, hemorrhagic, or sclerotic arrangements may be seen
- Bland cells that are either surface or stromal cells
- Cuboidal surface resembles type II pneumocytes with plump pink to clear cytoplasm, oval nuclei, and prominent nucleoli
- Intranuclear pseudoinclusions and multinucleation can be seen
- Cytologic atypia is generally mild and lacks marked pleomorphism and necrosis
- Prominent nucleoli and mitotic figures can be seen

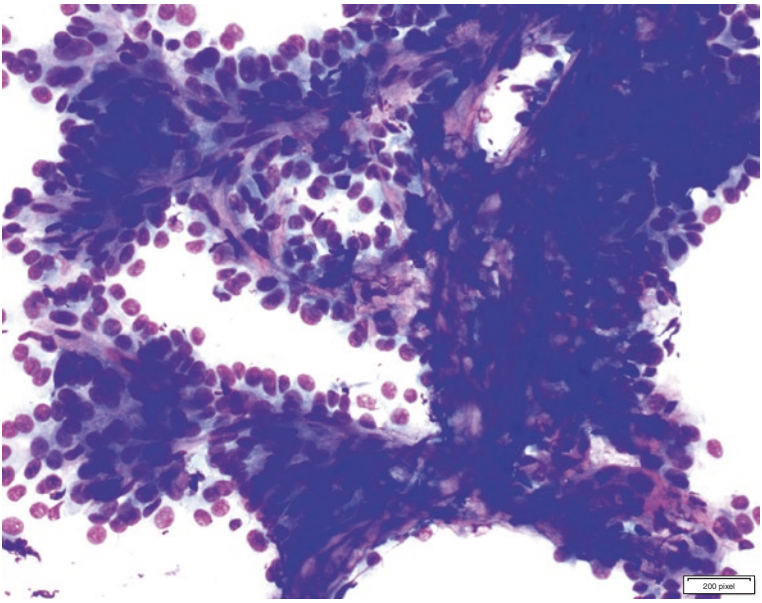

Fig. 6.15 Sclerosing pneumocytoma. Papillary arrangement of neoplastic cells. Note two layers of bland cells line the papillae. Note metachromatic matrix (Diff-Quik) within the papillae, which represents the sclerotic component of these tumors

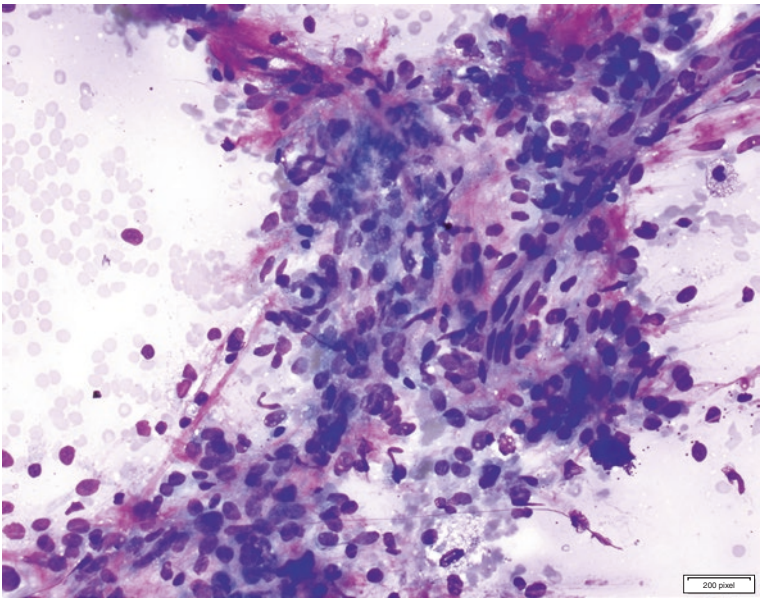

Fig. 6.16 Sclerosing pneumocytoma. Flat sheets and tri-dimensional pattern. Note two cell population

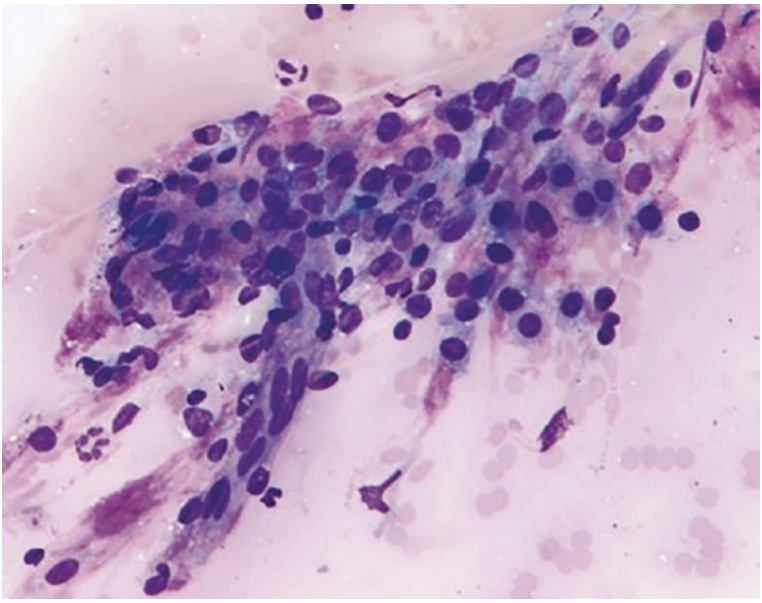

Fig. 6.17 Sclerosing pneumocytoma. Flat sheet of bland epithelial cells. It is difficult to recognize a second population. The differential diagnosis in this case is reactive type II pneumocytes or a well-differentiated adenocarcinoma. Correlation with imaging studies may be helpful to avoid this pitfall

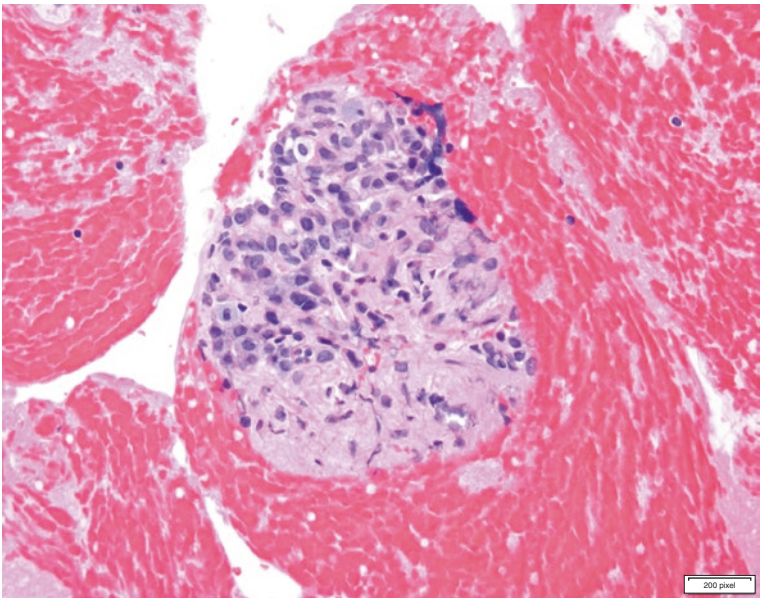

Fig. 6.18 Sclerosing pneumocytoma. Histological section of a cell block showing two cell population of superficial and stromal cell. The cells become more evident in IHC studies

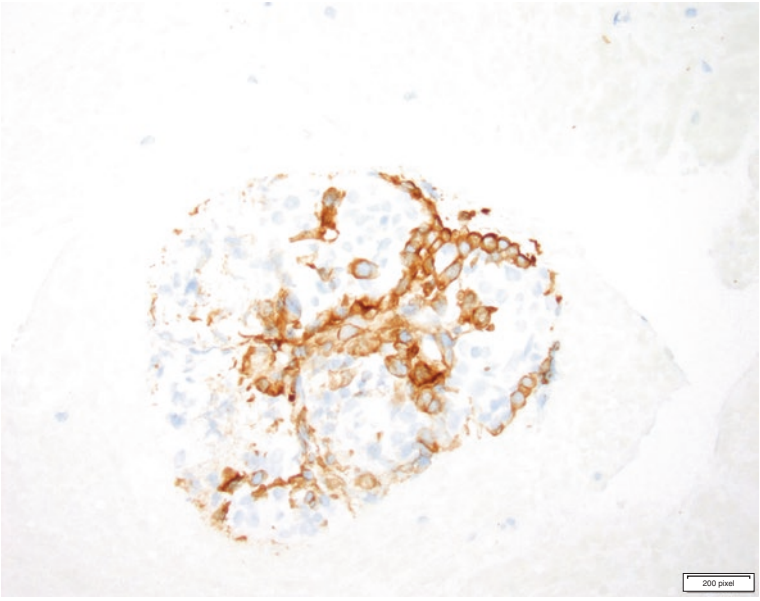

Fig. 6.19 Sclerosing pneumocytoma. Pattern of immunoreactivity from a cell block section. AE1/AE3 pancytokeratin stains only superficial cells

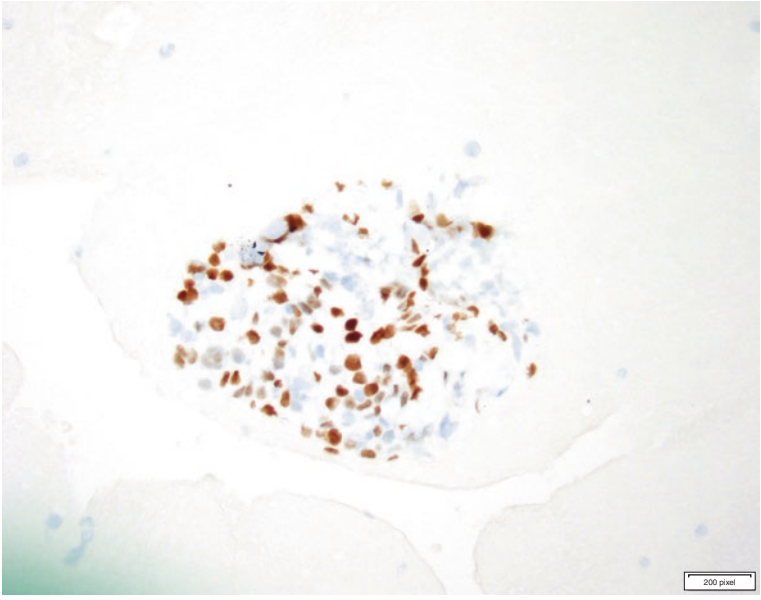

Fig. 6.20 Sclerosing pneumocytoma. Pattern of immunoreactivity from a cell block section TTF-1 stains superficial and stromal cells

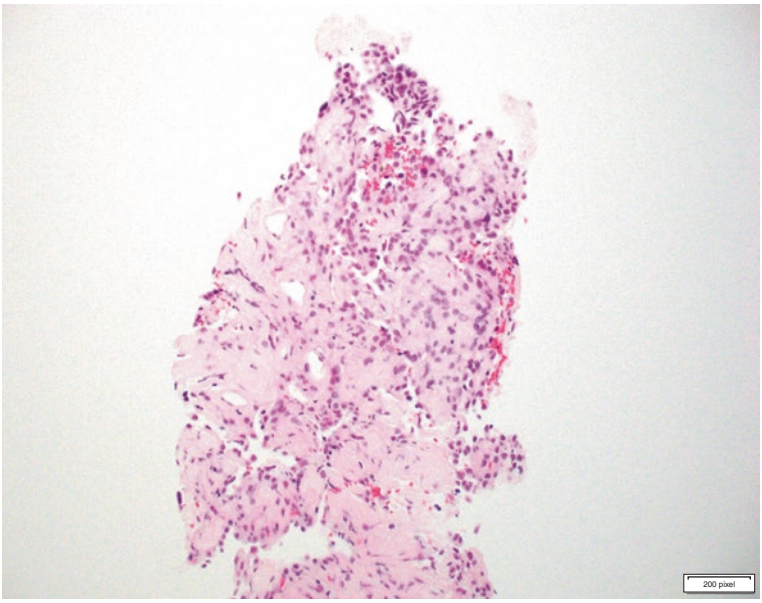

Fig. 6.21 Sclerosing pneumocytoma. Core biopsy. Sclerosing and papillary patterns. Note two cell population. Superficial cells that resemble type 2 pneumocytes and stromal cells

- Surface cells may be round, polygonal, or spindled with well-defined borders, oval or round nuclei, and inconspicuous nucleoli
- Nuclei may have smooth contours or display nuclear grooves
- Hemosiderin-laden macrophages or foamy macrophages may appear in the background
- Psammoma bodies may be seen

Explanatory Notes

Sclerosing pneumocytomas have a "coin-like" lesion appearance in radiographic studies, whereas well-differentiated adenocarcinomas are often described as ground-glass lesion. Knowledge of radiographic description of the lesion can be of great help in reaching the correct diagnosis. This is an important criterion for pathologists and cytotechnologists performing rapid on-site evaluation (ROSE).

Management

Surgical excision is curative.

Primary Pulmonary Meningioma

Primary pulmonary meningiomas are very rare! The diagnosis can only be made after exclusion of a primary meningioma in the central nervous system (CNS) including the

spinal cord, where the tumor is more commonly found. Metastatic meningiomas to the lung, although rare, are more common than primary pulmonary meningiomas. The tumor occurs in both genders; similar to other borderline tumors, it is often asymptomatic and discovered incidentally and described radiographically as a "coin lesion."

Similar to CNS tumors, these lesions consist of whorls or nests of elongated medium-sized cells with eosinophilic cytoplasm and oval nuclei with a fine chromatin. Poorly defined cytoplasmic borders (syncytial growth pattern), bland ovoid nuclei with inconspicuous nucleoli, occasional nuclear grooves, and intranuclear inclusions provide clues to a correct diagnosis. The tumor cells are positive for vimentin, EMA, CD56, and progesterone receptor by immunohistochemical stains but are negative for keratin, S100, or neuroendocrine markers [9, 17, 18].

Cytological Criteria: Meningioma

Cytological Criteria [9]: Meningioma (Figs. 6.22 and 6.23)

- Cohesive clusters of spindled cells arranged in intercepting sheets
- Whorls can be seen
- Cells have fine chromatin, and bland ovoid nuclei with inconspicuous nucleoli, nuclear grooves, and occasional intranuclear inclusions can be seen

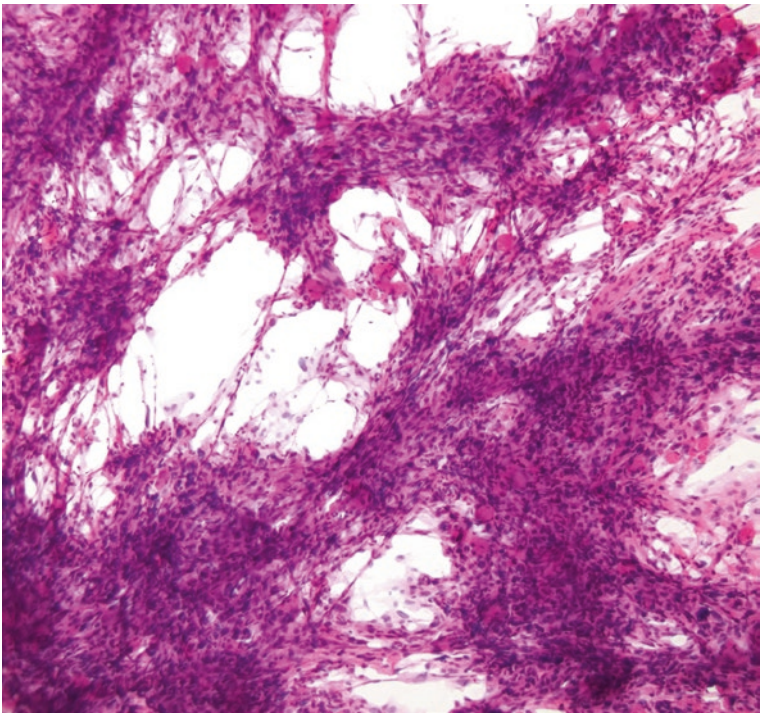

Fig. 6.22 Primary pulmonary meningioma. Cohesive clusters of spindled cells are arranged in intercepting sheets with meningothelial whorls and poorly defined cytoplasmic borders (hematoxylin and eosin)

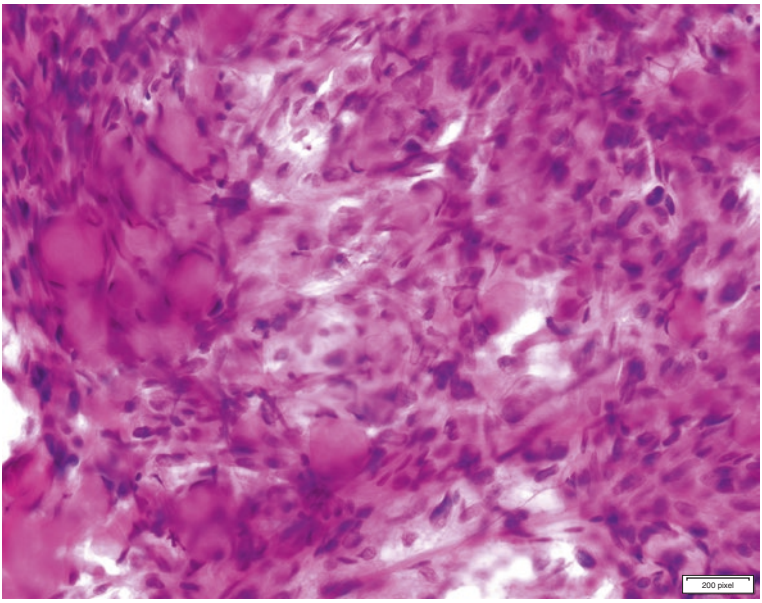

Fig. 6.23 Primary pulmonary meningioma. Cohesive clusters of spindle-shaped cells with poorly define cell borders. Note discrete clusters psammoma bodies

- Cytoplasmic borders are poorly defined
- Psammoma bodies may be present
- Mitosis is rare

Explanatory Note

The origin of primary pulmonary meningioma is unknown. The differential cytological diagnosis of meningiomas includes other spindle cell neoplasms of malignant or low malignant potential. These include solitary fibrous tumors, which are negative for keratins but positive for STAT6 and CD 34, inflammatory myofibroblastic tumors that are immunoreactive for smooth muscle actin and ALK and lack EMA positivity seen in meningiomas, and sarcomatoid carcinomas and metastatic sarcomas to the lung which have higher degree of cytological atypia, mitotic figures, and necrosis.

Management

Complete surgical resection is curative.

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH), previously pulmonary eosinophilic granuloma, is currently considered a clonal histiocytic neoplastic proliferation by the World Health Organization.

LCH is often associated with smoking and occurs most often in the mid to upper lung zones. Radiographically, LCH displays nodular occasionally cystic chest lesions on high-resolution CT. Regional lymph node involvement is uncommon. Stellate scars containing Langerhans histiocytes are the hallmark of LCH. LCH cells demonstrate abundant pale cytoplasm with grooved nuclei. Typically, Langerhans cells will stain positively with CD1a and S-100 protein. The presence of eosinophils is a valuable diagnostic clue. While LCH may be present in pleural fluids or bronchoalveolar lavage specimens, achieving the diagnosis on cytology is uncommon and difficult. Eosinophils, in a fluid specimen may however be a clue to the diagnosis [2, 19].

Cytological Criteria: Langerhans Cell Histiocytosis

Cytological Criteria [2, 3, 20]: Langerhans Cell Histiocytosis (Figs. 6.24, 6.25, and 6.26)

- Moderate to high cellularity
- Large cells with pale eosinophilic cytoplasm and distinct nuclear grooves/ folding of nuclear membrane
- Langerhans cells can be seen as isolated cells or in small clusters in smears
- Size variation and anisonucleosis
- Binucleation or multinucleated cells can be present
- Mixed inflammatory background with eosinophils

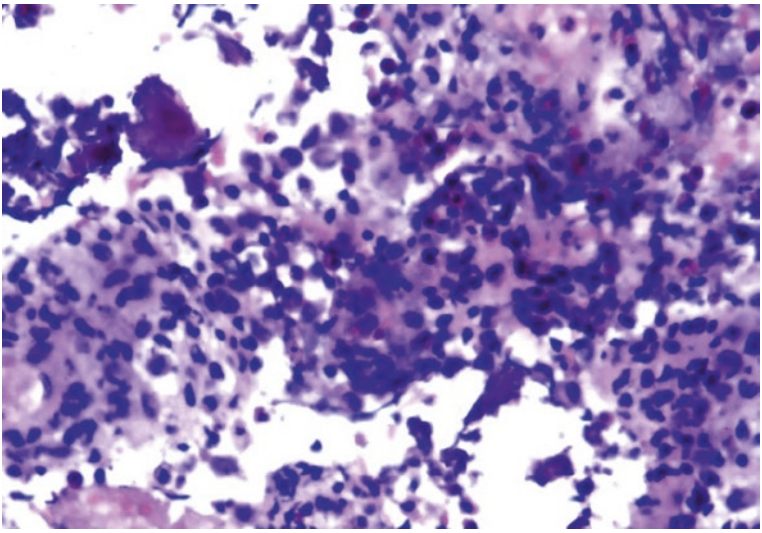

Fig. 6.24 Langerhans cell histiocytosis. Large cells with pale eosinophilic cytoplasm and distinct nuclear folding can be seen with eosinophils in the background

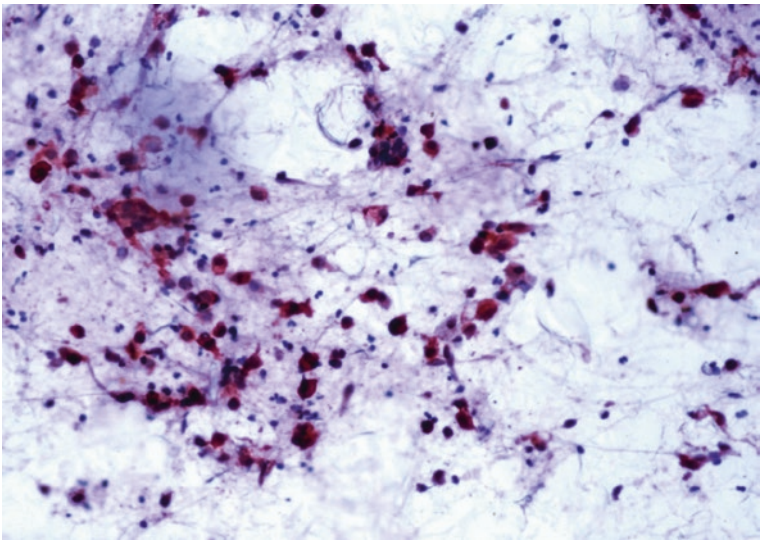

Fig. 6.25 Langerhans cell histiocytosis. Immunohistochemical stain for S100 protein is positive in tumor cells

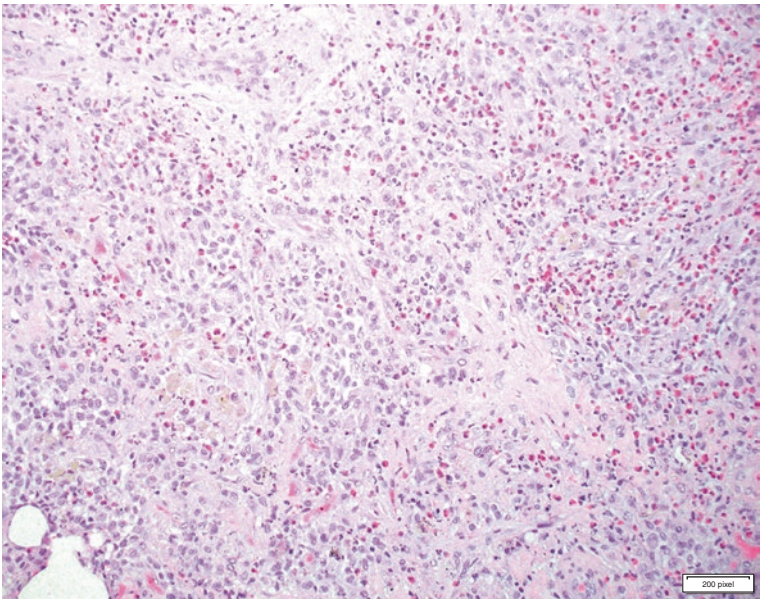

Fig. 6.26 Eosinophilic granuloma. Histological features. Numerous Langerhans cell and eosinophils within alveolar spaces and pulmonary parenchyma

Explanatory Note

The most common differential diagnosis is Hodgkin lymphoma that shows scattered large atypical cells in an inflammatory background. The typical Reed-Sternberg cells of Hodgkin lymphoma are often binucleated with prominent nucleoli; the latter is not seen in Langerhans cell histiocytosis. Hodgkin cells are positive for CD30 and CD15, which are not expressed in Langerhans cells, and are negative for Cd1a and S100.

Management

There is no specific therapy for Langerhans cell histiocytosis. Most lesions regress spontaneously, resulting in a stellate scar seen in resection specimens.

Smoking cessation is recommended. Some studies have shown a benefit from steroid therapy.

Rarely, these tumors are resected, which can occur if the tumor presents as a cystic mass in imaging studies, raising suspicion for a malignant neoplasm.

Solitary Fibrous Tumor (SFT)

These tumors are more commonly found in the pleura; intrapulmonary SFT are rare. These tumors can be large and present as a "lung mass." Histologically, these neoplasms show a uniform population of spindle cells interspersed with sclerotic stroma [1]. Cellularity of the neoplasm is variable with the cellular architecture varying from the so-called patternless pattern to a branching hemangiopericytomatous pattern with varying-sized vessels. Perivascular hyalinization is common. The individual cells have tapering nuclei and scant to modest amounts of cytoplasm. Mitotic index is usually less than three mitotic figures per $2mm^2$. Cytologic atypia is modest and necrosis is usually absent.

When malignant SFT occurs, there is increased mitotic activity, >4 mitotic figures per high-power field, high cellularity, pleomorphism, and necrosis.

Cytologic Criteria: Solitary Fibrous Tumor

Cytologic Criteria [1]: Solitary Fibrous Tumor (Figs. 6.27, 6.28, 6.29, and 6.30)

- Variable cellularity
- Cells lie singly and in tight fascicular clusters
- Uniform cell population composed of bland spindle cells
- Spindle-shaped nuclei
- Stripped nuclei
- Inconspicuous nucleoli
- Ropy collagen fibers
- Mast cells often present

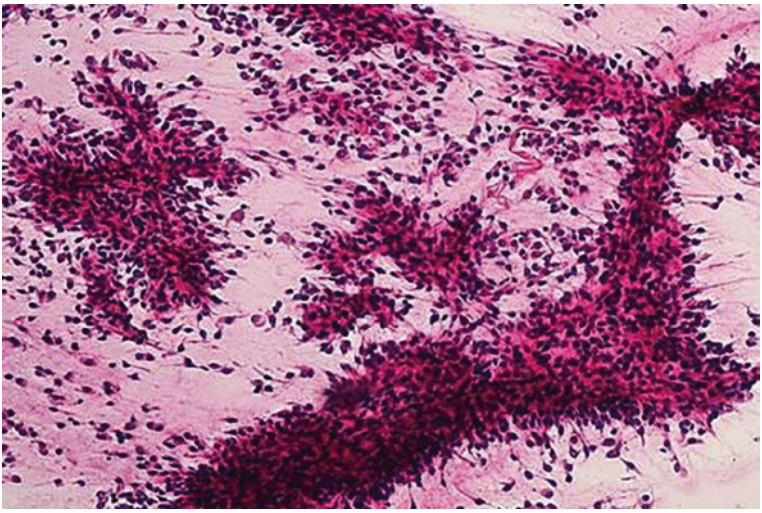

Fig. 6.27 Solitary fibrous tumor. Smear shows cohesive clusters of bland uniform spindled cells around collagenized matrix. Note naked spindled nuclei in the background

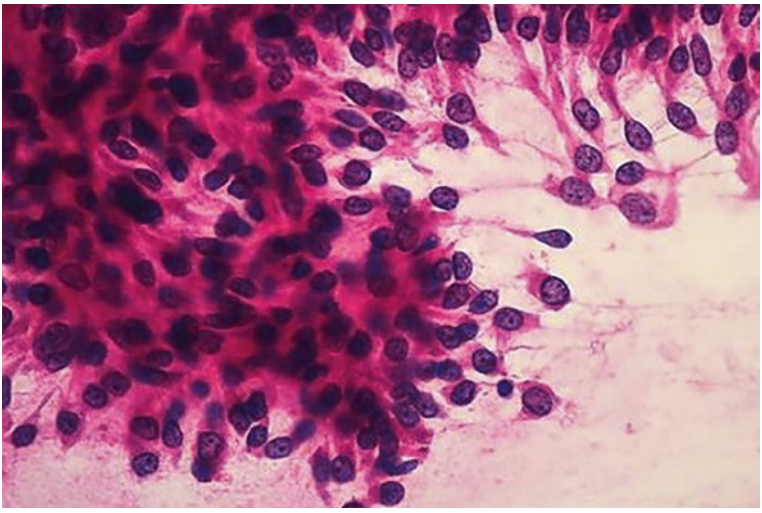

Fig. 6.28 Solitary fibrous tumor. Higher-power image showing cohesive clusters of bland uniform spindled cells

Explanatory Note

Tumor cells are immunoreactive for CD34 and STAT6. The main differential diagnoses are metastatic sarcoma to the lung, sarcomatoid carcinoma and sarcomatoid mesothelioma, and desmoid tumors.

The bland nature of the SFT cells is in contrast to pronounced atypia and cellularity seen in sarcoma and sarcomatoid carcinoma or mesothelioma. SFTs are

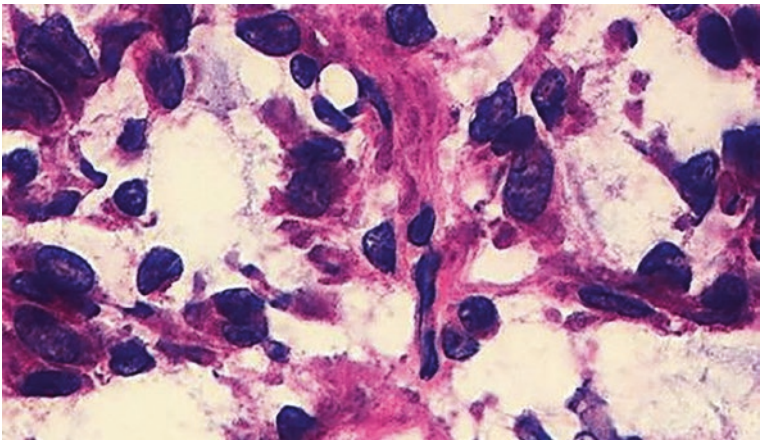

Fig. 6.29 Solitary fibrous tumor. Smear shows clusters of uniform spindled cells with cytological atypia. Atypia is not common in solitary fibrous tumor; its presence raises the possibility of a sarcoma or a malignant solitary fibrous tumor. Both tumors (borderline and malignant) share the same immunoreactivity profile (nuclear positivity for STA6 is diagnostic)

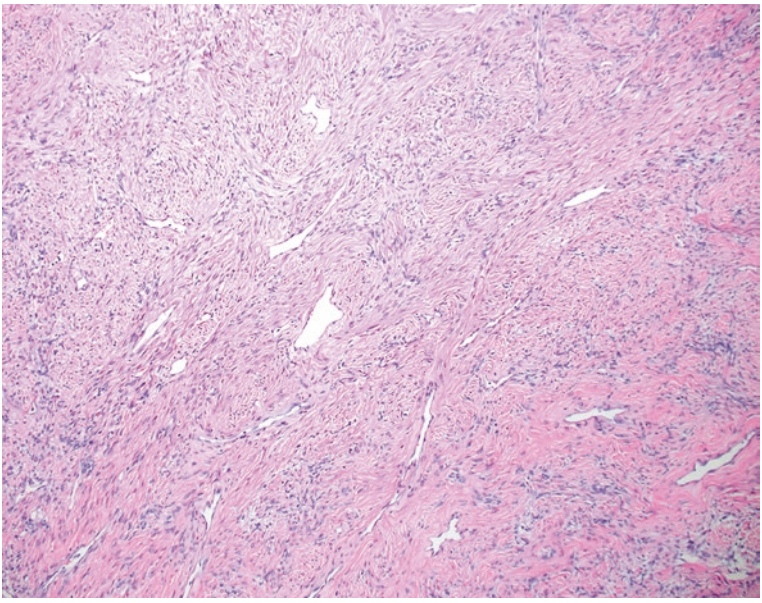

Fig. 6.30 Solitary fibrous tumor. Histological section showing characteristic blood vessels (staghorn appearance), variation in cellularity, and spindled cells arranged around ropy collagen fibers

negative for keratin which is often retained in sarcomatoid carcinoma and mesothelioma.

Desmoid tumors are negative for STAT6 and express nuclear positivity for beta-catenin.

Management

Complete resection is associated with good prognosis. Tumors with infiltrative borders or incomplete resection are prone to local recurrences, spread to lung and distant metastases.

Inflammatory Myofibroblastic Tumor (IMT)

These tumors often present as solitary, well-circumscribed nodules in the periphery of the lung. Most patients are younger than 30 years of age, but the tumor can occur in all age groups. Histologically, these neoplasms are composed of spindle- to ovoid-shaped cells with pale cytoplasm and indistinct cell borders [1]. The nuclei are tapered to ovoid in shape with a vesicular appearance. Nuclear atypia is minimal. Architecturally, the cells form a fascicular pattern or less commonly a storiform pattern. Chronic inflammation is invariably present and includes foamy histiocytes, neutrophils, and histiocytic giant cells. Fifty percent of cases are positive for ALK by immunohistochemistry which correlates with ALK gene rearrangement.

Most inflammatory myofibroblastic tumors behave in an indolent fashion, but recurrence and metastases have been reported especially with larger tumors [2, 21].

Cytologic Features: Inflammatory Myofibroblastic Tumor

Cytologic Features: Inflammatory Myofibroblastic Tumor [3, 21] (Figs. 6.31, 6.32, 6.33, 6.34, and 6.35)

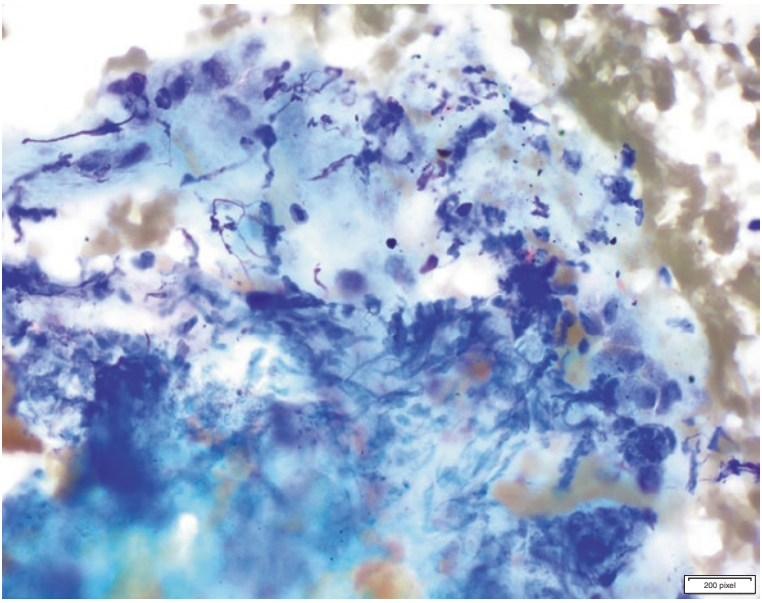

Fig. 6.31 Inflammatory myofibroblastic tumor. Bland spindle cells with fine chromatin. Admixed with inflammatory infiltrate

- Smears are often highly cellular
- Mixture of plump oval to spindle-shaped cells with fine chromatin pattern
- Cells may be scattered on the smear or in small clusters
- Inflammatory cells are prominent including lymphocytes and plasma cells, and the presence of histiocytic giant cells, macrophages, and neutrophils can be seen
- Myxoid or fibrous stromal fragments can be seen in the background
- Tumor cells show variable positivity for smooth muscle actin, desmin, and keratin, thus consistent with myofibroblast differentiation

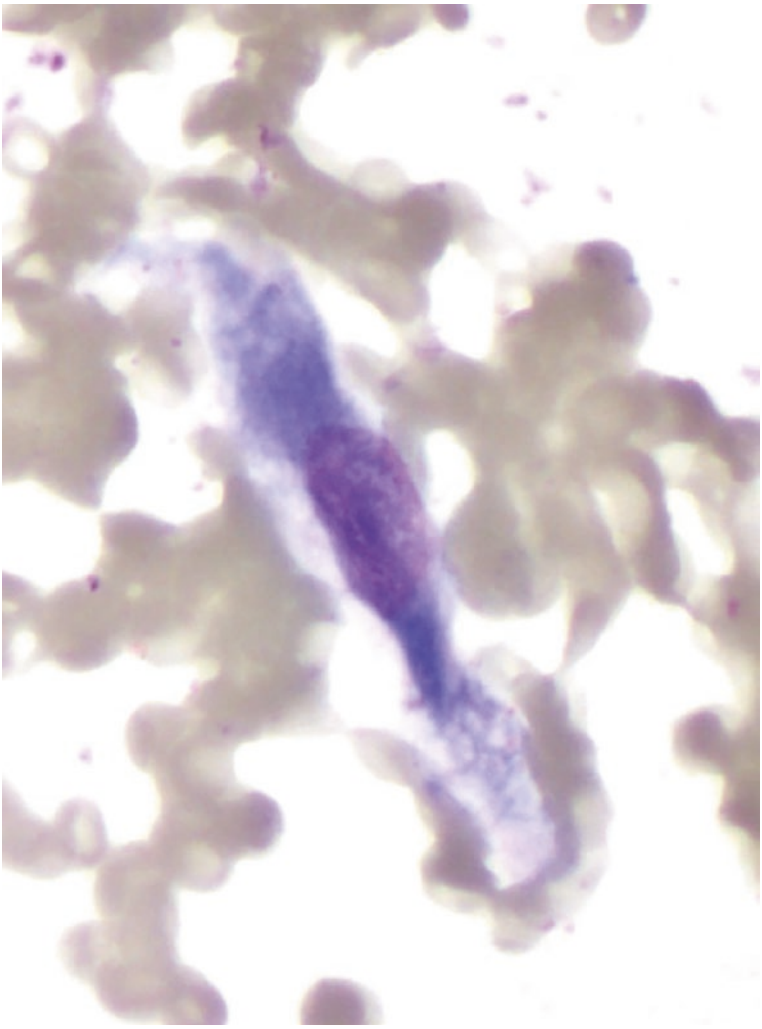

Fig. 6.32 Inflammatory myofibroblastic tumors showing cells with isolated bipolar eosinophilic cytoplasm are seen (Diff-Quik)

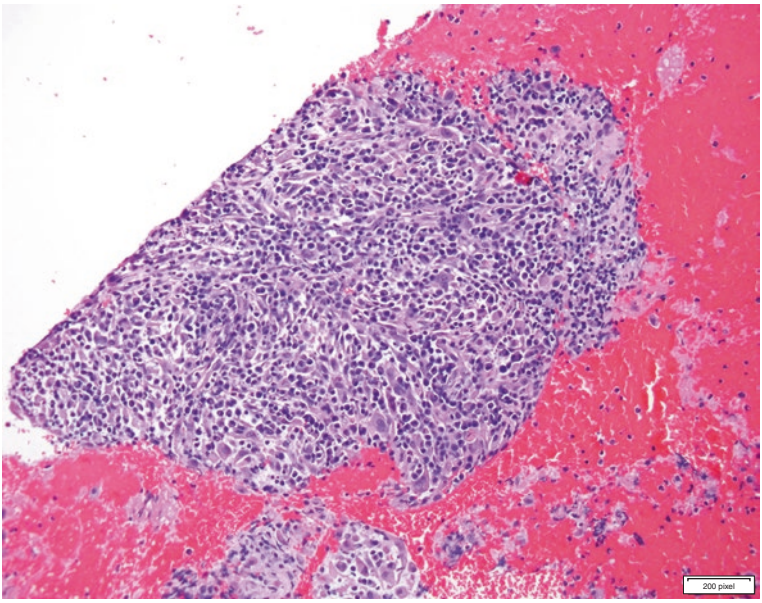

Fig. 6.33 Inflammatory myofibroblastic tumor. Storiform growth pattern can be seen on cell block. Note the inflammatory infiltrate admixed with tumor cells

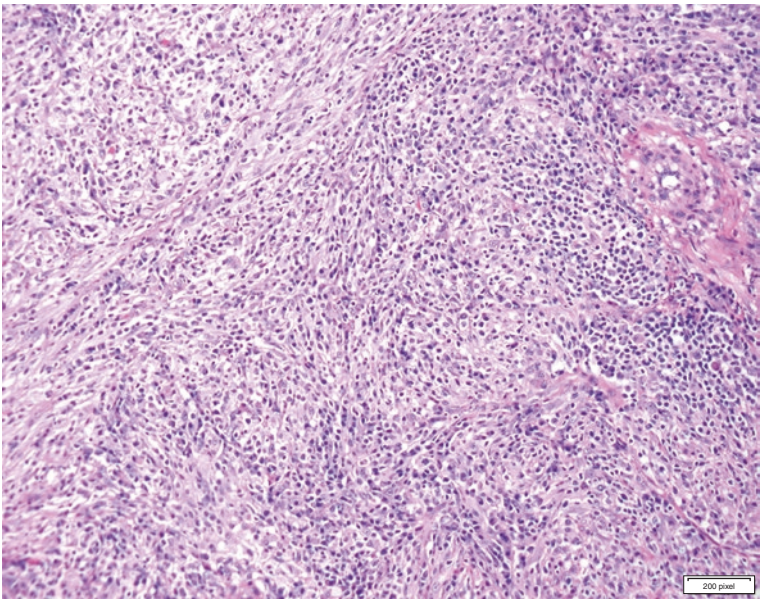

Fig. 6.34 Inflammatory myofibroblastic tumor. Histological features show a pattern less pattern of growth and inflammatory infiltrate

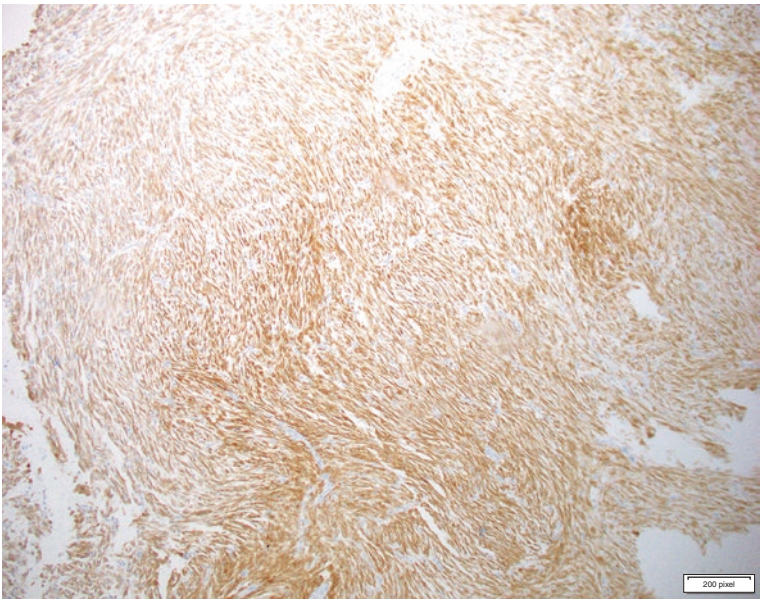

Fig. 6.35 Inflammatory myofibroblastic tumor. Immunohistochemical stain shows positivity for ALK (clone D5F3) in this excised tumor

Explanatory Notes

IMTs often occur in the periphery of the lung, but other sites such as endobronchial and tracheal lesions can occur. Brushings of tracheobronchial tree are often nondiagnostic. These neoplasms represent a group of lesions where biologic behavior is difficult to predict. Most follow an indolent course, but some recur or metastasize. Recurrence is associated with incomplete resection, large tumor size, and nonsurgical treatment.

Management

Complete surgical resection is the treatment of choice.

Myoepithelial Neoplasms

Myoepithelial tumors of the lung are rare but can arise in the peribronchial location (central) and more rarely can present as peripheral tumors. Any salivary-type tumor can occur in the lungs including malignant neoplasms, but here we will cover only tumors of borderline potential.

Pleomorphic adenomas or myoepitheliomas although rare are the most common types. Pleomorphic adenomas are more frequent in men with a mean age of 50 years. Patients are often asymptomatic but can present with productive cough, wheezing, and rarely hemoptysis. Symptoms are more common in centrally located tumors.

Pleomorphic adenomas are biphasic tumors containing varying proportions of epithelial and myoepithelial cells mixed with stromal components. Contrary to the salivary gland tumor, pleomorphic adenomas of the lung have sparse stromal components and are generally more cellular, which may be difficult to differentiate in a cytology specimen from a myoepithelioma. Malignant transformation in the lung has not been reported.

The cytomorphology is similar to that seen in salivary gland tumors. Epithelial or myoepithelial cells with plasmacytoid features, some with cytoplasmic hyaline inclusions, are arranged in sheets associated with a fibrillar chondromyxoid matrix, which is metachromatic in Diff-Quik stain.

Unlike mixed tumors, myoepithelial tumors lack ductal differentiation. The tumor cells are epithelioid or spindled, and the nuclei are uniform, with eosinophilic or clear cell cytoplasm. Majority show positive immunohistochemistry staining for keratin, S100, and calponin. Smooth muscle actin and p63 (or p40) may also be positive [2, 22–24].

Cytological Criteria: Myoepithelial Neoplasms

Cytological Criteria [2, 3]: Myoepithelial Neoplasms (Figs. 6.36 and 6.37)

- Pleomorphic adenomas are biphasic containing epithelial and myoepithelial cells mixed with stromal components
  - The epithelial component often forms tubules or stellate-shaped clusters
  - The stromal component shows metachromatic chondromyxoid matrix

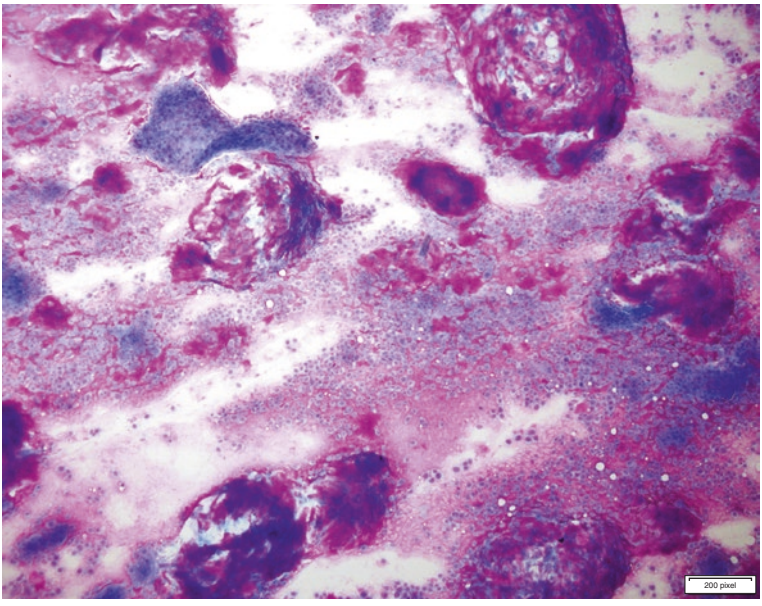

Fig. 6.36 Pleomorphic adenoma. Biphasic neoplasm containing epithelial and myoepithelial cells mixed with stromal components. The stromal component shows metachromatic chondromyxoid matrix

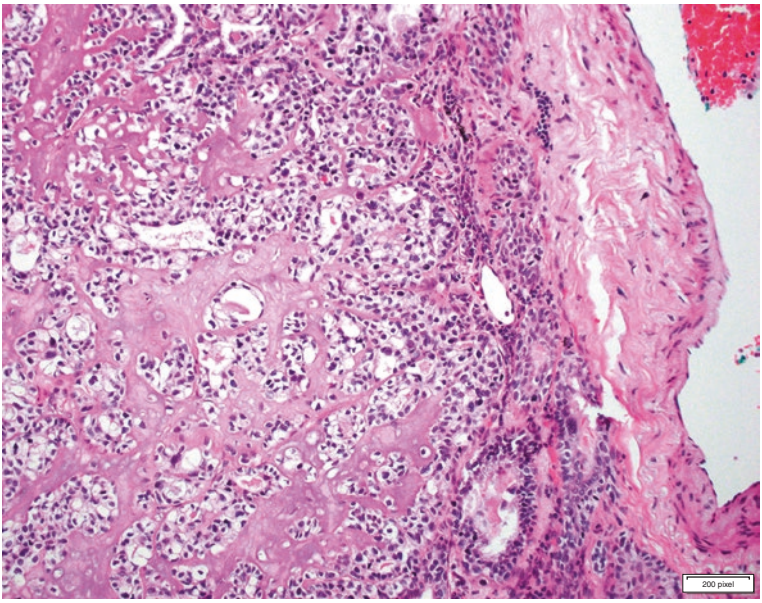

Fig. 6.37 Myoepithelial neoplasm. Slow-growing tumors showing a biphasic pattern with epithelial and myoepithelial cells. Myoepithelial cells can be plasmacytoid with clear cell features. Often the sclerotic stroma is less pronounced than salivary gland tumors

- Low mitotic rate
- Myoepithelial tumors lack ductal differentiation of mixed tumors
  - Epithelioid or spindle cells with uniform nuclei and clear to eosinophilic cytoplasm
  - Plasmacytoid cells with cytoplasmic hyaline inclusions may be seen

Explanatory Note

EWSR1 gene fusion has been reported in malignant pulmonary myoepithelial tumors but not in myoepithelioma and pleomorphic adenoma.

Management

Surgical resection is curative.

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