56

Mesenchymal Tumors

Cesar A. Moran

Primary pulmonary mesenchymal tumors, whether benign or malignant, are rare. Because the same histologic criteria are used to diagnose these tumors in the lung as in their soft tissue locations, the pathologist is often confronted with the dilemma of determining whether the lesion is primary or metastatic.

Unlike the much more common epithelial malignancies, the rarity of sarcomatous lesions and the lung's predilection for metastases makes the physician hesitant to describe any mesenchymal lesion as primary, and it becomes essential to rule out an extrapulmonary site of origin. It is possible that many cases, especially in referral institutions, are regarded as metastases of undetermined origin because of their unusual location, and the true incidence of these neoplasms in the lung may be higher than is acknowledged. Moreover, with the new methods available in diagnostic surgical pathology, past descriptions of some pulmonary sarcomas would probably not withstand the modern standards of classification. In this chapter, sarcomatous lesions that occur primarily in the lung are described to highlight their specific features and to increase the awareness of the existence of these tumors (Table 56-1).

BENIGN NEOPLASMS

Leiomyoma

Primary intrapulmonary leiomyoma is a rare, benign smooth muscle tumor.[1-4] It appears to be more common in women than in men. The tumors are more often found in parenchymal than bronchial locations. Although it can occur at any age, leiomyoma is more commonly seen in adults. One explanation for the higher incidence of these tumors in women may be because of confusion with the benign metastasizing leiomyoma, which is histologically

undistinguishable from leiomyomas arising in lung.[5] Some authorities think that multiple pulmonary lesions in a premenopausal woman with a history of uterine leiomyomas, abdominal surgery, or pregnancy indicates a benign metastasizing leiomyoma. Others have raised the possibility of multifocality to explain the presence of similar tumors in diverse parts of the body (see Chap. 60).[6] Deciding whether these tumors represent metastases from low-grade leiomyosarcoma, benign metastasizing leiomyoma, multifocal leiomyoma, or *de novo* intrapulmonary leiomyoma is difficult and attempted only with careful evaluation of the individual case.

Pulmonary leiomyomas produce symptoms according to their location. Most peripheral tumors are discovered on a routine chest x-ray film. Those located intraluminally present with symptoms of cough and hemoptysis. Clubbing of the fingers has been reported in pediatric patients.[7] Radiologic evaluation is essential to determine the location of the tumor and to assess the number of pulmonary lesions, but no radiographic features can differentiate benign from malignant lesions.[8] Histologic evaluation is the only means of arriving at a definitive diagnosis.

The tumors are of various sizes, well circumscribed, firm, and white. Histologically, they share features with leiomyomas arising elsewhere: spindle cell proliferation arranged in fascicles, with cigar-shaped, blunted nuclei, eosinophilic cytoplasm, and no evidence of significant mitotic activity or pleomorphism (Figs. 56-1 and 56-2). Occasionally, nuclear palisading and vacuolization of the nuclei are observed. Necrosis and hemorrhage are usually not found.

In most cases, the diagnosis can be established by light microscopy, but the use of immunohistochemical stains, including those for desmin and muscle-specific actin, may be helpful in supporting the diagnosis.[9] Ultrastructurally, peripheral aggregates of thin cytoplasmic filaments, pinocytotic vesicles, and incomplete basal lamina are consistent with a smooth muscle tumor.[10]

It is important to differentiate leiomyomas from other spindle cell neoplasms, such as neurofibroma and the intrapulmonary localized fibrous tumor (*i.e.*, fibrous mesothelioma). For neurofibroma, the wavy spindle cell proliferation and positive staining for the S-100 protein lead to the correct diagnosis. For the intra-

TABLE 56-1
Pulmonary Tumors of Mesenchymal Origin

Phenotypic Expression	Benign	Malignant
Fibrous tissue	Fibroma	Fibrosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Skeletal muscle		Rhabdomyosarcoma
Adipose tissue	Lipoma	Liposarcoma
Nerve sheath	Neurilemoma, neurofibroma, granular cell tumor	Neurofibrosarcoma
Cartilage	Chondroma, chondroblastoma	Chondrosarcoma
Bone	Osteochondroma	Osteosarcoma
Histiocyte	Benign histiocytoma	Malignant fibrous histiocytoma, hemangiopericytoma
Vascular and pericytic	Lymphangioma, glomangioma	Hemangioendothelioma, angiosarcoma, Kaposi sarcoma, hemangiopericytoma
Combined tissue	Hamartoma (fibrochondrolipoma)	Mesenchymoma

Adapted from Saldana MJ, Wright JL, Thurlbeck WM. Localized lesions of the bronchi and lungs. In Silverberg SG, ed. Principles and practice of surgical pathology. vol. 1. New York: John Wiley & Sons, 1983:563.

pulmonary localized fibrous tumor, although positive staining for smooth muscle actin or desmin can rarely be observed, the histologic characteristics of the tumor, such as ropelike collagen bundles between tumor cells, and ultimately the lack of smooth muscle features on ultrastructural examination can establish the correct diagnosis.

The most important diagnostic consideration is assessing the malignant potential of the tumors. High mitotic activity, nuclear pleomorphism, necrosis, and hemorrhage indicate malignancy. The treatment of choice for these tumors appears to be surgical excision, and the clinical course is probably similar to that of soft tissue leiomyomas.
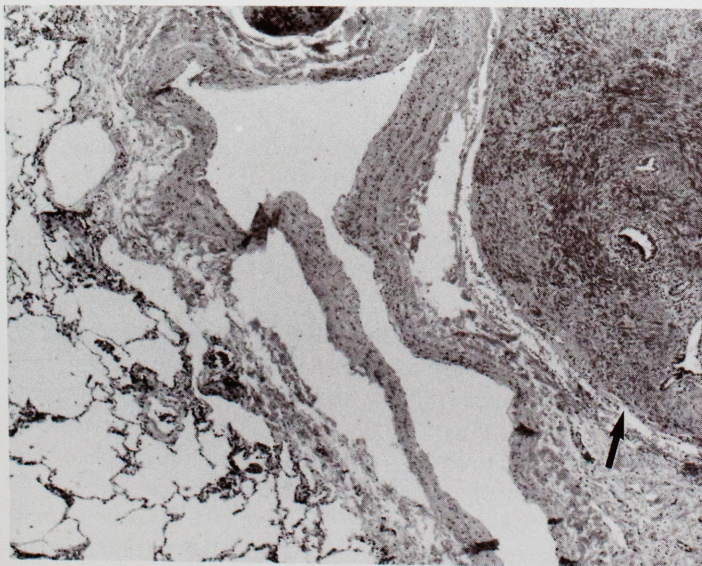
Lipoma

Lipomas are uncommon primary lung tumors.[11–14] They may appear to be an intrapulmonary lesion or an endobronchial tumor (Color Fig. 56-1). The patients may present with symptoms of cough and chest pain or be asymptomatic. Men are more frequently affected than women, and the patients are usually adults. The tumors have been associated with obesity in some cases.

Grossly, the tumors are soft, yellow, and well circumscribed. Microscopically, they show features similar to those in lipomas elsewhere: proliferation of mature fat cells. Even though the clinical course of these tumors is indolent, a radical procedure such as
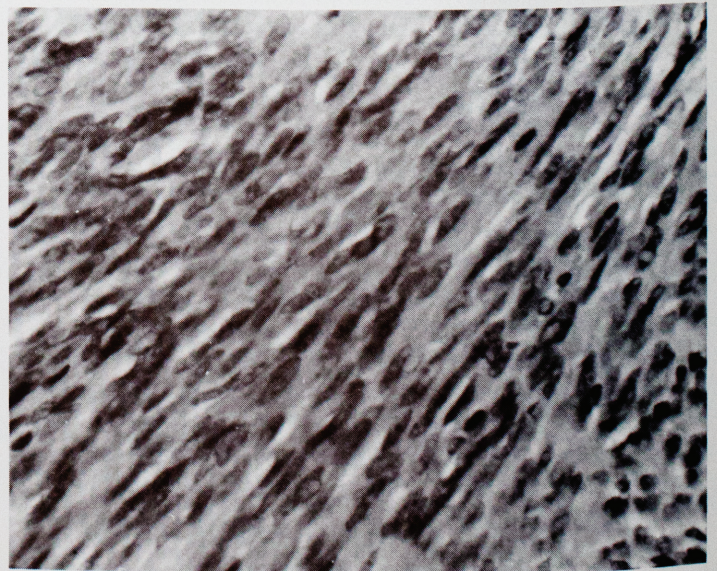

FIGURE 56-1. The intrapulmonary leiomyoma (*arrow*) is composed of a dense spindle cell proliferation. (H & E stain; low magnification.)

FIGURE 56-2. The detail of an intrapulmonary leiomyoma shows the bland appearance of the cells. Notice the absence of mitosis. (H & E stain; high magnification.)

lobectomy has been performed for some patients. Endoscopic resection is an appropriate treatment for endobronchial lesions.

Intrapulmonary Localized Fibrous Tumor

Localized fibrous tumors are neoplasms most commonly arising on the pleural and other serosal surfaces, but some arising in intrapulmonary locations have been documented.[15–20] The intrapulmonary fibrous tumors were probably interpreted as intrapulmonary fibromas in the past. Great caution must be exercised in categorizing these neoplasms as intrapulmonary, because tumors arising on the pleura may invade the lung parenchyma.

Intrapulmonary localized fibrous tumors have been found in adult patients, and the clinical presentation has varied from asymptomatic to symptoms related to airway obstruction. Grossly, the different-sized tumors have a firm, white, well-circumscribed appearance (Color Fig. 56-2). Microscopically, as with those in pleural locations, they are composed of a spindle cell proliferation showing a variety of patterns (Fig. 56-3). Areas of hypocellularity and hypercellularity and deposits of wavy collagen fibers admixed with areas of myxoid stroma and a marked vascular component may be seen. It is logical to assume that these tumors in intrapulmonary locations may show the same variety of histologic growth patterns seen in the tumors arising on the pleura.[21] Immunohistochemically, vimentin appears to be the only marker that consistently produces a positive reaction, but other markers, such as smooth muscle actin, have been positive in a few cases. Ultrastructurally, studies of pleural tumors have shown prominent rough endoplasmic reticulum, sparse mitochondria, microtubules, scattered ribosomes, micropinocytotic vesicles, and lack of desmosomes, microvilli, or basement membrane–like material in tumoral cells. They may arise from ectopic nests of mesothelial cells in the interlobular septa or from subpleural fibroblasts growing inward.

Even though the tumors described so far have been histologically benign, the existence of malignant variants is a logical possibility. However, the criteria employed to assess malignancy of these tumors in the pleura may not be applicable to the intrapulmonary lesions. For example, tumors in pleural locations presenting as easily resectable, polypoid, or pedunculated lesions behave as benign despite their mitotic activity, nuclear pleomorphism, or necrosis.[21] A similar clinical course may not be shared by the neoplasms with malignant cytologic features deep within the lung substance. Localized fibrous tumors should be differentiated from other neoplasms, such as smooth muscle and neural tumors. Immunohistochemical studies may help in arriving at a correct diagnosis (see Chap. 57).

MALIGNANT NEOPLASMS

Fibrosarcoma

Intrapulmonary fibrosarcomas are no longer commonly diagnosed. One explanation may be the use of immunohistochemical techniques, which can detect markers of differentiation not previously available.

Fibrosarcomas have been described as endobronchial or intraparenchymal tumors.[22–24] Symptoms depend on the location of the tumor. The tumors are slightly soft and white, but they may
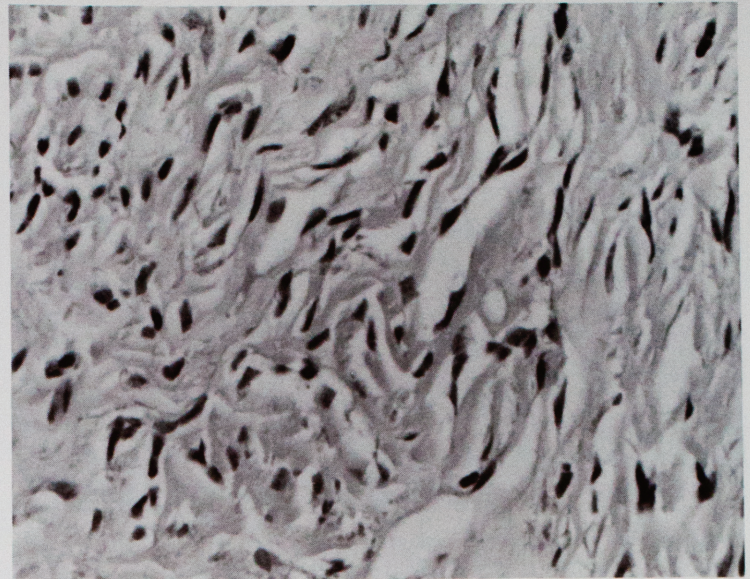

FIGURE 56-3. The microscopic appearance of a localized fibrous tumor shows the characteristic spindle cell proliferation admixed with ropes of collagen bundles (see Color Fig. 56-2). (H & E stain; intermediate magnification.)

show areas of necrosis or hemorrhage. Histologically, fibrosarcomas consist of a spindle cell proliferation arranged in interlacing fascicles. The cells have scant cytoplasm, round nuclei, and prominent nucleoli, and they characteristically form a herringbone pattern. Mitoses are numerous, and collagen is deposited between tumor cells. Immunohistochemically, tests for vimentin appear to be consistently positive, but other muscle, neural, or epithelial markers are negative. This immunoprofile and many of the histologic features are similar to those of the localized fibrous tumor, and some investigators contend that fibrosarcoma represents one end of the spectrum of such tumors.

Primary fibrosarcomas of the lung should be differentiated from other spindle cell neoplasms, such as spindle cell carcinomas and other sarcomas. Immunohistochemical stains and electron microscopy may help in diagnosing poorly differentiated tumors.

Leiomyosarcoma

Primary leiomyosarcomas occur in the lung, and they are more common than their benign counterpart, leiomyoma.[4–9,24–30] Men appear to be more often affected than women, and the tumor occurs more often in adults, but a few occurrences in the pediatric age group have been reported. The tumor may present as an intraparenchymal, endobronchial, or pulmonary artery mass. The tumor has no preference for a particular side or lobe.

The symptoms correlate with the locations of the tumors. Chest pain, cough, and hemoptysis may occur regardless of the location of the neoplasm. Grossly, the intraparenchymal tumor is firm, tan to yellow, and well circumscribed; necrosis and hemorrhage may be observed (Fig. 56-4). In an endobronchial location, the tumor is slightly softer and polypoid. Those arising in the pulmonary artery may appear as a lobulated mass growing from the vessel in a polypoid fashion. The tumor may be a few centimeters to larger than 20 cm in diameter; those in an intraparenchymal location reach a larger size.

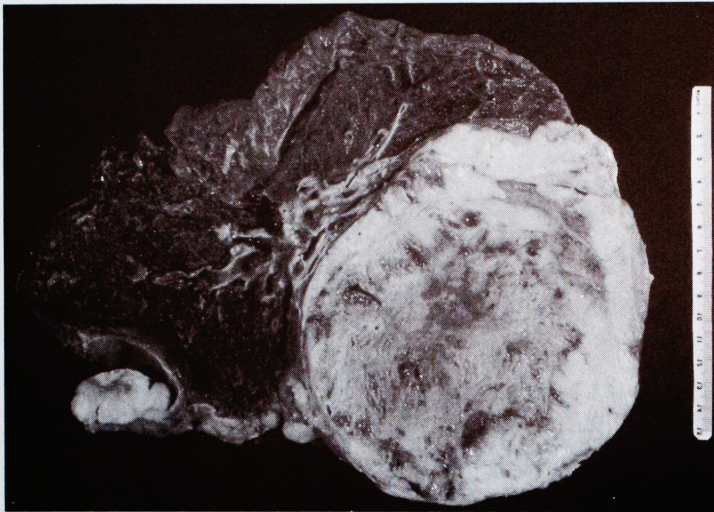Microscopically, leiomyosarcomas consist of a spindle cell

FIGURE 56-4.   This primary leiomyosarcoma occupied much of the left lower lobe. There was extensive necrosis and foci of hemorrhage (see Color 56-3). (Contributed by the editor.)

proliferation arranged in a fascicular pattern composed of cells with cigar-shaped nuclei, prominent nucleoli, and eosinophilic cytoplasm (Color Fig. 56-3). Although these features are also seen in leiomyomas, there are other features that help in arriving at a correct interpretation: mitotic activity, which could be as high as 10 per 10 high-power field (HPF); nuclear pleomorphism; hemorrhage; and necrosis. Larger tumors (>10 cm) with a high mitotic activity (>10/10 HPF) are thought to follow a more aggressive course.

Careful attention to histologic and cytologic detail is essential for a diagnosis of leiomyosarcoma, but immunohistochemical studies, including stains for smooth muscle actin and desmin, can aid the diagnosis. Electron microscopic study is useful for demonstrating cytoplasmic filaments with focal condensations (*i.e.*, dense bodies). Lesions that may be confused with leiomyosarcoma include malignant fibrous histiocytoma (MFH), fibrosarcoma, and neurogenic sarcoma.

Pulmonary Artery Sarcoma

Primary sarcomas arising in the pulmonary artery are uncommon.[31–37] These tumors probably arise from the intima or subintima of the vessel. Women are slightly more affected than men, and adults are more likely to have these tumors than children.

The patients may present with dyspnea, shortness of breath, chest pain, cough, weight loss, hemoptysis, or cardiac abnormalities. Chest x-ray studies may demonstrate a hilar mass, hilar infiltrate, or nodules. Other radiographic studies useful in the diagnosis of these tumors include computed tomography scans (Fig. 56-5*A*), angiography, and echocardiography.

Grossly, the tumors appear as polypoid intraluminal masses (Color Fig. 56-4) with nodularity extending along the intima of the vessel. Microscopically, a wide spectrum of histologic differentiation has been described, including leiomyosarcoma (Fig. 56-5*B*), rhabdomyosarcoma, angiosarcoma, chondrosarcoma, and osteosarcoma. Immunohistochemical and ultrastructural findings depend largely on the histologic characteristics and differentiation of the tumor. Although rare, metastatic lesions in brain, lymph nodes, pericardium, pleura, adrenal, thyroid, kidney, and small intestine have been documented.

Surgery has been used to treat these tumors, and some patients have received adjuvant radiation therapy or chemotherapy. There is no evidence that irradiation or chemotherapy significantly altered the clinical course of these patients. After the diagnosis is established, the prognosis for these patients is poor, with no reports of 5-year survival.

Rhabdomyosarcoma

Primary pulmonary rhabdomyosarcomas are unusual neoplasms.[38–43] They have been described in children and adults. There are some conditions, especially in children, that have been associated with the development of these tumors, such as congenital cystic adenomatoid malformation and congenital bronchogenic cysts. However, some of these neoplasms may represent pulmonary blastomas (see Chap. 54).
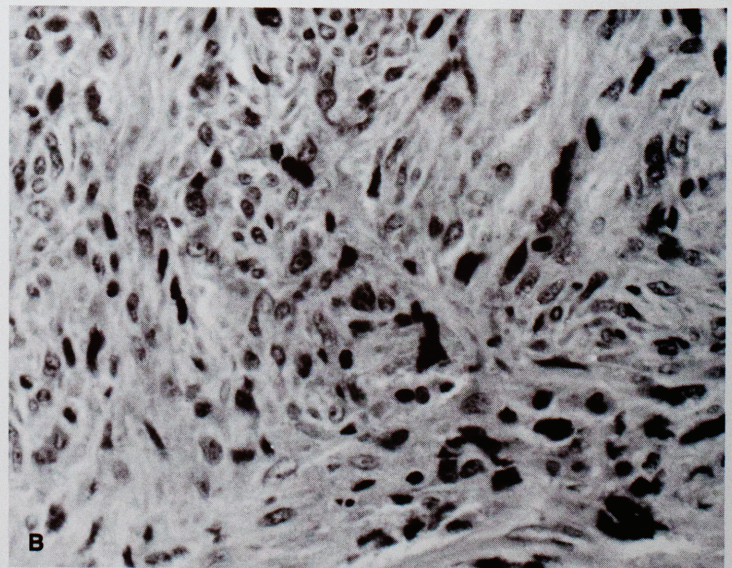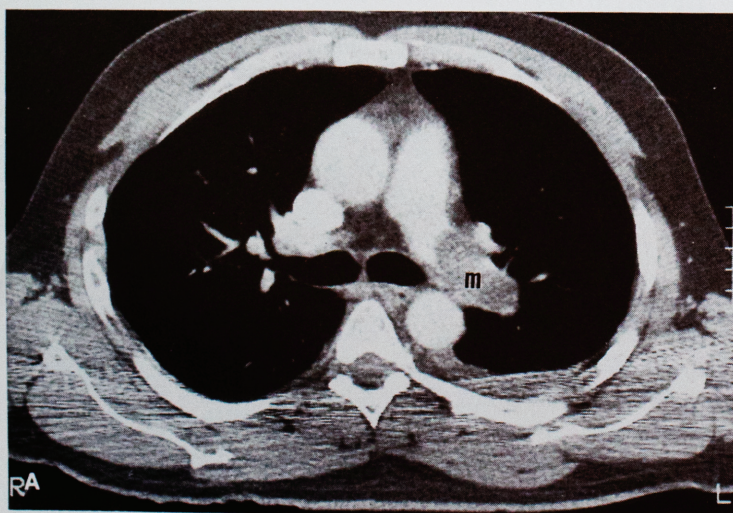

FIGURE 56-5.   Pulmonary artery sarcoma (see Fig. 56-4). (**A**) The contrast-enhanced chest CT scan shows a nonenhancing soft tissue mass in the lumen of the left pulmonary artery (m). There is also left pleural effusion. (**B**) A microscopic view of the tumor in **A** shows a leiomyosarcoma with pleomorphic features. (H & E stain; intermediate magnification.)

The clinical presentation depends on the location of the neoplasm. Grossly, these tumors appear cystic or solid with areas of hemorrhage or necrosis (Fig. 56-6A). Embryonal and alveolar variants have been described (Fig. 56-6B). Although difficult to identify, rhabdomyoblasts may be seen easier with a phosphotungstic acid-hematoxylin (PTAH) stain. Electron microscopy may reveal the presence of Z discs, linear ribosomes, or primitive cell junctions. Immunohistochemically, positive staining for desmin and myoglobin may support the diagnosis.

Because rhabdomyosarcomas may be associated with other neoplasms such as carcinosarcomas, extensive sampling is necessary to classify the tumor as a pure rhabdomyosarcoma. Other neoplasms such as primitive neuroectodermal tumors (PNET) may be confused with rhabdomyosarcoma. Immunohistochemical and ultrastructural examination help to establish the correct diagnosis.

Angiosarcoma

Malignant primary vascular tumors of the lung are uncommon neoplasms.[44–48] Most of the tumors known to have arisen as a primary in the lung are sporadic case reports, and a comprehensive study of these neoplasms in the lung is still lacking. Because this tumor may arise as a primary pulmonary artery sarcoma, it should be differentiated from those not related to the pulmonary artery.

The tumors are more often seen in young adults and may be associated with chest pain, hemoptysis, pleural effusion, pulmonary hemorrhage, embolism, and infarction. Chest x-ray studies may be remarkable for a reticulonodular or alveolar infiltrate. Microscopically, the tumors are characterized by an atypical cellular infiltrate distributed along vascular spaces. These vascular spaces are lined by neoplastic endothelial cells disclosing the true vascular nature of this neoplasm. The cellular infiltrate is usually distributed in a nodular pattern and is composed of oval or spindle cells with scant cytoplasm, hyperchromatic nuclei, and conspicuous nucleoli. These nodules or sheets of tumor cells are often separated or interconnected by slitlike spaces or vascular channels. Hemorrhage or areas containing pigment-laden macrophages may also be seen. Immunohistochemically, positive reactions to factor VIII and *Ulex europaeus* appear to be the most reliable markers for this tumor.

Angiosarcomas may be confused with hemangiomas. This benign vascular neoplasm does not show the atypical neoplastic endothelium seen in angiosarcomas. Primary or metastatic Kaposi sarcoma may demonstrate similar histologic features (Fig. 56-7). However, Kaposi sarcoma is an unusual primary lung neoplasm and is most often associated with cutaneous lesions in patients with AIDS (Color Fig. 56-5; see Chap. 45). Probably the most important question is whether the neoplasm is primary, an extension from a heart primary, or a metastasis from a soft tissue tumor. A detailed clinical evaluation is necessary. The prognosis for this tumor may be similar to those in soft tissue, which is generally poor.

Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma has also been known by other names, including intravascular bronchioloalveolar tumor, intravascular and sclerosing bronchioloalveolar tumor, sclerosing interstitial vascular sarcoma, sclerosing angiogenic tumor, and sclerosing endothelial tumor.[49–52] It has also been confused with chondrosarcoma and with pulmonary deciduosis.[53,54] The primary tumor can occur in the liver, soft tissue, and bone.[55–57] In the lung, the tumor is more frequently seen in young women.

The patients may be asymptomatic or present with respiratory symptoms such as cough, pleuritic pain, and dyspnea. Radiographically, the most common finding is multiple nodules that vary in size and number. Grossly, the tumors may have a rubbery consistency with focal calcification. Microscopically, the tumor nodules show plump cells with a round to oval nuclei and inconspicuous nucleoli. Mitoses are rare. This cellular proliferation may be embedded in a myxoid or cartilaginous stroma, and the
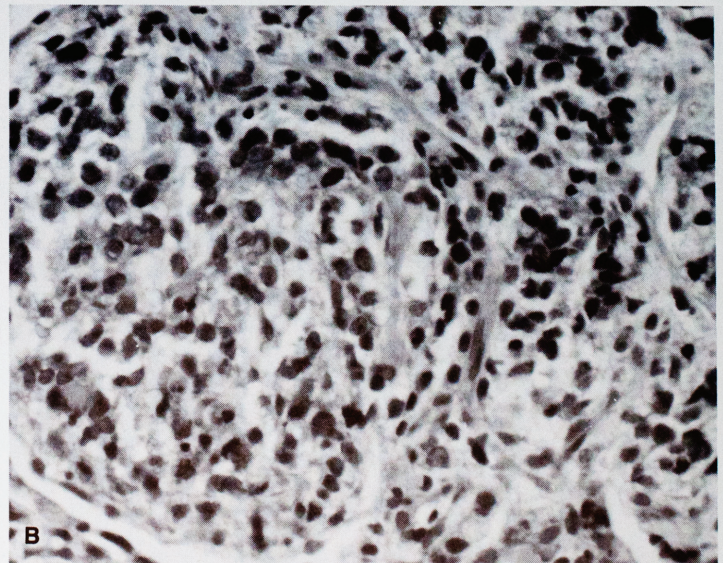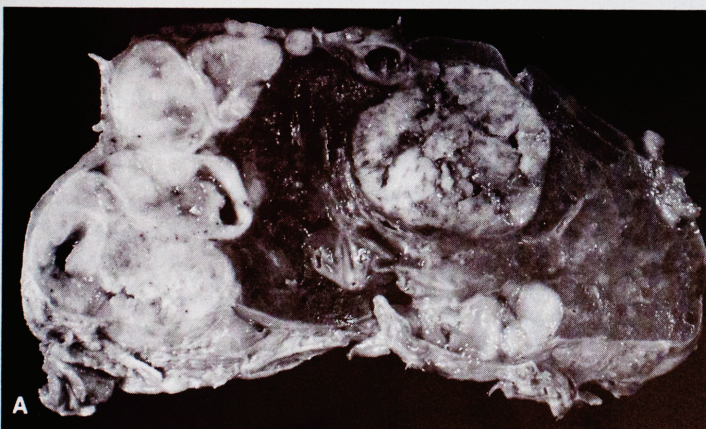
FIGURE 56-6. (**A**) Rhabdomyosarcoma of lung presented as a round mass in the upper lobe. There was extensive seeding of the pleura by tumor cells and organizing pleuritis. (**B**) Histologically, the tumor had an alveolar pattern and was composed of small neoplastic cells with round nuclei and scant cytoplasm. (H & E stain; intermediate magnification.)
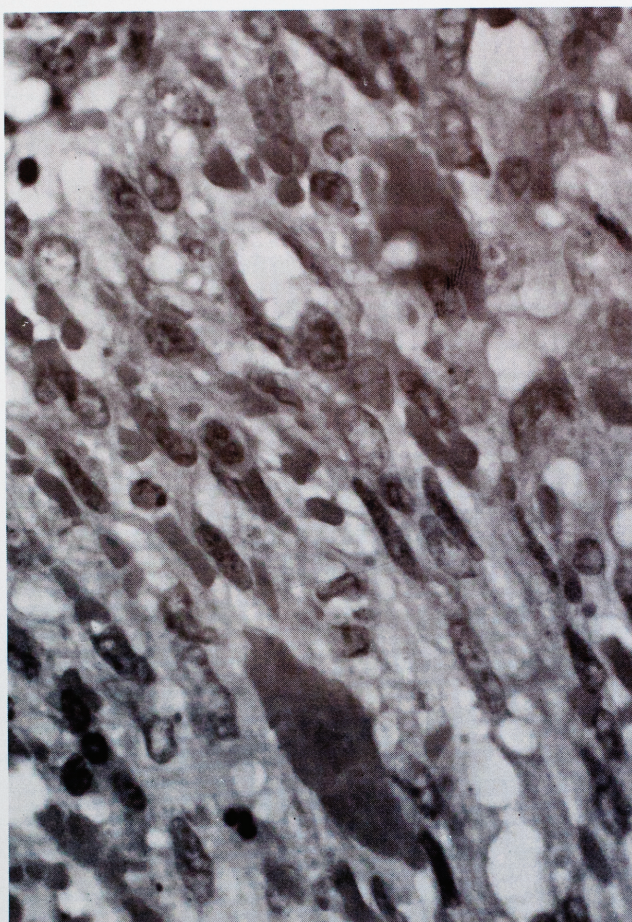
FIGURE 56-7. Microscopic appearance of the lung in adult patient with AIDS and Kaposi sarcoma (see Color Fig. 56-5). (H & E stain; high magnification; contributed by the editor.)

tumor may appear to have an intraalveolar polypoid distribution (Fig. 56-8).

Ultrastructurally, filaments, pinocytotic vesicles, intercellular junctions, lumina formation, and Weibel Palade bodies indicate an endothelial origin. Immunohistochemically, the positive reaction obtained using factor VIII and *Ulex europaeus* favor an endothelial origin. The neoplasm may follow an aggressive course, leading to death due to respiratory insufficiency, or the tumor may follow a protracted course.

Tumors that may be confused with this neoplasm include chondrosarcoma, hamartoma, or metastatic chordoma. Chondrosarcoma is an unusual primary lung neoplasm and is unlikely to present as a multinodular tumor unless it is a metastasis from an osseous primary lesion. The plump cells surrounding the acellular matrix are not a feature of chondrosarcoma. Immunohistochemical studies for factor VIII are negative for chondrosarcomas. A hamartoma presents as a solitary mass and histologically reveals cartilage and fatty tissue with invaginations of respiratory epithelium. Immunostains for factor VIII are also negative. Immunohistochemical stains for factor VIII and a previous history of chordoma elsewhere are helpful in diagnosing metastatic chordoma. Chemotherapy has been employed in advanced cases of epithelioid hemangioendotheliomas without evidence of significant improvement.

Hemangiopericytoma

Hemangiopericytomas are unusual primary lung neoplasms.[58-64] They occur more often in soft tissue, and eliminating a soft tissue source is important in designating this tumor a primary lesion in the lung.[65] The tumors are thought to be derived from the pericytes found around small vessels.

The tumor appears to affect men and women equally, usually in the fifth or sixth decade of life. The patients may be asymptomatic or present with cough, dyspnea, hemoptysis, or chest pain. Radiologically, a mass is found in a central or peripheral location. In a few cases, the tumor may present as an endobronchial polypoid tumor. Grossly, the tumors appear to be well circumscribed, with or without areas of hemorrhage or necrosis, and it may be a few centimeters in diameter to 10 cm or larger.

Microscopically, the tumor shows the classic vascular pattern with prominent vascular channels and stag horn–like vessels surrounded by a spindle cell proliferation. The spindle cells have oval to round nuclei with small nucleoli and scant cytoplasm. A large mass (>8 cm), high mitotic activity, necrosis, and bronchial or pleural involvement are associated with malignant behavior. However, it is wise to consider all pulmonary hemangiopericytomas as potentially malignant tumors. Ultrastructural and immunohistochemical studies offer little help for making the diagnosis.

Because many tumors may mimic the pattern of a hemangiopericytoma, it is prudent to perform immunohistochemical and electron microscopic studies to rule out alternate possibilities. However, the diagnosis of hemangiopericytoma must be based on light microscopy, and the physician must be familiar with other neoplasms that may show this growth pattern. Complete surgical resection appears to be the treatment of choice, and for aggressive disease, chemotherapy and radiation therapy may be helpful.

Malignant Fibrous Histiocytoma

MFH has a ubiquitous distribution, and there have been numerous reports of this neoplasm in the lung.[66-74] The tumors appear to affect male and female adults equally. Patients may present with dyspnea, cough, chest pain, hemoptysis, fever, and weight loss. Grossly, the tumors are grayish and vary in size.

Microscopically, MFH in the lung appears morphologically similar to MFH in soft tissue; it is a spindle cell proliferation arranged in a storiform pattern and displaying cellular pleomorphism with numerous multinucleated giant cells and variable amounts of collagen deposition. Mitoses are common and numerous, and vascular permeation often is observed. The storiform-pleomorphic, myxoid, and inflammatory histologic variants of the lung tumors have been described. The clinical course depends largely on the stage of the disease at the time of diagnosis. Chest wall or mediastinal involvement, extension of the neoplasm outside the thoracic cavity, recurrence, or distant metastases are features that portend a poor prognosis.

It is important to differentiate MFH from pleomorphic carcinoma. Pleomorphic carcinoma may have a spindle cell component arranged in a storiform pattern admixed with numerous pleomorphic, multinucleated giant cells against an inflammatory background. Immunohistochemical studies may help to differentiate this tumor, because epithelial markers such as keratin or epithelial membrane antigen react positively with the tumor cells. Although histiocytic markers such as α_1-antichemotrypsin and
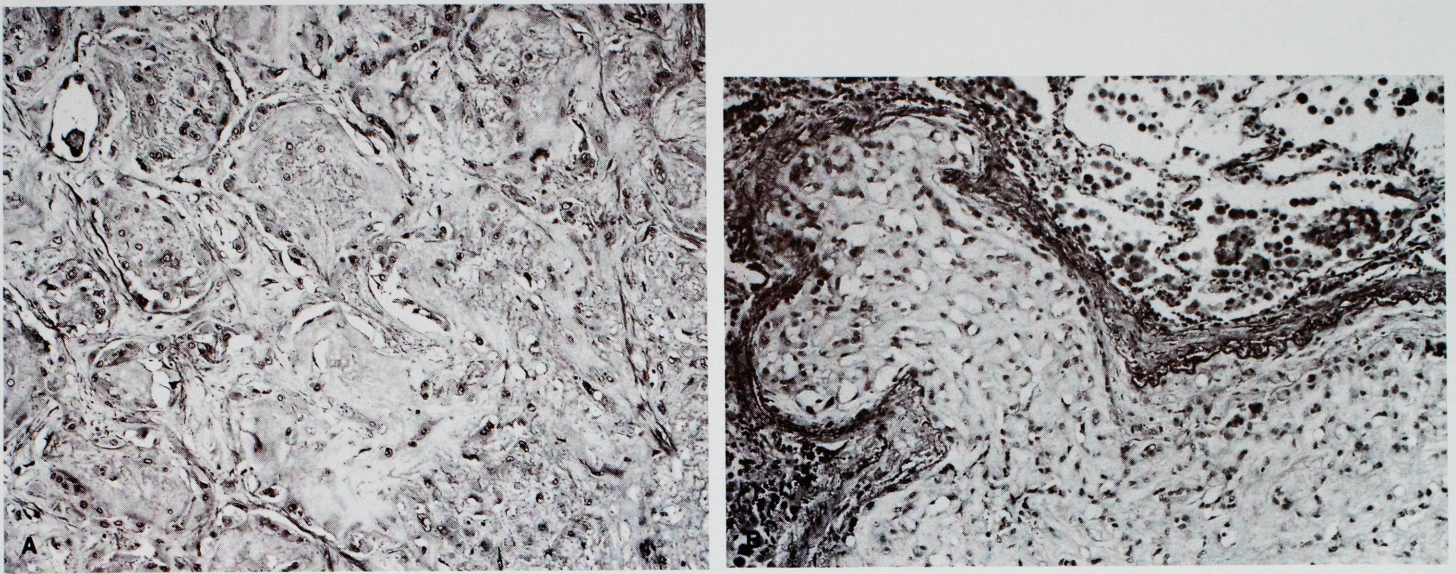
FIGURE 56-8. (**A**) Epithelioid hemangioendothelioma is composed of intraalveolar nodules made up of small round cells with eosinophilic cytoplasm embedded in a chondromyxoid stroma. (H & E stain; low magnification.) (**B**) The pulmonary vessel is invaded by a vascular proliferation of epithelioid hemangioendothelioma. (H & E stain; low magnification.)

α_1-antitrypsin react positively with MFH cells, they are not specific markers for this tumor.

MFH must also be differentiated from benign fibrous histiocytoma (*i.e.*, inflammatory pseudotumor, plasma cell granuloma). Nuclear pleomorphism, mitoses, and giant cells are the distinguishing features that separate these tumors from MFH.

Treatment consists of surgical resection by means of lobectomy or pneumonectomy, often with chemotherapy and radiation therapy. The prognosis depends on the extent of the spread of the tumor at the time of diagnosis.

Liposarcoma

Liposarcomas of the lung are highly unusual primary tumors; only a few cases have been reported.[75,76] Because of its rarity, no meaningful conclusions about its incidence and management can be reached. However, it is logical to think that liposarcomas may follow a clinical course similar to comparable tumors in soft tissues.

The patients may present with nonspecific symptoms such as cough, chest pain, and hemoptysis. As with pulmonary lipomas, liposarcomas may present as endobronchial masses. Microscopically, the typical vascular network, lipoblasts, and in some cases, cellular pleomorphism are features that help to differentiate this neoplasm from a benign lipomatous lesion.

Chondrosarcoma

Cartilaginous tumors develop rarely in extraosseous sites, and primary malignant cartilaginous tumors, called chondrosarcomas, in the lung are so unusual that there has not been a large, comprehensive study of them.[77-82] There is a semantic controversy about labeling the tumors primary or secondary. Some investigators believe that primary neoplasms are only those that arise from bronchial cartilage and that secondary tumors are those that occur in preexisting chondromas or hamartomas. A more important consideration is the exclusion of an osseous primary before labeling the lesion in the lung a primary tumor.

The tumor occurs equally in men and women and is probably more commonly seen in older persons. The patients may present with cough, chest pain, or hemoptysis, or they may be asymptomatic. Radiologically, a calcified intrapulmonary mass may be evident. Grossly, the tumor appears firm, whitish, and lobulated. Microscopically, these tumors are usually the well-differentiated type, with atypical and pleomorphic chondrocytes in lacunae (Fig. 56-9). The tumor may extend into pulmonary vessels, producing tumoral emboli.

The only significant differential diagnoses are chondromas and hamartomas. The atypical and pleomorphic nature of the chondrocytes help establish the correct diagnosis. Because of the rarity of this neoplasm in an intrapulmonary location, it is difficult to draw meaningful conclusions regarding their clinical behavior and treatment. In the cases reported, some patients have had several years survival, but others have died a few months after the diagnosis. Distant metastases have been reported. The surgical approach appears to be the only treatment used, but it is likely that these tumors may respond to chemotherapy or radiation therapy as their counterpart in skeletal locations do.

Osteosarcoma

Extraskeletal osteosarcomas arising primarily in the lung parenchyma are extremely rare; only a few cases have been reported.[83-86] Because of the osteosarcomatous component in other tumors that are relatively more common, such as carcinosarcoma or pulmonary blastoma, extensive sampling is necessary before rendering a definitive diagnosis of pulmonary osteosarcoma.

The tumor seems to affect adult men and women equally. The symptoms include chest pain, hemoptysis, dyspnea, fever, and pleural effusion. Grossly, the tumor may appear lobulated, firm, and yellowish or pink. Microscopically, the features are similar to
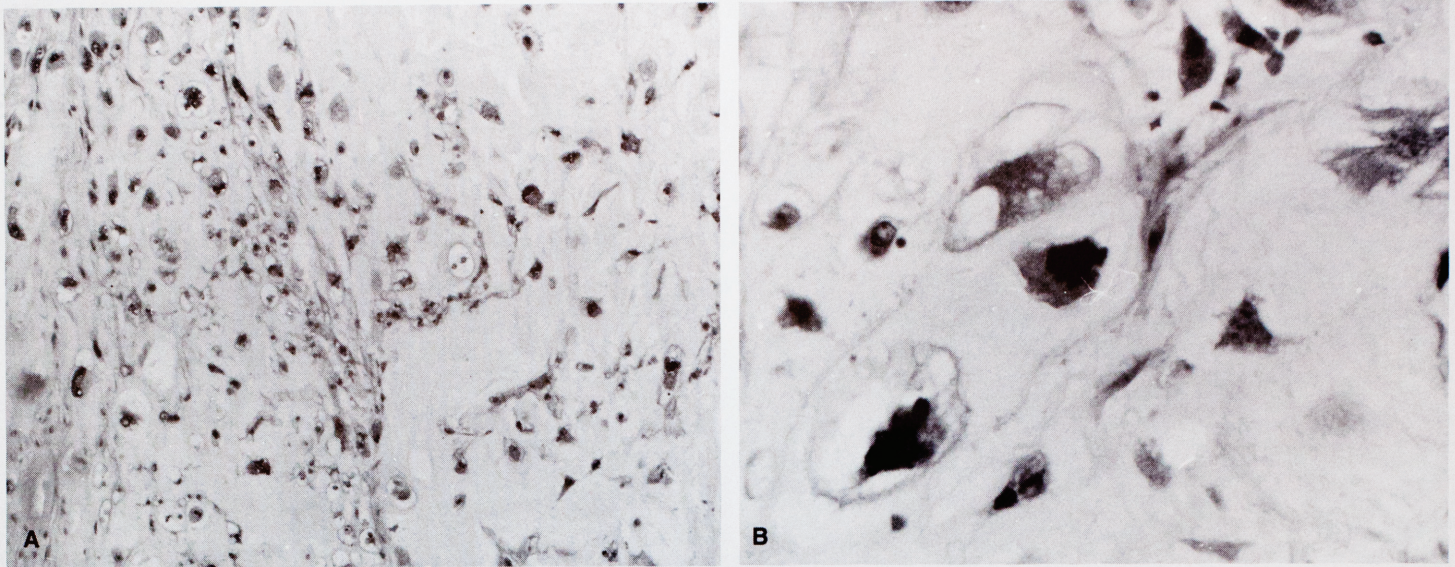
FIGURE 56-9. Pulmonary chondrosarcoma. (**A**) Numerous atypical chondrocytes are embedded in a cartilaginous stroma. (H & E stain; intermediate magnification.) (**B**) Another area in the chondrosarcoma shows highly atypical chondrocytes. (H & E stain; high magnification.)

those in osseous sites: spindle cell proliferation with areas of malignant osteoid. Areas of malignant chondroid tissue may be seen.

These tumors follow a malignant course, with documented metastases to lymph nodes and heart. Because of their rarity, it is difficult to assess specific treatment, but it is logical to expect them to behave like those arising in osseous sites. Although this tumor is diagnosed by light microscopy, it should not be confused with a malignant mesothelioma with osseous differentiation.[87] In malignant mesothelioma, the radiologic evidence of diffuse pleural thickening and a history of asbestos exposure help to determine the true nature of the neoplasm. In cases of mesothelioma with osseous differentiation, immunohistochemical stains for keratin react positively.

Neurogenic Tumors

Malignant and benign primary intrapulmonary neurogenic tumors are rare.[88–90] They have been classified as schwannomas (*i.e.*, neurilemomas) or neurofibromas. Although it is logical to think that patients with neurofibromatosis (*i.e.*, von Recklinghausen disease) are more prone to develop these neoplasms, the tumors have also been described in persons without the disease.

The patients may be asymptomatic or present with cough and chest pain. Grossly, these tumors are encapsulated, lobulated, tan, and soft with a glistening surface. Cystic degeneration may be observed, and careful examination is recommended if hemorrhage or necrosis is found, because these features are usually seen in malignant neurogenic tumors. Microscopically, the classic schwannoma is characterized by a spindle cell proliferation with Antoni A and Antoni B areas, palisading nuclei, areas of myxoid change, and hyalinization of blood vessels. Malignant transformation is identified by cellular atypia, mitoses, necrosis, or hemorrhage.

Neurofibromas characteristically show a pattern of wavy, spindle cell proliferation. The diagnosis of these neoplasms should be based on careful light microscopic evaluation. Immunohisto-

chemistry may be of value in the diagnosis of neurofibromas. Schwann cells express S-100 protein, which is expressed to a much lesser degree in the cells of neurofibroma, but S-100 protein reactivity may not of help in the diagnosis of malignant schwannomas, because this antigen is expressed in fewer than 50% of these neoplasms. The management and prognosis for these tumors are expected to be the same as for those in soft tissue locations.

Primitive Neuroectodermal Tumors

Although neuroectodermal rather than mesenchymal in origin, PNETs are reviewed here because of their resemblance to rhabdomyosarcoma and other small cell neoplasms of the lung (see Chap. 76). PNETs encompass tumors that through the years have been known by many other names, including extraskeletal Ewing sarcoma, paravertebral round cell tumor, neuroepithelioma, and small cell tumor of the thoracopulmonary region (*i.e.*, Askin tumor).[91–94] These neoplasms occur more often in the thoracopulmonary region or in the soft tissue of the chest wall. An intrapulmonary location has not been described as a primary site for this type of tumor.

We have observed several cases of this neoplasm in intrapulmonary locations without bone involvement. All the tumors occurred in young adults and were characterized by histopathologic features similar to those seen in skeletal Ewing sarcoma: neoplastic cell proliferation composed of round to elongated cells with scanty cytoplasm and round nuclei with moderate amounts of chromatin and inconspicuous nucleoli (Fig. 56-10). The number of mitoses ranged from few to numerous. Rosettes, necrosis, and hemorrhage were also seen in the tumors examined. Immunohistochemically, the neoplasms were negative for muscle and epithelial markers.

Lesions that must be ruled out before making a definitive diagnosis of this entity include rhabdomyosarcoma, undifferentiated small cell carcinoma, neuroblastoma, and lymphoma. Immunohistochemical studies and electron microscopy help in narrowing the differential diagnosis.
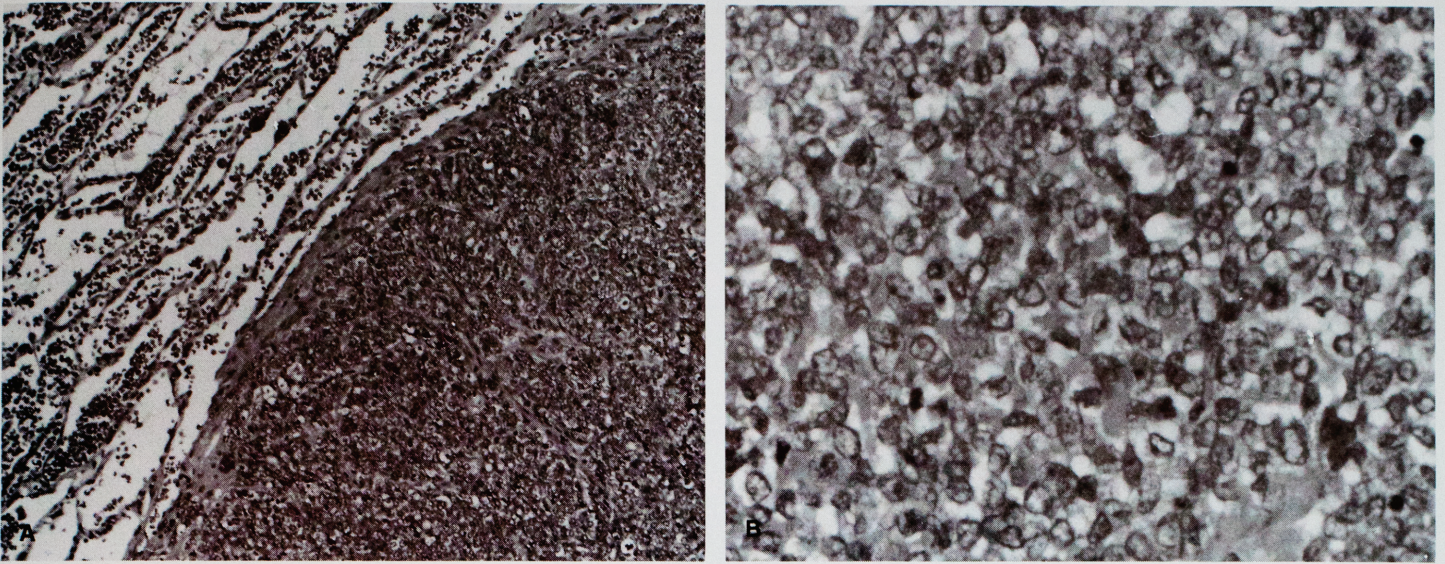
FIGURE 56-10. (**A**) Intrapulmonary malignant primitive neuroectodermal tumor is composed of a dense proliferation of small neoplastic cells. (H & E stain; low magnification.) (**B**) The detail of the same tumor reveals a proliferation of small cells with round to ovoid nuclei, inconspicuous nucleoli, and scant cytoplasm. (H & E stain; high magnification.)

Combined Mesenchymal Tumors

Combined mesenchymal tumors include the benign cartilaginous hamartoma or fibrochondrolipoma and malignant mesenchymoma.[95–100] The former lesion was considered for many years to represent a hamartoma or abnormal combination of benign tissues. However, the histology of the lesion has been reinterpreted, and it has been designated a neoplasm. The main histologic component consists of a myxoid mesenchymal tissue that undergoes maturation toward cartilage, mature fibrous tissue, and fat in different combinations.

Most fibrochondrolipomas occur in the periphery of the lung and are unrelated to bronchi (Color Fig. 56-6). They are surrounded by a fibrous capsule and can be neatly enucleated from the pulmonary tissue. They may be a few millimeters to 4 cm in diameter. As the lesion grows, it incorporates in its center clefts or slitlike channels lined by benign bronchial epithelium, but this is not an intrinsic component of the lesion (Fig. 56-11 and 56-12).

The cartilage of fibrochondrolipomas contains hyperchromatic or atypical chondrocytes, sometimes more than one in a lacuna; such changes should not be interpreted as malignancy (Fig. 56-13). The cartilaginous component of the lesion has the ability to calcify and ossify. Under the electron microscope, a cell population composed of mature fibroblasts, and glycogen-containing primitive mesenchymal elements are recognized immediately beneath the epithelial channels of the lesion.[97]

Most fibrochondrolipomas occur in the periphery of the lung, but 15% of the lesions grow endobronchially. Rarely, the lesions are multiple and cystic and lack the prominent cartilaginous component of the single lesion.[99] Carney described a triad of gastric epithelioid leiomyosarcomas, functioning extraadrenal paraganglioma, and fibrochondrolipoma in two girls and referred to a total of 15 such patients in the literature.[98]

Fibrochondrolipoma represents the most common benign neoplasm of the lung, but it is frequently excised because it resembles carcinoma (*i.e.*, coin lesion) radiographically (Fig. 56-14).
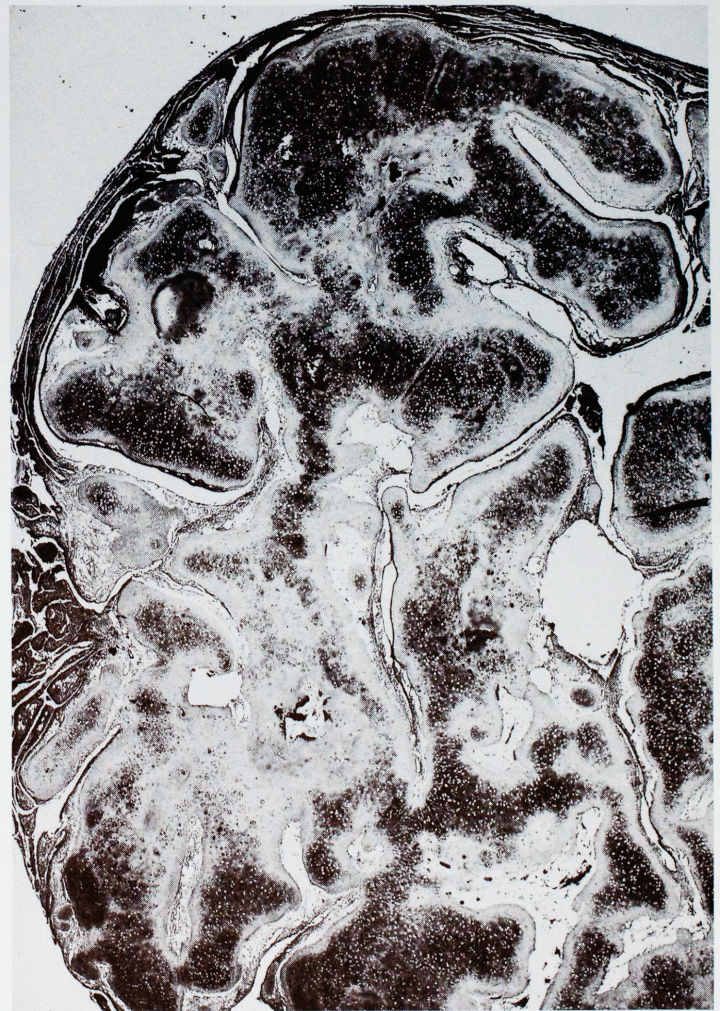

FIGURE 56-11. In this fibrochondrolipoma, the interconnecting lobules of cartilage are separated by narrow epithelial channels covered by respiratory epithelium. (H & E stain; panoramic view; from Saldana MJ. Localized diseases of the bronchi and lungs. In: Silverberg SG, ed. Principles and practice of surgical pathology, vol 1. New York: Churchill-Livingstone, 1990:713.)
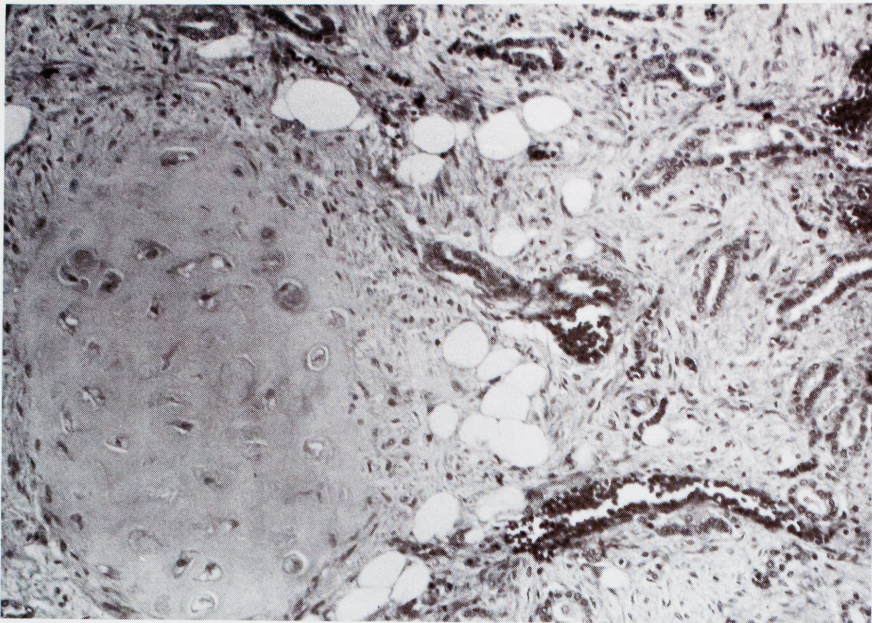
FIGURE 56-12. Cartilage, fat cells, mesenchyma, and epithelial-lined channels are characteristic of fibrochondrolipoma. (H & E stain; intermediate magnification; from Saldana MJ. Localized diseases of the bronchi and lungs. In: Silverberg SG, ed. Principles and practice of surgical pathology, vol 1. New York: Churchill-Livingstone, 1990:713.)
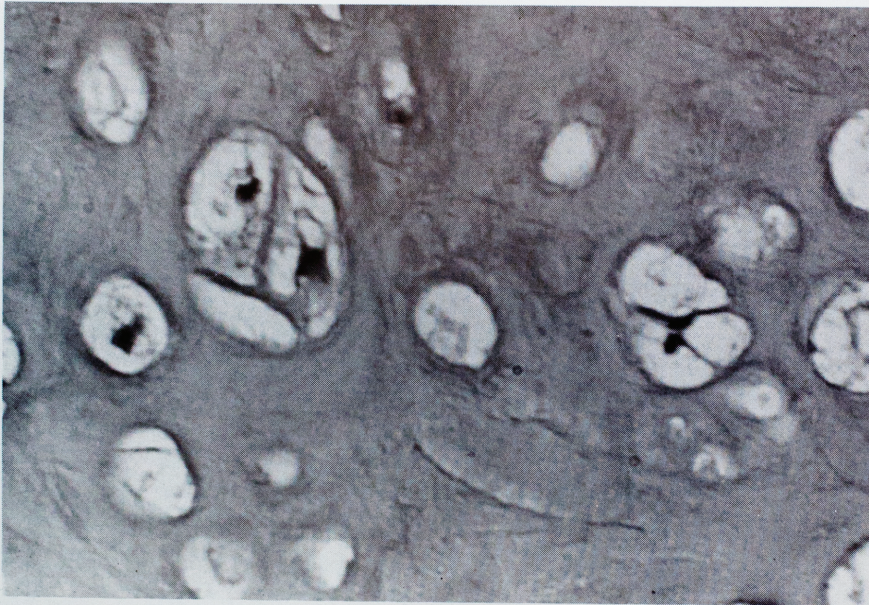

FIGURE 56-13. Atypical chrondrocytes in fibrochondrolipoma should not be misinterpreted as chondrosarcoma. (H & E stain; high magnification; contributed by the editor.)
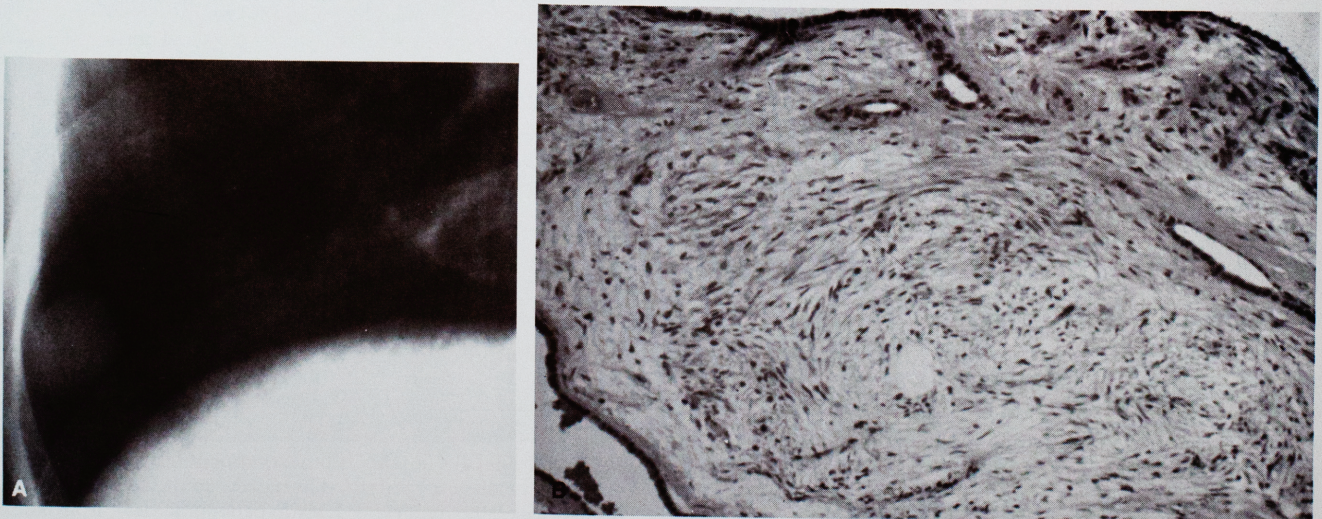

FIGURE 56-14. (**A**) Fibrochondrolipoma appears as a perfectly round coin lesion in a woman. (**B**) Histologically, the tumor consisted of myxoid tissue with entrapped epithelial channels, with no evidence of cartilage or adipose tissues. (H & E stain; low magnification; contributed by the editor.)

Mesenchymoma

Kalus and colleagues described a unique case of malignant mesenchymoma consisting of an admixture of undifferentiated malignant mesenchyme, osteosarcoma, chondrosarcoma, and rhabdomyosarcoma.[100] As expected from this histology, the tumor behaved aggressively and resembled carcinosarcoma.

Acknowledgment

REFERENCES

1. Taylor TL, Miller DR. Leiomyoma of the bronchus. J Thorac Cardiovasc Surg 1969;57:284.
2. Orlawsky TD, Stasiak K, Kolodzeij J. Leiomyoma of the lung. J Thorac Cardiovasc Surg 1978;76:257.
3. Vera-Roman JM, Sobonya RE, Gomez-Garcia JL, Sanz-Bondia JR, Paris-Romeu F. Leiomyoma of the lung. Cancer 1983;52:936.
4. Yellin A, Rosenman Y, Lieberman Y. Review of smooth muscle tumors of the lower respiratory tract. Br J Dis Chest 1984;78:337.
5. Steiner PE. Metastasizing fibroleiomyomas of the uterus: report of a case and review of the literature. Am J Pathol 1939;15:89.
6. Cho KR, Woodruff D, Epstein JI. Leiomyoma of the uterus with multiple extrauterine smooth muscle tumors: a case report suggesting multifocal origin. Hum Pathol 1989;20:80.
7. Lynn RB, MacFayden DJ. Solitary primary leiomyoma of the lung. Can J Surg 1958;2:93.
8. Sherman RS, Malone BH. A roentgen study of muscle tumors primary in the lung. Radiology 1950;54:507.
9. Gal AA, Brooks JSJ, Pietra GG. Leiomyomatous neoplasms of the lung: a clinical, histologic, and immunohistochemical study. Mod Pathol 1989;2:209.
10. Morales AR, Fine G, Pardo V, Horn RCC. The ultrastructure of smooth muscle tumors with a consideration of possible relationship of glomangiomas, hemangiopericytomas and cardiac myxomas. In: Sommers S, ed. Pathology annual. New York: Appleton-Century-Crofts, 1975:65.
11. Plachta A, Hershey H. Lipoma of the lung. Am Rev Respir Dis 1962;86:912.
12. Politis J, Funahashi A, Gehlsen JA, De Cock D, Stengel BF, Choi H. Intrathoracic lipomas. J Thorac Cardiovasc Surg 1979;77:550.
13. Eastridge CF, Young JM, Steplock AL. Endobronchial lipoma. South Med J 1984;77:759.
14. Schraufnagel DE, Morin JE, Wang NS. Endobronchial lipoma. Chest 1979;75:97.
15. Scharifker D, Kaneko M. Localized fibrous "mesothelioma" of pleura. Cancer 1979;43:627.
16. Dalton WT, Zolliker AS, McCaughey WTE, Jacques J, Kannerstein M. Localized primary tumors of the pleura. Cancer 1979;44:1465.
17. Hernandez FJ, Fernandez BB. Localized fibrous tumors of the pleura. Cancer 1974;43:1667.
18. England DM, Hochholzer L, McCarthy MJ. Localized benign and malignant fibrous tumors of the pleura. Am J Surg Pathol 1989;13:640.
19. Briselli M, Mark EJ, Dickersin GR. Solitary fibrous tumor of the pleura. Cancer 1981;47:2678.
20. Yousem SA, Flynn SD. Intrapulmonary localized fibrous tumor. Am J Clin Pathol 1988;89:365.
21. Moran CA, Suster S, Koss MN. Histologic growth patterns of localized fibrous tumors of the pleura. Semin Diagn Pathol 1992;9:169.
22. Guccion JG, Rosen SH. Bronchopulmonary leiomyosarcoma and fibrosarcoma. Cancer 1972;30:836.
23. Gebauer C. The postoperative prognosis of primary pulmonary sarcoma. J Thorac Cardiovasc Surg 1982;16:91.
24. Nascimiento AG, Unni KK, Bernatz PE. Sarcomas of the lung. Mayo Clin Proc 1982;57:355.
25. Wick MR, Scheithauer BW, Piehler JM, Pairolero PC. Primary pulmonary leiomyosarcomas. Arch Pathol Lab Med 1982;106:510.
26. Jimenez JF, Uthman EO, Townsend JW, Gloster ES, Seibert JJ. Primary bronchopulmonary leiomyosarcoma in childhood. Arch Pathol Lab Med 1984;78:337.
27. Patel SR, Jindrak KF, Anandarao N. Primary pedunculated leiomyosarcoma of the lung. N Y State J Med 1991;91:30.
28. Akamine S, Uchiyama Y, Kimino K, et al. Two cases of pulmonary leiomyosarcoma. Nippon Kyobu Geka Gakkai Zasshi 1990;38:1203.
29. Morgan PGM, Ball J. Pulmonary leiomyosarcomas. Br J Dis Chest 1980;74:245.
30. Ramanathan T. Primary leiomyosarcoma of the lung. Thorax 1974;29:482.
31. Baker PB, Goodwin RA. Pulmonary artery sarcoma. Arch Pathol Lab Med 1985;109:35.
32. Bleisch VR, Kraus FT. Polypoid sarcoma of the pulmonary trunk. Cancer 1980;46:314.
33. Henrichs KJ, Wenisch HJC, Hofmann W, et al. Leiomyosarcoma of the pulmonary artery. Virchows Arch A Pathol Anat Histopathol 1979;383:207.
34. Murthy MSN, Meckstroth CV, Merkle BH, et al. Primary intimal sarcoma of pulmonary valve and trunk with osteogenic sarcomatous elements. Arch Pathol Lab Med 1976;100:649.
35. Hayes WL, Farha SJ, Brown RL. Primary leiomyosarcoma of the pulmonary artery. Am J Cardiol 1974;34:615.
36. Di Gilio MM, Lee HJ, Tatooles CJ, et al. Myxosarcoma of the pulmonary artery. J Thorac Cardiovasc Surg 1972;63:587.
37. Nerlich A, Permanetter W, Ludwig B, Remberger K. Primary leiomyosarcoma of the truncus pulmonalis. Pathol Res Pract 1990;186:296.
38. Lee SH, Renhachary SS, Paramesh J. Primary pulmonary rhabdomyosarcoma. Hum Pathol 1979;12:92.
39. Allan BT, Day DL, Dehner LP. Primary pulmonary rhabdomyosarcoma of the lung in children. Cancer 1987;59:1005.
40. Avagnina A, Elsner B, De Marco L, Bracco AN, Nazar T, Paulausky H. Pulmonary rhabdomyosarcoma with isolated small bowel metastasis.
41. Erikson A, Thunell M, Lundquist G. Pedunculated endobronchial rhabdomyosarcoma with fatal asphyxia. Thorax 1982;37:390.
42. Krouss HF, Sezauer CHL. Endobronchial rhabdomyosarcoma arising within a congenital bronchogenic cyst in a child. J Pediatr Surg 1981;16:506.
43. Shariff S, Thomas JA, Shetty N, D'Cunha S. Primary pulmonary rhabdomyosarcoma in a child with a review of the literature. J Surg Oncol 1988;38:261.
44. Tralka GA, Katz S. Hemangioendothelioma of the lung. Am Rev Respir Dis 1963;87:107.
45. Spragg RG, Wolf PL, Haghighi P, et al. Angiosarcoma of the lung with fatal pulmonary hemorrhage. Am J Med 1983;74:1072.
46. Yousem SA. Angiosarcoma presenting in the lung. Arch Pathol Lab Med 1986;110:112.
47. Plaaut A. Hemangioendothelioma of the lung: report of two cases. Arch Pathol 1931;12:517.
48. Guarda LA, Ordonez NG, Smith L, Hanssen G. Immunoperoxidase localization of factor VIII in angiosarcomas. Arch Pathol Lab Med 1982;106:515.
49. Dail DH, Liebow AA, Gmelich JT, et al. Intravascular bronchiolar and alveolar tumor of the lung. Cancer 1983;51:452.
50. Azumi N, Churg A. Intravascular and sclerosing bronchioloalveolar

tumor. A pulmonary sarcoma of probable vascular origin. Am J Surg Pathol 1980;5:587.

51. Ferrer-Roca O. Intravascular and sclerosing bronchioloalveolar tumor. Am J Surg Pathol 1980;4:375.

52. Corrin B, Manners B, Millard M, Weaver L. Histogenesis of the so-called "intravascular bronchioloalveolar tumor." J Pathol 1979; 128:163.

53. Farinacci DJ, Blauw AS, Jennings EM. Multifocal pulmonary lesions of possible decidual origin (so-called pulmonary deciduosis). Am J Clin Pathol 1973;59:508.

54. Weiss SW, Ishak KG, Dail DH, Sweet DE, Enzinger FM. Epithelioid hemangioendothelioma and related lesions. Semin Diagn Pathol 1986;3:259.

55. Bhagavan BS, Murthy MNS, Dorfman HD, Eggleston JC. Intravascular bronchiolo-alveolar tumor (IVBAT): a low grade sclerosing epithelioid angiosarcoma of lung. Am J Surg Pathol 1982;5:41.

56. Miettinen M, Collan Y, Halttunen P, Maamies AT, Vilko P. Intravascular bronchoalveolar tumor. Cancer 1987;60:2471.

57. Weldon-Linne CM, Victor TA, Christ ML, Fry WA. Angiogenic nature of the "intravascular bronchioloalveolar tumor" of lung. An electron microscopic study. Arch Pathol Lab Med 1981;105:174.

58. Shinn MS, Ho KJ. Primary hemangiocytoma of lung. Radiography and pathology. Am J Roentgenol 1979;133:1077.

59. Razzuk MA, Nassur A, Gardner MA, Martin J, Gohara SF, Urchel HC. Primary pulmonary hemangiopericytoma. J Thorac Cardiovasc Surg 1977;74:227.

60. Feldman F, Seaman WB. Primary thoracic hemangiopericytoma. Radiology 1964;998.

61. Meade JB, Whitwell F, Bickford JKB. Primary hemangiopericytoma of lung. Thorax 1974;29:1.

62. Davis Z, Berliner WP, Weiland LH, Clagett OT. Primary pulmonary hemangiopericytoma. J Thorac Cardiovasc Surg 1972;64:882.

63. Yousem SA, Hochholzer L. Primary pulmonary hemangiopericytoma. Cancer 1987;59:549.

64. Alt B, Huffer WE, Belchis DA. A vascular lesion with smooth muscle differentiation presenting as a coin lesion in the lung: glomus tumor versus hemangiopericytoma. Am J Clin Pathol 1983;80:765.

65. Enzinger FM, Smith BH. Hemangioendothelioma: an analysis of 106 cases. Hum Pathol 1976;7:61.

66. Paulsen SM, Egeblad K, Christensen J. Malignant fibrous histiocytoma of the lung. Virchows Arch A Pathol Anat Histopathol 1981;394:167.

67. Misra DP, Sunderriajan EV, Rosenhaltz MJ, Hurst DJ. Malignant fibrous histiocytoma in the lung masquerading as recurrent pulmonary thromboembolism. Cancer 1983;51:538.

68. Silverman JF, Coalson JJ. Primary malignant myxoid fibrous histiocytoma of the lung. Arch Pathol Lab Med 1984;108:49.

69. Bedrossian CWM, Veroni R, Unger KM, Salman J. Pulmonary malignant fibrous histiocytoma. Chest 1979;75:186.

70. Kern WH, Hughes RK, Meyer BW, Harley DP. Malignant fibrous histiocytoma of the lung. Cancer 1979;44:1793.

71. Lee JT, Shelburne JD, Linder J. Primary malignant fibrous histiocytoma of the lung. Cancer 1984;53:1124.

72. Sajjad SM, Begin LR, Dail DH, Lukeman JM. Fibrous histiocytoma of the lung. Histopathology 1981;5:325.

73. Mc Donnell T, Kyriakos M, Royer C, Mazoujian G. Malignant fibrous histiocytoma of the lung. Cancer 1988;61:137.

74. Yousem SA, Hochholzer L. Malignant fibrous histiocytoma of the lung. Cancer 1987;60:2532.

75. Sawamura K, Hashimoto T, Nanjo S, et al. Primary liposarcoma of the lung. J Surg Oncol 1982;19:243.

76. Ruiz-Palomo F, Alleja JL, Fogue L. Primary liposarcoma of the lung in a young woman. Thorax 1990;45:298.

77. Morgan AD, Salama FD. Primary chondrosarcoma of the lung. J Thorac Cardiovasc Surg 1972;64:460.

78. Sun CCJ, Kroll M, Muller JE. Primary chondrosarcoma of the lung. Cancer 1982;50:1864.

79. Lowell LM, Tuby JG. Primary chondrosarcoma of the lung. J Thorac Surg 1946;68:476.

80. Stanfield BL, Power CN, Disch CE, Brooks JW, Frable WJ. Fine-needle aspiration cytology of an unusual primary lung tumor, chondrosarcoma. Diagn Cytopathol 1991;7:423.

81. Rees GM. Primary chondrosarcoma of lung. Thorax 1970;25:366.

82. Smith EAC, Cohen RV, Peale AR. Primary chondrosarcoma of the lung. Ann Intern Med 1960;53:838.

83. Reingold IM, Amromin GD. Extraosseous osteosarcoma of the lung. Cancer 1971;28:491.

84. Greenspan EB. Primary osteoid chondrosarcoma of the lung. Am J Cancer 1933;18:603.

85. Nasanchuk JS, Weatherbee L. Primary osteogenic sarcoma in lung. J Thorac Cardiovasc Surg 1969;58:242.

86. Yamashita T, Kiyota T, Ukishima G, Hayama T, Yobuki E. Autopsy of a case of chondro-osteoid sarcoma originating in the lung. J Shonai Med Assoc 1964;23:472.

87. Yousem SA, Hochholzer L. Malignant mesothelioma with osseous and cartilaginous differentiation. Arch Pathol Lab Med 1987;111:62.

88. Bartley TD, Arean VM. Intrapulmonary neurogenic tumors. J Thorac Cardiovasc Surg 1965;50:114.

89. Roviaro G, Montorsi M, Varoli F, Binda R, Cecchetto A. Primary pulmonary tumors of neurogenic origin. Thorax 1983;38:942.

90. Unger PD, Geller SA, Anderson DJ. Pulmonary lesions in a patient with neurofibromatosis. Arch Pathol Lab Med 1984;108:654.

91. Angervall L, Enzinger FM. Extraskeletal neoplasm resembling Ewing's sarcoma. Cancer 1977;101:446.

92. Askin FB, Rosai J, Sibley R, Dehener LP, McAlister W. Malignant small cell tumor of the thoracopulmonary region in children. Cancer 1979;43:2438.

93. Hashimoto H, Enjoi M, Nakajima T, Kiryu H, Daimoru Y. Malignant neuroepithelioma. Am J Surg Pathol 1983;7:309.

94. Tefft M, Vawter GF, Metus A. Paravertebral "round cell" tumors in children. Radiol 1969;92:1051.

95. Bateson EM. So-called hamartoma of the lung—a true neoplasm of fibrous connective-tissue of the bronchi. Cancer 1973;31:1458.

96. Ramchand S, Baskerville L. Multiple hamartomas of the lung. Am Rev Respir Dis 1969;99:932.

97. Stone FJ, Churg AM. The ultrastructure of pulmonary hamartoma. Cancer 1969;39:932.

98. Carner JA. The triad of gastric epithelioid leiomyosarcoma, functioning extra-adrenal paraganglioma, and pulmonary chondroma. Cancer 1979;43:374.

99. Tomashefski JF Jr. Benign endobronchial mesenchymal pulmonary hamartomas. Am J Surg Pathol 1982;6:531.

100. Kalus M. Rahman F, Jenkins DE, et al. Malignant mesenchymoma of the lung. Arch Pathol 1973;95:199.