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54

Mixed Epithelial-Mesenchymal Tumors

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True mixed epithelial-mesenchymal tumors occur infrequently in the lung as primary neoplasms. They include pulmonary blastomas, carcinosarcomas, and teratomas. Teratomas are rare in the lung, occurring much less frequently than their mediastinal counterparts.[1] Pleuropulmonary blastomas, even though they are purely mesenchymal tumors, are discussed in this chapter because they are part of the spectrum of blastomatous lesions; however, the relatively common pulmonary hamartoma whose epithelial components are entrapped or represent hyperplastic bronchial epithelium are discussed in Chapter 56.

PULMONARY BLASTOMAS

Pulmonary blastoma is a type of tumor in which the glandular or mesenchymal components appear primitive or embryonal.[1] The glycogen-rich, nonciliated tubules or embryonic stroma resemble fetal lung between 10 and 16 weeks of gestation (*i.e.*, pseudoglandular stage of lung development).

The first report of pulmonary blastoma was by Barnett and Barnard in 1945.[2] The pathology of the tumor was revisited by Barnard in 1952, who coined the term "embryoma" in appreciation of its resemblance to embryonic lung.[3] Almost a decade later, Spencer described three additional cases and first used the name "blastoma" in the assumption that the tumor arose from a primitive blastema, in the manner of nephroblastoma.[4] By 1983, 83 cases had been published.[5] Pulmonary blastoma was initially thought to be always biphasic in its appearance, but in the 1980s, variants of pulmonary blastoma consisting exclusively of malignant glandular or of malignant "embryonic" mesenchyme were reported.[6–9] Tumors consisting of malignant glands were given a variety of names: pulmonary adenocarcinoma of fetal type, well-differentiated adenocarcinoma simulating fetal lung tubules, pulmonary endodermal tumor resembling fetal lung, and well-differentiated fetal adenocarcinoma (WDFA).[6–8] Malignant mesenchymal tumors were characterized by embryonic stroma without neoplastic epithelium; they were called pleuropulmonary blastoma.[9]

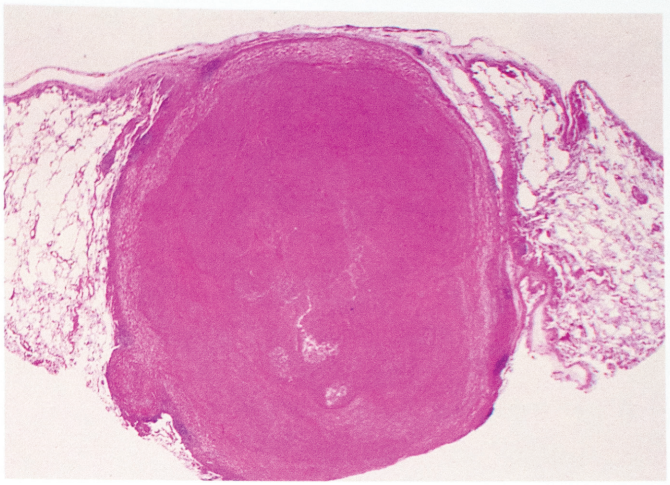
Clinical Features

The relative frequency of biphasic and purely epithelial blastomas is still not clear. Only 10 bona fide cases of WDFA have been reported in the literature as of 1990, compared with over 80 blastomas by 1983.[10] However, the ratio of WDFA to biphasic blastomas in the 52 cases reported from the Armed Forces Institute of Pathology is approximately one, and this appears to be a more realistic figure.[8]

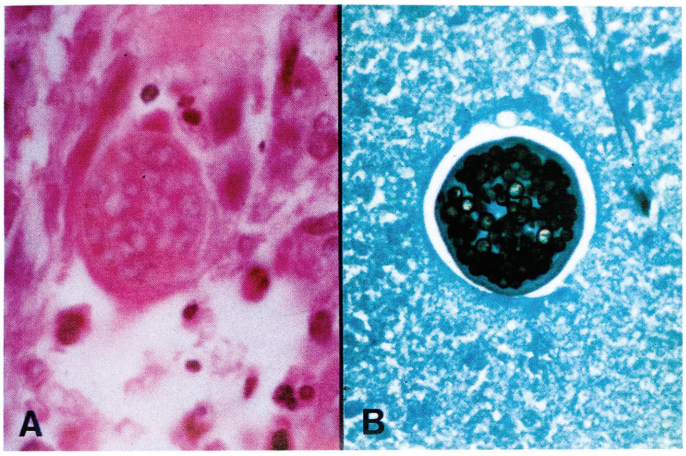
In published reports, biphasic blastomas and WDFA affect women more commonly than men by a ratio of over 2:1.[5,10]

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Navy, the Department of the Army, or the Department of Defense.

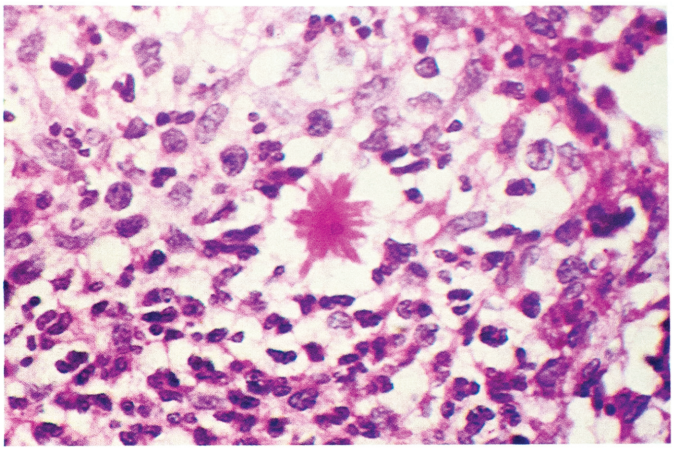
COLOR FIGURE 43-1. A fibrocaseous nodule of histoplasmosis (*i.e.*, histoplasmoma) has concentric laminations; the lesion increased in size over time. (Contributed by the editor.)



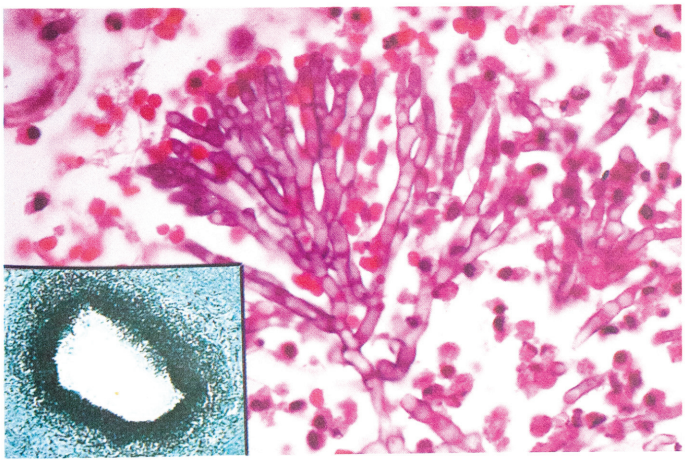
COLOR FIGURE 43-2. A fibrocaseous nodule of *Coccidioides immitis* in a lung. (H & E stain; low magnification.)



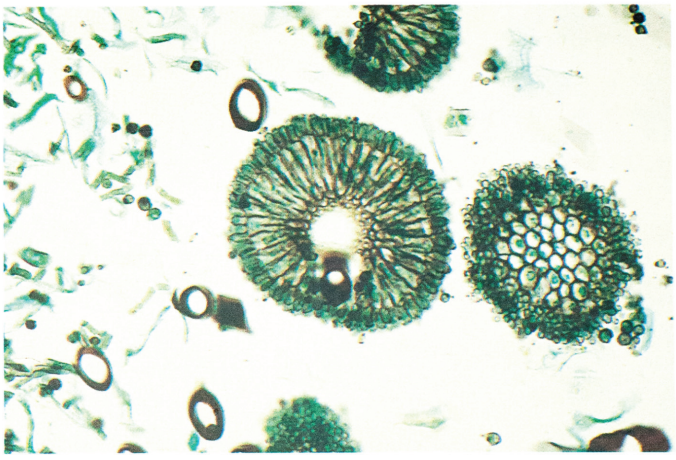
COLOR FIGURE 43-3. A mature spherule of *Coccidioides immitis* with endospores in caseous material. (**A**: H & E stain; high magnification; courtesy of P. Angritt, M.D., Washington, DC.) (**B**: GMS stain; high magnification.)



COLOR FIGURE 43-4. An asteroid body of *Sporothrix schenckii*. (PAS stain; intermediate magnification.)



COLOR FIGURE 43-5. A bundle of septated hyphae of *Aspergillus* are characterized by Y-shaped dichotomous branching. (H & E stain; high magnification.) *Aspergillus* vasculitis is seen in a patient with generalized infection (*inset*). (GMS stain; low magnification; courtesy of Peter Angritt, M.D., Washington, DC.)



COLOR FIGURE 43-6. The conidial heads of *Aspergillus niger* are composed of a vesicle and two rows of phialides (*i.e.*, sterigmata). The large, thick oval structures are transverse sections of conidiophores. (GMS stain; intermediate magnification.)

TABLE 54-1
Clinical Features of Blastomas by Histologic Subtype

Clinical Feature	WDFA[8]	Biphasic Blastomas[8]	Pleuropulmonary Blastomas[9]
Number of cases	28	24	11
Percent of patients younger than 10 years of age	0	8	91
Male/female	13/15	11/13	5/6
Caucasian/black	17/8	13/5	NA
Smoker/nonsmoker	19/4	14/3	0/11

NA, not available; WDFA, well-differentiated fetal adenocarcinoma.
Data from Koss M, Hochholzer L, O'Leary T. Pulmonary blastomas. Cancer 1991;67:2368 and Manivel JC, Priest JR, Watterson J, et al. Pleuropulmonary blastoma. The so-called pulmonary blastoma of childhood. Cancer 1988;62:1516.

However, data from the Armed Forces Institute of Pathology demonstrate an almost equal gender ratio for both tumors (Table 54-1).[8]

Pulmonary blastoma is largely a tumor of adults. According to the published cases, only 20% of blastomas occur in persons younger than 20 years of age, and the mean age at presentation is 43 years.[11] However, 4% of epithelial and biphasic blastomas occur in children younger than 10 years of age (see Table 54-1).[8] The youngest reported patient with WDFA was 12 years of age.[8]

Approximately 80% of the patients with epithelial and biphasic pulmonary blastomas are smokers (see Table 54-1).[8,10] Cigarette smoking probably plays a role in the pathogenesis of these tumors despite their embryonic appearance. Between 25% to 40% of patients with blastomas are asymptomatic. Patients who are asymptomatic more commonly have the epithelial variant (*i.e.*, WDFA) of blastoma (Fig. 54-1). Presumably, the lack of symptoms is caused by the smaller size of the epithelial tumors compared with biphasic or pleuropulmonary tumors. The slow growth of blastomas in adults is not rare; in one large series, 21% of patients with gradually enlarging pulmonary masses were followed for as long as 6 years.[8] The most frequent symptoms in adults and children are cough, chest pain, and hemoptysis, presumably provoked by a mass in lung impinging on bronchi or pleura.[8,9]

The most frequent chest x-ray presentation is that of a solitary peripheral or midlung mass, an appearance that is of little aid in the differential diagnosis (Table 54-2). The WDFA variant of blastoma averages about one half of the size of biphasic tumors. A correct or suggestive preoperative diagnosis of blastoma, typically made by bronchoscopic or needle biopsy, was reported for only one third of published cases.

The primary treatment of blastomas is surgical extirpation or combination chemotherapy for distant metastasis.[8] Patients with biphasic blastomas generally have poor rates of survival.[5,8] The prognosis of patients with these neoplasms is as bad as that for common lung carcinomas. Although there are individual reports of long-term tumor-free survival, two thirds of patients with biphasic tumors die within 2 years of diagnosis, 16% survive for 5 years, and only 8% survive for 10 years.[5,12] Survival depends partially on the stage of the tumor; for stage I blastomas, there is a 5-year survival rate of about 25%.[8]

For WDFA, Nakatani and colleagues determined a tumor-associated mortality rate of only 10% for 10 cases of "pulmonary endodermal tumor."[10] Koss and associates showed a tumor-induced mortality rate of only 14% for 21 patients with WDFA after adequate follow-up (mean/median follow-up, 97/95 months).[8] When recurrences happen, as they do in about 30% of these patients, they are usually within the lung and can be surgically extirpated, a fact that may also explain the longer survival of these patients.

The established ominous prognostic factors for pulmonary blastomas are metastasis at the initial presentation, tumor recurrence during the clinical course, and a tumor size greater than 5 cm.[8,12,13] Tumor size is a significant predictor for patients with biphasic tumors but apparently not for those with epithelial tu-

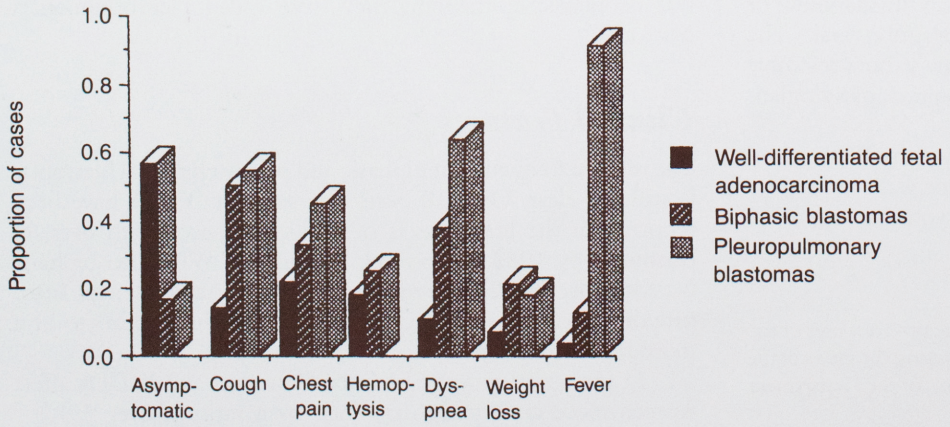
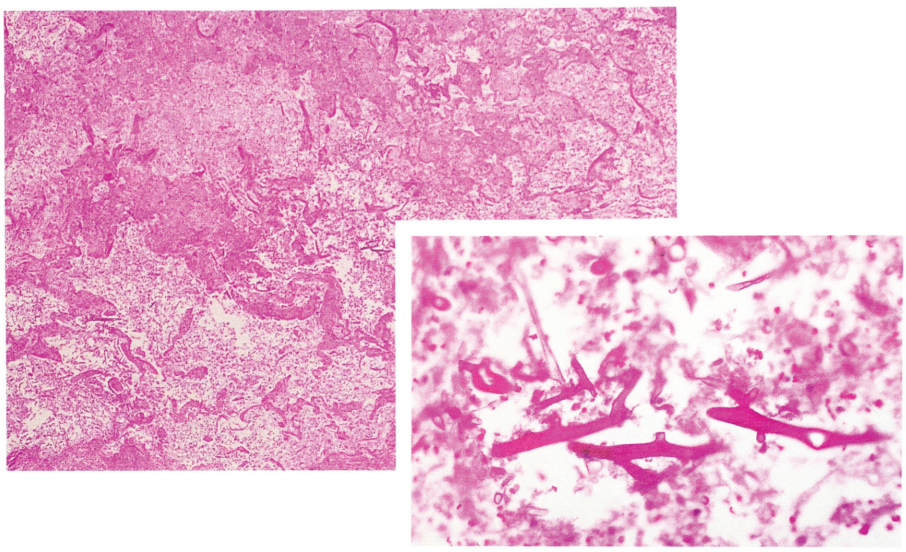
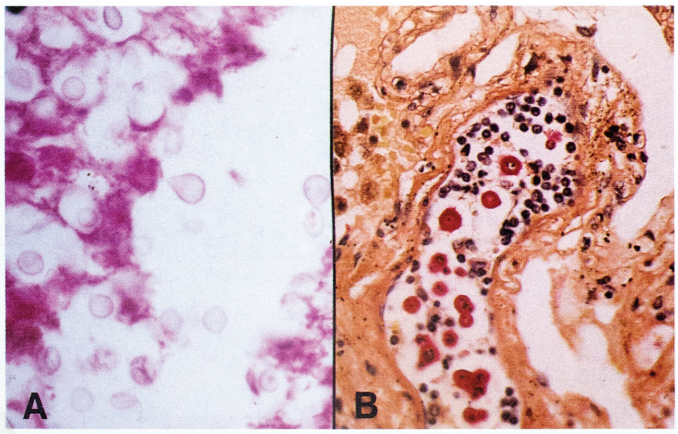


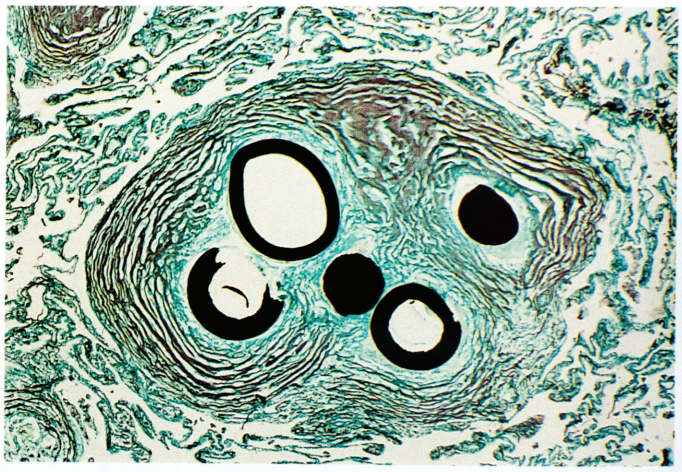
FIGURE 54-1. Comparison of the symptoms of pulmonary blastomas by histologic subtype.



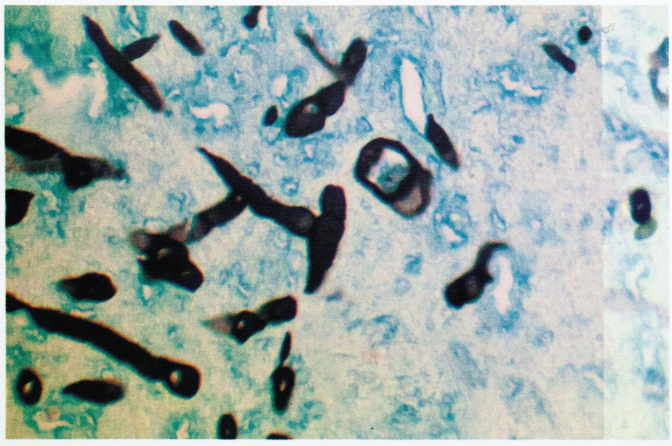
COLOR FIGURE 43-7. Numerous hyphae of *Rhizopus* are seen in a necrotic area of the lung. Hyphae stain well with H & E. (H & E stain; low magnification.) Broad hyphae in greater detail (*inset*). (H & E stain; intermediate magnification.)



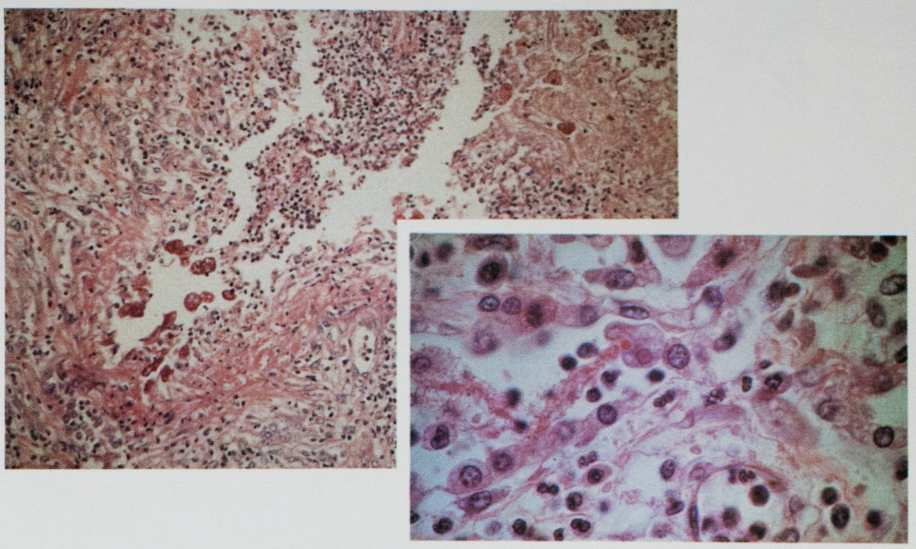
COLOR FIGURE 43-8. (**A**) Numerous yeast forms of *Cryptococcus neoformans* with narrow-necked budding in necrotic tissue are perfectly discernible. (H & E stain; high magnification.) (**B**) Confirmation of the diagnosis is made by brilliant mucicarmine staining in another patient with intravascular invasion by the fungus. (Mucicarmine stain; high magnification; contributed by P. Angritt, M.D., Washington, DC.)



COLOR FIGURE 43-9. A lesion of adiaspiromycosis shows several adiaspores of *Chrysosporium* in granuloma of lung. The adiaspores are large and have thick, GMS-positive walls. (GMS stain; intermediate magnification.)

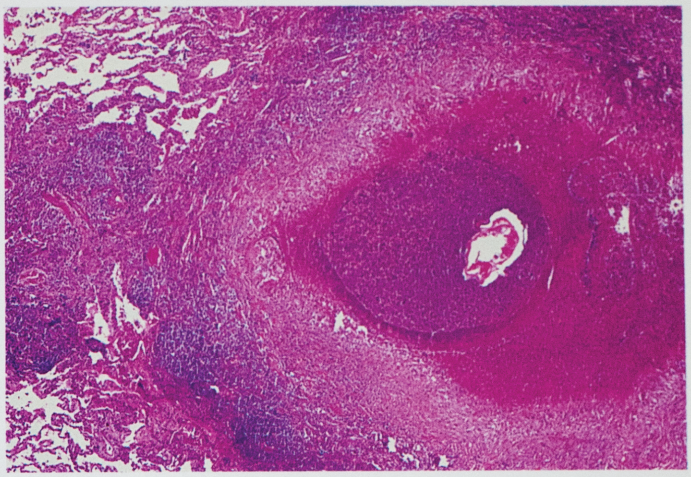


COLOR FIGURE 43-10. A pulmonary lesion of invasive phaeohyphomycosis caused by *Alternaria* sp. (GMS stain; intermediate magnification; contributed by the editor.)



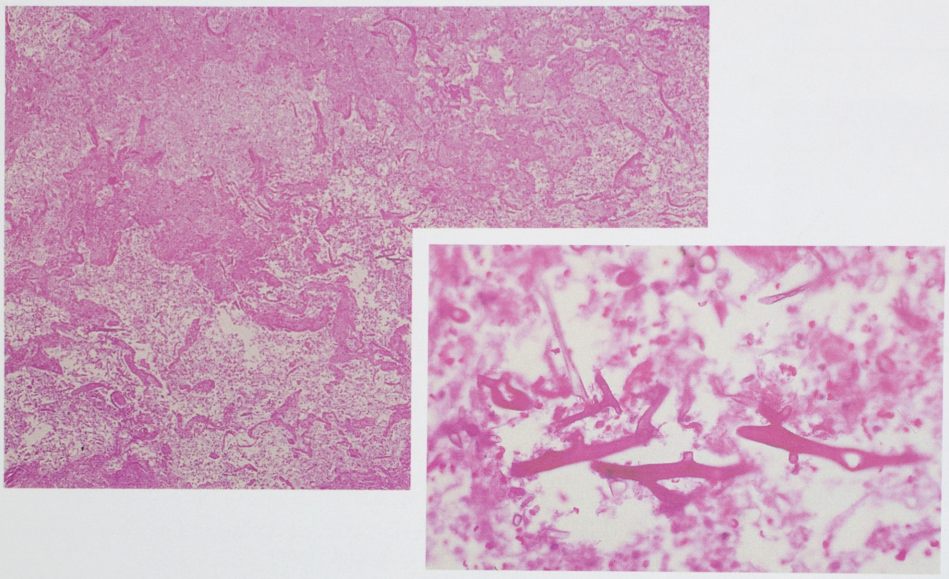
COLOR FIGURE 44-1. Numerous trophozoites of *Entamoeba histolytica* are present in the center of a pulmonary abscess. (H & E stain; intermediate magnification.) The inset shows a single trophozoite with a characteristic nucleus with fine chromatin, lining nuclear membrane, tiny central karyosome, and engulfed red blood cell in cytoplasm. (H & E stain; high magnification; contributed by P. Angritt, MD., Washington, DC.)

COLOR FIGURE 44-2. Left upper lobe contains a large hydatid cyst of *Echinococcus granulosus*. The punctate granules on the inner lining represent scolices. (From Saldana MJ. Localized diseases on bronchi & lungs. In: Silverberg SE, ed. Principles and practices of surgical pathology. vol. 1. 2nd ed. New York: Churchill-Livingstone, 1990.)



COLOR FIGURE 44-3. An adult gravid female *Enterobius vermicularis* provokes extensive necrosis and organization of lung tissue. (H & E stain; low magnification.)

COLOR FIGURE 44-4. A cross section of the worm that appears in Color Figure 44-3. The worm has green, single, lateral alae, a yellow cuticle, and several eggs in uterus. (Movat stain; low magnification.)



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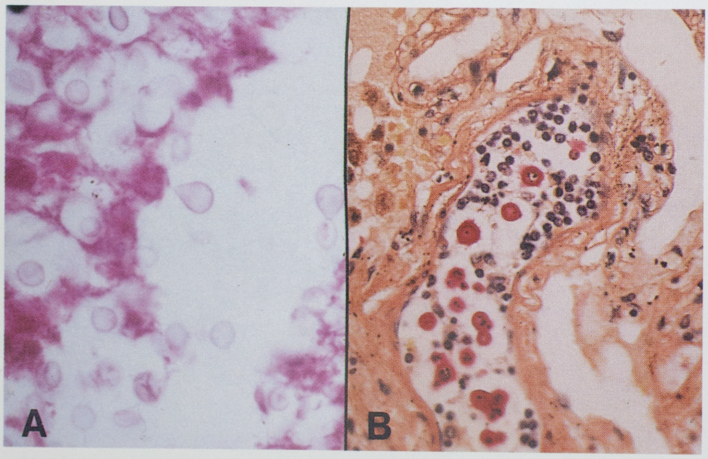
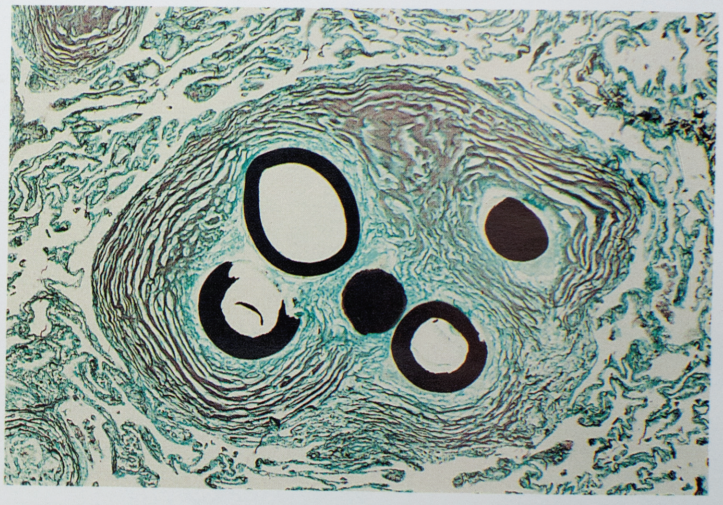
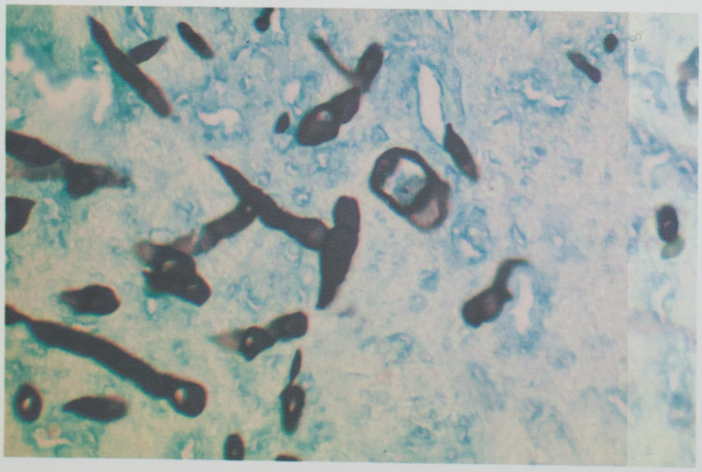


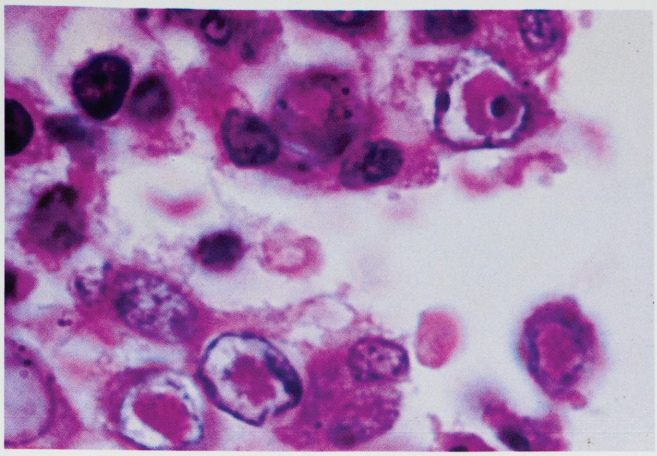
COLOR FIGURE 43-8. (**A**) Numerous yeast forms of *Cryptococcus neoformans* with narrow-necked budding in necrotic tissue are perfectly discernible. (H & E stain; high magnification.) (**B**) Confirmation of the diagnosis is made by brilliant mucicarmine staining in another patient with intravascular invasion by the fungus. (Mucicarmine stain; high magnification; contributed by P. Angritt, M.D., Washington, DC.)



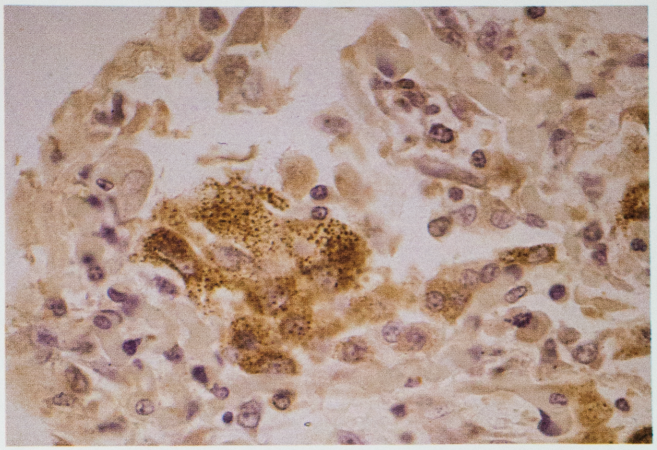
COLOR FIGURE 43-9. A lesion of adiaspiromycosis shows several adiaspores of *Chrysosporium* in granuloma of lung. The adiaspores are large and have thick, GMS-positive walls. (GMS stain; intermediate magnification.)



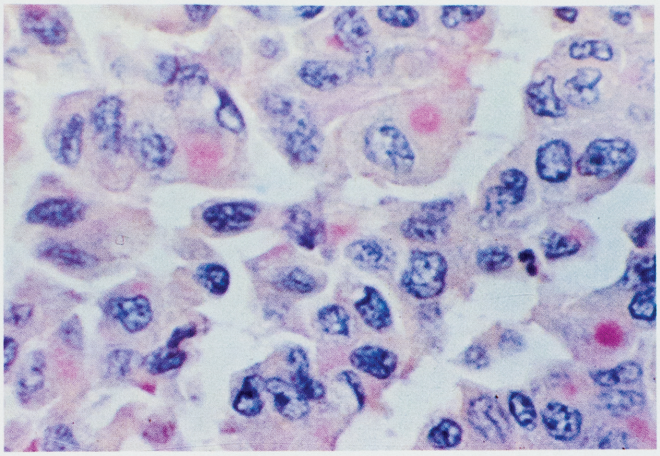
COLOR FIGURE 43-10. A pulmonary lesion of invasive phaeohyphomycosis caused by *Alternaria* sp. (GMS stain; intermediate magnification; contributed by the editor.)



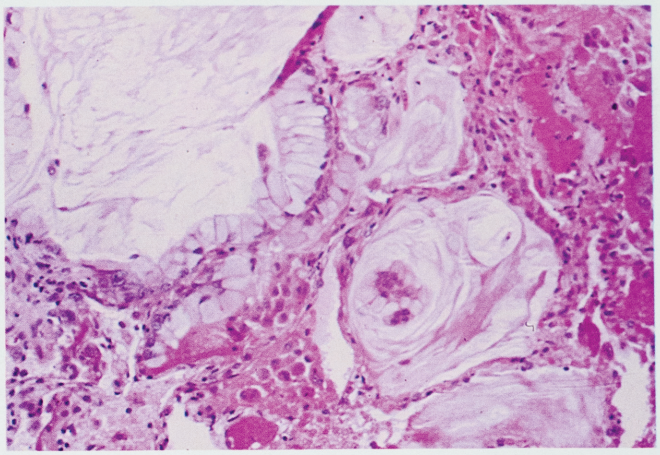
COLOR FIGURE 45-5. Pink intranuclear inclusions are characteristic of herpesvirus in a patient with pulmonary infection. (H & E stain; high magnification; contributed by the editor.)



COLOR FIGURE 45-6. *Mycoplasma fermentens* organisms, *incognitus* strain, are demonstrated in lung tissue. (Immunoperoxidase stain; high magnification.)

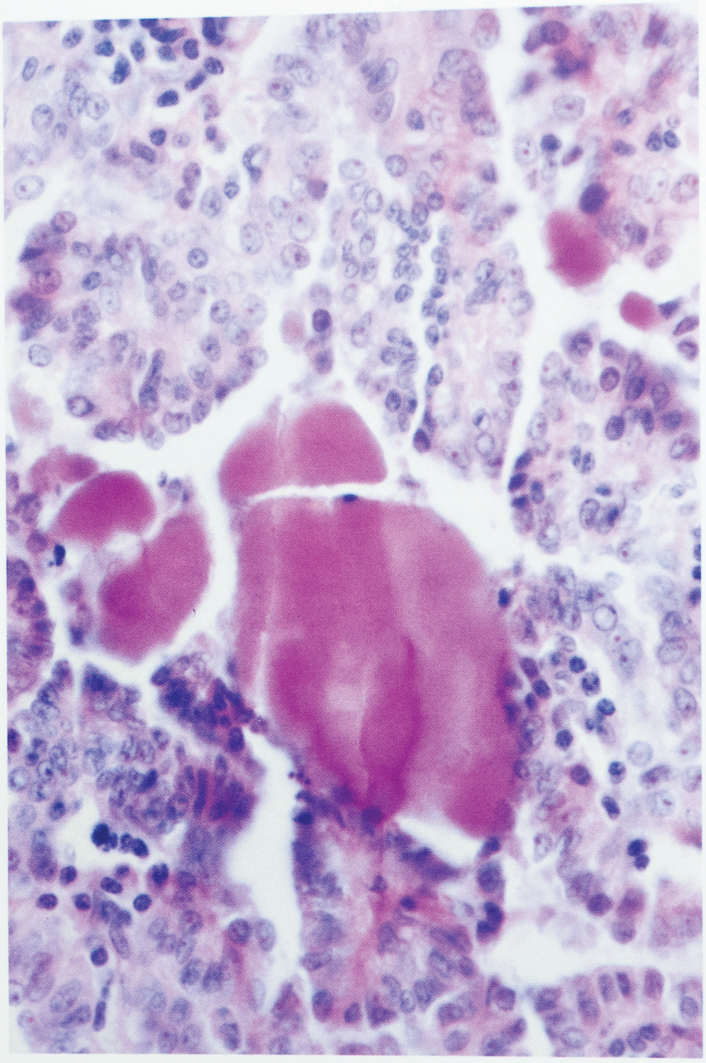


COLOR FIGURE 47-1. Poorly differentiated adenocarcinomas with intracellular mucin production were previously designated large cell undifferentiated carcinomas, but because of the mucin production, they are presently recognized as adenocarcinomas. (Mucicarmine stain; intermediate magnification.)

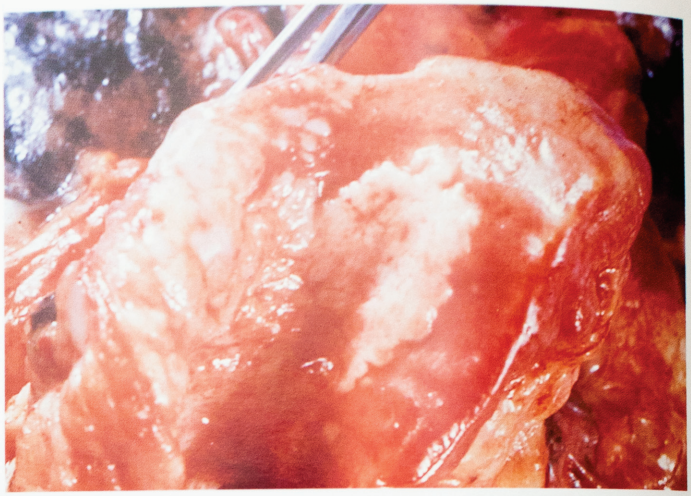


COLOR FIGURE 47-2. Histologically, a colloid carcinoma has large pools of mucin and relatively bland cells. (H & E stain; intermediate magnification.)

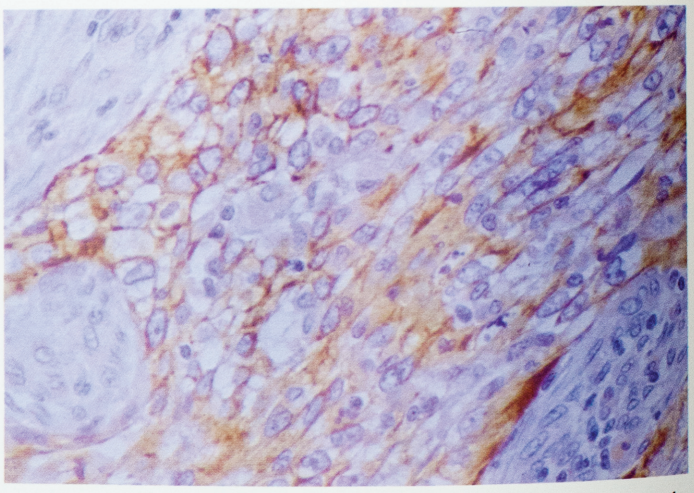
COLOR FIGURE 47-3. Dense alveolar infiltrate is present in a patient with bronchioloalveolar carcinoma composed of Clara cells.



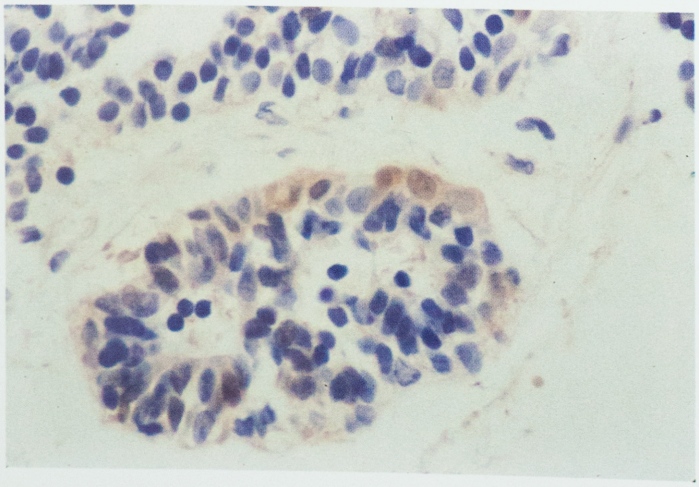
COLOR FIGURE 47-4. In this papillary Clara cell tumor, deposits of a colloidlike secretion stain positively with PAS-diastase. (Low magnification.)



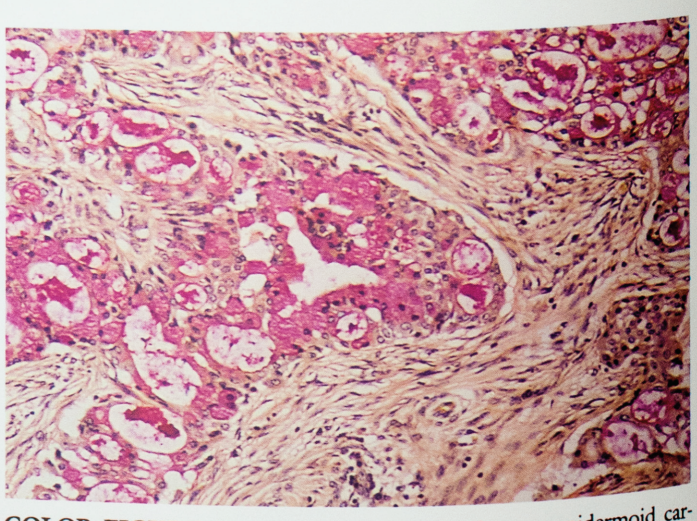
COLOR FIGURE 48-1. Bronchus with squamous cell carcinoma *in situ* presents as a broad leukoplakia patch extending several centimeters in a patient with squamous cell carcinoma at a distal location.



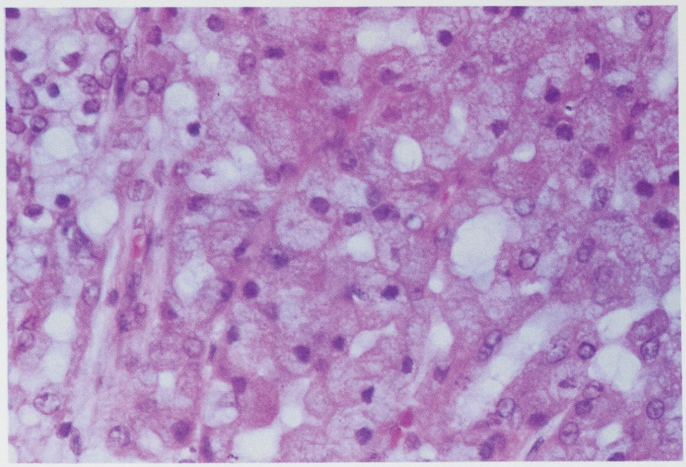
COLOR FIGURE 48-2. A squamous cell carcinoma with pseudosarcomatous features is positive for keratin by the immunoperoxidase technique (see Fig. 48-10). (Immunoperoxidase stain; intermediate magnification.)



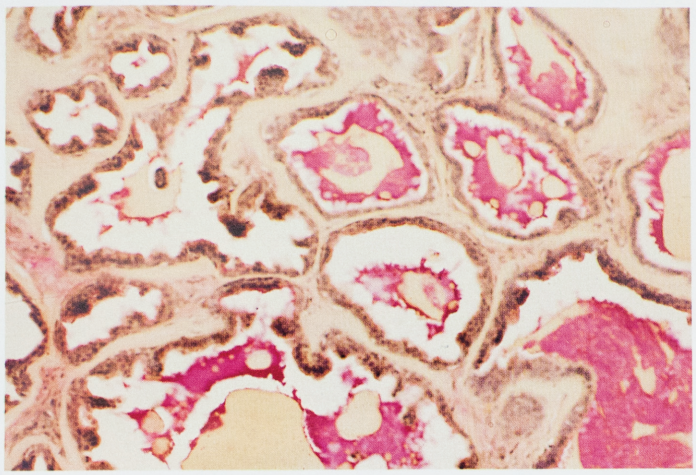
COLOR FIGURE 52-1. The myoepithelial cells of a pleomorphic adenoma exhibit immunoreactivity with antibodies to S-100 protein. (Intermediate magnification.)



COLOR FIGURE 52-2. Glands of low-grade mucoepidermoid carcinoma with mucin secretion. (Mucicarmine stain; low magnification.)

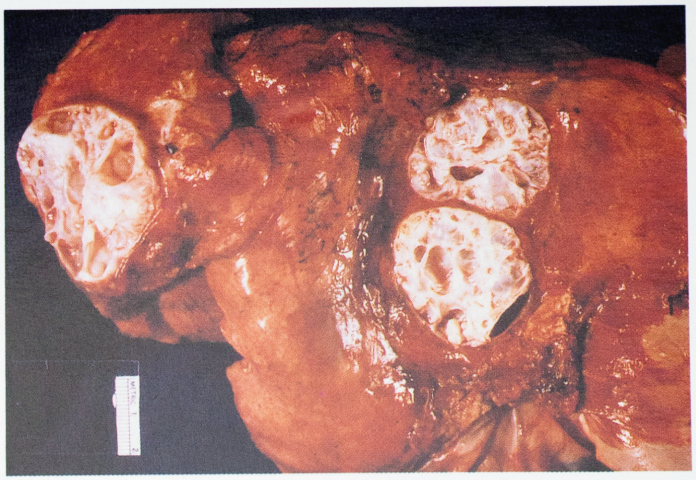


COLOR FIGURE 52-3. Acinic cell carcinoma of bronchial origin is composed of cuboidal cells with basophilic and clear cytoplasm. (H & E stain; low magnification.)

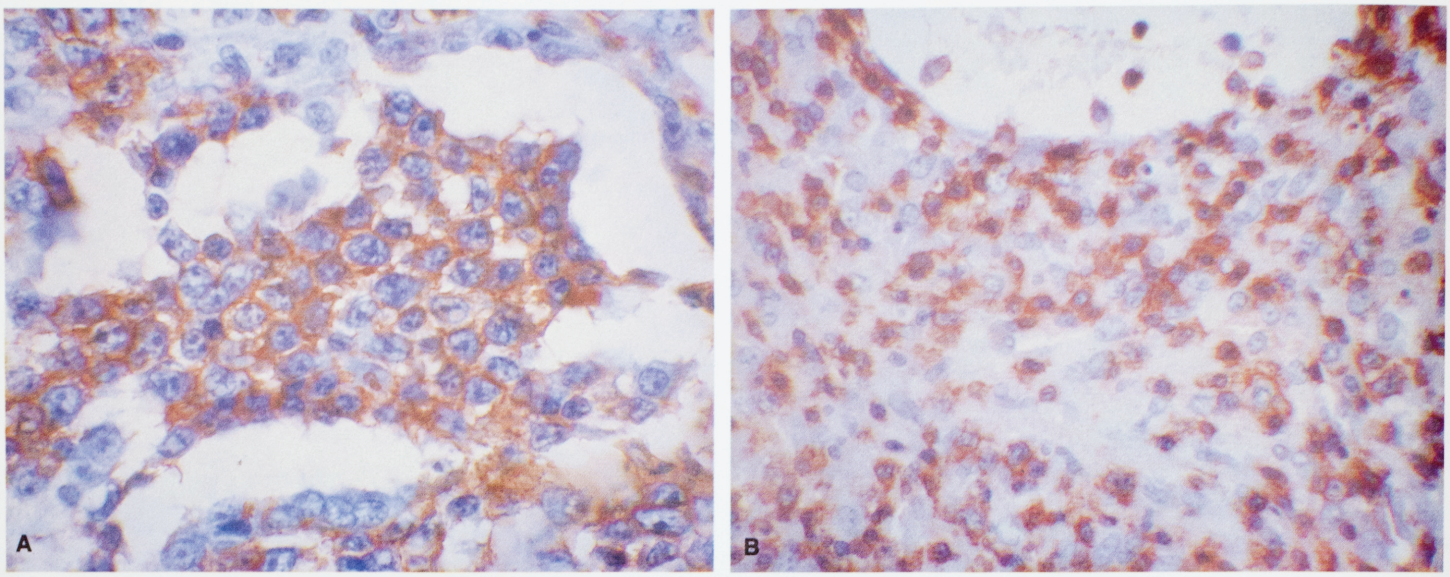


COLOR FIGURE 53-1. A mixed-type papilloma associated with mucous gland cystadenoma shows mucicarmine-positive material in the glandular spaces (see Fig. 53-3). (Mucicarmine stain; intermediate magnification.)

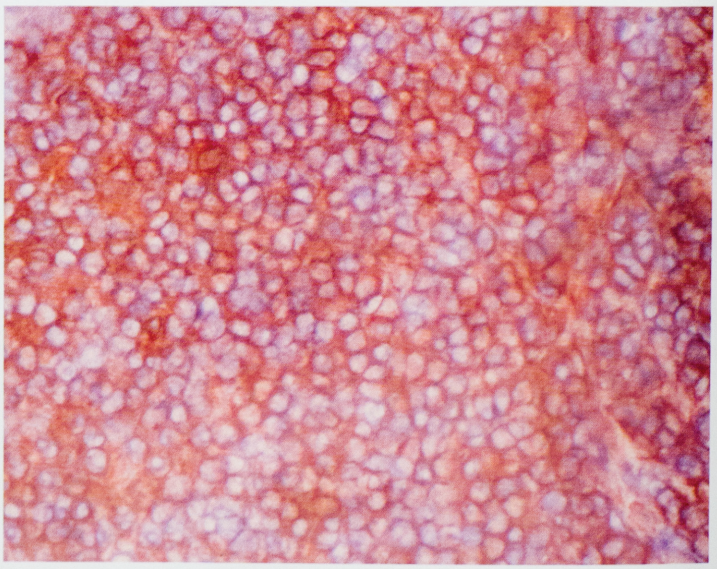
COLOR FIGURE 53-2. Gross appearance of papillary adenocarcinoma shows marked distension of bronchi; notice the striking papillarity of the lesion (see Fig. 53-5).



COLOR FIGURE 54-1. Two well-demarcated masses showing cystic structures and solid areas are seen in this metastatic mature teratoma.



COLOR FIGURE 55-1. (**A**) CD20-positive cells (*i.e.*, B cells) are present in large cell immunoblastic lymphoma of the lung. (Immunoperoxidase with hematoxylin counterstain in paraffin-embedded tissue; high magnification.) (**B**) Lymphomatoid granulomatosis of lung exhibits numerous CD43-positive cells (*i.e.*, T cells) in a vascular wall. (Immunoperoxidase with hematoxylin counterstain in paraffin-embedded tissue; high magnifications.)



COLOR FIGURE 55-2. In this B-cell lymphoma, neoplastic cells exhibit positivity for one light chain only. (Direct immunoperoxidase stain and hematoxylin counterstain in frozen tissue; high magnification.)

TABLE 54-2
Chest X-ray Features of Patients With Blastomas by Histologic Subtype

Chest X-ray Feature	WDFA[8] (n = 28)	Biphasic Blastoma[8] (n = 24)	Pleuropulmonary Blastoma[9] (n = 11)
Solitary lesion	96%	100%	Opacification
Average size (cm)	4.5	10.1	NA
Location			
Lung only	78%	96%	9%
Lung-mediastinum	12%	4%	45%
Mediastinum only	0%	0%	45%
Upper lobe-lower lobe	13/10	13/9	3/3
Right lung-left lung	11/12	13/10	10/1
Hilar-peripheral	6/14	3/8	NA
Adenopathy	7%	8%	NA
Pleural effusion	0%	46%	10%

NA, not available; WDFA, well-differentiated fetal adenocarcinoma.
Data from Koss M, Hochholzer L, O'Leary T. Pulmonary blastomas. Cancer 1991;67:2368 and Manivel JC, Priest JR, Watterson J, et al. Pleuropulmonary blastoma. The so-called pulmonary blastoma of childhood. Cancer 1988;62:1516.

mors.[8] Nakatani and colleagues have also suggested that there are morphologically anaplastic variants of WDFA that lack a periglandular myofibroblastic proliferation and that may be better classified as clear cell adenocarcinomas with associated poorer prognoses.[10] Some of the cases reported by Kodama and associates probably fall into this category.[6]

Pathology

Grossly, pulmonary blastomas are large, well-demarcated but unencapsulated solitary peripheral masses.[8] Pleuropulmonary blastomas are described as multilobated masses.[9] A polypoid intrabronchial component may be found in some cases of adult blastomas, but the tumors do not typically present as intrabronchial neoplasms. The cut surface is often bulging and white, tan, or brown, with areas of cystic breakdown and hemorrhage.

The epithelial component of pulmonary blastomas can have a variety of appearances. The characteristic features are branching tubules lined by stratified columnar cells with clear cytoplasm and relatively little nuclear hyperchromasia or pleomorphism (Fig. 54-2). The glands have an endometrioid appearance heightened by subnuclear and supranuclear cytoplasmic vacuoles within lining epithelial cells (Fig. 54-3). There can also be solid cords, ribbons, or nests of epithelial cells that show a basaloid pattern or contain minute rosettelike glands.[8] The clear appearance of the cytoplasm of the neoplastic glands is caused by abundant intracytoplasmic glycogen, which is demonstrated by periodic acid-Schiff stains. Small amounts of mucin frequently are seen within the glandular

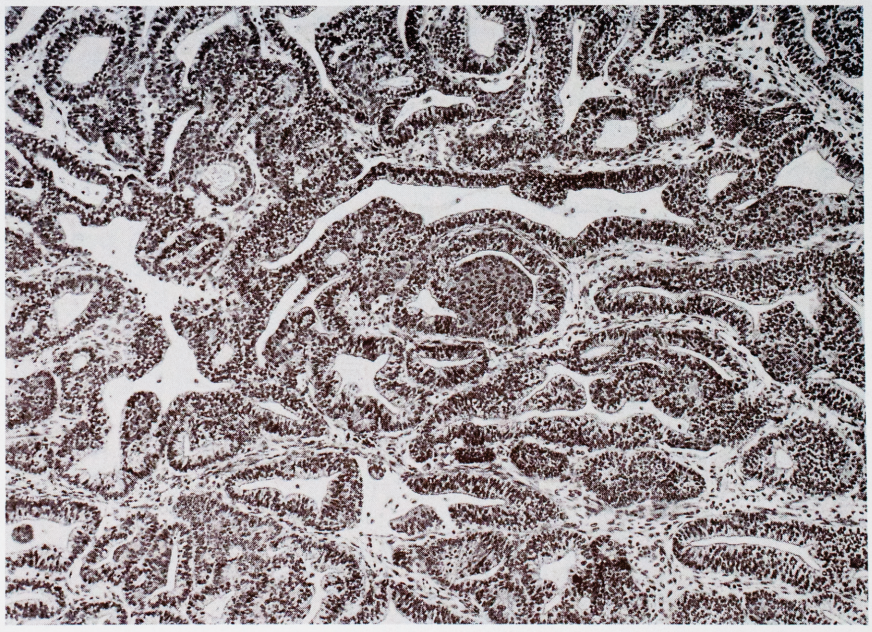


FIGURE 54-2. Microscopic view of a well-differentiated fetal adenocarcinoma variant of pulmonary blastoma shows branching tubules with a scant, benign stroma. (H & E stain; low magnification.)

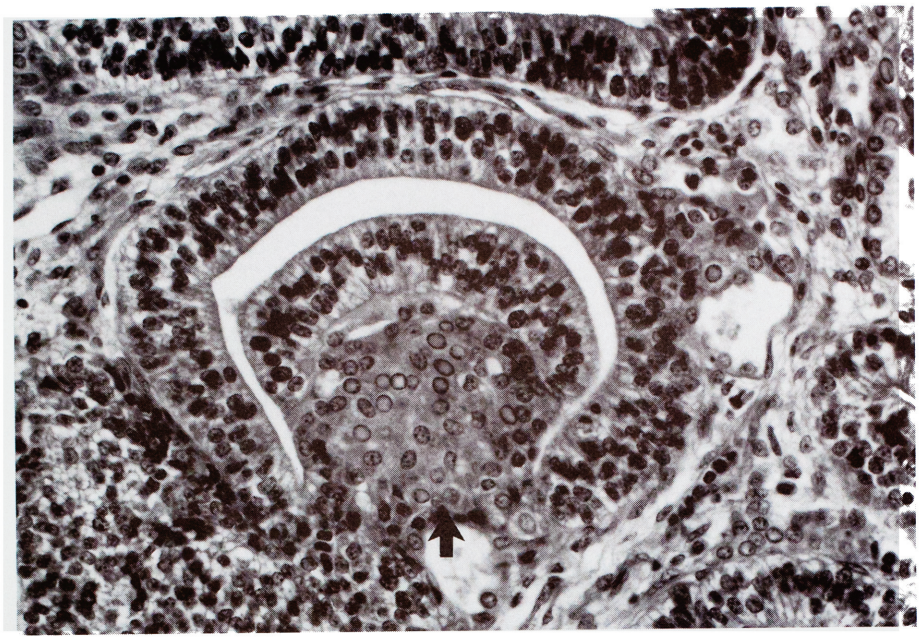


FIGURE 54-3. A well-differentiated fetal adenocarcinoma variant of pulmonary blastoma shows stratified epithelium, uniform, dark nuclei, and focally clear cytoplasm. Notice the morule (*arrow*) consisting of a solid nest of cells with optically clear nuclei beneath the glandular epithelium. (H & E stain; intermediate magnification.)

lumens, but intracellular mucin is unusual. Solid cell balls (*i.e.*, morules) with a vaguely squamous appearance and with optically clear nuclei can be seen at the base of well-ordered glands (see Fig. 54-3). Nakatani and associates localized surfactant apoprotein within morules and reported ultrastructural evidence of type 2 cell differentiation in them.[10]

In WDFA, the stroma is typically scant, mature, and consists of spindled myofibroblastic cells (see Fig. 54-3). Nakatani and colleagues have argued that these stromal cells are a component of the tumor, despite their benign appearance.[10]

The mesenchyme of biphasic blastomas typically consists of an embryonic or primitive stroma with small oval and spindled cells in a myxoid matrix (Figs. 54-4 and 54-5). An adult-type sarcoma, most commonly spindle cell sarcoma, can be found, including foci of immature striated muscle, cartilage, bone, and fat (Fig. 54-6).[8]

Argyrophilic granules can sometimes be seen within scattered glandular cells of blastomas by light microscopy. Immunohistochemical studies show chromogranin and neuron-specific enolase in glandular epithelial cells and often in morules in 64% to 72% of these cases (Fig. 54-7).[8] More detailed immunohistochemical studies show small numbers of cells containing calcitonin, gastrin-releasing peptide, leucine enkephalin, methionine enkephalin, somatostatin, or serotonin.[6,14] Cytokeratin and carcinoembryonic antigen (CEA) are found in the epithelium of blastomas, and surfactant apoprotein is present in tubular epithelial cells and particularly in morules.[10,15] Vimentin and muscle-specific actin and less frequently desmin are found in the stromal cells of WDFA and biphasic blastomas. Myoglobin and S-100 can be seen if there is striated muscle and cartilage differentiation, respectively. One study reported specific staining for mesenchymal markers in the surface epithelium of biphasic blastomas and reactivity to keratin in the stroma.[15]

The histogenesis of blastomas is unclear. Because the bron-

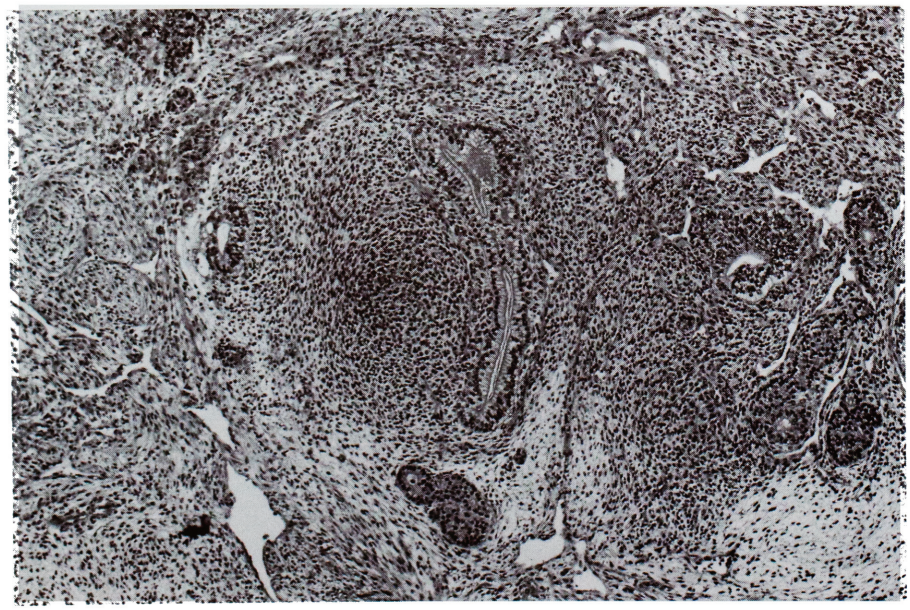


FIGURE 54-4. In a biphasic variant of pulmonary blastoma, the centrally placed gland is lined by cells with clear cytoplasm and surrounded by condensed, primitive stroma. (H & E stain; low magnification.)

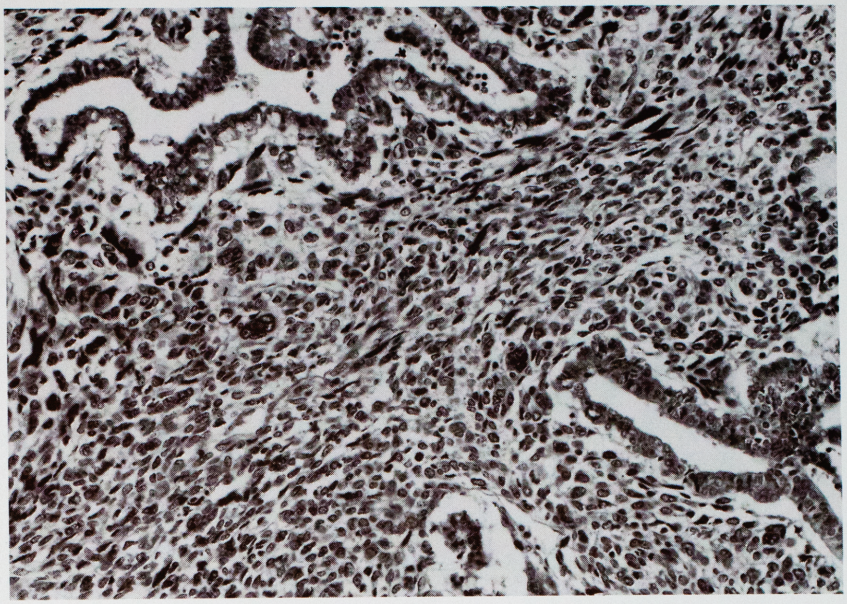


FIGURE 54-5. In this embryonic stroma in a biphasic blastoma, giant tumor cells are seen with oval and spindle stromal cells. (H & E stain; intermediate magnification.)

chial structures of the lung derive from endoderm, origin in a primitive mesenchymal blastema seems questionable. Two cases of combined yolk sac tumor and blastoma have been found, raising the possibility of an origin in a pluripotential stem cell.[16] It seems likely that biphasic and purely epithelial tumors are probably not histogenetically distinct, because composite forms of these tumors occur.

Pulmonary Blastomas of Childhood

Pulmonary blastomas in children, particularly those younger than 12 years of age, often present a clinical and pathologic picture distinct from those seen in adults. Although the adult type of pulmonary blastoma can rarely occur in older children, most childhood cases are lesions ranging from thin-walled cysts with foci of rhabdomyosarcoma to solid masses of blastemal and mesenchymal sarcomatous elements involving the pleura and lung. The latter form was called pleuropulmonary blastoma by Manivel and associates (see Chap. 75).[9] At one end of the spectrum, children 1 to 4 years of age are found to have cystic lung lesions on routine chest x-ray films or present with cough, fever, shortness of breath, or rarely with severe dyspnea secondary to pneumothorax (Fig. 54-8*A*).[17] The cysts are single or multiloculated, involving one or more lobes, and display focal thickening of their walls or discrete 1-to 2-cm nodules (Fig. 54-8*B*). The walls, lined by alveolar or ciliated columnar epithelial cells, are composed of loose

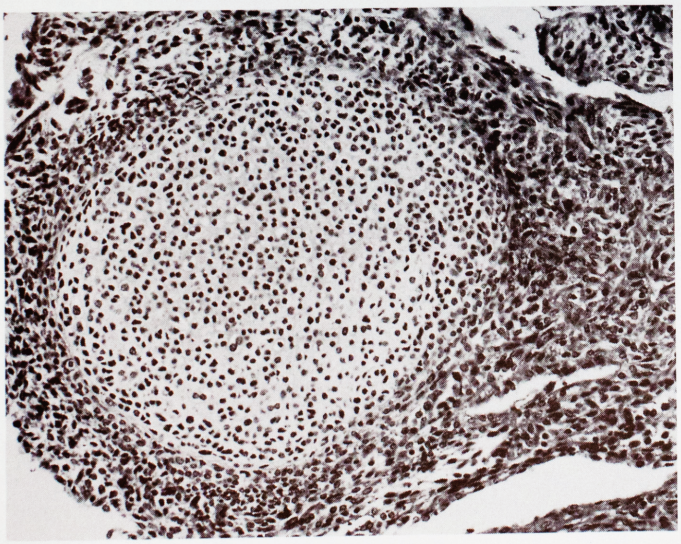


FIGURE 54-6. In this biphasic variant of pulmonary blastoma, an island of immature cartilage is seen within the stroma. (H & E stain; low magnification.)

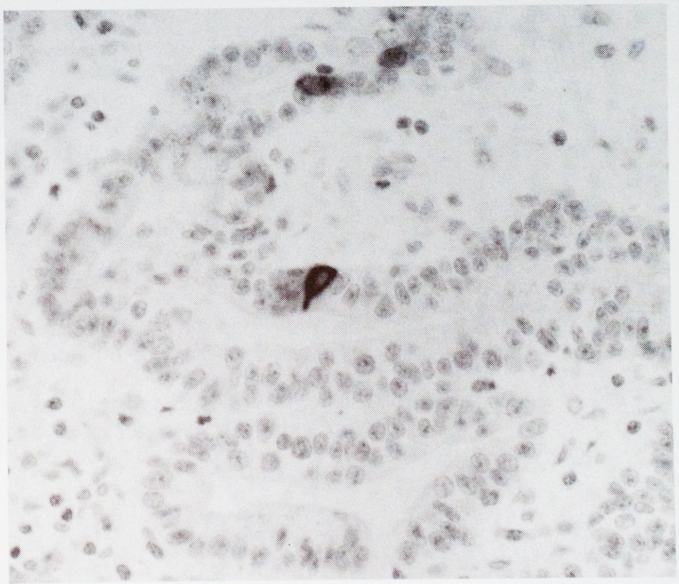


FIGURE 54-7. Scattered neuroendocrine cells line the glands of this well-differentiated fetal adenocarcinoma. (Immunoperoxidase stain for chromogranin; intermediate magnification.)

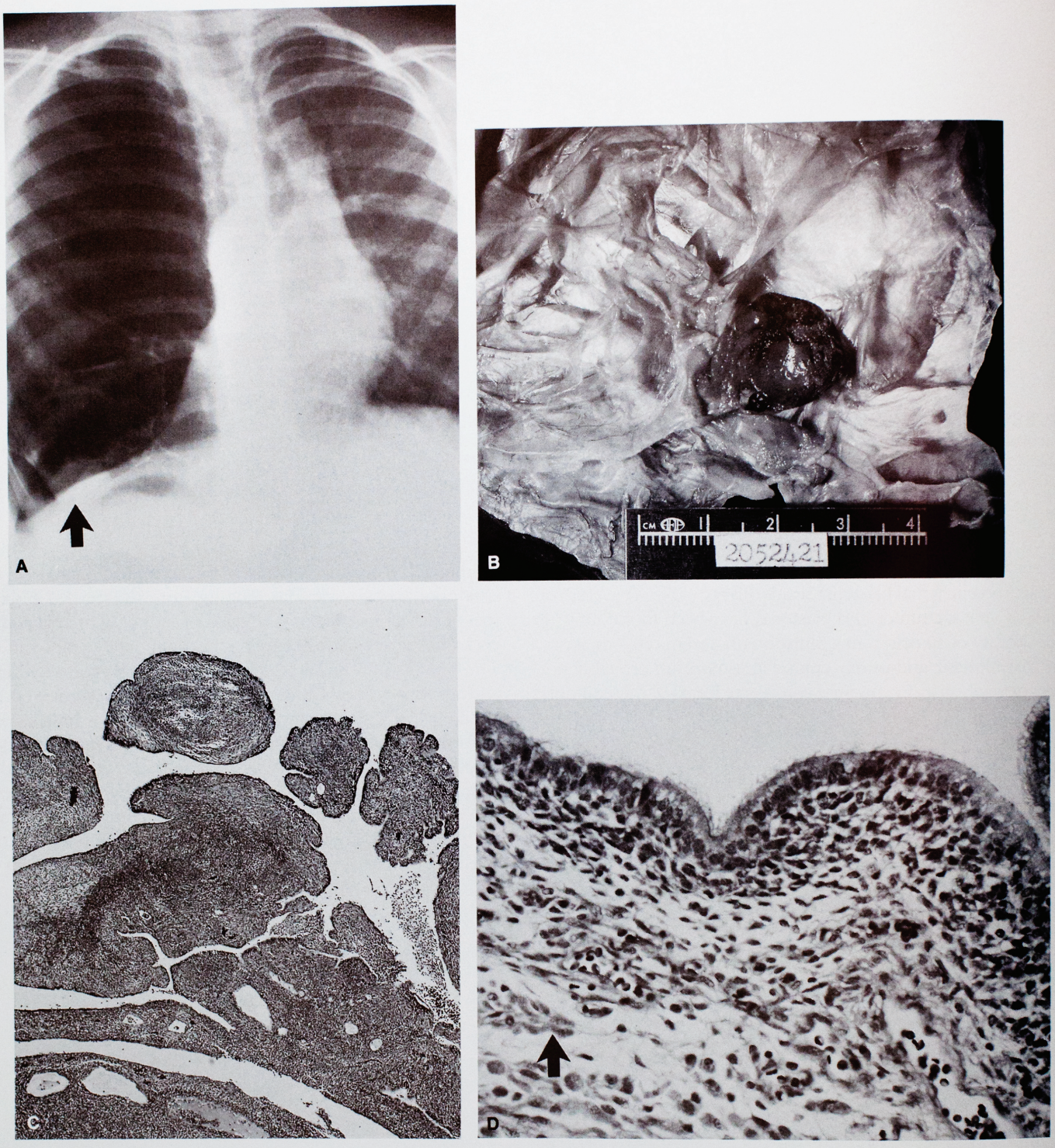


FIGURE 54-8. This pulmonary blastoma is the childhood, thin-walled cyst type. (**A**) Multiple thin-walled cysts and a solid component (*arrow*) are present in the right lung of a 2-year-old boy with mild shortness of breath. Notice the shifted mediastinum. (**B**) A 2-cm pedunculated mass is attached to the wall of a large, multiloculated cyst. (**A, B:** From Stocker JT. The respiratory tract. In: Stocker JT, Dehner LP, eds. Pediatric pathology. vol. 1. Philadelphia: JB Lippincott, 1992:564.) (**C**) The solid component is composed of blastemal cells and loose mesenchymal cells and is covered by cuboidal-to-columnar epithelium. (H & E stain; low magnification.) (**D**) Beneath the ciliated columnar epithelium of a thin-walled cyst is a cambium layer of rhabdomyoblasts and a deeper layer of strap cells (*arrow*). (H & E stain; intermediate magnification.)

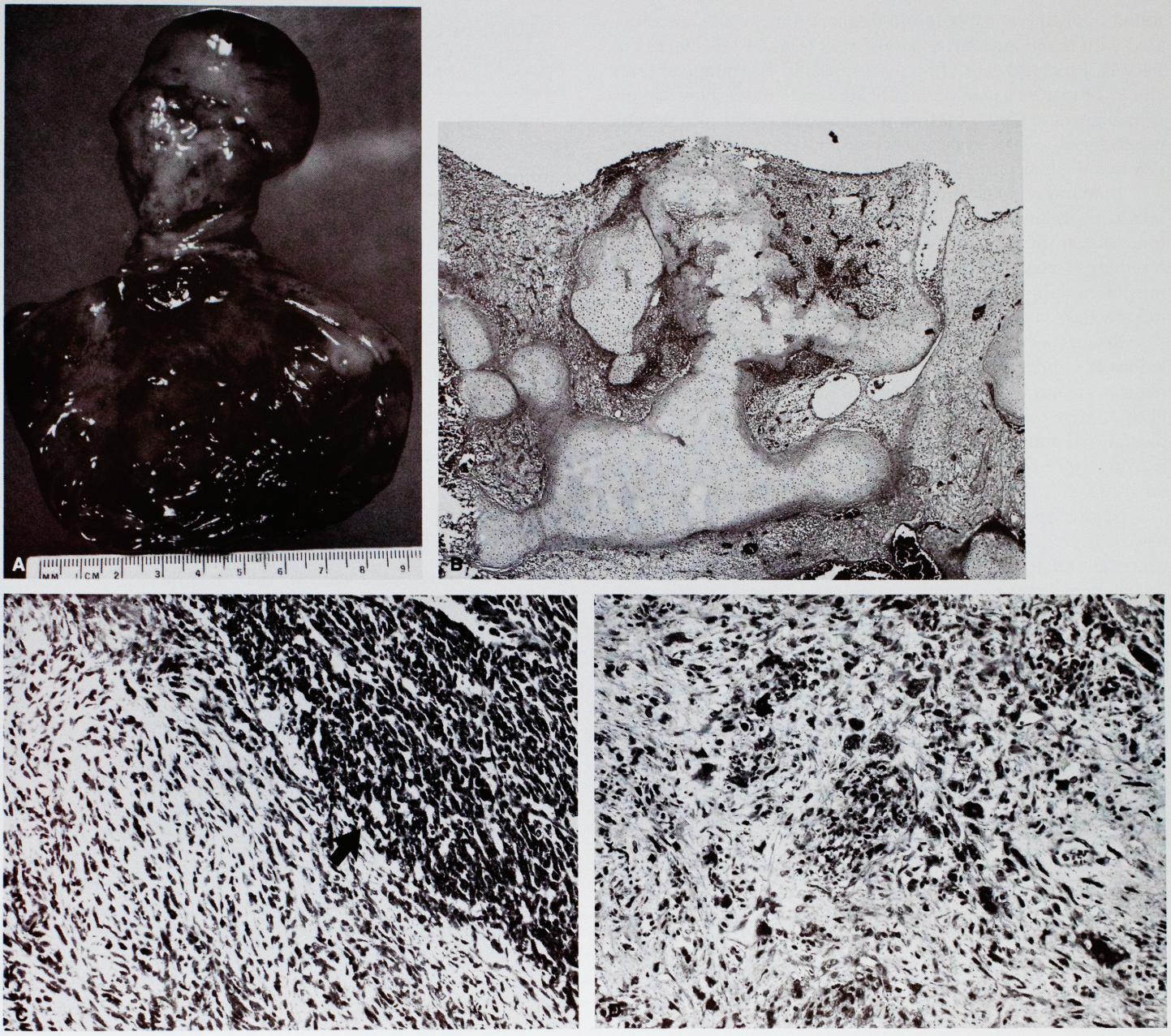


FIGURE 54-9. This pulmonary blastoma is the childhood pleuropulmonary blastoma type. (**A**) This hemorrhagic and focally necrotic solid mass was resected from the pleura of a 1-year-old boy. (From Stocker JT. The respiratory tract. In: Stocker JT, Dehner LP, eds. Pediatric pathology. Vol. 1. Philadelphia: JB Lippincott, 1992:562.) (**B**) The lesion is composed of masses of immature cartilage and mesenchymal and blastemal components. (H & E stain; low magnification.) (**C**) Blastemal cells (*arrow*) with hyperchromatic nuclei and numerous mitoses lie adjacent to rhabdomyoblasts and strap cells, representing an area of rhabdomyosarcoma. (H & E stain; low magnification; from Stocker JT. The respiratory tract. In: Stocker JT, Dehner LP, eds. Pediatric pathology. Vol. 1. Philadelphia: JB Lippincott, 1992:562.) (**D**) Bizarre, multinucleated giant cells are surrounded by a loose mesenchymal stroma. (H & E stain; intermediate magnification.)

or dense fibrovascular tissue that has bands of subepithelial rhabdomyoblasts in a typical cambium layer (Fig. 54-8*C*, *D*). Differentiating muscle fibers with prominent cross striations are often present beneath the immature cells of the upper cambium layer (Fig. 54-8*D*). The solid or nodular elements are composed of blastemal cells with immature and occasionally malignant mesenchymal tissue. The cysts, although superficially resembling congenital cystic adenomatoid malformation, type I, lack a number of features, including mucogenic cells, polypoid epithelium, mature cartilage plates, and fibromuscular walls, and they may represent a cystic change in a pulmonary blastoma rather than a malignant transformation of a congenital cyst.[18]

At the other end of the spectrum are predominantly solid lesions that may be mediastinal, pleural-based, or intrapulmonary. Manivel and colleagues and others have described multilobulated masses in children 30 months to 11 years of age who presented with nonproductive cough, fever, chest pain, or a combination of symptoms lasting days or weeks (see Tables 54-1 and 54-2).[9,19–21] The solid to cystic lesions were 8 to 23 cm in diameter and weighed up to 1100 g (Fig. 54-9*A*). Blastemal elements are consistently

found but display anaplasia and frequent mitoses and are associated with rhabdomyosarcomatous areas (Fig. 54-9*B–D;* see Fig. 54-9*A*). Epithelial cells, if present, appear to be entrapped bronchioles or mature squamous epithelium and do not show features of malignancy. Large, bizarre, multinucleated and pleomorphic mesenchymal cells are seen in most cases, and sarcomatous cartilage is detected in about 25% of the specimens (see Fig. 54-9*B, D*).

Immunoreactivity in the blastemal and sarcomatous areas is seen with α_1-antitrypsin, α_1-antichymotrypsin, desmin, myoglobin, neuron-specific enolase, S-100 protein, and vimentin. No reactivity is seen in these areas for CEA, α-fetoprotein, epithelial membrane antigen (EMA), or cytokeratin, although the latter two may be seen in the benign components.[9,19]

Recurrences and metastases may develop in patients with lesions at either end of the spectrum, although the younger patients with intrapulmonary, thin-walled cystic lesions are more likely to have surgically resectable tumors than those with solid, pleural, and pulmonary-based lesions. The long-term survival rate is 25% to 50% for children with solid lesions and more than 50% for those with thin-walled cystic lesions.

Neither thin-walled cystic types nor pleuropulmonary blastomas of a predominantly solid character are likely to be histogenetically related to the other types of pulmonary blastoma. This is suggested by the extrapulmonary (*e.g.*, pleural, mediastinal) location of many of the pleuropulmonary tumors, their occurrence in a completely different age group, and the absence of a carcinomatous component.

PULMONARY CARCINOSARCOMA

The history of pulmonary carcinosarcoma in the medical literature antedates that of pulmonary blastoma, and it is quite as confusing. Kika apparently described the first case in 1908.[22] In 1938, Saphir and Vass reviewed previously reported cases and repudiated them, suggesting that many were carcinomas; this problem has returned to plague modern students of the disease.[23] Bergmann and associates reported two new cases in 1951, resurrecting the concept.[24] In 1961, Moore reported a case that had a differentiated malignant stroma and proposed a bipartite classification of the tumor based on its location in the lung.[25] Modern consideration of biphasic pulmonary tumors has focused on the application of immunostains to them.[26] The result has been the use of terms such as pulmonary carcinomas with sarcomatoid elements to describe these tumors.

According to the 1981 World Health Organization (WHO) definition, pulmonary carcinosarcomas are malignant tumors consisting of an admixture of malignant epithelial and mesenchymal elements.[1] Unlike pulmonary blastomas, the neoplastic components are of the type ordinarily seen in malignancies of adults: well-defined carcinomas and sarcomas like those seen in the soft tissues. The WHO study group noticed the difficulty of separating carcinosarcomas from spindle cell carcinomas of lung, which are relatively more common tumors. They suggested that carcinosarcoma must show differentiation of the mesenchymal component into specific tissues, such as neoplastic bone, cartilage, and striated muscle.[1] A subsequent definition recognizes carcinosarcoma as a biphasic tumor by light microscopy, but support for the presence of definitive sarcomatous differentiation can also be given by immunohistochemical staining for specific mesenchymal markers such as myoglobin and S-100.[27]

TABLE 54-3
Pulmonary Carcinomas With Sarcomalike Features Determined by Light Microscopy

Investigation	Number of Patients	Patients With Definite Sarcomatous Differentiation (%)
Davis et al.[31]	16	19
Stackhouse et al.[34]	9	33
Humphrey et al.[27]	8	13
Ishida et al.[28]	8	25

An important corollary to these definitions is that evaluating the reports of carcinosarcoma is treacherous, because many of the tumors are biphasic tumors without definitive sarcomatous differentiation (Table 54-3); some of them could be spindle cell carcinomas. Investigators have used "pulmonary carcinomas with sarcoma-like or sarcomatoid element" to describe a spectrum of lesions: carcinosarcomas showing definitive mesenchymal differentiation, possible or probable spindle cell carcinomas that fail to show definite mesenchymal or epithelial differentiation of the malignant spindle cell component, and pleomorphic (*i.e.*, spindle cell) carcinomas that show immunohistochemical evidence of epithelial markers in the spindle cells.[27,28]

Clinical Features

Approximately 48 pulmonary carcinosarcomas were reported in the world literature by 1985, and 76 cases were reported by 1989.[24,30] They constitute between 0.2% and 0.6% of resected lung cancers in United States and Japanese series.[28,31] The lung is the fourth most common site for these unusual neoplasms.[32]

Men are affected 5 to 11 times as frequently as women.[29,31,33,34] Most patients are in their sixth decade or, if one uses the strict WHO definition of the tumor, seventh and eighth decades of life (Fig. 54-10).[31] Cabarcos observed that 85% of these patients were

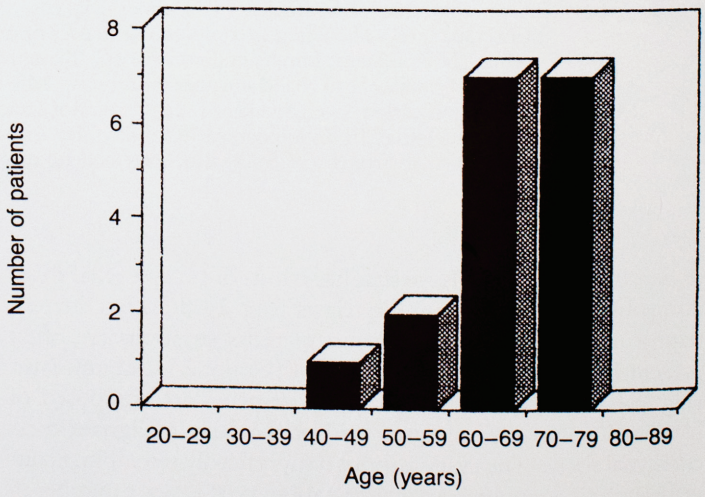


FIGURE 54-10. Age distribution by decade of patients with pulmonary carcinosarcomas.

between 50 and 80 years of age at diagnosis.[29] There is a strong association with heavy smoking.[31]

The chest x-ray film usually shows a well-demarcated, lobulated solitary mass, most frequently in the upper lobes (Fig. 54-11). For example, 10 (59%) of 17 patients reported by Davis and colleagues from the Mayo clinic, 69% of the 48 literature cases reviewed by Cabarcos and associates, and 16 (69%) of 23 endobronchial carcinosarcomas reviewed by Ludwigsen occurred in the upper lobes.[29,31,33] A single case of extensive pleural involvement was reported.[35]

The symptoms that patients develop are typical of pulmonary neoplasms: cough followed by chest pain, dyspnea, fever, and hemoptysis.[29] The symptoms are diagnostically nonspecific.

Bronchoscopy yields a positive diagnosis for malignancy in 40% to 66% of patients in which it is attempted.[31,34] Transthoracic fine needle aspiration can be used in the diagnosis of more peripheral tumors. At least four cases have been diagnosed by this technique.[29,31] However, bronchoscopy and fine needle aspiration are infrequently accurate because they produce fragments of tissue that are too small and too necrotic to show both components of the neoplasm.

Surgical resection is both diagnostic and the initial treatment in many cases, supplemented by radiation therapy. Ludwigsen, in in many cases, supplemented by radiation therapy. Ludwigsen, in reporting a series of endobronchial tumors, observed that 91% of the patients had lesions that could be resected with a potential for cure, a frequency that is twice as high as that seen for squamous cell carcinomas of lung.[31,33] The most common operation is pneumonectomy, followed by lobectomy. The clinical symptoms, chest x-ray film appearance, and possible evolution of the clinical course reflect the location of tumor in lung.

Moore was the first to suggest that carcinosarcomas could be divided into two clinicopathologic groups on the basis of the tumor's location in the lung: a solid parenchymal type and a central or endobronchial lesion.[25] The solid parenchymal type was more frequent (62% of cases) and typically presented as a peripheral, often large mass in lung. It was usually asymptomatic in the early stages; it could later invade mediastinum, pleura, and chest wall, producing chest pain; it metastasized early; and it had a poor prognosis. Central or endobronchial lesions were often pedunculated with limited extension into the lung; frequently presented with symptoms such as wheezing, dyspnea, and hemoptysis due to an obstructing airway tumor; and had infrequent metastases and a relatively good prognosis. Subsequent studies of small groups of patients led to a dispute about the value of this bipartite schema, particularly regarding the relation between location and prognosis. For example, endobronchial tumors are reported to have a more favorable prognosis by some researchers, but others noticed that some patients with endobronchial lesions have no better outcome than others.[28,31,32,36] Davis and associates suggested that the stage of the tumor should be explored as an alternative means of establishing prognosis.[31]

Although there is still uncertainty about the factors determining prognosis, there is general agreement that the outcome of carcinosarcomas of lung is poor despite surgery, radiation therapy, and chemotherapy.[31] A variety of sites of recurrence can occur, most commonly lung, but also lymph nodes, chest wall, spinal cord, adrenals, and brain. The average postoperative survival of patients with pulmonary carcinosarcoma is 9 months, and fewer than 10% of patients survive 2 years.[37] Cabarcos, in reviewing published reports, observed that only 7 (27%) of 26 patients survived more than 6 months.[29]

Pathology

Carcinosarcomas typically present as gray-white masses with red-brown areas of hemorrhage and yellow zones of necrosis. They are well-circumscribed, single peripheral masses or, in about 25% of patients, central tumors that are largely or focally endobronchial and polypoid (Fig. 54-12).[31,33] The tumors are between 1.5 and 15 cm; 43% are 2 to 6 cm in their maximal diameter. The mean diameter is 6 to 6.9 cm in different studies.[28,31] Microscopically, they have a biphasic appearance (Fig. 54-13). The demarcation between the microscopic phases may be sharp or focally ill defined. Evaluation of the older published reports shows that the most

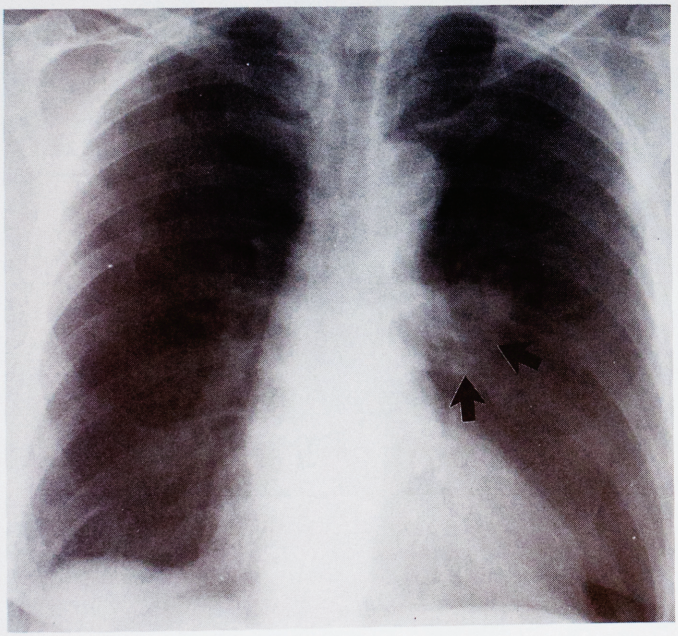


FIGURE 54-11. Posteroanterior chest x-ray film of a patient with carcinosarcoma of the lung shows a well-marginated mass (*arrows*) in the medial aspect of the left upper lobe. Postbiopsy pneumothorax is also seen (*left*).

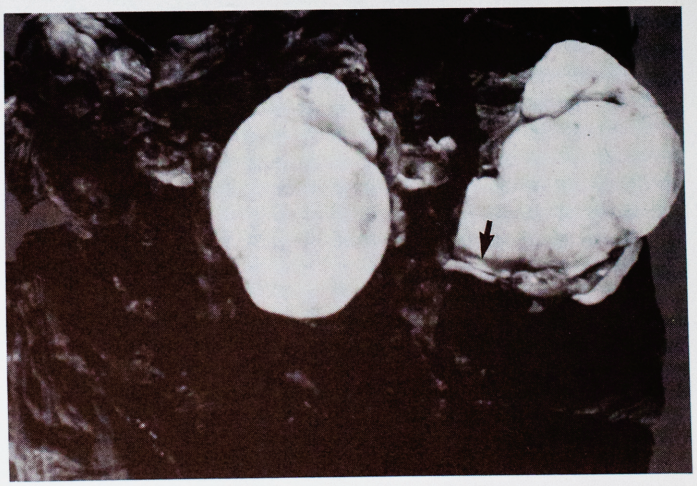


FIGURE 54-12. This bisected tumor specimen was taken from the patient in Figure 54-11. A lobulated mass fills the bronchus and extends into the adjacent lung tissue. Notice the bronchial cartilage (*arrow*).

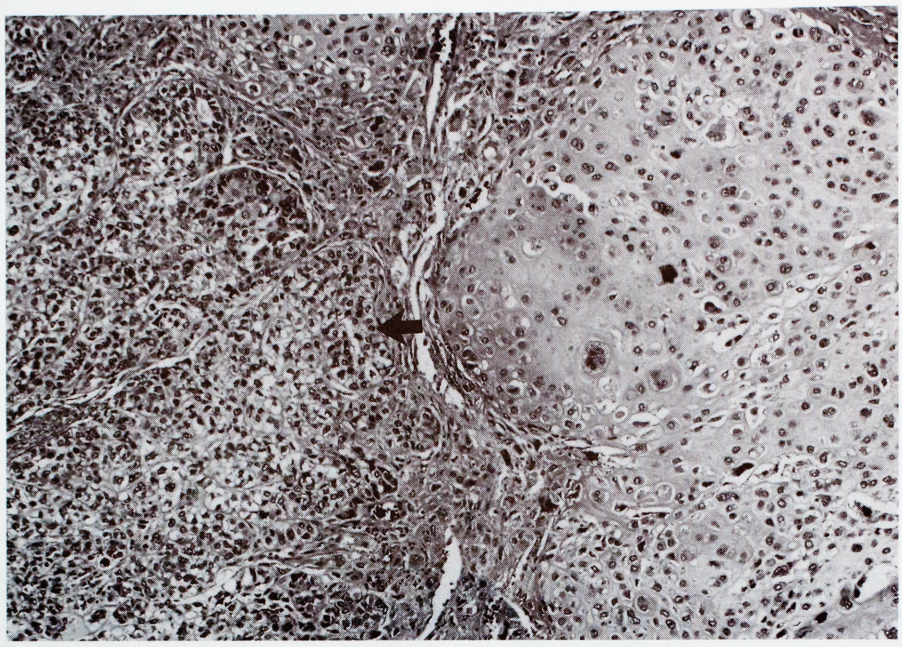


FIGURE 54-13. This carcinosarcoma of the lung, showing definitive sarcomatous differentiation, has a typical biphasic appearance. Chondrosarcoma lies contiguous to squamous cell carcinoma (*arrow*). (H & E stain; low magnification.)

frequently encountered types of carcinoma and sarcoma are squamous cell carcinoma and fibrosarcoma, respectively. Differentiated sarcomas include osteosarcoma, chondrosarcoma, and rarely rhabdomyosarcoma (Fig. 54-14).[25,35]

On the basis of more recent studies using light, electron, and immunohistochemical microscopy, it appears that the tumors can be divided into three groups according to the differentiation in the spindle cell component: carcinosarcomas that show distinct sarcomatous differentiation (*e.g.*, muscle, bone, cartilage) by light microscopy or by ancillary studies; possible or probable spindle cell carcinomas showing vimentin-positive, keratin-negative spindle cells, which show no other evidence of sarcomatous differentiation; and spindle cell carcinoma, in which the spindle cells are keratin positive and presumably have an epithelial phenotype.[27,28,38,39] The histologic features of these tumors are compared in Table 54-4. For carcinosarcomas, the most frequent epithelial component is squamous cell carcinoma, and the most common mesenchymal components are osteosarcoma or chondrosarcoma. It may appear that the spectrum of epithelial phenotypes in this subgroup is relatively restricted, but it is possible to find other epithelial phenotypes. For example, there can be carcinosarcomas consisting of salivary gland–like epithelium, adenosquamous carcinoma, and malignant myoepithelial stroma or of adenocarcinoma and rhabdomyosarcoma.

Possible spindle cell carcinomas appear to show a greater range of epithelial differentiation than definitive carcinosarcomas (see Table 54-4). Adenocarcinomas are more common in these tumors, but undifferentiated large cell carcinomas, adenosquamous carcinoma, and, in one unusual case, small cell carcinoma have been reported. Mixtures of more than one type of carcinoma can be found.[31] However, these neoplasms show a more restricted range of spindle cell patterns: fascicles suggestive of fibrosarcoma

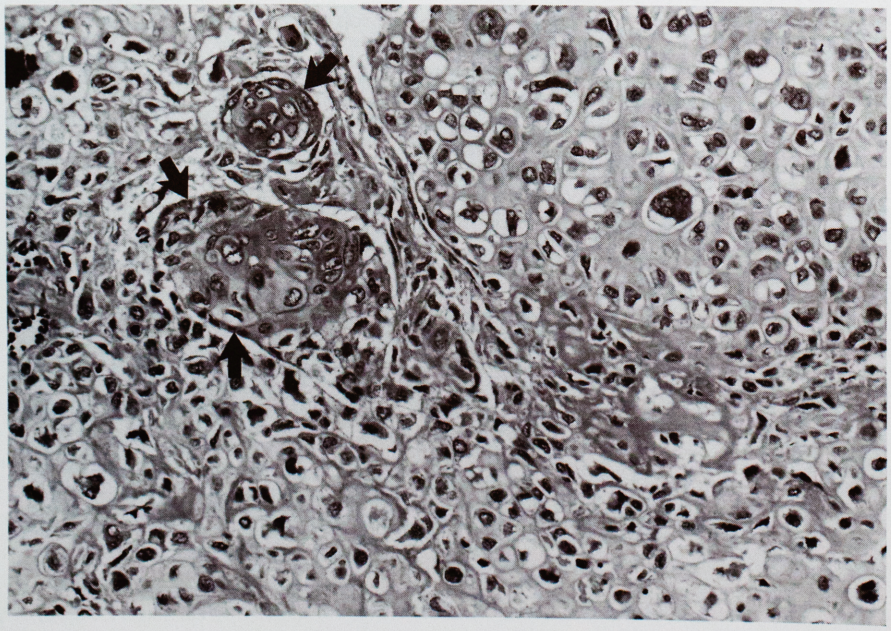


FIGURE 54-14. The microscopic view of the carcinosarcoma shown in Figure 54-13 shows islands of squamous cell carcinoma (*arrows*) lying next to large masses of malignant cartilage. (H & E stain; intermediate magnification.)

TABLE 54-4
Histologic Findings In Pulmonary Carcinosarcomas

Cell Type	CS	PPCA	Pleo CA (AFIP)	Lit
EPITHELIAL				
Squamous	8	3	7	8
Adenocarcinoma	1	5	20	4
Large cell	0	0	19	5
Adenosquamous	0	0	0	2
STROMAL				
Fibrosarcoma	0	7	0	2
Osteosarcoma	5	0	0	0
Chondrosarcoma	4	0	0	0
Rhabdomyosarcoma	3	0	0	0

*AFIP, unpublished AFIP series; CS, definitive carcinosarcoma; Lit, literature series; PPCA, probable or pleomorphic carcinoma; Pleo CA, pleomorphic (*i.e., *spindle cell) carcinoma.*
Data from references 25, 27, 28, 31, 34, 38, 39, and 58.

TABLE 54-5
Outcome of Selected Cases of Pulmonary Carcinomas With a Sarcomalike Component

Diagnosis	Number of Patients Alive/Dead	Median Follow-Up (mo)
Carcinosarcoma*	4/4	22
Possible spindle cell†	0/7	9
Spindle cell carcinoma	4/16	2

** Tumors with definitive mesenchymal differentiation (*e.g., *bone, cartilage, muscle).*
† Biphasic tumors showing no evidence of epithelial immunophenotype in the spindle cell component but lacking definitive mesenchymal differentiation.
Data from references 24, 25, 27, 28, 31, 38, 39, and 58.

or a storiform pattern resembling that seen in malignant fibrous histiocytoma.

This schema seems reasonably simple, but it is important to emphasize that reliance on keratin immunostains alone as the distinguishing marker can produce problems. In one study, only 9 of 12 sarcomatoid carcinomas of lung were keratin positive; the remaining three keratin-negative cases stained with antibody to EMA.[38] There are also reports in which the epithelial component of carcinosarcoma failed to stain for keratin but stained for CEA.[27,28] A battery of epithelial markers (*e.g.*, EMA, CEA, Ber Ep4, surfactant apoprotein) should be used to define the phenotype of the spindle cells.[28] Electron microscopy can be employed in doubtful cases.[27,28] The number of cases classified using these techniques is relatively small, and definite conclusions regarding the clinical usefulness of the schema are lacking. From the small amount of data available, it appears that 75% of cases of carcinosarcomas with definitive mesenchymal differentiation show the classic endobronchial location originally reported by Moore, and spindle cell carcinomas are more frequently located peripherally.[25,27]

Carcinosarcomas are usually smaller than spindle cell carcinomas (4.7 cm *versus* 8.5 cm).[27] Whether the classification is of prognostic use is still unclear. Ishida concluded that definitive sarcomatous differentiation was associated with a poorer prognosis, but a review combining a number of small series and individual case reports suggests that these tumors may have a better prognosis than other types of biphasic lesions (Table 54-5).[28] More work needs to be done to determine the prognostic value of this classification.[27]

The histogenetic value of the classification scheme can also be questioned. A variety of undoubted mesenchymal neoplasms can express keratin, and rarely the same phenomenon can occur in carcinosarcomas with areas of differentiated stroma.[40–42] Some investigators argue that carcinosarcoma and spindle cell carcinoma are merely windows along a spectrum of biphasic lesions, and they use the terms "carcinoma with a sarcomatoid element" or "pulmonary carcinoma with sarcoma-like lesions" to describe all of these tumors, including spindle cell carcinomas.[27,28] We think that the names "carcinosarcoma" and "spindle cell carcinoma" should be retained if they can be proven to have clinical and prognostic meaning.

PULMONARY TERATOMAS

Primary teratomas in the lung parenchyma are highly unusual neoplasms.[43–55] Because of their rarity, it is important to exclude the presence of similar tumors in more common sites, such as the testes and the mediastinum, before definitely classifying a teratoma as a primary lung neoplasm. We have observed several cases of completely mature teratomas appearing in the lung parenchyma after a testicular embryonal tumor or teratocarcinoma has been surgically removed.[56] This phenomenon may be an effect of the treatment that patients undergo after surgical resection of their primary neoplasm, but it has also been reported in a patient without a history of additional treatment after resection of the primary testicular tumor.[57] Whatever the mechanism may be, mature teratoma metastatic to the lung should not be confused with a primary lung neoplasm.

Most primary teratomas of lung appear in the adult population, but cases of benign and malignant teratomas in the pediatric age group have been documented.[48,49] The patients may present with chest pain, cough, weight loss, fever, hematemesis, and hemoptysis. The tumors present most commonly in the lung parenchyma, but cases with endobronchial location have been reported. It has been stated that lung teratomas have a greater predilection for the left upper lobe.

Radiologically, no definite criteria exist to separate lung teratomas from other more common lung neoplasms. Grossly, these tumors may appear cystic with hair, teeth, and sebaceous material. They present as a single lesion in the lung parenchyma, a feature that may help to differentiate primary from metastatic tumors, which are more frequently multiple masses. Otherwise, primary lung teratomas cannot be differentiated from metastatic teratomas on the basis of gross inspection.

Microscopically, two variants–completely mature teratomas (Fig. 54-15) and malignant teratomas–have been reported. As would be expected, a range of tissues from the three germinal layers can be involved, but as in the case of analogous tumors in the testes or mediastinum, pulmonary teratomas are not specific for the presence of a determined tissue. The presence of teeth, thymus,

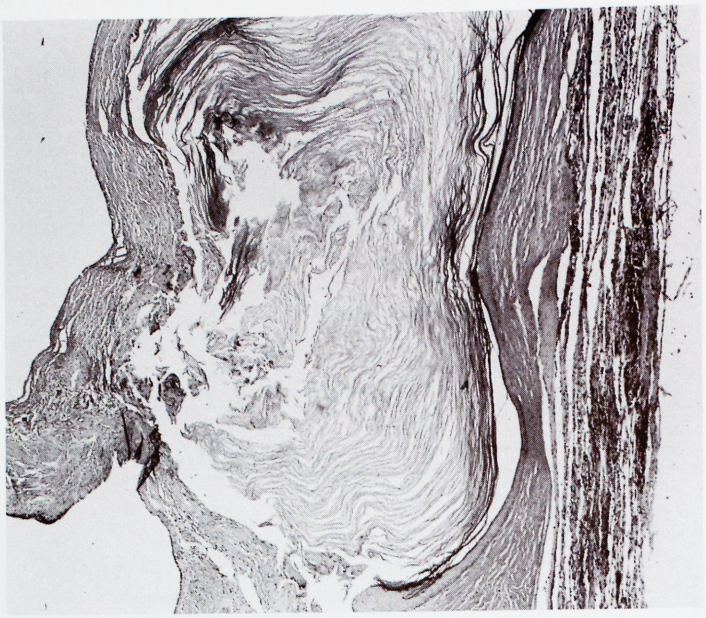


FIGURE 54-15. Cystic structures are lined by flattened squamous epithelium in a mature teratoma of lung. (H & E stain; panoramic view.)

hair, and sebaceous material has been documented in mature teratomas, and malignant cartilage, sarcomatous stroma, neural tissue, and adenocarcinoma have been reported in its malignant counterpart.

The only differential diagnosis to consider in cases of pulmonary teratoma is a metastatic teratoma from a possible testicular or mediastinal location. We have observed that more than one lesion in the lung parenchyma (Color Fig. 54-1) is more consistent with a metastasis and that a single tumoral mass is more consistent with a primary tumor, but in a patient with a history of gonadal neoplasm, mature or immature, a teratoma in the lung is most likely the result of metastasis.

Complete surgical excision appears to be the treatment of choice for benign tumors. Adjuvant chemotherapy with possible postoperative radiation therapy for patients with residual disease or lymph node metastases is reserved for malignant tumors. With evidence of chest wall involvement, preoperative radiation therapy may be considered. In addition, measurements of α-fetoprotein and CEA appear to be good markers for determining recurrence or metastases of these neoplasms.

OTHER COMPLEX MIXED TUMORS

Curious examples of complex mixed tumors of the lung have sporadically appeared, and their position in the spectrum of lesions already described awaits clarification. For instance, in the report of Vadillo-Briceno and colleagues, a tumor arose in the right middle lobe of a 67-year-old man and evolved into extensive metastatic disease.[59] Histologically, the tumor consisted of a combination of three carcinomatous components (*i.e.*, small cell carcinoma, squamous cell carcinoma, adenocarcinoma); there was also an admixture of benign mesenchymal tissues (*i.e.*, cartilage, adipose tissue, myxoid tissue).

Edwards and associates reported a case of a malignant lung tumor consisting of squamous cell carcinoma, undifferentiated carcinoma, and clefts lined by bland epithelial cells.[60] The tumor stroma consisted of pleomorphic sarcoma, fibrosarcoma, chondrosarcoma, osteosarcoma, and undifferentiated mesenchymal tissue. Multiple metastases of the tumor showed only the pleomorphic sarcoma.

A 40-year-old man with a lung mass was described by Flanagan and colleagues; the tumor consisted of squamous cell carcinoma and osteocartilaginous stroma.[61] The investigators ruled out the possibility of carcinosarcoma because of the absence of malignant features in the stromal component. The tumor described by Oyasu and colleagues consisted of a polypoid endobronchial mass from the left lower lobe, showing a population of mononuclear cells admixed with multinucleated giant cells identical to those of giant cell tumors of the bone.[62] There were also components of typical and spindle cell squamous carcinoma. The researchers concluded that the tumor represented a metaplastic squamous cell carcinoma with mesenchymal cell differentiation.

REFERENCES

1. Robin LH, Yesner R. International histological classification of tumors, no 1. Histological typing of lung tumors. Geneva: World Health Organization 1981:30.
2. Barnett NR, Barnard W. Some unusual thoracic tumors. Br J Surg 1945;32:447.
3. Barnard WG. Embryoma of the lung. Thorax 1952;7:229.
4. Spencer H. Pulmonary blastomas. J Pathol Bacteriol 1961;82:161.
5. Francis D, Jacobsen M. Pulmonary blastoma. Curr Top Pathol 1983; 73:265.
6. Kodama T, Shimosato Y, Watanabe S, Koide T, Naruke T, Shimose J. Six cases of well differentiated adenocarcinoma simulating fetal lung tissues in pseudoglandular stage: comparison with pulmonary blastoma. Am J Surg Pathol 1984;8:725.
7. Kradin RL, Young RH, Dickersin GIC, Kirkham SE, Mark EJ. Pulmonary blastoma with argyrophil cells lacking sarcomatous features (pulmonary endodermal tumor resembling fetal lung). Am J Surg Pathol 1982;6:165.
8. Koss M, Hochholzer L, O'Leary T. Pulmonary blastomas. Cancer 1991;67:2368.
9. Manivel JC, Priest JR, Watterson J, et al. Pleuropulmonary blastoma. The so-called pulmonary blastoma of childhood. Cancer 1988; 62:1516.
10. Nakatani Y, Dickersin GR, Mark EJ. Pulmonary endodermal tumor resembling fetal lung: a clinicopathologic study of five cases with immunohistochemical and ultrastructural characterization. Hum Pathol 1990;21:1097.
11. Dail DH. Uncommon tumors. In: Dail DH, Hammar SP, eds. Pulmonary pathology. New York: Springer-Verlag, 1987:874.
12. Gibbons JRP, McKeown F, Field TW. Pulmonary blastoma with hilar lymph node metastases: survival for 24 years. Cancer 1981;47:152.
13. Fung CH, Lo JW, Yonan TN, Milloy FJ, Hakami MH, Changus GW. Pulmonary blastoma: an ultrastructural study with a brief review of literature and a discussion of pathogenesis. Cancer 1977; 39:153.
14. Manning JT Jr, Ordonez NJ, Rosenberg HS, Walker WE. Pulmonary endodermal tumor resembling fetal lung. Arch Pathol Lab Med 1985;109:48.
15. Yousem SA, Wick MR, Randhawa P, Manivel JC. Pulmonary blastoma. An immunohistochemical analysis with comparison with fetal lung in its pseudoglandular stage. Am J Clin Pathol 1990;93:167.
16. Siegel RJ, Bueso-Ramos C, Cohen C, Koss M. Pulmonary blastoma with germ cell (yolk sac) differentiation: report of two cases. Mod Pathol 1991;4:566.
17. Hedlund GL, Bisset GS, Bove KE. Malignant neoplasms arising in cystic hamartomas of the lung in childhood. Radiology 1989;173:77.

18. Stocker JT. The respiratory tract. In: Stocker JT, Dehner LP, eds. Pediatric pathology. Philadelphia: JB Lippincott, 1992:559.
19. Cohen M, Emms M, Kaschula ROC. Childhood pulmonary blastoma: a pleuropulmonary variant of the adult-type pulmonary blastoma. Pediatr Pathol 1991;11:737.
20. Dehner LP. Tumors and tumor-like lesions of the lung and chest wall in childhood: clinical and pathologic review. In: Stocker JT, Dehner LP, eds. Pediatric pathology. Philadelphia: JB Lippincott, 1992:232.
21. Jimenez JF. Pulmonary blastoma in childhood. Cancer 1988;62:1516.
22. Herxheimer G, Reinke F. Pathologie des Krebses. Ergeb Allg Pathol Anat 1912;16:281.
23. Saphir O, Vass A. Carcinosarcoma. Am J Cancer 1938;33:331.
24. Bergmann M, Ackerman LV, Kemler RL. Carcinosarcoma of the lung. Cancer 1951;4:919.
25. Moore T. Carcinosarcoma of the lung. Surgery 1961;50:886.
26. Addis BJ, Corrin B. Pulmonary blastoma, carcinosarcoma, and spindle-cell carcinoma: an immunohistochemical study of keratin intermediate filaments. J Pathol 1985;147:291.
27. Humphrey P, Scroggs M, Roggli V, Shelburne J. Pulmonary carcinomas with a sarcomatoid element: an immunocytochemical and ultrastructural analysis. Hum Pathol 1988;19:155.
28. Ishida T, Tateishi M, Kaneko S, et al. Carcinosarcoma and spindle cell carcinoma of the lung. Clinicopathologic and immunohistochemical studies. J Thorac Cardiovasc Surg 1990;100:844.
29. Cabarcos A, Gomez DM, Lobo BJ. Pulmonary carcinosarcoma: a case study and review of the literature. Br J Dis Chest 1985;79:83.
30. Heremans A, Verbeken E, Deneffe G, Demedts M. Carcinosarcoma of the lung. Report of two cases and review of the literature. Acta Clin Belg 1989;44:110.
31. Davis MP, Eagan RT, Weiland LH, Pairolero PC. Carcinosarcoma of the lung: Mayo Clinic experience and response to chemotherapy. Mayo Clin Proc 1984;59:598.
32. Haque S. Carcinosarcoma of the lung: report of a case and review of the literature. JPMA J Pak Med Assoc 1980;30:91.
33. Ludwigsen E. Endobronchial carcinosarcoma. A case with osteosarcoma of pulmonary invasive part, and a review with respect to prognosis. Virchows Arch [A] 1977;373:293.
34. Stackhouse EM, Harrison EG, Ellis FH. Primary mixed malignancies of lung: carcinosarcoma and blastoma. J Thorac Cardiovasc Surg 1969;57:385.
35. Zimmerman KG, Sobonya RE, Payne CM. Histochemical and ultrastructural features of an unusual pulmonary carcinosarcoma. Hum Pathol 1981;12:1046.
36. Bull J, Grimes OF. Pulmonary carcinosarcoma. Chest 1974;65:9.
37. Gebauer C. The postoperative prognosis of primary pulmonary sarcomas. Scand J Thorac Cardiovasc Surg 1982;16:91.
38. Ro J, Chen J, Lee J, Sahin A, Ordonez N, Ayala A. Sarcomatoid carcinoma of the lung: immunohistochemical and ultrastructural studies of 14 cases. Cancer 1992;69:376.
39. Suster S, Huszar M, Herczeg E. Spindle cell squamous carcinoma of the lung. Immunocytochemical and ultrastructural study of a case. Histopathology 1987;11:871.
40. Miettinen M, Tapola J. Immunohistochemical spectrum of rhabdomyosarcoma and rhabdomyosarcoma-like tumors. Expression of cytokeratin and the 68-kd neurofilament protein. Am J Surg Pathol 1989;13:120.
41. Litzky LA, Brooks JJ. Cytokeratin immunoreactivity in malignant fibrous histiocytoma and spindle cell tumors: comparison between frozen and paraffin-embedded tissues. Mod Pathol 1992;5:30.
42. Cupples J, Wright J. An immunohistological comparison of primary lung carcinosarcoma and sarcoma. Pathol Res Pract 1990;186:326.
43. Bateson EM, Hayes JA, Woo-Ming M. Endobronchial teratoma with bronchiectasis and bronchiolectasis. Thorax 1968;23:69.
44. Berghout A, Mallens WM, te-Velde J, Haak HL. Teratoma of the lung in a hemophilic patient. Acta Haematol 1968;70:330.
45. Day DW, Taylor SA. An intrapulmonary teratoma associated with thymic tissue. Thorax 1975;30:582.
46. Gautam H. Intrapulmonary malignant teratoma. Am Rev Respir Dis 1969;100:863.
47. Holt S, Deverall PB, Boddy JE. A teratoma of the lung containing thymic tissue. J Pathol 1978;126:85.
48. Jamieson MPG, McGowan AR. Endobronchial teratoma. Thorax 1982;37:157.
49. Pound AW, Willis RA. A malignant teratoma of the lung in an infant. J Pathol 1968;98:111.
50. Saruk M, Stern H, Tronic B, Neumann RD, LiVolsi V. Intrapulmonary benign cystic teratoma. Conn Med 1980;44:687.
51. Stair CJ, Stevenson RD, Schaefer RF, Fullenwider JP, Campbell GS. Primary teratocarcinoma of the lung. J Surg Oncol 1986;33:262.
52. Steir K. Benign cystic teratoma of the lung. Postgrad Med 1988;83:85.
53. Trivedi SA, Mehta KN, Nanavaty JM. Teratoma of the lung. Br J Dis Chest 1966;60:156.
54. Walrond ER, Prussia PR. Pulmonary teratoma. West Indian Med J 1987;36:39.
55. Zachar CK. Intrapulmonary dermoid cyst. Semin Roentgenol 1987; 22:231.
56. Moran CA, Travis WD, Carter D, Koss MN. Metastatic mature teratoma in lung following testicular embryonal carcinoma and teratocarcinoma. Arch Pathol Lab Med 1993;117:641.
57. Skinner DG, Leadbetter WF, Wilkins EW. The surgical management of testis tumors metastatic to the lung: a report of 10 cases with subsequent resection of from one to seven pulmonary metastases. J Urol 1971;105:275.
58. Prive L, Tellem M, Meranze D, Chodoff R. Carcinosarcoma of the lung. Arch Pathol 1961;72:351.
59. Vadillo-Briceno F, Feder W, Albores-Saavedra J. Malignant mixed tumor of the lung. Chest 1970;58:84.
60. Edwards CW, Saunders AM, Collins F. Mixed malignant tumor of the lung. Thorax 1979;34:629.
61. Flanagan P, McCracken AW, Cross RM. Squamous cell carcinoma of the lung with osteocartilaginous stroma. J Clin Pathol 1965;18:403.
62. Oyasu R, Battifora HA, Buckingham WA, et al. Metaplastic squamous cell carcinoma of bronchus simulating giant cell tumor of the bone. Cancer 1977;39:1119.