Pathology of Pulmonary Disease, edited by Mario J. Saldana.
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58

Miscellaneous Tumors

Nicholas J. Hruby
Michael J. Gaffey
Stacey E. Mills

In this chapter, a group of pulmonary neoplasms characterized by their rarity, uncertain histogenesis, and characteristic and sometimes unique histologic appearance is discussed (Display 58-1).

CLEAR CELL TUMOR

Clear cell (*i.e.*, sugar) tumors of the lung (CCTL) are rare pulmonary neoplasms originally described in abstract form by Liebow and Castleman in 1963.[1] Approximately 46 examples have been reported, excluding a single histologically identical tumor that arose in the trachea and a case reported by Ozdemir and colleagues, which probably represents a clear cell adenocarcinoma.[2–29] Sugar tumor is a term that was coined by Liebow and Hubbell because of the lesion's substantial glycogen content.[1] Biochemical analysis revealed one CCTL to contain 10,657 μmol of hexose per 100 g of wet tissue; normal lung tissue and other pulmonary tumors to contain at most 27.5 μmol of hexose per 100 g of wet tissue.[30]

The reported patients with CCTL include 21 males and 25 females ranging in age from 8 to 70 years (median, 51 years of age). Patients are typically asymptomatic and present with incidentally discovered, peripheral, solitary lesions found on chest roentgenogram. The tumors are small, ranging from 0.7 to 6.5 cm in their greatest dimension (median, 2.0 cm) and have no lobar predilection.

CCTL are traditionally considered benign, and almost all CCTL patients are cured by simple excision. In 1988, Sale and Kulander described a symptomatic patient with CCTL who died of hepatic and peritoneal metastases 17 years after resection of the primary tumor.[20] In this case, the primary CCTL was unusually large (*i.e.*, 4.5 cm in diameter) and necrotic but immunohistochemically and ultrastructurally indistinguishable from its benign counterparts. The presence of symptoms attributable to the CCTL was unique and probably related to the larger size of the lesion. Gaffey and colleagues suggested that CCTLs greater than 2.5 cm in diameter with necrosis or symptoms should be regarded as potentially metastasizing neoplasms.[7]

Grossly, CCTL are well-circumscribed, red-tan nodules that easily shell out the surrounding pulmonary parenchyma (Fig. 58-1). Most are homogenous and devoid of hemorrhage or necrosis on the cut surface. Microscopically, CCTL are unencapsulated but sharply demarcated from the surrounding parenchyma. They consist of sheets and cords of uniform cells arranged around large, sinusoidal, thin-walled vessels with focal perivascular hyalinization (Fig. 58-2). CCTL are unassociated with nerves, bronchi, or major blood vessels; because of their peripheral location, epithelial-lined tubules representing entrapped alveolar epithelium are frequently found in these tumors.

The neoplastic cells are polygonal with clear to eosinophilic cytoplasm and prominent cell borders. Nuclei are oval and mildly irregular with finely granular chromatin and inconspicuous nucleoli. Rare CCTL are predominantly composed of cells with eosinophilic cytoplasm; others may show spindled cells that merge with

DISPLAY 58-1. MISCELLANEOUS TUMORS

Clear cell tumor
Meningothelial-like nodules
Meningioma
Paraganglioma
Sclerosing hemangioma
Malignant melanoma
Alveolar adenoma
Papillary adenoma
Choriocarcinoma
Ependymoma

FIGURE 58-1. A clear cell tumor of the lung forms a sharply circumscribed, unencapsulated mass unassociated with major vessels or bronchial structures. (From Gaffey MJ, Mills SE, Zarbo RJ, Weiss LM, Gown AM. Clear cell tumor of the lung: immunohistochemical and ultrastructural evidence of melanogenesis. Am J Surg Pathol 1991;15:644.)

the more characteristic polygonal cells. Mitotic figures are rare or absent. Large tumor cells with linear arrays of cytoplasm radiating from the nucleus (*i.e.*, spider cells) or large nuclei and homogenous eosinophilic cytoplasm (*i.e.*, neuroid cells) have been described. The cytoplasm of the neoplastic cells is intensely positive with the periodic acid-Schiff (PAS) stain and sensitive to diastase predigestion because of their high glycogen content.[30] Most CCTL studied immunohistochemically have been positive with HMB-45 and S-100 protein (Fig. 58-3). A minority have been positive for vimentin, and some are positive for α_1-antitrypsin, HAM-56, factor XIIIA, neuron-specific enolase (NSE), synaptophysin, cathepsin B, and Leu-7.[6,7,8,15] All CCTL have been nonreactive with antibodies to keratin, epithelial membrane antigen (EMA), chromogranin, neurofilament, and glial fibrillary acidic protein.

Ultrastructurally, the cells of CCTL are arranged in nests and have short cytoplasmic processes that interdigitate with those of neighboring cells (Fig. 58-4). Poorly developed cellular junctions of the macula adherens type are occasionally seen. The most striking and characteristic feature of CCTL is the large amounts of monogranular and rosette-forming cytoplasmic glycogen, which is removed to some degree by processing. Occasional 900- to 1400-nm, membrane-bound vesicles containing monogranular glycogen–like material may be seen. Rare 120- to 280-nm,

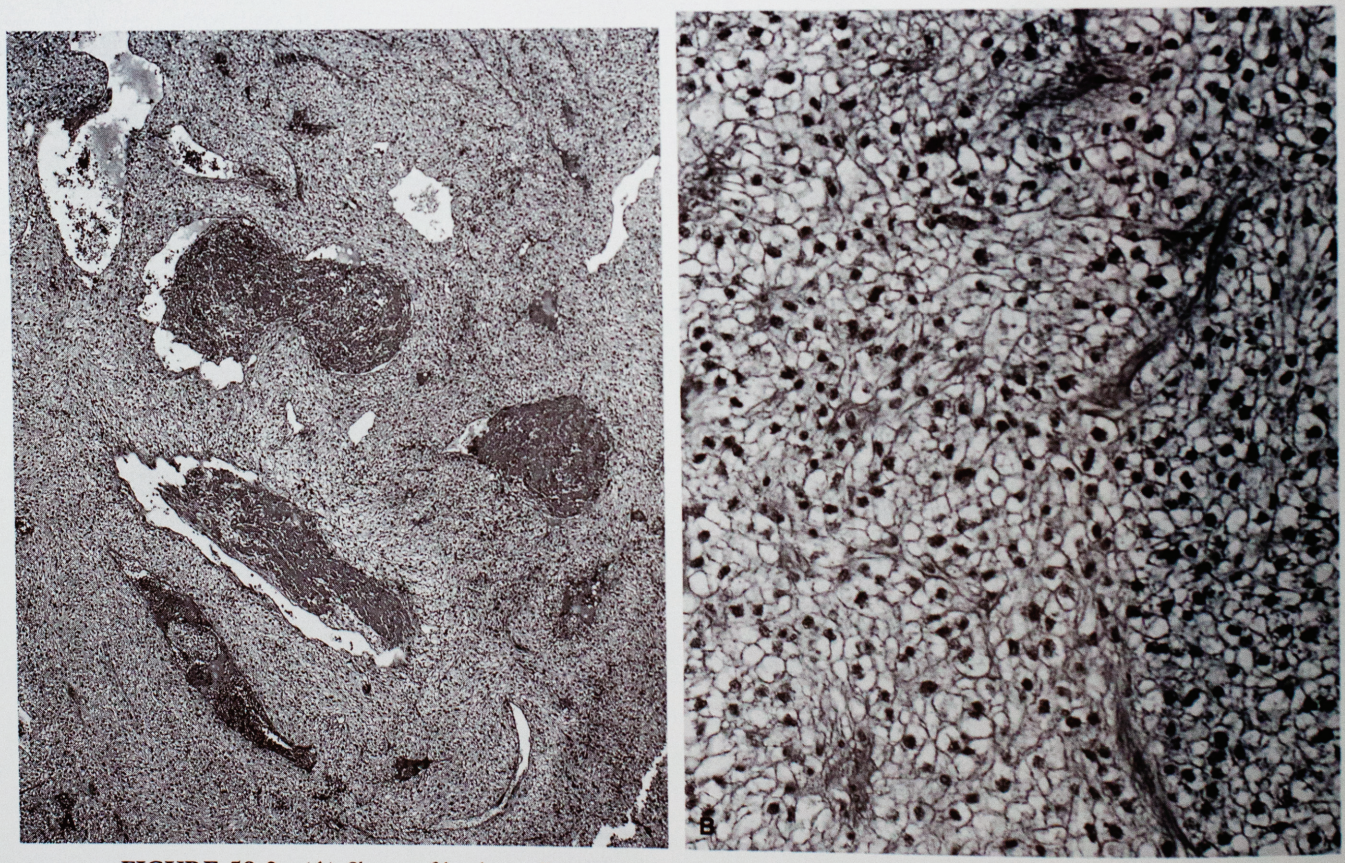

FIGURE 58-2. (**A**) Sheets of haphazardly arranged neoplastic cells in a clear cell tumor of the lung surround characteristic sinusoidal vessels, some of which contain thrombi. (H & E stain; low magnification.) (**B**) The tumor cells are uniform, with cytologically bland nuclei and prominent cell borders. (H & E stain; intermediate magnification; from Gaffey MJ, Mills SE, Zarbo RJ, Weiss LM, Gown AM. Clear cell tumor of the lung: immunohistochemical and ultrastructural evidence of melanogenesis. Am J Surg Pathol 1991;15:644.)

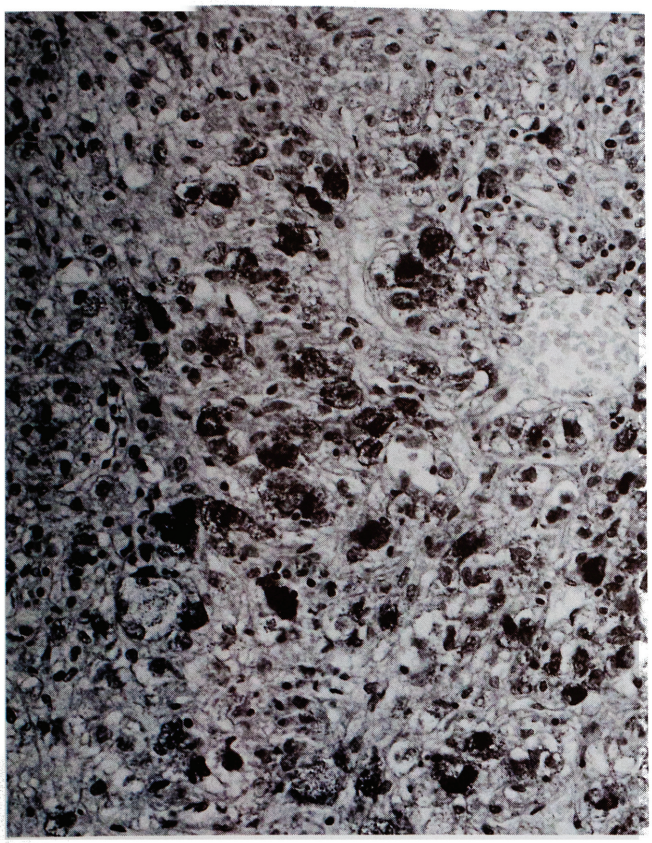

FIGURE 58-3. Immunohistochemical staining of a clear cell tumor of the lung with HMB-45 labels most tumor cells in a granular, cytoplasmic pattern. (HMB-45 stain and hematoxylin counterstain; intermediate magnification; from Gaffey MJ, Mills SE, Zarbo RJ, Weiss LM, Gown AM. Clear cell tumor of the lung: immunohistochemical and ultrastructural evidence of melanogenesis. Am J Surg Pathol 1991;15:644.)

membrane-bound, neurosecretory-type granules have been reported.[2,3,6,9–11] Two optimally fixed CCTL specimens showed oval to ellipsoidal, membrane-bound intracytoplasmic structures consistent with melanosomes, and aberrant melanosomal forms were identified in a third case.[7] Other cellular organelles were sparse.

Early proposals for the origin of CCTL included myogenic or pericytic cells, the Kulchitsky cell, and the Clara cell.[2,3,5,9,11] The recent demonstration of melanosomes in some CCTL and their immunoreactivity with HMB-45 and for S-100 protein suggests melanocytic or neuroectodermal differentiation.[7] The neuroendocrine features of CCTL also support this concept, because neuroendocrine-type granules and immunoreactivity for NSE and synaptophysin have been reported in clear cell sarcoma of tendon sheath and malignant melanoma.[31–33] However, nonmelanocytic tumors such as breast and hepatocellular carcinomas may stain with HMB-45, and melanosomes have been reported in several nonmelanocytic tumors, such as pulmonary carcinoids and pigmented dermatofibrosarcoma protuberans.[17,34–38] Premelanosomelike structures and HMB-45 reactivity have been reported in angiomyolipomas.[17,39] Consequently, the characteristic immunophenotype of CCTL should be regarded as suggestive but not conclusive evidence of melanocytic differentiation.

The differential diagnosis of CCTL includes clear cell carcinoma, carcinoid tumor, granular cell tumor, oncocytoma, acinic cell tumor, and metastatic renal cell carcinoma. Clear cell carcinoma is not considered a distinct clinicopathologic entity, because areas of squamous or glandular differentiation are usually identified. Clear cell and oncocytic carcinoid tumors lack the sinusoidal pattern of CCTL, are frequently invasive, and immunohistochemically stain with markers of epithelial differentiation. Oncocytomas, granular cell tumors, and acinic cell tumors are easily differentiated from eosinophilic CCTL by the absence of intracytoplasmic glycogen and their typical ultrastructural characteristics.[40–42] Differentiating CCTL from metastatic renal cell carcinoma is difficult but can be accomplished immunohistochemically, because the latter tumor is frequently positive for keratin and EMA.[43,44] Rare vimentin-positive, keratin-negative, and EMA-negative renal cell carcinomas have been reported but can be separated by the immunoreactivity of most CCTL with HMB-45 and S-100 protein.[7,8]

MINUTE PULMONARY MENINGOTHELIAL-LIKE NODULES

In 1960, Korn and associates described a distinctive pulmonary interstitial lesion composed of multiple, small, cell nests (*i.e.*, Zellballen) that were invariably associated with small veins.[45] The lesions bore a striking resemblance to carotid body tumors and were designated "minute pulmonary tumors resembling chemodectomas," although their precise nature remained unknown.[45] Spain and Ichinose and colleagues observed that the nodules were associated with pulmonary thromboemboli, leading to the speculation that embolic occlusion produced a hyperplastic proliferation of chemoreceptor elements in normal lung parenchyma.[46,47] In 1964, Barroso-Moguel and Costero supported this concept with a report of focal argentaffin positivity in five tumors.[48] In a 1972 publication, the same investigators failed to observe nerve fibers or secretory granules within the nodules and proposed that they represented hamartomas of mesothelial derivation.[49] In 1975, a chemoreceptor derivation was questioned by Churg and Warnock, who observed a histologic and ultrastructural resemblance to meningothelial cells.[50] In 1988, Gaffey and colleagues confirmed earlier ultrastructural observations and demonstrated an immunohistochemical similarity with meningothelial cells.[51] On the basis of their findings, the term "minute pulmonary meningothelial-like nodules" (MPMN) was introduced as a more accurate reflection of the morphologic nature of these lesions.[51]

Approximately 89 adequately documented cases of MPMN have been reported.[46–50,52,53] The nodules are typically incidental findings in lung biopsies and in surgical and autopsy specimens; they show a marked female predominance (*i.e.*, 5.4 : 1). The age at diagnosis is between 12 and 91 years (mean, 58 years of age), with most patients in their sixth decade of life. The reported incidence of MPMN varies from 1 in 300 to 1 in 25 lung specimens, a variation undoubtedly related to the diligence with which the lesions are searched for.[45,46] The teams led by Gaffey and Churg reported incidences of 1 in 60 autopsies and 1 in 33 autopsies, respectively, if the nodules were searched for specifically.[50,51] The nodules have been identified in all pulmonary lobes. In the series of 26 MPMN reported by Churg and associates, 46% were located in the lower lobes, 38% in the upper lobes, and 15% the middle lobes.[50] Most cases are subpleural, but the location within the pulmonary parenchyma varies, and examples of exclusively deep, intraparenchymal MPMN have been described.[51]

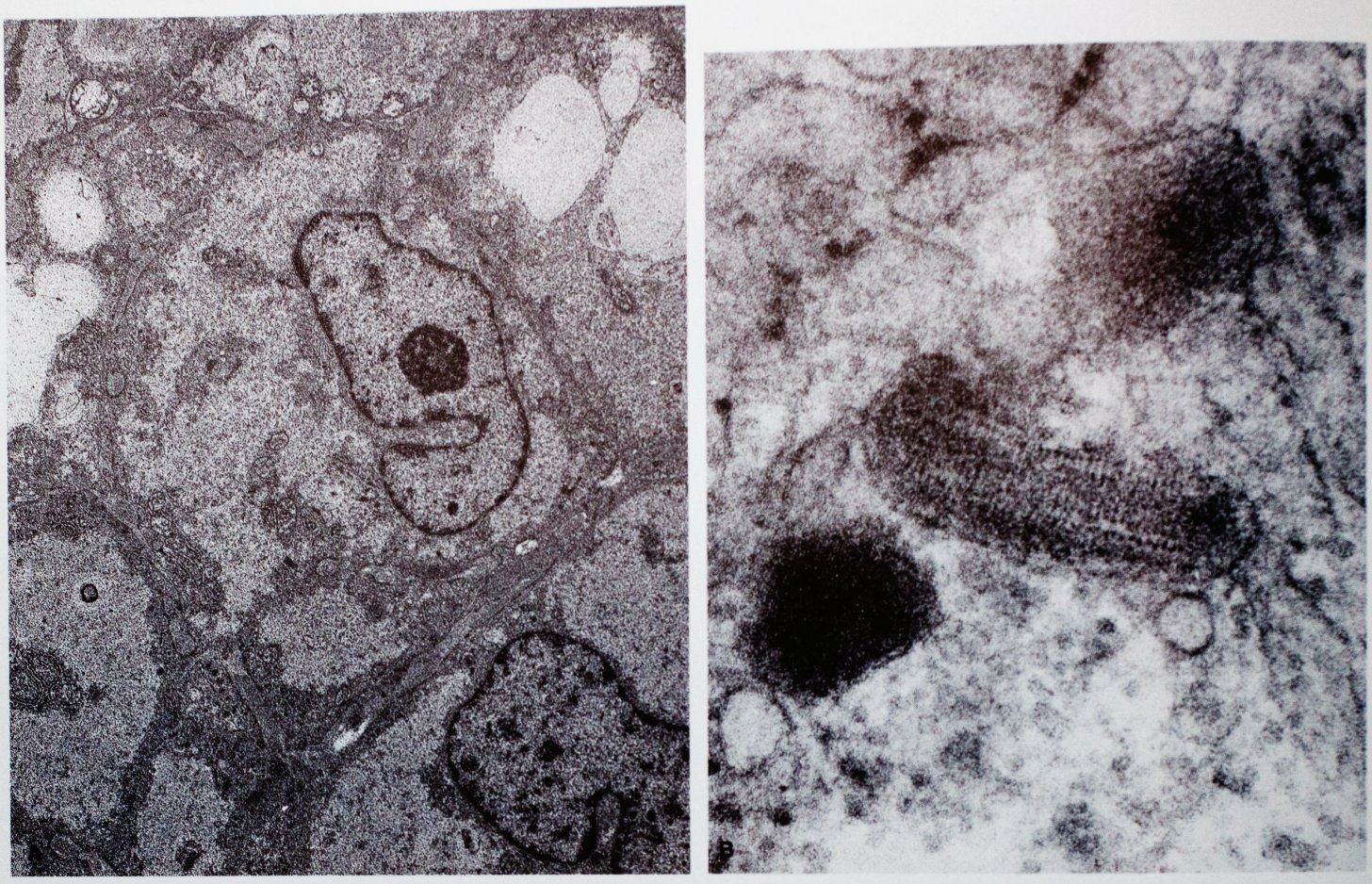

FIGURE 58-4. (**A**) Electron microscopic view of a clear cell tumor of the lung shows the cytoplasm of the tumor cells distended with glycogen. (Original magnification × 7000; from Gaffey MJ, Mills SE, Askin FB, et al. Clear cell tumor of the lung: a clinicopathologic, immunohistochemical, and ultrastructural study of eight cases. Am J Surg Pathol 1990;14:248.) (**B**) Higher magnification showed an elliptical, stage 2 premelanosome with internal periodicity adjacent to a partially pigmented, stage 3 melanosome. (Original magnification; × 110,000; from Gaffey MJ, Mills SE, Zarbo RJ, Weiss LM, Gown AM. Clear cell tumor of the lung: immunohistochemical and ultrastructural evidence of melanogenesis. Am J Surg Pathol 1991;15:644.)

Grossly, the lesions appear as firm, ovoid, gray-white subpleural nodules that are 1 to 3 mm in their greatest diameter. Within the parenchyma, MPMN appear as slightly smaller, tan-yellow, poorly defined nodules that characteristically protrude from the cut surface (Fig. 58-5).

Microscopically, the nodules are composed of cell nests usually associated with small veins. The nests characteristically expand the surrounding alveolar septa, displacing the capillary to one side. Most nodules appeared as multiple cell nests interconnected by variably dense collagenous bands containing parallel arrays of spindled cells similar to those in the nests. Larger lesions occasionally show intervening air space obliteration and fibrosis that appears to retract the surrounding parenchyma, imparting a stellate configuration to the lesion (Fig. 58-6). Other presumably early nodules show closely apposed, whorled cell nests with little intervening connective tissue.

The tumor cells are ovoid to predominantly spindled, with eosinophilic cytoplasm and indistinct cell borders (Fig. 58-7). Nuclei are oval with occasional indentations and finely granular to vesicular chromatin. Most cells show small, indistinct nucleoli, and mitotic figures are not seen. Reticulin preparations show distinct fibrils surrounding the cell nests with fine fibers surrounding individual cells within the nests.

In the only detailed immunohistochemical study of MPMNs, Gaffey and colleagues reported 12 of 14 nodules that were positive for EMA (Fig. 58-8) and 10 of 12 that were positive for vimentin.[51] Staining for cytokeratin, NSE, S-100, and actin was uniformly negative.

Ultrastructurally, the tumor cells extend complex, branching cytoplasmic processes that interdigitate extensively with those of neighboring cells (Fig. 58-9).[50–52] The cell processes are joined by numerous, well-formed desmosomes, without associated basement membrane material. The nuclei are often indented up to one half of the nuclear diameter with peripherally clumped chromatin and well-formed nucleoli. Cell organelles are sparse, with scattered mitochondria, Golgi apparatuses, and loose, parallel bundles of intermediate filaments occasionally seen in a paranuclear location. Specialized structures such as glycogen inclusions, pinocytotic vesicles, and neurosecretory-type granules have not been identified.

The ultrastructural features of MPMN are quite similar to those of meningothelial cells.[50–54] The immunophenotype of MPMN resembles that of meningothelial cells. As with MPMN, most meningiomas are immunoreactive for EMA and vimentin, and a few are positive for keratin and S-100 protein.[55–62]

It is not clear whether MPMN represent benign neoplasms or hamartomatous proliferations, and their origin is unresolved. The

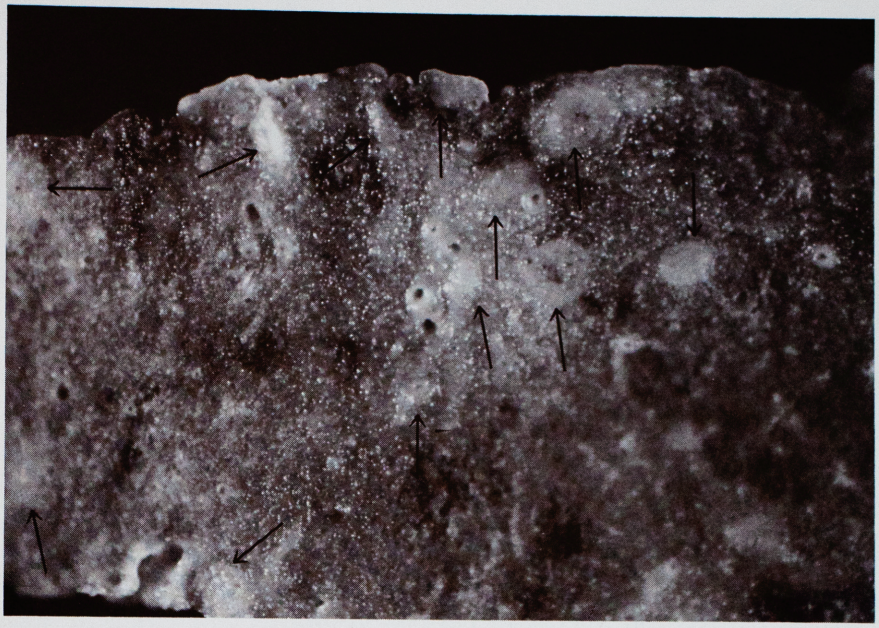

FIGURE 58-5. In a portion of lung at postmortem from a patient with pulmonary fibrosis, careful inspection reveals several, ill-defined, white-tan nodules, each less than 2 to 3 mm in diameter, histologically corresponding to MPMNs. There were hundreds of these nodules throughout the lung tissue (*arrows*). (Contributed by the editor.)

tumor cells bear no resemblance to a recognized normal pulmonary cell type. The relation of MPMN to pulmonary meningiomas remains unclear.[63–67] The possibility that MPMN may represent a precursor lesion is unlikely in view of the relatively high prevalence of MPMN compared with the rarity of pulmonary meningiomas. Pulmonary meningiomas are solitary and are, on average, 4 cm in diameter, but MPMN are frequently multiple and typically are 1.0 to 3.0 mm; larger MPMN should exist if the nodules were precursor lesions with the capacity for further growth.

The differential diagnostic considerations are few and primarily include pulmonary carcinoid tumorlets and sclerosing hemangioma (SH). Pulmonary carcinoid tumorlets may superficially resemble MPMN but are bronchocentric, in contrast to the perivenular, interstitial location of MPMN. Tumorlets may be differentiated by immunohistochemical or ultrastructural evidence of neurosecretory differentiation. SH may be subpleural and occasionally diminutive, but most show areas with papillae, hemorrhage, and central sclerosis.[68]

PRIMARY PULMONARY MENINGIOMA

Meningiomas account for approximately 15% of intracranial neoplasms.[69] An extracranial origin is unusual, and most of these tumors have been described in the head and neck region.[69–73] Extracranial meningiomas arising in sites distant from the neural axis are exceedingly rare, and virtually all of these have been reported in the posterior mediastinum, pleura, or lung. In 1982, Kemmitz and associates first reported a primary pulmonary men-

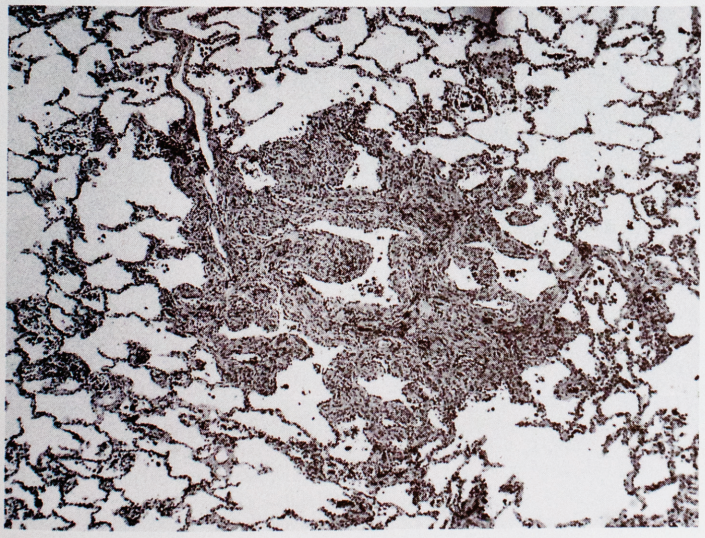

FIGURE 58-6. The microscopic view of an intraparenchymal meningothelial-like nodule shows an irregular, stellate configuration in continuity with adjacent alveolar septa. (H & E stain; low magnification; from Gaffey MJ, Mills SE, Askin FB. Minute pulmonary meningothelial-like nodules. A clinicopathologic study of so-called minute pulmonary chemodectoma. Am J Surg Pathol 1988;12:167.)

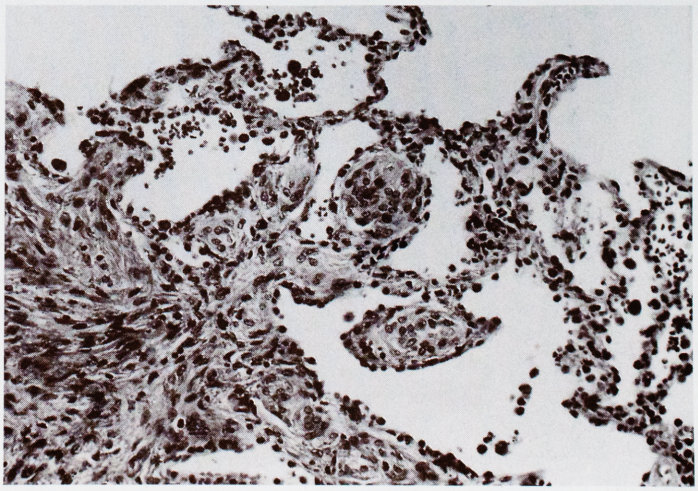

FIGURE 58-7. The meningothelial-like cellular nests characteristically expand the alveolar septa. (H & E stain; low magnification; from Gaffey MJ, Mills SE, Askin FB. Minute pulmonary meningothelial-like nodules. A clinicopathologic study of so-called minute pulmonary chemodectoma. Am J Surg Pathol 1988;12:167.)

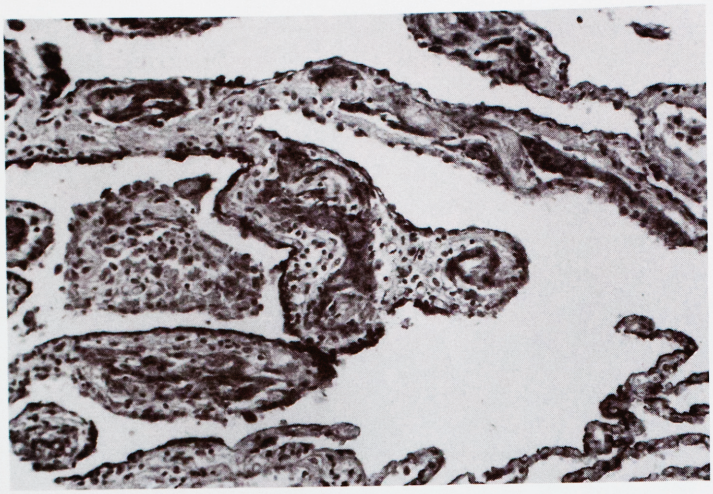

FIGURE 58-8. Immunohistochemical staining for epithelial membrane antigen labels the meningiothelial-like cell nests and the alveolar lining epithelium. (Anti-EMA stain and hematoxylin counterstain; low magnification; from Gaffey MJ, Mills SE, Askin FB. Minute pulmonary meningothelial-like nodules. A clinicopathologic study of so-called minute pulmonary chemodectoma. Am J Surg Pathol 1988;12:167.)

ingioma.[74] The tumor arose in the right lower lobe of an asymptomatic 59-year-old woman. Sequential radiographs had documented that the tumor was unchanged for 4 years before excision. Clinical and radiologic examination revealed no evidence of a central nervous system component, and the patient was alive without evidence of disease 2.5 years after excision.

Since the initial report, 10 primary pulmonary meningiomas have been described in patients without evidence of intracranial tumors.[74–78] Another pulmonary meningioma was reported in a patient with neurofibromatosis and intracranial meningiomas; metastasis cannot be excluded in this case.[79] The 10 patients include 8 women and 2 men who were between 41 and 74 years of age (median, 59 years). The lesions typically appeared radiographically as well-circumscribed, opaque nodules unassociated with major bronchi or vessels. All lesions were incidentally discovered during routine examinations or evaluations of other, apparently unrelated complaints. Seven nodules have been reported in the left lung and three in the right. Most were peripherally placed; one was subpleural.[75] Because of the innocuous radiologic appearance of their tumors, 4 patients were followed for 3 to 17 years.[75–77] During this time, two tumors slightly increased in size. Nine patients were treated with surgical excision and were free of disease after a follow-up period of 1 to 7 years (median, 3.5 years). The remaining case was diagnosed at autopsy, 6 years after its initial radiographic discovery.[76]

Grossly, the tumors were well-circumscribed, firm, gray-white nodules without evidence of hemorrhage or necrosis (Fig. 58-10). They ranged from 1.7 to 6.0 cm (median, 3.0 cm) in the greatest dimension. Histologically, the tumors were indistinguishable from their intracranial counterparts and consisted of cytologically bland neoplastic cells arranged in lobules and concentric whorls. In three cases, the classic, whorled architecture was found primarily at the tumor's periphery, with the central portions of the tumor showing a more haphazard proliferation of polygonal to spindled cells. The cytoplasm was typically eosinophilic, with inapparent cell borders. The nuclei were elongated and uniform, with frequent cytoplasmic inclusions and finely granular chromatin without nucleoli (Fig. 58-11). Mitotic figures were not found. A few psammoma bodies were found in 9 of the 10 tumors.

Six pulmonary meningiomas were examined by electron microscopy.[74–76,78] Although the examination was suboptimal in two cases because of poor preservation of paraffin-embedded material, the remaining four tumors showed complex interdigitations of cellular membranes and well-formed desmosomes, features consistent with meningiomas. Various degrees of intracytoplasmic bundles of intermediate filaments, concentric membranes of smooth endoplasmic reticulum, and mitochondria were

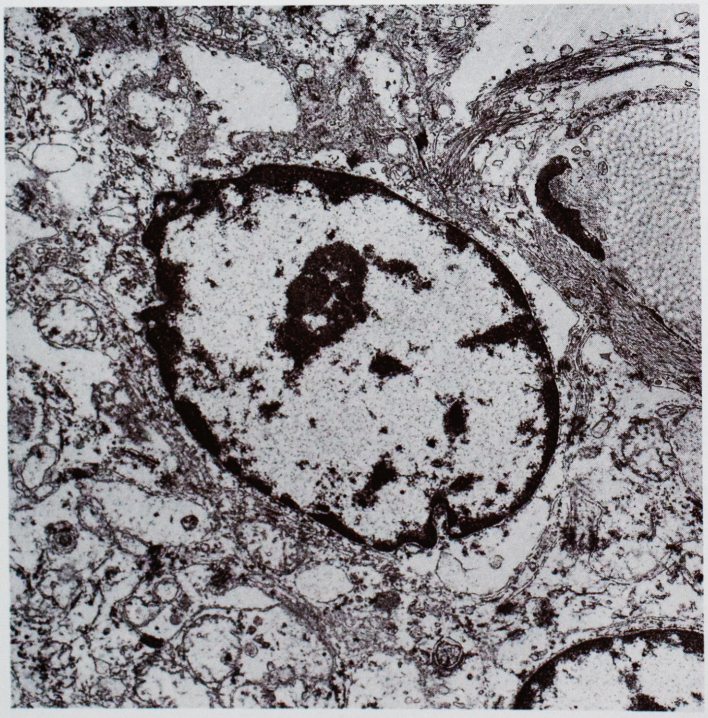

FIGURE 58-9. Ultrastructurally, the meningothelial-like cells show complex, interdigitating cytoplasmic processes joined by true desmosomes. (Original magnification ×7000; from Gaffey MJ, Mills SE, Askin FB. Minute pulmonary meningothelial-like nodules. A clinicopathologic study of so-called minute pulmonary chemodectoma. Am J Surg Pathol 1988;12:167.)

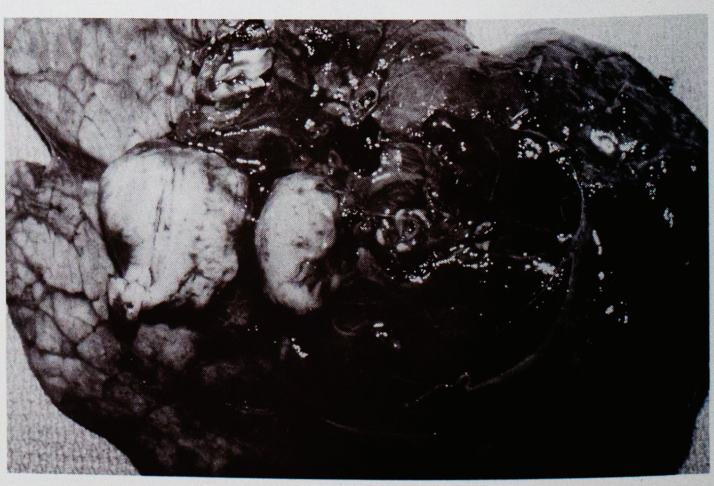

FIGURE 58-10. Pulmonary meningiomas characteristically appear as well-circumscribed, intraparenchymal, homogeneous masses with no association with bronchi, vessels, or pleura. (From Flynn SD, Yousem SA. Pulmonary meningiomas: a report of two cases. Hum Pathol 1991; 22:469.)

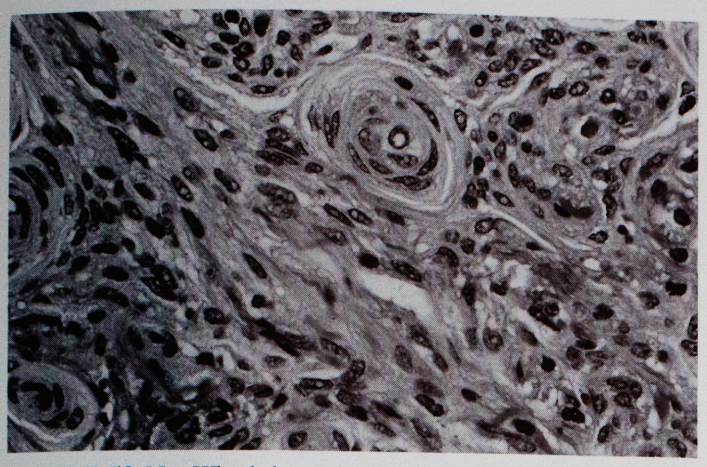

FIGURE 58-11. Whorled neoplastic cells have uniform nuclei with finely granular chromatin and occasional intranuclear inclusions. (H & E stain; intermediate magnification; from Flynn SD, Yousem SA. Pulmonary meningiomas: a report of two cases. Hum Pathol 1991;22:469.)

seen. Basal lamina material, microvilli, and neurosecretory-type granules were not seen. Five cases have been examined by immunohistochemistry, all of which showed diffuse reactivity for vimentin and limited positivity for EMA, particularly within the whorled areas (Fig. 58-12).[75,76] Staining for keratin, S-100 protein, NSE, chromogranin, and bombesin was uniformly negative. Most intracranial meningiomas have been positive for vimentin and EMA, with limited reactivity for keratin, S-100 protein, NSE, and Leu-7 found in a few lesions.

Intracranial meningiomas arise from cells lining the external layer of the arachnoid membrane and the arachnoidal villi.[71] The origin of extracranial meningiomas, however, is problematic. In 1960, Hoye subdivided extracranial meningiomas into four groups: primary intracranial tumors with extracranial extension through foramina or other bony defects; tumors derived from arachnoidal cell nests located along cranial nerve sheaths with extracranial growth; extracranial growth of embryologically displaced (*i.e.*, ectopic) arachnoidal cells without apparent continuity with foramina or cranial nerves; and metastases from benign-appearing primary intracranial meningiomas.[70] Although applicable to ectopic meningiomas of the head and neck, the latter theories do not account for meningiomas occurring away from the neural axis and without a demonstrable intracranial primary lesion. As discussed earlier, primary pulmonary meningiomas are probably not derived from MMPN.

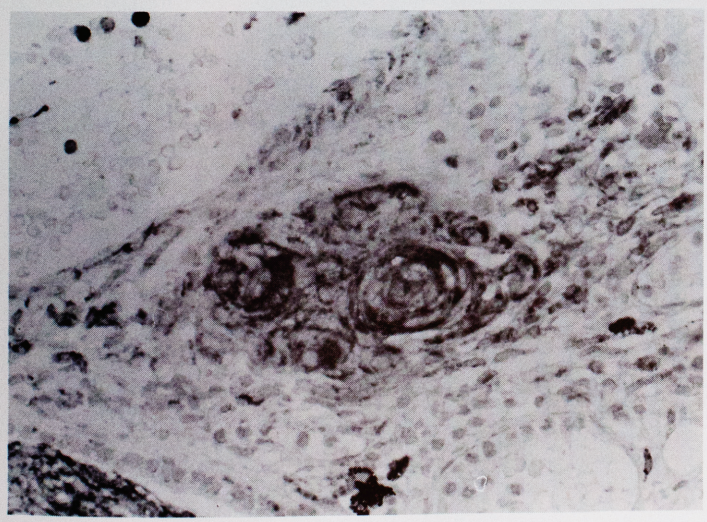

FIGURE 58-12. Immunohistochemical staining for epithelial membrane antigen shows strong cytoplasmic positivity within the neoplastic cells. (Anti-EMA stain and hematoxylin counterstain; intermediate magnification; from Flynn SD, Yousem SA. Pulmonary meningiomas: a report of two cases. Hum Pathol 1991;22:469.)

PRIMARY PULMONARY PARAGANGLIOMA

Primary pulmonary paragangliomas (PPPG; *i.e.*, chemodectoma) are extremely rare, controversial lesions, with a total of nine purported cases in the English language literature.[80–87] These reports are of interest, because the existence of normal paraganglia in human lungs is debatable. Preliminary physiologic evidence from animal studies and a single ultrastructural report of paraganglialike structures in human fetal lung constitute the only evidence.[88,89]

Most reported PPPG are difficult to evaluate, because the pathologic descriptions are limited. The well-documented tumors have typically been incidentally discovered as solitary, well-circumscribed, peripheral lesions in asymptomatic patients. Grossly, they were well-demarcated but unencapsulated, gray-white, firm tumors ranging in size from 1 to 5 cm (mean, 3.2 cm).

Histologically, reported PPPG consisted of epithelioid cell nests surrounded by a richly vascular stroma, often associated with sinusoidal vessels. The tumor cells were polyhedral, with ample eosinophilic cytoplasm and indistinct cell borders. The nuclei were centrally placed, with finely granular chromatin and a few nucleoli. Mitotic figures and necrosis were absent. Intracellular argentaffin granules were observed in one of four PPPG in which they were searched for, all of which were negative for the Gomori chromaffin reaction. All reported PPPG have antedated the immunohistochemical era. One PPPG was studied ultrastructurally and found to contain neurosecretory-type granules, ranging from 120 to 140 nm in diameter.[87]

The differential diagnosis of PPPG includes carcinoid tumor, melanoma, benign CCTL, granular cell tumor, and metastatic renal cell carcinoma. Well-documented paragangliomas at other anatomic locations are differentiated from the latter four tumors by their organoid appearance; combined immunoreactivity for vimentin, NSE, chromogranin, and synaptophysin, but not keratin; and the ultrastructural presence of neurosecretory-type granules. Differentiation from peripheral carcinoid tumors is problematic but would be supported by the immunohistochemical demonstration of keratin in carcinoid tumors but not in paragangliomas. Well-differentiated paragangliomas at other locations have contained S-100–positive sustentacular cells that encircle the tumor cell nests. Rare sustentacular cells may be observed in carcinoids in a randomly scattered, nonencompassing pattern.[90,91]

The possibility that most or all reported pulmonary paragangliomas are carcinoid tumors cannot be easily discounted. An analogous situation exists in the larynx, a site at which paragangliomas were initially found to have a rather high metastatic rate. Some laryngeal paragangliomas were shown to be carcinoid tumors. In our opinion, an optimally documented PPPG has not been reported.

SCLEROSING HEMANGIOMA

The term "sclerosing hemangioma" (SH) was originally coined by Liebow and Hubbell based on a series of seven cases reported in 1956.[92] Before their report, SH had been referred to as histiocytomas, xanthomas, or fibroxanthomas because of the large numbers of foamy histiocytes, siderophages, and chronic inflammatory cells characteristically in these lesions.[93–110]

SH occur over a wide age range; combined data from 130 patients in seven series shows an average age of 44 years (range, 15–83 years of age), and women are affected five times as often as men.[68,98,100] Most patients are asymptomatic, and when present, symptoms are nonspecific and typically include cough, chest pain, and hemoptysis. Chest roentgenograms usually show a circumscribed, solitary, peripheral mass that rarely contain focal calcifications. In a few patients studied with serial chest radiographs, SH remained stable or grew slowly.

Two SH said to be metastatic to hilar lymph nodes were reported, but we do not regard the bland, subcapsular collection of polygonal cells illustrated by Spencer and colleagues as convincing evidence of a lymph node metastasis.[98] The hilar metastasis illustrated by Tanaka and associates consisted of subcapsular aggregates of foamy and eosinophilic polygonal cells forming papillations; the cells were immunoreactive for surfactant apoprotein and provide convincing evidence for metastatic disease.[99] None of the remaining SH reported in the English literature have recurred or metastasized after surgical excision. Few patients have had multiple or bilateral tumors, usually occurring as a single dominant tumor with smaller, peripheral lesions.[95,98,100–102]

SHs have been reported in all lobes, and some tumors have occurred within interlobar fissures. There is a slight predilection for the lower and right middle lobes (*i.e.*, right lower lobe, 26%; left lower lobe, 21%; right middle lobe, 21%; left upper lobe, 16%; right upper lobe, 12%; interlobar fissures, 5%). Dail and Hammar proposed that SH may have a right middle lobe preference.[100]

SH lesions have an average diameter of 2.8 cm (range, 0.4–8.0 cm). SHs are typically well circumscribed, unencapsulated, and gray-white on cut section, with areas of yellow and mottled red-brown discoloration.

Microscopically, the tumors are well demarcated and are surrounded by a fibrous pseudocapsule because of compression of the surrounding parenchyma. Four major histologic patterns are usually seen: solid, hemorrhagic, papillary, and sclerotic. At least two patterns are usually encountered in a given tumor, although the relative proportion of each component varies markedly. Regardless of the histologic pattern or patterns present, the key to diagnosis rests on the identification of the underlying tumor cells. The neoplastic cells are uniform and polygonal, with abundant pale to faintly eosinophilic cytoplasm and indistinct cell borders. Nuclei are round with finely granular chromatin and small, basophilic nucleoli. Intracytoplasmic vacuoles with nuclear compression (*i.e.*, signet-ring appearance) and intranuclear cytoplasmic invaginations are rarely seen. Nuclear pleomorphism is minimal and mitotic figures are typically absent. A proportion of SH show cells with PAS and diastase-sensitive positivity, which is consistent with intracytoplasmic glycogen.

The solid pattern of SH is characterized by sheets and clusters of round, pale cells embedded in a variably dense fibrous stroma (Fig. 58-13). The sheets of cells are occasionally interrupted by irregular clefts lined by smaller cuboidal cells with dark nuclei that probably represent entrapped alveolar epithelium (Fig. 58-14). Peripherally, the tumor cells extend into adjacent alveolar septa lined by hyperplastic type II pneumocytes.

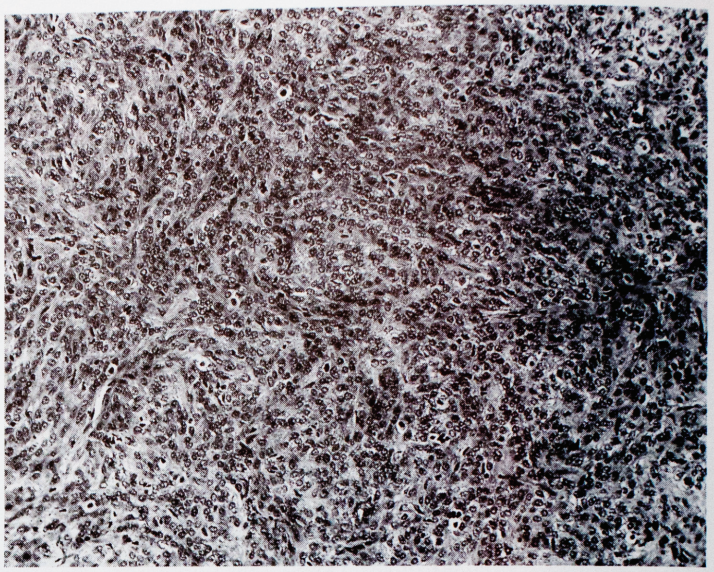

FIGURE 58-13. The solid variant of sclerosing hemangioma shows sheets of diagnostic, round, pale tumor cells intermixed with occasional chronic inflammatory cells. (H & E stain; low magnification.)

Papillary areas in SH consist of closely packed, variably sclerotic papillary processes that project into cleftlike spaces (Fig. 58-15). The cores contain clusters of round, pale tumor cells interspersed with the fibrous stroma; a few papillations are totally sclerotic. The papillary processes and cleft spaces are lined by medium-sized cuboidal cells similar to those lining the entrapped alveolar spaces.

The hemorrhagic (*i.e.*, angiomatous) areas of SH consist of variably sized, blood-filled spaces separated by broad fibrous septa

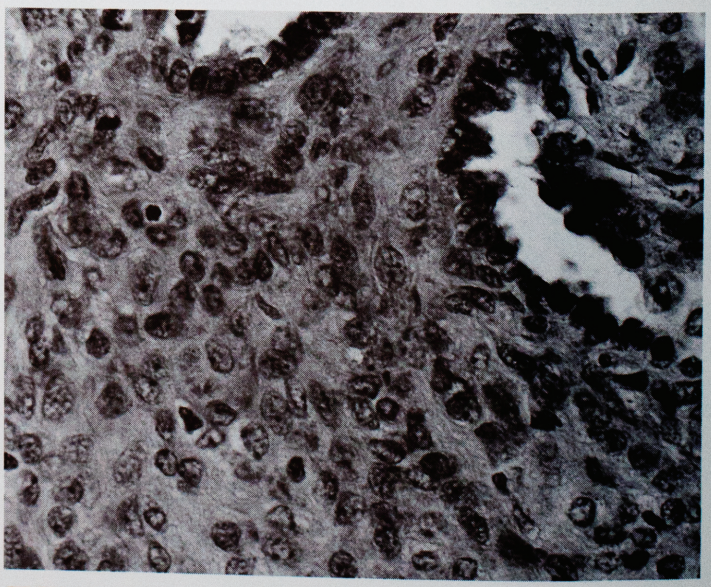

FIGURE 58-14. At high magnification, the round tumor cells of sclerosing hemangioma are easily differentiated from the smaller, darker, cuboidal epithelial cells lining the entrapped alveolar spaces. (H & E stain; high magnification.)

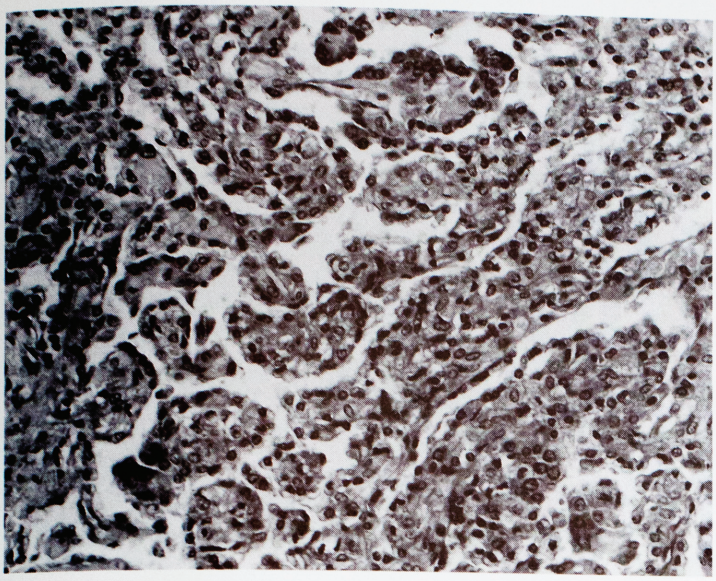

FIGURE 58-15. In papillary areas of sclerosing hemangioma, papillations lined by alveolar epithelial cells with cores of round neoplastic cells project into dilated air spaces. (H & E stain; intermediate magnification.)

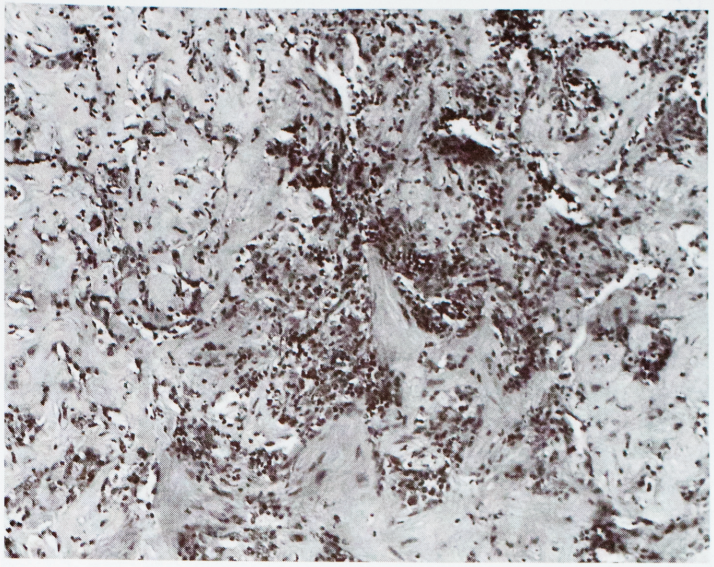

FIGURE 58-16. Sclerotic areas in sclerosing hemangioma tend to be paucicellular, and diagnostic tumor cells are often difficult to find. (H & E stain; low magnification.)

lined by cuboidal to flattened pneumocytes. The round, pale tumor cells are found within the intervening fibrous septa with scattered erythrocytes and inflammatory cells. The overall appearance is that of a cavernous hemangioma and probably accounts for the variegated red-brown discoloration seen.

Sclerotic areas in SH are typically paucicellular, with single cells and small nests of cells embedded in a dense, hyalinized fibrous stroma (Fig. 58-16). Areas of sclerosis may be extensive and often appear to arise out of solid or hemorrhagic areas. Entrapped alveolar epithelial clefts may be distorted by the sclerosing process and resemble an infiltrating glandular neoplasm. The round, pale tumor cells and the cuboidal, darker alveolar pneumocytes appear distinct, but transitional forms between the two cell types have been observed.[95–103] Other features found in all histologic areas include often numerous mast cells, foci of necrosis, calcification, and inflammation consisting mainly of lymphocytes and plasma cells (Fig. 58-17). Cholesterol clefts with foreign-body giant cells and hemosiderin-laden or foamy histiocytes are most common in hemorrhagic areas, but they may be seen in other regions as well. Concentric, laminated whorls of eosinophilic material and mature adipose tissue have been rarely observed in areas of sclerosis.

Many immunohistochemical studies of SH have shown that the round, pale tumor cells and cuboidal lining cells are positive for epithelial markers.[93,94,96,97,103,104] The cuboidal lining cells are variably reactive for keratin, EMA, surfactant apoprotein, and secretory component, a staining pattern also seen in reactive pneumocytes. The round tumor cells are immunoreactive for EMA, surfactant apoprotein, secretory component, CEA, and Clara cell antigen. Results of keratin immunostaining in the tumor cells are conflicting, with various studies reporting the presence or absence of keratin immunoreactivity using paraffin-embedded and cryostat sections. The tumor cells have been reported as reactive and negative with *Ulex europaeus* lectin, but this marker is not specific for endothelial cells and may bind to epithelial cells as well. Staining for factor VIII–related antigen, actin, desmin, and S-100 protein has been uniformly negative.

Most ultrastructural studies of SH have shown similar findings, although their interpretation has varied markedly. Two cell types have been identified, dark cells and light cells, labeled as such because of the relative quantity of intracytoplasmic organelles.[95,105–107] The dark cells typically show lipid-type vacuoles, concentrically whorled, laminated bodies, and large numbers of intracytoplasmic organelles. The nuclei are occasionally indented with peripherally clumped chromatin and prominent nucleoli. The cell borders possess abundant microvilli and occasional cytoplasmic processes that interdigitate with those of adjacent cells. A discontinuous basal lamina and rudimentary desmosomes without associated filaments are often seen.

The light cells have scanty cytoplasmic organelles and ovoid nuclei with a single nucleolus and peripheralized, aggregated chro-

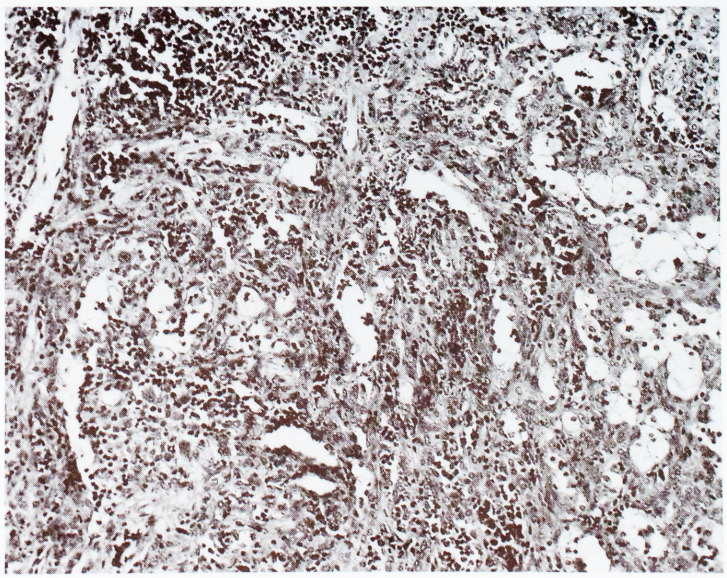

FIGURE 58-17. Some sclerosing hemangiomas are infiltrated by chronic inflammatory cells and foamy histiocytes (*right*) that may focally obscure the underlying tumor. (H & E stain; low magnification.)

matin. Surface microvilli and osmiophilic lamellar inclusions are seen, although in fewer numbers than in the dark cells. The cell margins also display interdigitating cell processes, a basal lamina, terminal bars, and primitive desmosomes. Transitional cells show the same ultrastructural features as the dark and light cells, with organelles quantitatively intermediate between the two.[112,113]

Some investigators consider the dark cells to represent the cuboidal lining cells and the light cells to represent the pale tumor cells.[94,105] However, both cell types may assume an attenuated, cuboidal, or tall columnar shape throughout the tumor, including the surfaces of papillations, in cavities and clefts, and within solid sheets of cells. The ultrastructural similarities between the two cell types and the intermediate forms indicate that the differentiation of tumor cells from reactive alveolar epithelium may not be clear-cut.

The differentiation of SH, often erroneously equated with origin, has been the overriding concern in most published studies. Liebow and Hubbell considered pulmonary SH to be analogous to SH of the skin and favored a reticuloendothelial origin.[92] Kay and colleagues proposed an endothelial origin, based on the observation of Weibel-Palade bodies within rare tumor cells.[108] Their illustrations, however, are not convincing, and the finding has not been confirmed. Haas also proposed an endothelial origin, based on the relation of the stromal cells to blood-filled spaces and a well-developed basement membrane, even though microvilli and poorly formed desmosomes were evident.[109] Another study favored an origin from mesothelium, based on the findings of microvilli and a compatible glycosaminoglycan electrophoresis pattern.[95] Most of the ultrastructural and immunohistochemical evidence delineated earlier indicates that SH is a lesion with epithelial features. Several investigators have proposed that SH are hamartomatous proliferations of distal respiratory epithelium and not true neoplasms.[98,106,110] Other than the mature adipose tissue in rare SH, there is little evidence to support this claim, and the issue remains unresolved.

Because of the histologically distinct features of SH, the differential diagnostic considerations are limited. Bronchoalveolar and other papillary adenocarcinomas may be initially confused with SH, but the other histologic patterns and the absence of anaplasia and mitotic figures are incompatible with the diagnosis of carcinoma. Plasma cell granulomas and other inflammatory pseudotumors may be confused with SH because of some solid areas mimicking SH. They are differentiated by the absence of blood-filled spaces, sclerotic areas, or epithelial-lined papillary processes. The intraalveolar, polypoid growth pattern of pulmonary epithelioid hemangioendothelioma may superficially resemble the papillary and solid patterns of SH. However, pulmonary epithelioid hemangioendothelioma often shows central zones of coagulative necrosis and a single neoplastic cell population, with the frequent formation of intracytoplasmic lumens.

PRIMARY MALIGNANT MELANOMA

Malignant melanoma primary in the lung or lower respiratory tract is uncommon, and many of the reported cases probably represent a solitary pulmonary metastasis from a regressed or occult primary cutaneous lesion.[111] Pulmonary metastases is the only clinical manifestation of primary cutaneous malignant melanoma in 7% to 9% of cases, and the possibility of metastasis should be methodically excluded. Jennings and associates have proposed a series of exclusionary criteria that we endorse: no previously removed pigmented skin lesions; no ocular tumors removed or enucleation; solitary tumor; compatible morphologic characteristics (*e.g.*, junctional changes and pagetoid spread favor a primary lesion, but cellular polymorphism favors a metastasis); and absence of demonstrable melanoma elsewhere at the time of operation or autopsy.[112]

Not all of these criteria are satisfied in every case. Some cases may be considered acceptable if most of the criteria are satisfied and information regarding one or two criteria is unknown or unavailable. There are approximately 20 cases reported in the English language literature that adequately fulfill the criteria for primary pulmonary malignant melanoma.[112–129] All patients were adults between 29 and 80 years of age (median, 47 years) at diagnosis. The 20 patients included 11 women and 9 men, most of whom presented with nonspecific symptoms such as cough, dyspnea, or hemoptysis. Four tumors arose in the trachea or carina, and the remaining 17 malignant melanomas were distributed throughout the lung without lobar predilection.[122,124,125,129] Eleven of the 17 lesions were centrally located.

Most patients received some type of surgical treatment, segmental resection, lobectomy, or pneumonectomy; a few patients received adjuvant irradiation or chemotherapy. Clinical follow-up was available for 17 patients, 8 of whom died of their disease within 14 months of diagnosis. Seven patients were alive, 1 with disease at 19 months, and 6 without evidence of disease an average of 5.2 years after diagnosis (range, 1.5–11 years). Of the remaining 2 patients, 1 died postoperatively, and 1 was diagnosed at autopsy.

On gross examination, primary pulmonary malignant melanomas are often polypoid, lobulated, tan-yellow, fleshy tumors that may show areas of tan-black discoloration. Virtually all pulmonary tumors are associated with bronchi, and most of these show polypoid intraluminal growth (Fig. 58-18). The histologic findings are analogous to those of cutaneous malignant melanoma. The neoplastic cells form cords, nests, and sheets underlying the junctional changes usually present in the overlying bronchial mucosa (Fig. 58-19). The neoplastic cells varied from polygonal to spindled shaped, with moderate amounts of eosinophilic cytoplasm. One bronchial malignant melanoma with a predominant spindled cell pattern has been reported.[125] Finely granular intracytoplasmic melanin pigment was observed in virtually every case.

Only two acceptable pulmonary malignant melanomas have been examined immunohistochemically.[112,117] The one reported by Jennings and colleagues was positive for S-100 protein and HMB-45, and it was negative for keratin, EMA, chromogranin, NSE, and calcitonin.[112] The example reported by Bagwell and associates was positive for S-100 protein and negative for keratin and leukocyte common antigen.[117]

Three pulmonary malignant melanomas have been studied ultrastructurally, all of which showed variable numbers of membrane-bound, electron-dense, ovoid inclusions with lamellar internal periodicity consistent with premelanosomes.[112,114,119] Irregular nuclei and numerous intracytoplasmic organelles, including mitochondria, smooth endoplasmic reticulum, and lysosomes, were found. Neurosecretory-type granules, desmosomes, or other cellular attachments were not observed.

Malignant melanoma is well known for its histologic variability, regardless of its site of origin. The differential diagnosis is therefore that of a poorly differentiated neoplasm with epithelioid, spindled, or small cell features. The diagnostic considera-

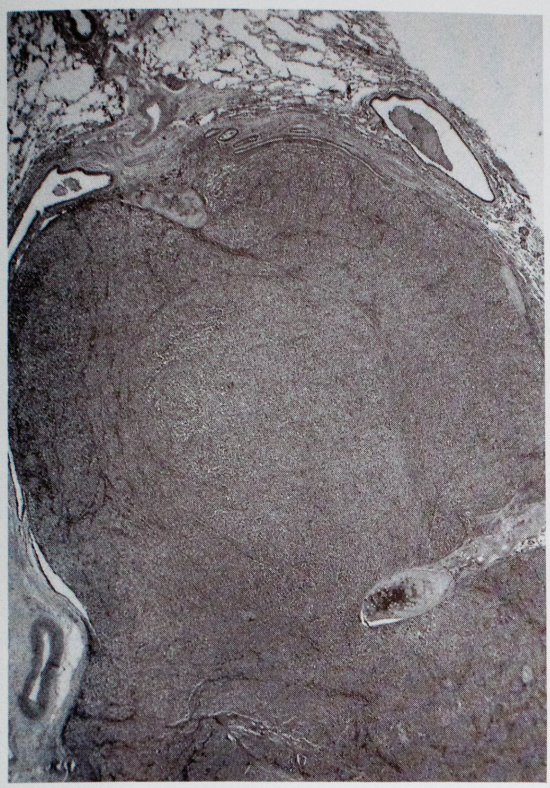

FIGURE 58-18. This bronchial malignant melanoma produced a large intraluminal mass. (H & E stain; low magnification; from Jennings TA, Axiotis CA, Kress Y, Carter D. Primary malignant melanoma of the lower respiratory tract. Report of a case and literature review. Am J Clin Pathol 1990;94:649.)

tions are broad and vary according to the cell type. Fortunately, problematic cases are easily resolved immunohistochemically, because malignant melanomas are invariably positive for vimentin and S-100 protein, with HMB-45 positivity in a high proportion of cases. Electron microscopy may be used for the identification of premelanosomes.

Several proposals have been formulated to explain the origin of malignant melanoma in the lower respiratory tract, but all remain speculative. Derivation from melanocytes or their precursors is unlikely, because such cells have not been identified as a normal constituent of the lower respiratory tract. Melanogenic metaplasia of epithelial, glandular, or neuroendocrine (*i.e.*, Kulchitsky) cells has been proposed, but precursor melanocytic proliferations or transitional forms have not been reported. Origin from a multipotential stem cell, a theory applied to every histogenetically problematic neoplasm, has the dubious advantage of being virtually impossible to prove or refute.

ALVEOLAR ADENOMA

The lesion we recognize as alveolar adenoma was originally described in 1974 by Wada and colleagues, who thought the lesion was a lymphangioma.[130] In 1986, Yousem and Hochholzer described six such benign neoplasms to which they applied the term alveolar adenoma.[131] All patients were asymptomatic and presented with an incidentally discovered, solitary, noncalcified coin lesion in the peripheral lung. Almost all lobes were involved, and the six lesions were surgically excised. Follow-up information was available for five patients, none of whom experienced recurrence or metastasis an average of 42.8 months (range, 13–120 months) after surgical excision.

Grossly, the resection specimens were well-circumscribed, gray-white nodules, averaging 1.8 cm in diameter (range, 1.2–2.5 cm). Most of the lesions were homogeneous, with hemorrhagic, cystic areas observed in two cases.

Microscopically, the proliferations appear spherical, multicystic, and well demarcated from the adjacent compressed pulmonary parenchyma (Fig. 58-20). Small central scars composed of granulation tissue, hemorrhage, and chronic inflammatory cells were observed in three cases. The cystic spaces were large and somewhat irregular in the central region and assumed a uniform microcystic to cribriform appearance toward the periphery. The centrally located cystic areas often contained amorphous, eosinophilic material that stained with PAS after diastase digestion. The intervening septa were usually thin and focally resembled normal alveolar walls (Fig. 58-21). The fibrovascular septal cores contained scant to

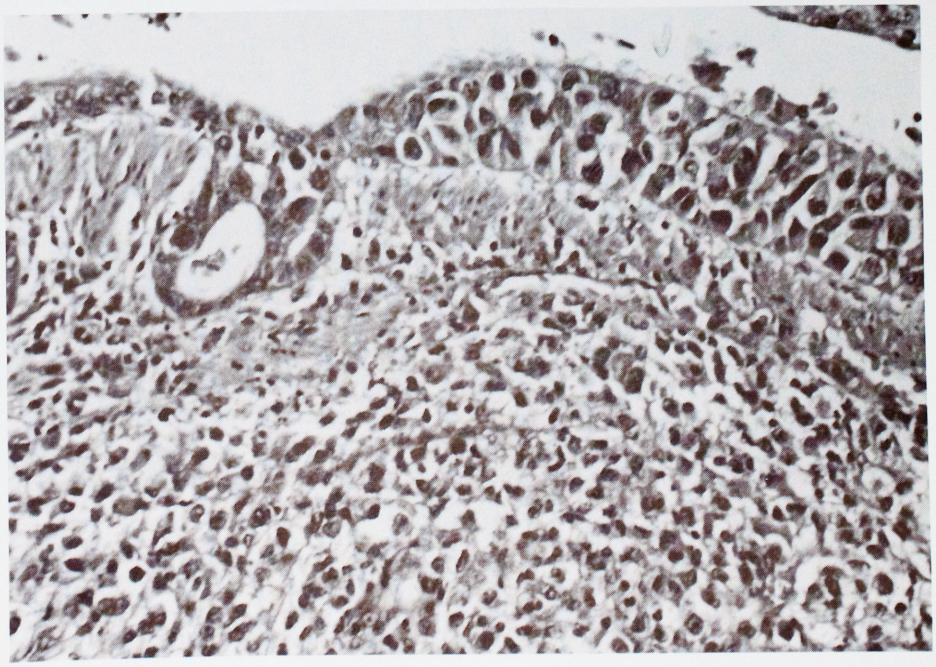

FIGURE 58-19. Malignant melanoma cells infiltrate the mucosa and submucosa of the bronchus. (H & E stain; intermediate magnification; from Jennings TA, Axiotis CA, Kress Y, Carter D. Primary malignant melanoma of the lower respiratory tract. Report of a case and literature review. Am J Clin Pathol 1990;94:649.)

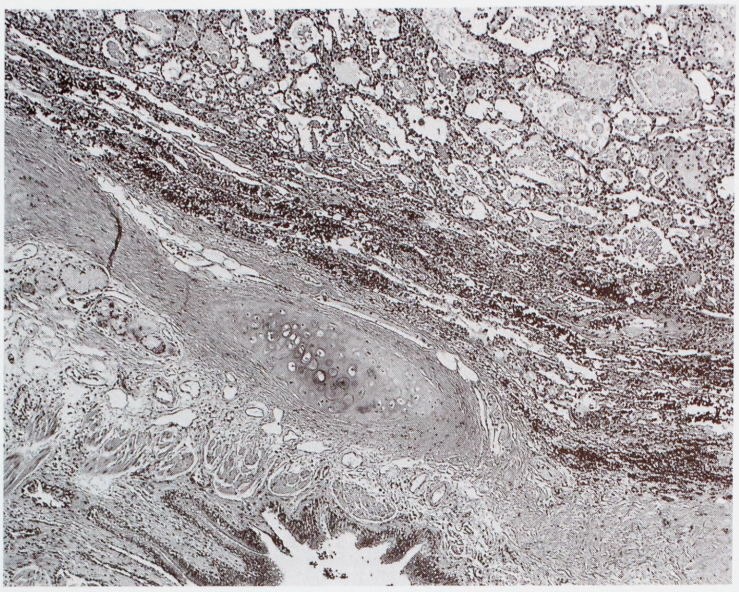

FIGURE 58-20. Alveolar adenomas (*top*) are characteristically well demarcated from the adjacent, compressed bronchus. (H & E stain; low magnification.)

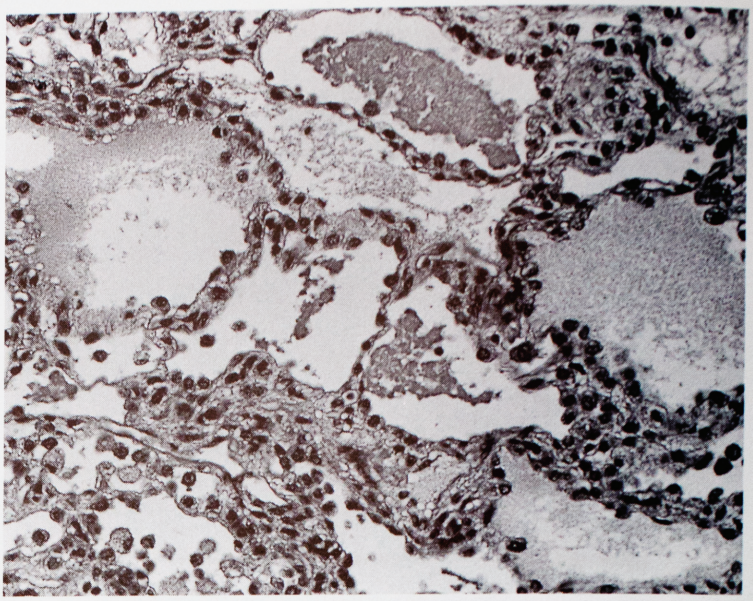

FIGURE 58-22. The cysts in this alveolar adenoma are lined by attenuated, flattened or cuboidal, cytologically bland alveolar pneumocytes and contain pink proteinaceous material. (H & E stain; intermediate magnification.)

moderate degrees of chronic inflammatory infiltrate, and interstitial hemorrhage was often seen.

The cells lining the cystic walls resemble alveolar pneumocytes and appeared hobnailed, cuboidal, or flattened. The cells had cytologically bland, ovoid nuclei with finely granular chromatin and occasional intracytoplasmic inclusions (Fig. 58-22). Mitotic figures were scarce, with fewer than one identified per 10 high-power fields. Conventional histochemical studies failed to demonstrate intracellular mucin within the lining or interstitial cells. Despite the well-circumscribed, low-power appearance, under high magnification, the tumor cells were occasionally found in direct continuity with neighboring alveolar epithelial cells.

Immunohistochemical examination of three cases in the Yousem and Hochholzer series demonstrated that the lining cells were strongly positive for cytokeratin and faintly reactive for CEA.[131] Staining for desmin and factor VIII–related antigen was uniformly negative in the neoplastic cells. Electron microscopy was performed in two cases, but the results were suboptimal because of poor preservation. Nonetheless, it supported an alveolar pneumocyte origin for the lining cells (see Chap. 47).

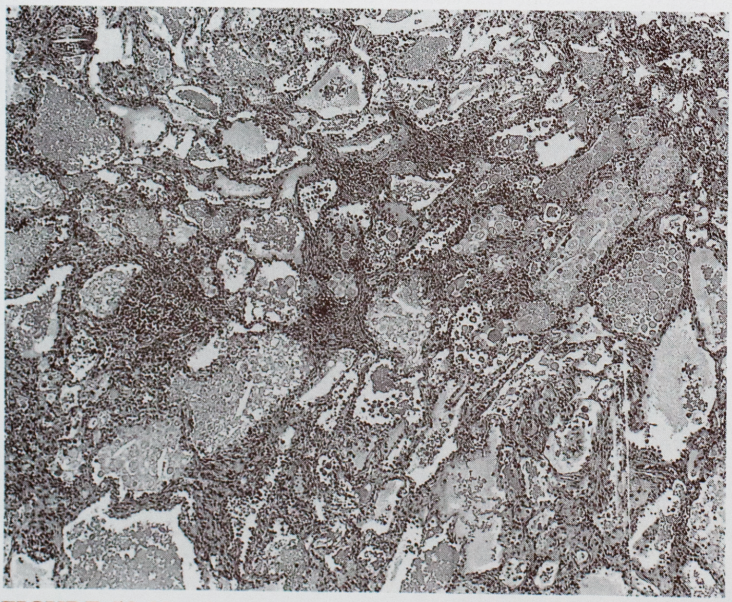

FIGURE 58-21. Cysts containing amorphous granular material are separated by fibrous septa in this example of alveolar adenoma. (H & E stain; low magnification.)

PAPILLARY ADENOMA

Three intrabronchial or bronchial-associated and four intraparenchymal papillary adenomas have been reported.[132–135] Two of the parenchymal tumors were subpleural.[132,133] All patients, including four females and three males ranging in age from 7 to 60 years (median, 26 years of age), presented with asymptomatic coin lesions discovered on routine chest roentgenograms. Follow-up was available for five patients, all of whom were free of recurrence or metastasis for 11 months to 10 years.

Grossly, papillary adenomas are well circumscribed but unencapsulated tumors ranging in diameter from 1.2 to 4.0 cm (Fig. 58-23). On cut section, the neoplasms are tan-brown and soft; grossly evident papillations are not seen. Microscopically, the tumors show well-defined, arborizing papillations with delicate to occasionally prominent fibrovascular cores (Fig. 58-24). Solid areas are evident. The epithelial cells are cuboidal with basally located nuclei and moderate amounts of eosinophilic cytoplasm. Nuclei are oval with finely granular chromatin and inconspicuous nucleoli. Pleomorphism is minimal, and mitotic figures are rare. Psammoma bodies have been not identified.

Papillary adenomas have morphologic, immunohistochemical, and ultrastructural features resembling Clara cells and type II pneumocytes. Four papillary adenomas were studied immunohistochemically, with immunoreactivity for Clara cell antigen demonstrated in one lesion and surfactant apoprotein observed in the neoplastic cells of another.[133,134] Four tumors were examined ultrastructurally.[132–134] Each showed cuboidal neoplastic cells con-

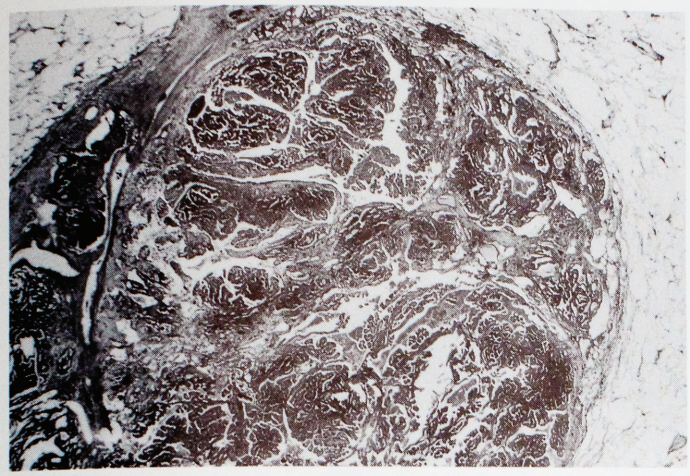

FIGURE 58-23. Papillary adenomas are sharply demarcated from the adjacent parenchyma. (H & E stain; low magnification; from Hegg CA, Flint A, Singh G. Papillary adenoma of the lung. Am J Clin Pathol 1992;97:393.)

nected by primitive or tight junctions with apical microvilli having filamentous cores and surrounding glycocalyces. Concentric, osmiophilic lamellar bodies and apical membrane-bound secretory granules were identified in three tumors.

Papillary adenomas and alveolar adenomas are morphologically distinct. Papillary adenomas lack the microcystic architecture, intracystic proteinaceous material, septal inflammation, and attenuated epithelial cells of alveolar adenomas and appear fundamentally different from the latter tumors. Continuity with adjacent alveolar epithelium has been observed in alveolar adenomas but not papillary adenomas. We believe that the two tumors are sufficiently distinct that the separate designations of alveolar and papillary adenoma should be retained.

Papillary adenoma resembles SH of the lung, because both neoplasms may show a prominent papillary growth pattern lined by bland cuboidal cells. The tumors are differentiated by the pale, round tumor cells in the papillae of SH but not papillary adenoma. SHs may show extensive solid, hemorrhagic, and sclerotic areas that are not present in papillary adenomas.

Some investigators have proposed that alveolar and papillary adenomas represent hamartomas, rather than neoplasms. In our opinion, the cystic configuration and the characteristic lining cells are sufficiently dissimilar from normal pulmonary parenchyma to support a neoplastic interpretation. Unlike pulmonary epithelial hyperplasia, however, alveolar and papillary adenomas are not associated with bronchioloalveolar carcinomas and do not appear to represent a premalignant lesion (see Chap. 47).

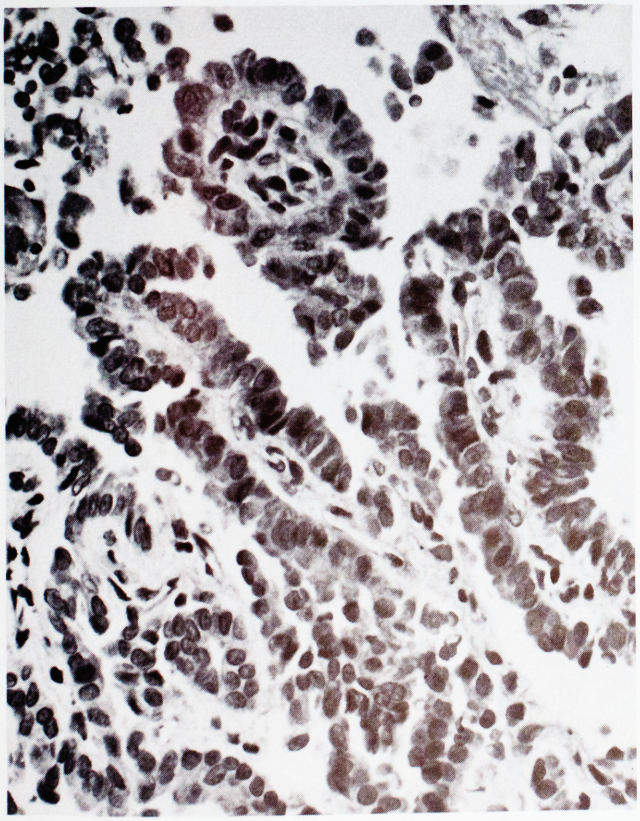

FIGURE 58-24. Papillae with delicate fibrovascular cores are lined by cytologically bland cuboidal or columnar cells in this example of papillary adenoma. (H & E stain; intermediate magnification; from Hegg CA, Flint A, Singh G. Papillary adenoma of the lung. Am J Clin Pathol 1992;97:393.)

CHORIOCARCINOMA

Choriocarcinoma arising as a primary lung tumor is exceedingly rare, and undifferentiated carcinoma of the lung with giant cell features should be ruled out in making the diagnosis. Because serum human chorionic gonadotropin (HCG) can also be elevated in undifferentiated large cell carcinoma of the lung, this important laboratory test is of little diagnostic help in separating these two tumors. In 1977, Hayakawa and associates reported two examples of primary pulmonary choriocarcinoma.[136] One patient was a 45-year-old man with a left upper lobe mass measuring 7 cm × 6 cm

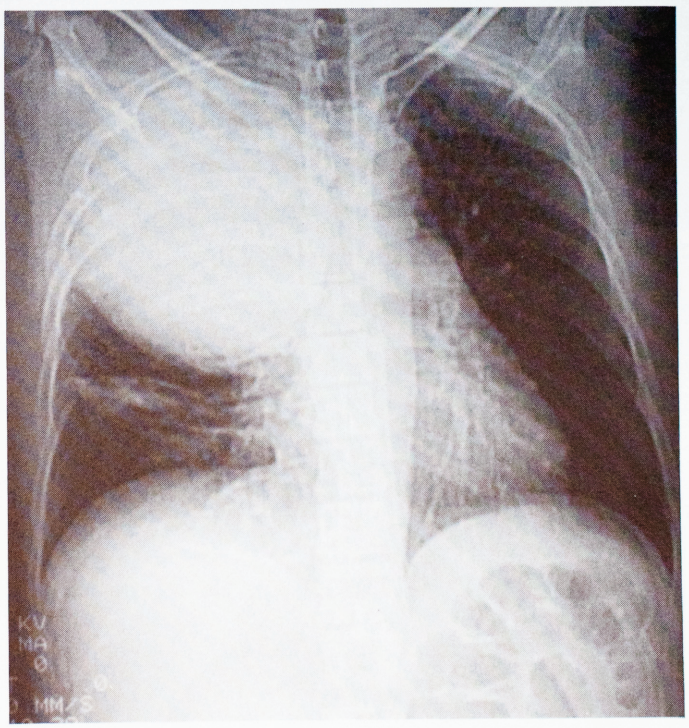

FIGURE 58-25. Primary choriocarcinoma of the lung presented as a huge mass replacing the right upper lobe of a woman. (Contributed by the editor.)

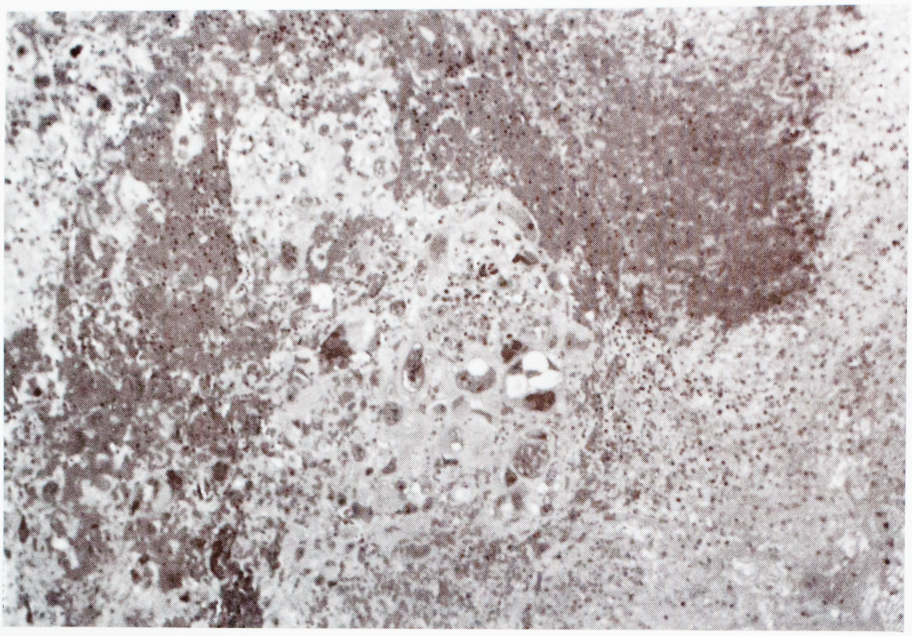

FIGURE 58-26. The mass in Figure 58-25 consisted of extensively necrotic and hemorrhagic tissue with islands of choriocarcinoma. (H & E stain; low magnification; contributed by the editor.)

× 5 cm. The second patient was a 57-year-old man with a 10 cm × 7 cm × 6.5 cm mass in the right lower lobe. The histologic appearance of the tumor was absolutely indistinguishable from choriocarcinoma arising in usual locations. Both patients in this study had gynecomastia, increased serum HCG levels, and disseminated lesions at necropsy.

In another case described by Saldana, the pulmonary choriocarcinoma was a huge hemorrhagic mass arising in the right upper lobe of a woman (Fig. 58-25) with no choriocarcinoma elsewhere and no history of having had such a tumor in the past.[137] Histologically, there was extensive hemorrhagic necrosis, but cellular islands unmistakable for choriocarcinoma were identified (Fig. 58-26). Malignant trophoblastic elements stained positively for HCG by the immunoperoxidase technique (Color Fig. 58-1; Fig. 58-27). A few months after extirpation of the lung mass, the patient developed massive metastatic disease to the brain and died despite extensive chemotherapy for choriocarcinoma.

Ependymoma

Crotty and colleagues recently have described a unique example of primary malignant ependymoma of the lung in a 60-year-old woman.[138] It presented as an isolated lesion 2.0 cm in diameter, after 30 months of combined chemotherapy and irradiation for small cell carcinoma of the ipsilateral lung. The histologic features of the tumor were comparable to those of ependymomas of the central nervous system, including strong reactivity for glial fibrillary acid protein. The patient died 6 months later, not from metastatic disease, but from a hypertensive cerebral hemorrhage.

Acknowledgments

We thank Ms. Ursula Miller for expert photographic support. Andrew Flint, M.D., Stuart A. Flynn, M.D, and Timothy A. Jennings, M.D. graciously supplied illustrative materials from their prior publications.

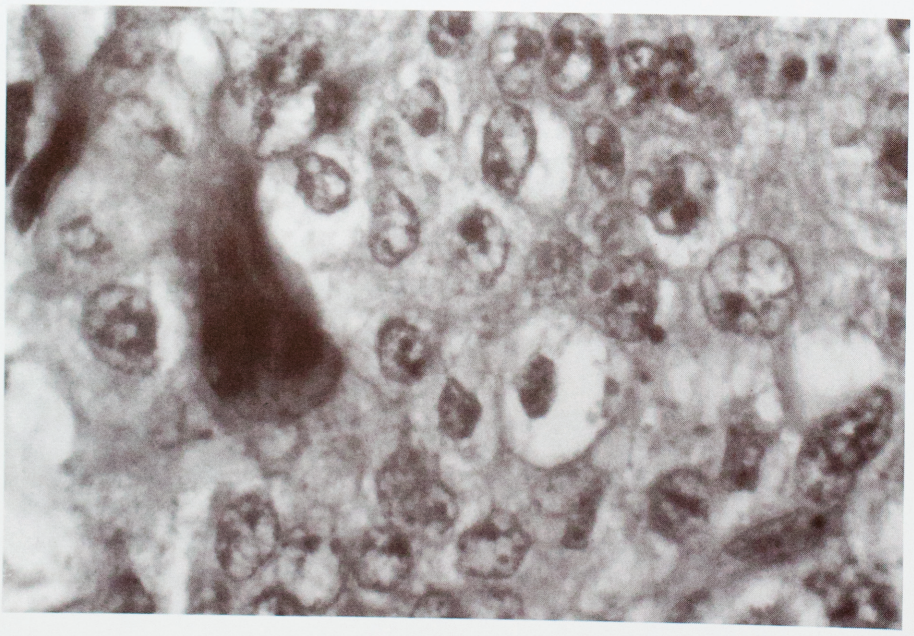

FIGURE 58-27. The choriocarcinoma is composed of clear cytotrophoblastic cells and darker syncytiotrophoblastic cells. (H & E stain; high magnification; contributed by the editor.)

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