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47
Adenocarcinoma

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Tumors with the architectural and cytologic features of adenocarcinoma, including the ability to form glands and secrete intracellular and extracellular mucins, represent the most common histologic type of lung cancer. Evidence accrued over the last 15 years indicates that adenocarcinoma has surpassed squamous cell carcinoma as the most common histologic type of lung cancer in some geographic areas of the United States.[1–7] Adenocarcinoma has been known for many years to be more common in women, in younger persons, and in those who have never smoked. However, most patients with this tumor do have a history of cigarette smoking, although the association is statistically not as strong as it is for squamous and small cell carcinoma.[8,9]

Does the emergence of adenocarcinoma reflect in any way the switch from traditional, nonfiltered, highly toxic cigarettes to refined, filtered brands?[10] Is adenocarcinoma becoming more frequent because of involuntary exposure to cigarette smoke (*i.e.*, passive smoking) at home and at work?[11] Equally intriguing are the roles of a host of poorly understood factors, such as genetic predisposition, radiation effects, occupational exposure, dietary habits, and viruses, which may act individually or in concert (see Chap. 46).[6] The pathologic classification of adenocarcinoma used in this chapter takes into account the site of origin, histologic features, and histogenesis (Display 47-1).[12]

PERIPHERAL BRONCHOGENIC ADENOCARCINOMA

Peripheral bronchogenic adenocarcinomas arise from bronchi much smaller than those giving rise to the usual squamous and small cell carcinomas. These bronchi are usually about 3 mm in diameter or smaller. Inspection and palpation disclose a localized, firm mass attached to and producing puckering of the pleura. On cut sections, these cancers are circumscribed, unencapsulated nodules or masses of white-gray tissue with ragged edges that infiltrate the surrounding lung parenchyma. Characteristically, there is a central stellate scar that produces the pleural retraction, hence the designation "scar carcinomas" (Fig. 47-1). Anthracotic pigment deposition varies from simple mottling to uniform black staining of the scar. The foci of necrosis within the scar are also a common finding, particularly in poorly differentiated tumors. Massive necrosis with cavitation is rare and should raise the suspicion of a peripheral squamous cell carcinoma, large cell undifferentiated carcinoma, or metastatic tumor. In Chaudhuri's study of 632 primary lung cancers with cavitation, there were only 7 adenocarcinomas (1%).[13]

In peripheral bronchogenic adenocarcinomas associated with a central scar, the scar has been traditionally interpreted as preceding the development of the adenocarcinoma[14]; but this view has undergone a drastic revision in recent years. Careful histologic observations by Shimosato and colleagues and biochemical and histologic studies by Madri and Carter and Barsky and associates led to the conclusion that the scar develops after the carcinoma.[15–17] For Kung and colleagues, the scar represents a collapse of lung tissue after obstruction of the airway by tumor.[18] Barsky and associates think that tumor-induced desmoplasia is probably the main mechanism of scar formation.[17] For Kolin and Koutoulakis, scar production in small peripheral adenocarcinomas with predominately intraalveolar growth patterns is caused by repeated episodes of neoplastic occlusion of arteries, producing areas of necrosis and infarction; after reabsorption of the necrotic debris, the existing lung parenchyma collapses, producing an elastic-rich anthracotic scar.[19]

We concur with Shimosato and colleagues that eventual infiltration by tumor leads to hyalinization of the scar, a mark of highly aggressive tumors.[15] We and others have observed that poorly differentiated scar adenocarcinomas with vascular invasion are associated with various degrees of necrosis and unfavorable prognoses.[12,19] Squamous cell carcinomas, large cell carcinomas, and some small cell carcinomas may have an associated central scar, the pathogenesis of which is probably not different from that of adenocarcinomas.[12]

DISPLAY 47-1. CLASSIFICATION OF LUNG ADENOCARCINOMA

- Peripheral bronchogenic adenocarcinoma (70%–80%)
  - Usual subtypes
    - Acinar
    - Papillary
    - Solid carcinoma with mucin production
    - Adenosquamous carcinoma
  - Unusual subtypes
    - Signet-ring cell carcinoma
    - Colloid carcinoma
    - Colonic-like carcinoma
    - Intestinal-like carcinoma
    - Hepatoid carcinoma
    - Endodermal tumor resembling fetal lung
    - Mesothelioma-like adenocarcinoma
- Central bronchogenic adenocarcinoma (rare)
- Bronchioloalveolar tumors (20%–30%)
  - Bronchioloalveolar carcinoma
    - Lepidic, with mucinous and non-mucinous variants
    - Papillary
    - Solid
  - Papillary adenoma
  - Pulmonary mucinous cystic tumor
  - Papillary nodules resembling bronchioloalveolar carcinoma
  - Alveolar adenoma
- Adenocarcinoma in diffuse interstitial fibrosis (rare)

Adapted from Saldana MJ. Localized diseases of the bronchi and lung. In: Silverberg SG, ed. Principles and practice of surgical pathology. 2nd ed. New York: Churchill-Livingstone, 1990:713.

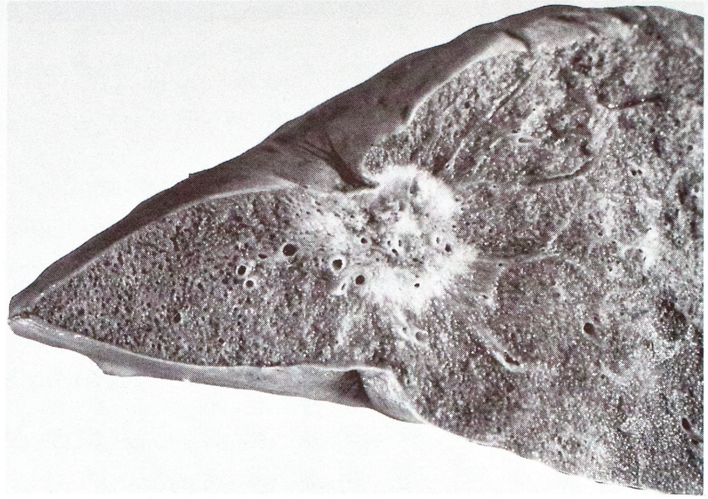

FIGURE 47-1. The characteristic appearance of peripheral adenocarcinoma of the lung includes a central, pigmented scar that is producing pleural retraction (*i.e.* scar carcinoma). The small bronchi from which this tumor arose are 1 to 3 mm in diameter. (From Saldana MJ. Localized diseases of the bronchi and lung. In: Silverberg SG, ed. Principles and practice of surgical pathology. 2nd ed. New York: Churchill-Livingstone, 1990:713.)

Usual Histologic Subtypes

Histologically, adenocarcinomas are usually acinar or gland forming, with or without a papillary component.[20–24] Depending on the predominant pattern, the lesions should be classified as acinar or papillary; acinar tumors are fourfold more common than papillary (Figs. 47-2 and 47-3).[25,26] The qualification of well, moderately, or poorly differentiated is based on cytologic features and architectural detail, as for adenocarcinomas of other organs. Mucin production is frequently found and should always be investigated with mucicarmine and with periodic acid-Schiff and diastase stains. If the results of staining are positive, immunoperoxidase stains are unnecessary for confirmation; immunoperoxidase staining is expected to be positive for low-molecular-weight keratins, carcinoembryonic antigen (CEA), epithelial membrane antigen, Leu M1, B72.3, and Ber-EP4.[27] Immunostains are frequently indispensable in differentiating adenocarcinomas from mesothelioma but of lesser value in separating primary from metastatic adenocarcinomas (see Chap. 57).[28]

Solid tumors lacking acinar or papillary features were once considered to be large cell undifferentiated carcinomas (Color Fig. 47-1), but according to the 1981 classification of the WHO, the tumors are designated as poorly differentiated adenocarcinomas if mucins are demonstrated in their cytoplasm.[24] Their incorporation into the adenocarcinoma group, however, is insufficient to explain the increased incidence of adenocarcinoma.[29] Solid adenocarcinomas can account for as many as 13% of all pulmonary adenocarcinomas in some series, and they are notorious for their highly malignant course.[25,26]

Adenosquamous carcinomas are characterized by the coexistence of adenocarcinoma and squamous cell carcinoma. They account for 0.6% to 4% of all lung cancers, depending on the diagnostic criteria used.[30–35] Tumors that combine the well-differentiated adenocarcinoma features of mucin production and gland formation with distinct keratinization are exceedingly rare, representing 0.6% of the total. They are adenocarcinomas with squamous differentiation, a view supported by their histologic features, by their occurrence at the periphery of the lung, and by a prognosis comparable to that of common adenocarcinoma (Fig. 47-4).[12]

Although rare, centrally located adenosquamous carcinomas do occur, probably because they arise from mucin-producing bronchial epithelium that has undergone squamous metaplasia. Linnoila observed that many typical squamous cell carcinomas of major bronchi frequently contain scattered mucicarmine-positive pools or cells, and only if this feature is extensive should the tumor be interpreted as adenosquamous.[6] A third condition in which distinct adeno and epidermoid components coexist is in bronchial gland tumors of the mucoepidermoid type (see Chap. 52). Ishida and associates identified three histologic subgroups in 11 patients with pulmonary adenosquamous carcinomas: those that were predominately glandular (5), those that were predominately squamous (3), and those that contained roughly equal amounts of adenocarcinoma and squamous carcinoma (3).[34] In the glandular-predominant group, four tumors were peripheral, and one was central; in the squamous-predominant group, two tumors were peripheral, and one was central; and in the mixed group, all tumors were peripheral. In the mixed group, the tumors were poorly differentiated and contained areas of undifferentiated carcinoma with no recognizable glandular or squamous components by light microscopy, but all were positive for keratin, epithelial membrane antigen, and CEA by immunohistochemical methods.

The researchers led by Ishida proposed that most adenosquamous carcinomas of the glandular-predominant type arise through squamous metaplasia in a preexisting adenocarcinoma. Adenosquamous carcinomas of the predominantly squamous type are characterized by squamous elements punctuated by

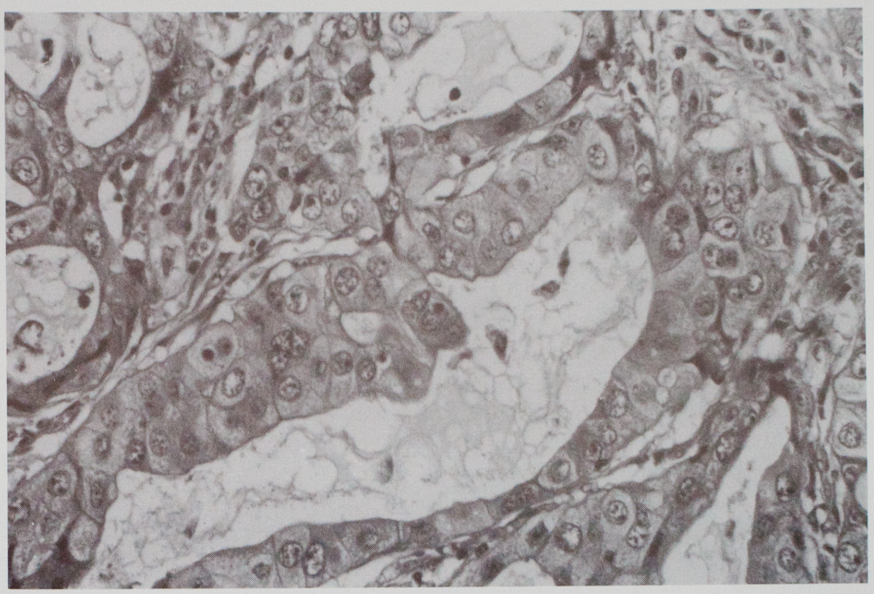

FIGURE 47-2. Moderately differentiated, mucin-producing acinar adenocarcinoma of the lung infiltrates an inflamed and fibrous stroma. (H & E stain; intermediate magnification.)

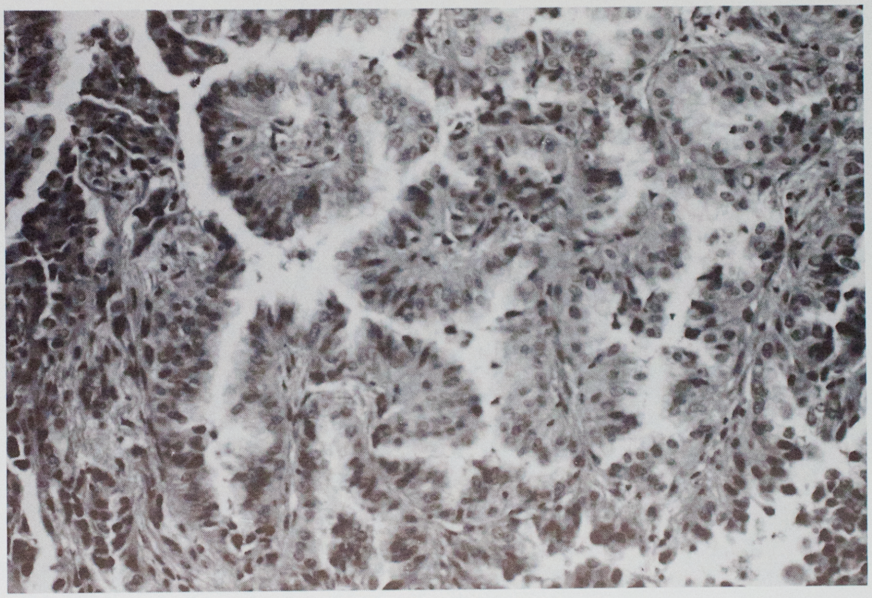

FIGURE 47-3. Papillary type of bronchogenic adenocarcinoma of the lung. Although the acinar and papillary patterns frequently coexist, purely papillary lesions represent only 20% of all bronchogenic adenocarcinomas. (H & E stain; intermediate magnification.)

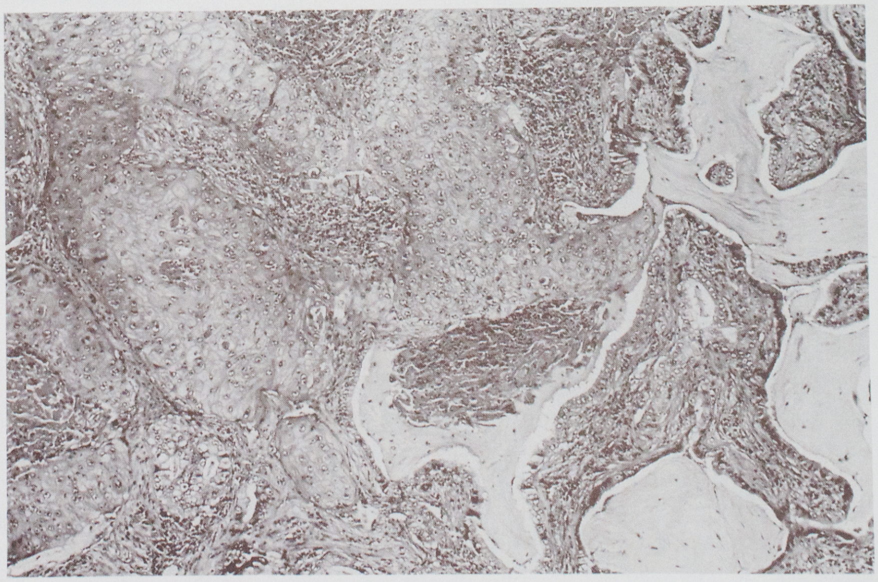

FIGURE 47-4. A peripheral lung adenosquamous carcinoma combines features of adenocarcinoma with mucin production (*right*) and squamous cell carcinoma (*left*). (H & E stain; intermediate magnification; from Saldana MJ. Localized diseases of the bronchi and lung. In: Silverberg SG, ed. Principles and practice of surgical pathology. 2nd ed. New York: Churchill-Livingstone, 1990:713.)

mucus-containing glands or cells, resembling mucoepidermoid carcinomas. All adenosquamous carcinomas of the mixed type contained undifferentiated carcinoma, suggesting that they arose from a multipotential stem cell capable of differentiating along glandular and squamous lines. The overall 5-year survival rate for patients with adenosquamous carcinoma in this small series was 35%, a figure similar for adenocarcinoma and squamous cell carcinomas. In the series of 127 patients with adenosquamous carcinoma of the lung reported by Sridhar and colleagues, smoking was a major etiologic factor. The patients with localized cancer had a projected 5-year survival rate of 62%, but the median survival for those with regional and distant disease was 8 and 4 months, respectively.[32] In the 56 patients described by Takamori and associates, the outcome for those with adenosquamous carcinoma was poorer than that for those with adenocarcinoma and squamous cell carcinoma of a comparable stage.[33]

In our experience, adenosquamous carcinomas in which both components are poorly differentiated occur more frequently than well-differentiated forms, and they are a source of confusion for the pathologist. They actually represent large cell undifferentiated carcinomas with partial differentiation along adenocarcinoma and squamous cell carcinoma lines. The squamous component can be recognized by features such as intracytoplasmic keratin production, intercellular bridges, and the characteristic layering and interlocking of the cells in a pavementlike fashion, resembling Malpighi stratum of the skin. The nuclear chromatin tends to be coarse and dark and the nucleoli indistinct.

The adenocarcinoma component may show mucin-containing cells or cells with abundant clear or basophilic cytoplasm, vesicular nuclei with distinct nuclear membrane, and prominent nucleoli. For a tumor to be considered poorly differentiated adenosquamous carcinoma, the adeno and squamous components must be clearly recognizable, whether or not an undifferentiated component exists in the lesion. In practice, a combination of histologic and cytologic criteria should be used to classify carcinomas composed of large cells among four situations that commonly arise:

- No clear evidence of squamous or adenocarcinoma differentiation should be interpreted as a large cell undifferentiated carcinoma.
- Large cell undifferentiated carcinoma with focal squamous differentiation should be called a poorly differentiated squamous cell carcinoma.
- Large cell undifferentiated carcinoma combined with poorly differentiated adenocarcinoma should be interpreted as a poorly differentiated adenocarcinoma.
- Large cell undifferentiated carcinoma combined with poorly differentiated adenocarcinoma and poorly differentiated squamous cell carcinoma can be designated poorly differentiated adenosquamous carcinoma.

The pathologist classifies a large cell tumor according to its most differentiated component and grades it by the poorest degree of differentiation of such a component.

Small, artifactually altered transbronchial specimens may be impossible to classify, but that should not be the case for thoroughly sampled, resected lesions. Immunohistochemical stains, particularly for demonstrating cytokeratins, CEA, and epithelial membrane antigen, may aid in the solution of these problems, but these stains are not required by the WHO to classify a lung tumor; nor is the electron microscope required, but it is a useful instrument for demonstrating intracellular organelles and intercellular attachments. As shown by McDowell and colleagues, the ultrastructural features in an astonishingly large proportion of non-small cell lung cancers (46%) are those of poorly differentiated adenosquamous tumors.[35]

Unusual Histologic Subtypes

The full range of histologic expression of pulmonary adenocarcinoma remains to be explored. We recognize signet ring and colloid adenocarcinomas, which mimic their counterparts in the gastrointestinal tract and breast, and their prognosis is equally poor.[36] Rare forms of pulmonary adenocarcinoma are morphologically indistinguishable from carcinomas of the colon (Color Fig. 47-2; Fig. 47-5), and immunohistochemistry may aid in their separation.[37] Tumors with small intestinal differentiation, including the presence of Paneth cells (*i.e.*, intestinal-like cells), and hepatoid carcinomas producing α-fetoprotein and pursuing a highly malignant course have also been documented.[38,39]

Another unusual variant of pulmonary adenocarcinoma designated endodermal tumor resembling fetal lung or blastomalike adenocarcinoma is composed of clear glands identical to those of blastomas (Fig. 47-6), complete with epithelial morulas and neuroendocrine features (see Chap. 54).[40]

Rare examples have been reported of aggressive peripheral adenocarcinomas displaying a pleural tropism and encase the lung in a shell-like layer of tumor, which resembles mesothelioma of the pleura.[41] The separation of this peculiar form of pulmonary adenocarcinoma from mesothelioma has been greatly facilitated by the use of immunoperoxidase stains.[28]

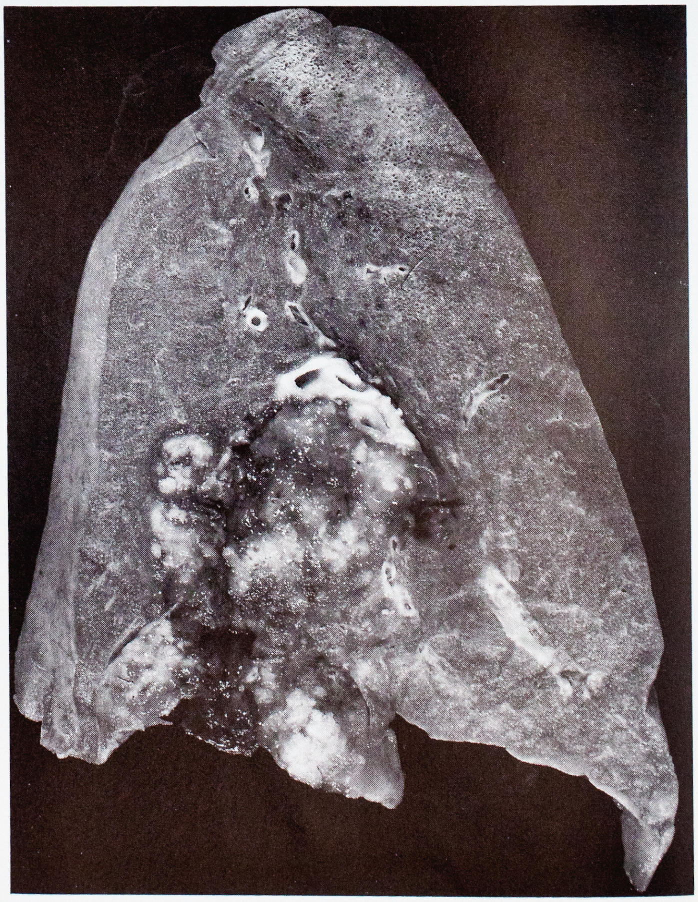

FIGURE 47-5. An adenocarcinoma of the lung with colloid features produces mucin, imparting a slimy consistency to the lesion. A metastatic lesion was carefully ruled out at necropsy.

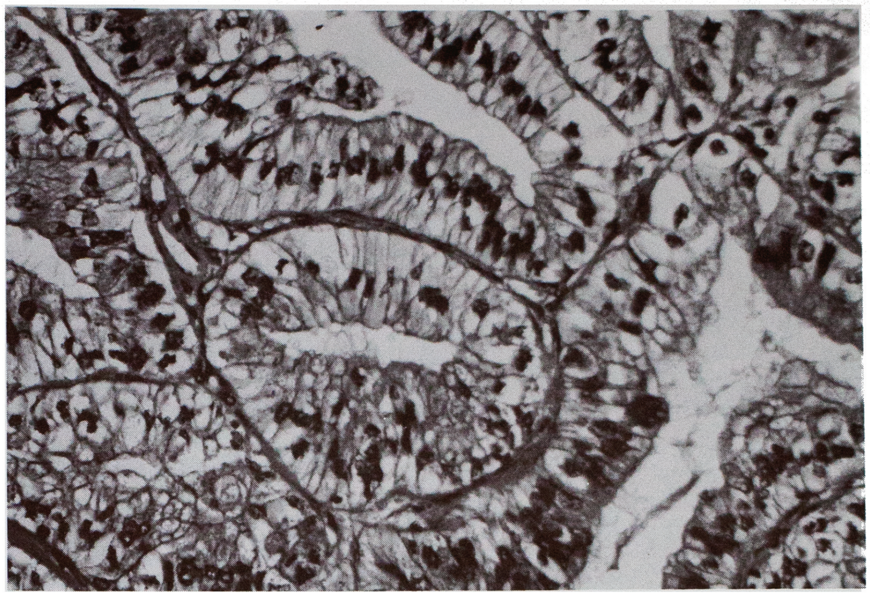

FIGURE 47-6. This type of adenocarcinoma is designated as an endodermal tumor resembling fetal lung or blastomalike adenocarcinoma because of its peculiar histologic features. (H & E stain; intermediate magnification.)

CENTRAL BRONCHOGENIC ADENOCARCINOMAS

Rarely, adenocarcinomas arise in large and medium-sized bronchi or the trachea, locations favored by squamous cell carcinomas.[42–44] In these cases, the possibility of a metastatic adenocarcinoma from elsewhere in the lung; metastases from breast, colon, kidney, or thyroid; or a malignant melanoma should be carefully considered. Primary adenocarcinomas of large bronchi can arise from the bronchial surface epithelium or from submucosal bronchial glands. They are frequently papillary or grow into bulky masses rich in mucins that have a lobular configuration or a complex cribriform appearance suggesting a bronchial gland origin (see Chap. 52).

Kodama and associates described five cases of adenocarcinoma of the lung with predominant endobronchial growth.[45] All were interpreted as well-differentiated papillary adenocarcinomas. Under the electron microscope, evidence of bronchial and bronchiolar differentiation was found, and mucus-producing cells were observed.

BRONCHIOLOALVEOLAR TUMORS

Bronchioloalveolar Carcinoma

Bronchioloalveolar carcinoma (BAC) is probably responsible for the rising overall incidence of pulmonary adenocarcinoma.[6,7] This tumor originates at the periphery of the lung beyond grossly recognizable, cartilage-bearing bronchi in the terminal membranous bronchioles, respiratory bronchioles, alveolar ducts, and alveoli. Originally described by Malassez in 1876, BAC has been the subject of numerous pathologic studies and reviews.[46–61] The development of this tumor in sheep and cattle (*e.g.*, Jaagsiekte, Maedi, Montana fever) has been associated with a viral agent.[62–65] In humans, Colson and colleagues observed particles with the morphologic and biologic characteristics of oncoviruses.[55] Perk and associates reported the remarkable occurrence of this tumor in a husband and wife within a year of each other.[64] These observations and the fact that the association between cigarette smoking and BAC is the weakest among all common lung cancers support the role of a different agent, perhaps a virus, in the genesis of this tumor, but this remains to be proven.

HISTOLOGIC SUBTYPES

We classify BAC in three variants according to their architectural features: lepidic (*i.e.*, classic), papillary, and solid (see Display 47-1).

Lepidic Forms. The lepidic variant of BAC is the most common form, and the tumor is characterized by spreading in a single cell layer on top of alveolar septa that serve as a scaffold for the malignant cell growth. The supporting alveolar walls may be of normal thickness or mildly thickened by chronic inflammation and fibrosis. Cytologically, more than one half of these cases are mucinous BAC, composed of tall, well-differentiated, mucin-producing cells with basally located nuclei (Figs. 47-7 and 47-8). They are thought to arise from bronchiolar epithelium undergoing mucinous metaplasia, a change common in bronchiolar epithelium even in nontumoral situations such as chronic bronchitis.

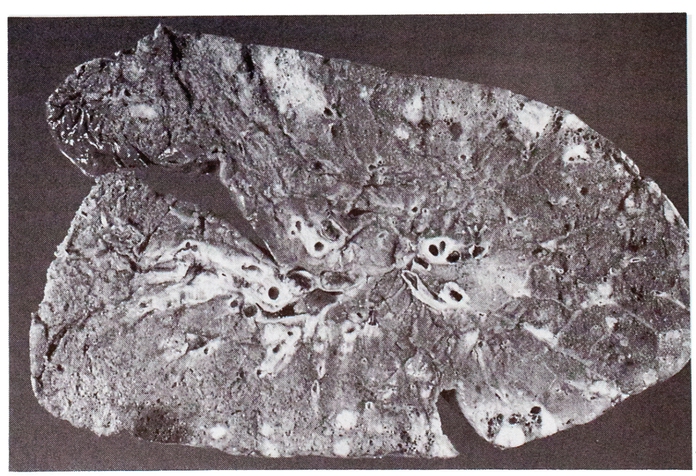

FIGURE 47-7. A multifocal bronchioloalveolar carcinoma composed of mucin-producing cells. Tumors with this gross appearance are more common and have a poorer prognosis than unifocal lesions.

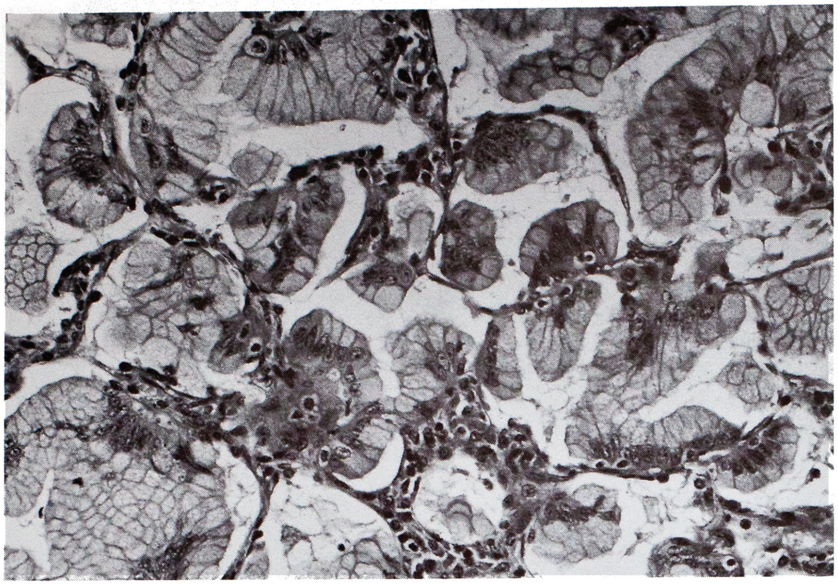

FIGURE 47-8. This mucin-producing bronchioloalveolar carcinoma has a striking lepidic type of growth. The lepidic designation alludes to the resemblance to butterflies sitting on a fence. (H & E stain; intermediate magnification; from Saldana MJ. Localized diseases of the bronchi and lung. In: Silverberg SG, ed. Principles and practice of surgical pathology. 2nd ed. New York: Churchill-Livingstone, 1990:713.)

The nonmucinous forms of lepidic BACs are derived from at least two cell types: tall columnar cells with a peglike configuration representing Clara cells indigenous to bronchioli, and type II pneumocytes that normally line alveoli. Among BACs of Clara cell origin, examples with apocrine and glycogen-rich features have been described, and the glycogen-rich forms should not be confused with mucinous BACs.[66–68]

A combination of cytologic features can be frequently observed in lepidic BACs by light or electron microscopy. Tumors composed primarily of Clara cells may show focal mucin production; by electron microscopy and immunohistochemistry, other tumors may demonstrate a combination of Clara cell and type II pneumocyte differentiation.[69] It seems reasonable to accept the existence of a totipotential cell as the source of these tumors, although the cell has not been identified.

Maeda and Sueishi, using monoclonal antibody KP8D4, which specifically reacts with basal cells of the bronchus, were able to stain positively, among other tumors, four examples of Clara cell adenocarcinoma.[70] It is possible that the basal cell of the bronchial epithelium, which for many researchers is the stem cell for most bronchogenic carcinomas, may be the primary source of BACs as well. However, no basal cells occur in the normal bronchiolar epithelium (see Chap. 1).

Grossly, lepidic BAC, regardless of cell of origin, can be classified as unicentric or multicentric. Overall, the unicentric lesion is two to three times more common than the multicentric. Tumors presenting as an isolated nodule or infiltrate have a resectability rate of about 80% and a 5-year survival rate in the range of 75%.[12] Tumors composed of mucinous cells are frequently multicentric and have a poorer prognosis than nonmucinous tumors.[61,71–73] Confluence of multiple mucinous lesions may progress to a lobar consolidation with a sticky, mucoid character that is classically compared with *Klebsiella* pneumonia.

The unicentric form of BAC is slow growing and often resectable. The tumor may recur after surgery, but it seems unlikely that the unicentric form evolves over time into the multicentric one.[73] In favor of this interpretation, Barsky and colleagues used the polymerase chain reaction to demonstrate that 75% of multifocal BAC specimens had evidence of multiclonality.[74] They recommended that multifocal BAC be treated as separate primaries with limited wedge resections to conserve lung tissue. Their observations also militate against the old view of intrapulmonary metastasis or aerosol spread of multifocal BAC.

Another variant, designated as sclerosing BAC, was proposed by Ohori and associates, and it may have a worse prognosis than the mucinous and nonmucinous forms.[75] In their study, the sclerosing BACs had central sclerotic areas with disruption of the basement membranes but with preservation of the same at the periphery of the lesion, features also seen in conventional adenocarcinomas. The existence of the sclerotic variant of BAC needs clarification, but it focuses attention on the subject of scar-associated BAC—a fact that is real in our experience but is seldom mentioned in the literature.[66]

Papillary Forms. Most BACs can be readily identified by their characteristic lepidic growth, which does not exclude some papillary tufting, a feature depicted by Malassez in his original description of this tumor in 1876.[46] Less well recognized is the existence of BAC with exuberant papillary features striking enough to suggest a papillary adenocarcinoma of bronchus or a metastasis from papillary carcinoma of the thyroid (Color Figs. 47-3 and 47-4; Figs. 47-9 through 47-12).[76–79] The latter possibility must be ruled out, because occult thyroid carcinoma may present as a solitary pulmonary nodule.[81,82] When examined with the electron microscope, some of these papillary tumors show cells with electron-dense granules at their apical portion, a feature of Clara cell differentiation.[76–79] Other tumors contain intracytoplasmic lamellar bodies or may be positive for surfactant apoprotein by the immunoperoxidase technique, indicating a type II pneumocyte lineage.[77,78] In our experience, most tumors have combined features.

Papillary BACs frequently exhibit psammoma bodies, but the diagnostic value of this finding is limited, because they also occur in papillary bronchogenic adenocarcinomas. In some studies, as many as 50% of BACs had psammoma bodies.[47,83] The group led by Silverman thought the finding of psammoma bodies with optically clear nuclei strongly suggested BAC.[84]

Solid Forms. Even more striking is a BAC with a solid histologic appearance, as originally described by Feldman and

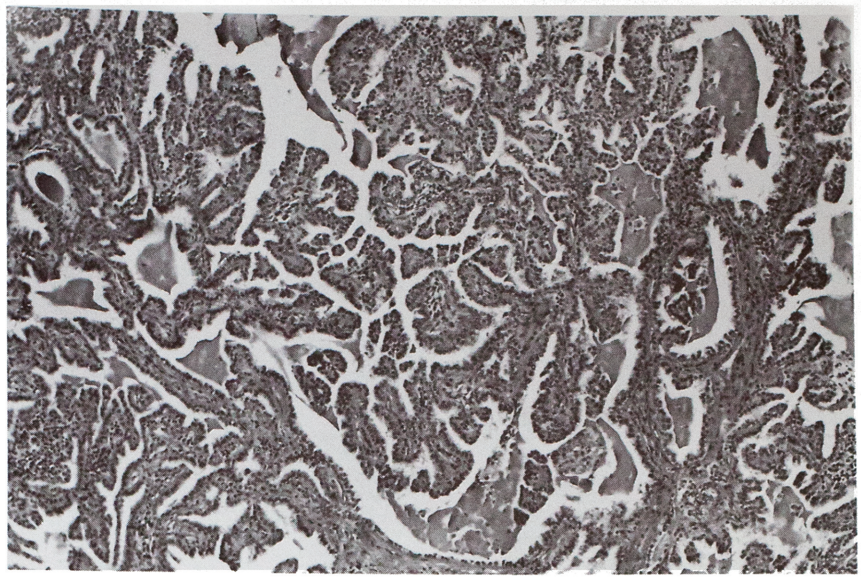

FIGURE 47-9. In this papillary bronchioloalveolar carcinoma of Clara cell origin, dense colloidlike material is seen between papillary fronds. (H & E stain; low magnification.)

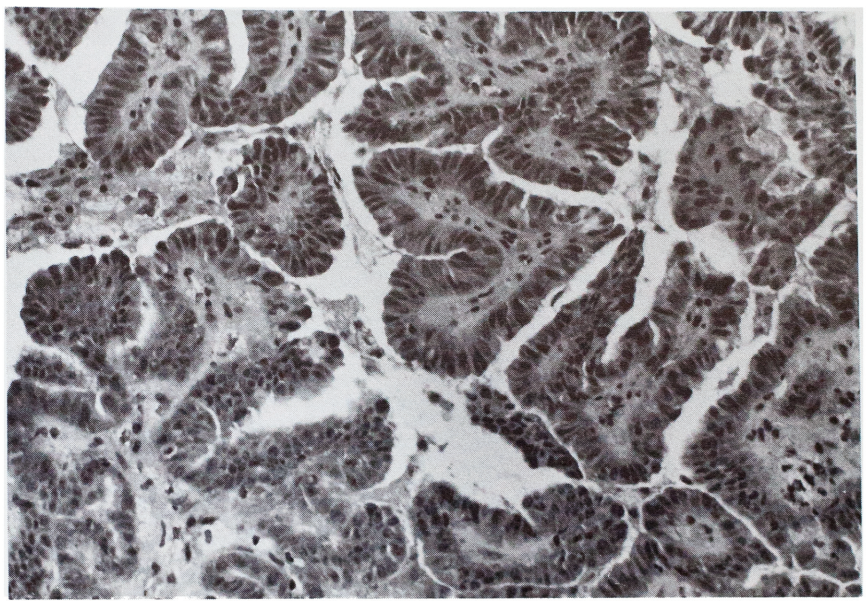

FIGURE 47-10. This bronchioloalveolar carcinoma of Clara cell origin is composed of tall columnar Clara cells with apocrine features. (H & E stain; intermediate magnification.)

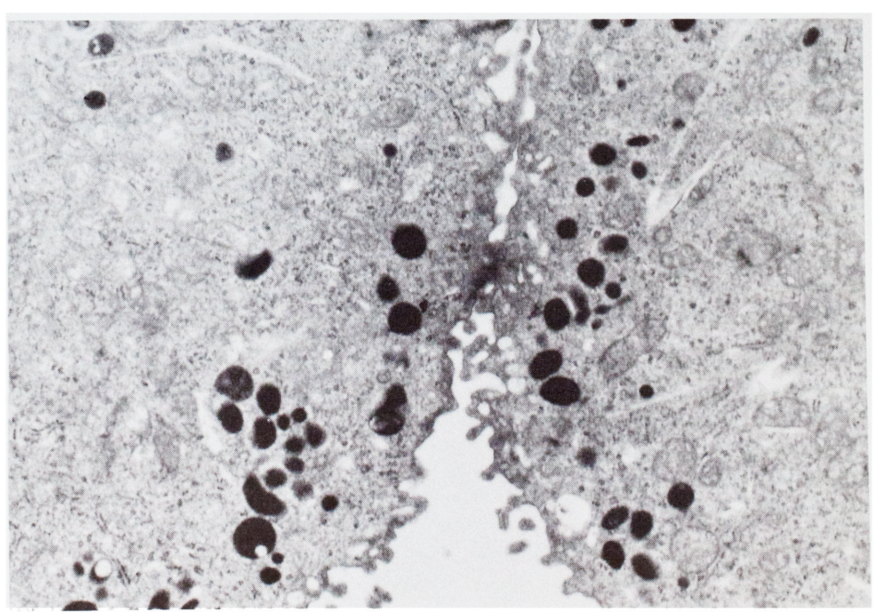

FIGURE 47-11. The electron microscopic view of the tumor in Figure 47-9 shows the characteristic electron-dense apical granules indicative of Clara cell differentiation. (Original magnification × 10,000.)

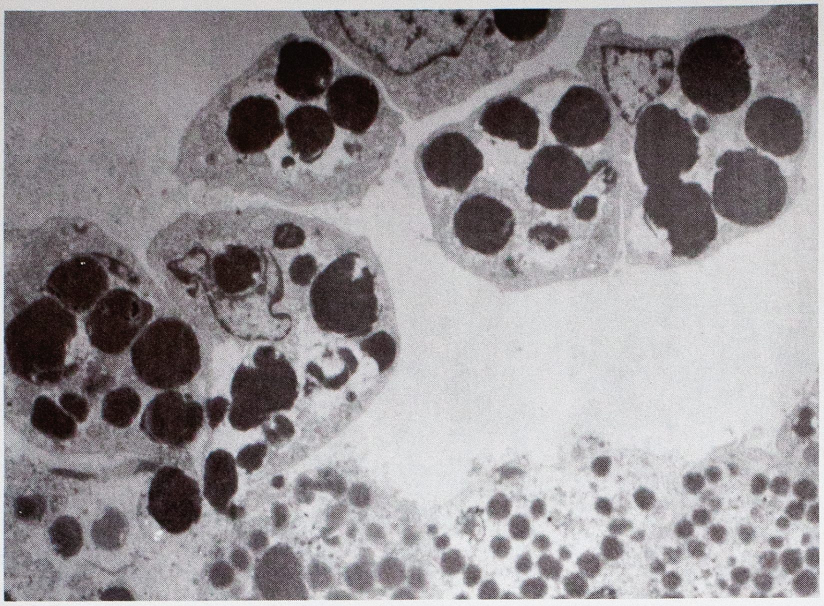

FIGURE 47-12. The electron microscopic view of the tumor in Figure 47-10 shows numerous Clara cell granules of various sizes. (Original magnification × 10,000.)

Innes.[84] By light microscopy, these tumors can be easily misinterpreted as large cell undifferentiated carcinomas (Fig. 47-13). Clara cell or type II pneumocyte differentiation has been demonstrated in some of these tumors by electron microscopy or by immunohistochemical methods.[79,86] A useful finding in recognizing type II pneumocyte tumors is the clear intranuclear inclusions shown by electron microscopy to be microtubular structures; they are positive for surfactant apoprotein by the immunoperoxidase technique.[86–89] Although papillary and solid tumors represent histologic variants of BAC, knowledge of their histogenesis, biologic behavior, and response to treatment is incomplete.

Insight into the morphogenesis of the papillary and solid

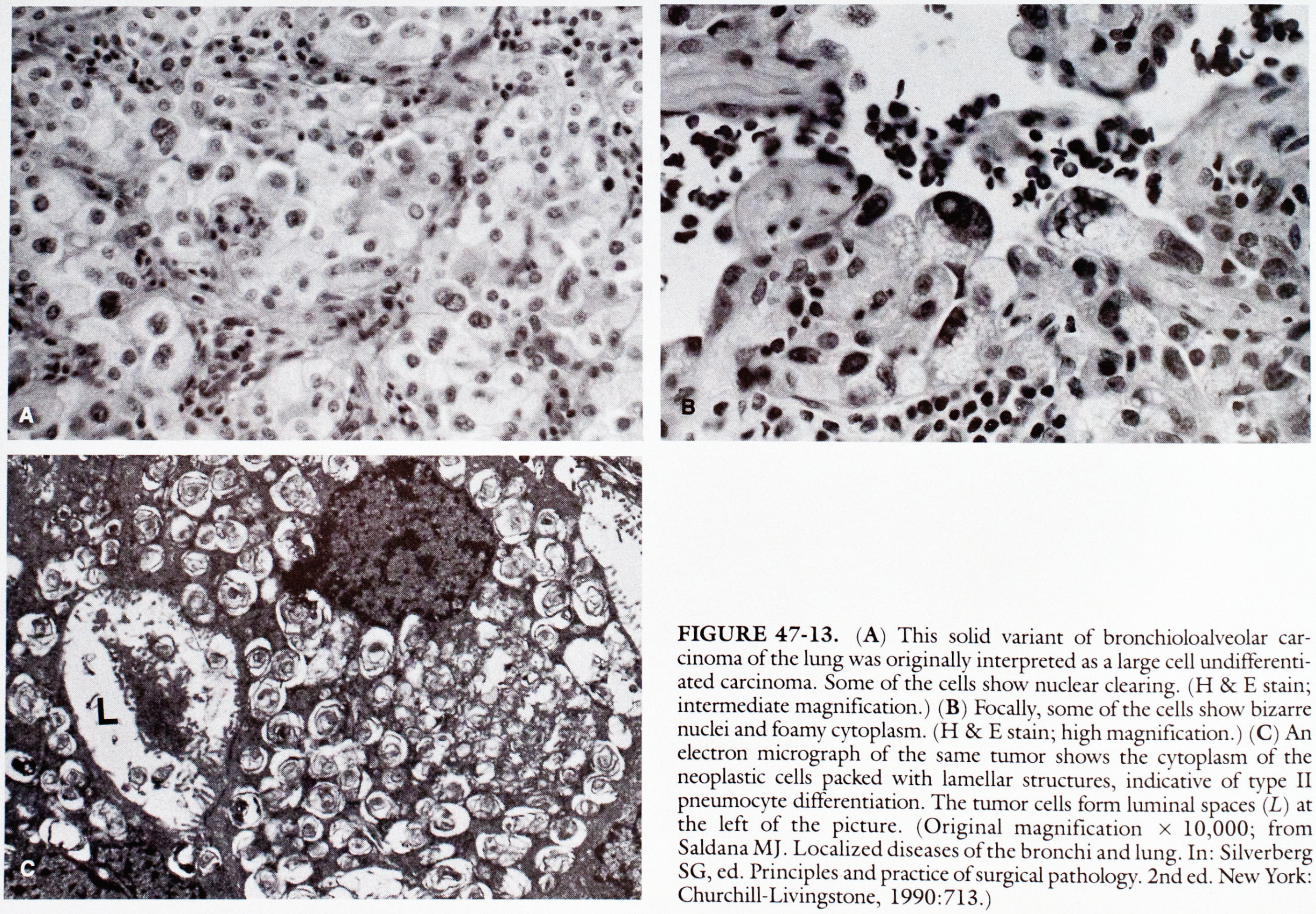

FIGURE 47-13. (**A**) This solid variant of bronchioloalveolar carcinoma of the lung was originally interpreted as a large cell undifferentiated carcinoma. Some of the cells show nuclear clearing. (H & E stain; intermediate magnification.) (**B**) Focally, some of the cells show bizarre nuclei and foamy cytoplasm. (H & E stain; high magnification.) (**C**) An electron micrograph of the same tumor shows the cytoplasm of the neoplastic cells packed with lamellar structures, indicative of type II pneumocyte differentiation. The tumor cells form luminal spaces (*L*) at the left of the picture. (Original magnification × 10,000; from Saldana MJ. Localized diseases of the bronchi and lung. In: Silverberg SG, ed. Principles and practice of surgical pathology. 2nd ed. New York: Churchill-Livingstone, 1990:713.)

forms of BAC can be gained from the experimental work of Rehm and colleagues, who induced lung tumors in rats by transplacental injection of *N*-nitrosoethylurea.[90] Solid and alveolar papillary tumors arose from the pulmonary acinus, invading the bronchioles as the tumor grew. Mixed solid and papillary patterns represent a progression from the solid to the papillary form rather than a merging of separate tumors. No typical features of mature Clara cells were detected ultrastructurally; instead, all tumors showed characteristic type II pneumocyte features. According to Thaete and Malkinson, urethane-induced pulmonary tumors in mice have two distinct histologic growth patterns; solid tumors arise from type II pneumocytes, and papillary tumors arise from Clara cells.[91] This simple rule may also apply to human BACs.

Langerhans Cells, Myoepithelial Cells, and Intracytoplasmic Bodies. The presence of Langerhans cells and their numbers have been the subjects of several studies, but the results are inconclusive.[92–98] In their study of 40 stage IA adenocarcinomas, Furukawa and associates, using S-100 protein for T-zone histiocytes (*i.e.*, Langerhans cells), demonstrated the cells in 31 (77.5%) of 40 patients. Patients with large numbers of T-zone histiocytes had a 5-year survival rate of 86.4%, compared with 38.9% for patients with none or slight infiltration.[97]

Fox and colleagues correlated survival for 41 lung tumors, 8 of which were adenocarcinoma, studied with the CD1 antibody Na1/34 that is specific for Langerhans cells.[98] Their results conflicted with those of Furukawa and associates; they found that patients whose tumors contained fewer than two Langerhans cells per high-power field had a better prognosis that those with more than two cells.[97] The significance of the presence and number of Langerhans cells in lung tumors needs clarification, as do the myoepithelial cells described in 1 of 100 BACs by Dekmezian and colleagues using the electron microscope. The patient's tumor recurred, suggesting a tendency toward multifocality.[99]

In their study of 105 lung tumors, Nakanishi and associates found large intracytoplasmic bodies in 27 tumors, 13 of which were adenocarcinomas.[100] These membrane-bound, electron-dense bodies had matrices with a fingerprint pattern and stained positively with acid hematin and Luxol fast blue, suggesting a phospholipid component as in Clara cells. However, 9 squamous cell carcinomas and 5 large cell undifferentiated carcinomas also had these bodies. This finding is probably unrelated to the presence of masses of alcoholic hyaline reported in one case of scar adenocarcinoma of the lung and the eosinophilic intracytoplasmic globules described by Scroggs and colleagues in six examples of mucin-producing adenocarcinomas of the lung.[101,102] The globules are similar to Russell bodies of plasma cells and the globules seen in hepatocytes of patients with α_1-antitrypsin deficiency.

MULTIFOCALITY

Observations by the teams led by Miller and McElvaney brought attention to the problem of multifocality in adenocarcinoma of the lung, a condition commonly identified with squamous cell carcinoma.[73,103] In a group of 62 patients with adenocarcinomas, these researchers showed that as many as 19% had multifocal tumors. Such a remarkable observation was possible in part because of careful slicing of resected specimens after inflation in Bouin solution, which hardens the organ and makes small lesions more distinct. They made several observations. In 4 of 50 patients with single tumors, 1- to 2-mm nodules designated as bronchioloalveolar tumors of uncertain malignant potential were discovered away from the main mass. Each of 7 (11%) of 62 patients had two adenocarcinomas; two of these were bronchial adenocarcinomas and were associated with multiple bronchioloalveolar tumors of uncertain malignant potential. Each of 5 patients (8%) had one dominant BAC and several independent nodules up to 1 cm in diameter with a similar histologic appearance; these were interpreted as multicentric BAC. The researchers compared their findings with those in studies of colonic neoplasia; single tumors of the colon, double tumors of the colon, and polyposis syndrome were analogous to their three groups.[73,103] The bronchioloalveolar tumors of uncertain malignant potential in this scheme would be equivalent to the familiar tubular adenomas of the colon.

Nakanishi studied a group of patients with lesions comparable to the bronchioloalveolar tumors of uncertain malignant potential described by Miller and associates and their relation to peripheral well-differentiated adenocarcinomas of the lung.[73,104] They differentiated typical alveolar epithelial hyperplasia (TAEH) from atypical alveolar epithelial hyperplasia (AAEH). In the typical lesions, the cells were uniform in distribution and appearance; in the atypical lesions, the distribution of the cells along the alveolar wall was irregular, with great variation in nuclear size. In both groups, the cells were Clara cells or type II pneumocytes. Although the TAEH cells maintained their A, B, and H blood group antigens, AAEH cells and the concomitant adenocarcinomas had lost these antigens, indicating malignant transformation. The only way to separate AAEH from adenocarcinoma was by morphometric analysis of mean nuclear area, which was significantly higher in the adenocarcinoma cells.

Nakayama and colleagues studied lesions designated as atypical adenomatous hyperplasia that were comparable to the bronchioloalveolar tumors of uncertain malignant potential studied by Miller and associates.[73,105] By cytofluorometric analysis of nuclear DNA content, they showed a clonal growth in 13 lesions and concluded that the tumors were closely related to well-differentiated adenocarcinomas.

In their study on precursors of pulmonary adenocarcinomas, Mikhail and Vuitch observed that 2 (33%) of 6 BACs showed type II pneumocyte dysplasia in areas adjacent to the tumor, which they defined as a pleomorphism and hyperchromasia of nuclei suggestive of malignancy.[106] Surprisingly, bronchiolar dysplasia and adenocarcinoma *in situ*, defined as markedly atypical or overtly malignant columnar epithelium within the bronchioli, with intact basement membrane and with transition of adjacent normal epithelium was a finding in 6 of 15 peripheral bronchogenic adenocarcinomas. Whether this represents a field effect or a bronchiolar origin for at least some peripheral adenocarcinomas must be determined. In the same study, they found an unusual case of peripheral adenocarcinoma with changes of Paget disease of the bronchial mucosa extending into submucosal glands. An identical finding had been reported by Higashiyama and colleagues.[107]

PROGNOSIS

Predicting the outcome of a resected adenocarcinoma of the lung depends on several factors. In their study of 75 patients with adenocarcinomas smaller than 2 cm in diameter, Takise and associates showed that the most important prognostic indicator was the pathologic stage determined by tumor size and extent, lymph node involvement, and metastasis.[108] Although vascular invasion occurred in 45 patients (60%), approximately one half of them were long-term survivors.

Among 259 patients with inoperable stage III adenocarcinomas studied by Sørensen and colleagues, those with BAC had the longest median survival (40 weeks).[25] The shortest median survival was for patients with solid carcinoma with mucin production (22 weeks). The median survival was 29 weeks for those with acinar adenocarcinomas and 31 weeks for those with papillary adenocarcinomas. When patients were grouped as those with well-differentiated tumors (*e.g.*, well-differentiated and moderately differentiated acinar and papillary adenocarcinomas and BACs) and poorly differentiated tumors (*e.g.*, poorly differentiated acinar and papillary adenocarcinomas and solid carcinoma with mucus production), the median survival was 31 weeks for patients with well-differentiated tumors and 27 weeks for the patients with poorly differentiated tumors. However, this difference was not statistically significant. Regardless of the difference in median survival, the difference in survival curves for the four main histologic subtypes of pulmonary adenocarcinoma were not statistically significant. Overall, 80% of the patients were dead by the fifth year.

In a complementary study, Sørenson and Olson studied 137 consecutive patients with radically resected stage I or II tumors.[26] The median survival times were 44 months for patients with BAC, 31 months for acinar adenocarcinoma, 32 months for papillary adenocarcinoma, and 10 months for solid carcinoma with mucus production. In the solid tumor group, there were significantly fewer 1-year survivors compared with the other groups. The researchers suggested that because of such an unfavorable prognosis, patients with solid carcinoma with mucin production may be potential candidates for adjuvant therapy.

Wilde and associates studied the prognosis for 1000 patients with resected lung cancers, 198 of which were adenocarcinomas.[109] These patients had 5- and 10-year survival rates of 42% and 25.3%, respectively, rates similar to those for patients who had been operated on for squamous cell carcinoma. Among patients with peripheral adenocarcinoma, the survival rates after 5 and 10 years were 42.4% and 26.6%, respectively. Of 10 patients with central adenocarcinomas, not a single patient survived more than 3 years. The survival rates after 5 and 10 years for patients with resected adenocarcinomas dropped steeply with increasing tumor stage. Although adenocarcinoma patients with stage I disease had the highest survival compared with other types, the survival curve of stage III patients with adenocarcinoma fell below that of small cell and large carcinoma patients. There was no prognostic difference between acinar and papillary subtypes, but patients with BAC had significantly higher survival rates.

Papillary Adenoma

There have been six examples of an interesting lung neoplasm to which the designation papillary adenoma has been applied.[110–114] They were all circumscribed, nonencapsulated tumors measuring up to 4.0 cm in diameter. All exhibited a striking papillary structure but no such histologic features of malignancy as cellular atypia, necrosis, or increased mitoses. Electron microscopic observations disclosed an origin from Clara cells, type II pneumocytes, or a combination of both. It is not yet clear whether these neoplasms represent the benign counterpart of unicentric papillary BAC or a low-grade form of this tumor. One of the tumors had been present for 10 years, unchanged, before resection (see Chap. 58).[112]

Pulmonary Mucinous Cystic Tumor

Mucinous cystadenoma of the lung is a benign pulmonary tumor; only a few examples have been described.[115–117] The well-circumscribed, small, peripheral masses usually are found in patients older than 60 years of age. The tumors are usually unilocular cysts but may be multilocular and demonstrate a characteristic stratified mucinous epithelial lining surrounding pools of mucus (Fig. 47-14). Rupture of the cyst wall may result in extravasation of mucin with fibrosis and granulomatous inflammation. Immunohistochemical and ultrastructural observations performed by Kragel and colleagues revealed a CEA-positive, surfactant apopro-

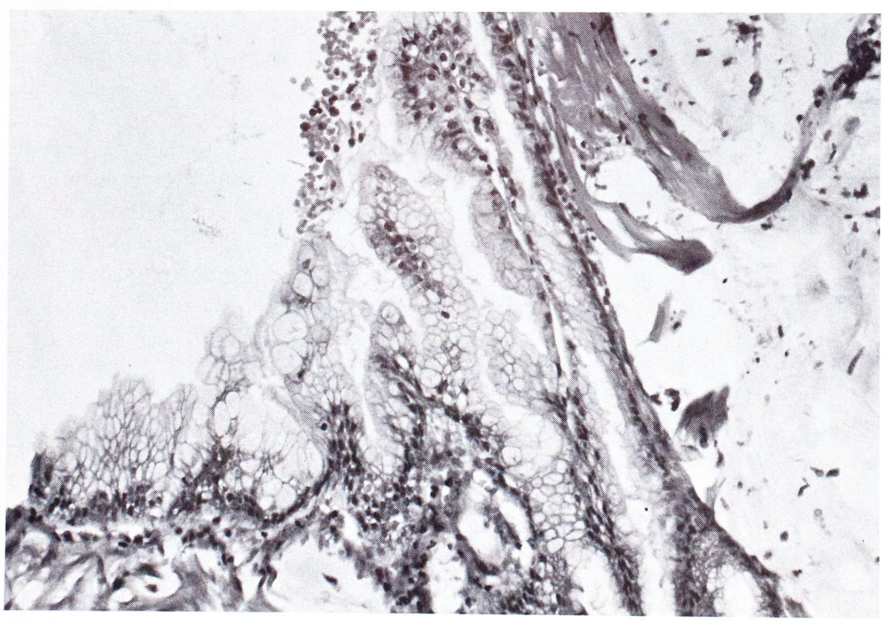

FIGURE 47-14. Histologic appearance of pulmonary mucinous cystic tumor presenting as a single peripheral mass in an older man. (H & E stain; intermediate magnification.)

tein-negative tumor in one of their patients.[115] Surface microvilli, junctional complexes, and abundant cytoplasmic mucus granules were seen. Follow-up studies of two other patients at 1 year and 3 years showed no evidence of disease.[115] In the patient described by Gower, there was seeding of the parietal pleura, but the patient remained asymptomatic for 5 years.[116] For the one patient described by Dail and Hammar, no follow-up information was available.[117]

Dixon and colleagues have recently reported the case of a 59-year-old man with a 4.5-cm pulmonary mucinous cystic tumor documented on chest x-ray films for 11 years before thoracotomy.[118] Although the resected lesion contained a focus of adenocarcinoma, the patient remained free of disease during five years of close follow-up. As noted by Dixon and colleagues,[118] by Graeme-Cook and Mark,[118a] and by Kragel and colleagues,[115] mucinous cystic tumors of the lung, like their ovarian and appendiceal counterparts, should be separated into three categories: cystadenoma, cystadenocarcinoma (frank carcinoma present), and tumors of borderline malignacy. Despite the presence of focal malignancy in the borderline category, their prognosis is remarkably favorable.

It is important to differentiate mucinous cystadenomas from mucinous cystadenocarcinomas of the lung (*i.e.*, colloid carcinomas), which may also present as solitary peripheral nodules.[118b] Colloid carcinomas are rather ill-defined and contain small clusters of atypical cells within intraalveolar pools of mucin. Foci of neoplastic columnar epithelium also line alveoli. It has been proposed that mucinous cystadenocarcinomas represent BAC of the mucinous type with a peculiar cystic structure.[118b] However, a bronchogenic origin is highly probable on the basis of the histologic findings and highly aggressive clinical course of these tumors.

Papillary Nodules Resembling Bronchioloalveolar Carcinoma

Travis and colleagues described papillary nodules resembling BAC in two adolescents who had received systemic chemotherapy.[119] They thought the nodules probably represent BAC, but the biology of these lesions is poorly understood.

Alveolar Adenoma

The lesion designated as alveolar adenoma by Yousem and Hochholzer had previously been called lymphangioma by Wada and associates (Fig. 47-15).[120,121] This is a benign neoplastic lesion that appears histologically different from the other tumors discussed in this section (see Chap. 58).

ADENOCARCINOMA ARISING IN DIFFUSE INTERSTITIAL FIBROSIS

In lungs with idiopathic interstitial fibrosis and honeycombing, there are frequently foci of atypical bronchiolar and alveolar proliferations, and considerable experience is required not to overdiagnose these lesions as carcinomas (see Chap. 31). Meyer and Liebow described the development of adenocarcinomas, frequently of the bronchioloalveolar type, in such lungs (Fig. 47-16), a condition already noted in cases of scleroderma with lung involvement.[122,123] However, Turner-Warwick and colleagues found no increased incidence in BACs among patients with diffuse interstitial fibrosis.[124] They did find an excess relative risk of lung cancer of 14.1 compared with the general population, but the distribution of lung cancer by histologic types was no different than that in the general population. This is also the case for lung cancer occurring in patients with asbestosis, which is a form of interstitial fibrosis of the lung (see Chap. 36). In the patient described by Kitamura and associates, a combined epidermoid and adenocarcinoma arose against a background of diffuse interstitial fibrosis. Histologically, the carcinoma grew extensively along dilated bronchioles and air spaces of the honeycomb lung.[125]

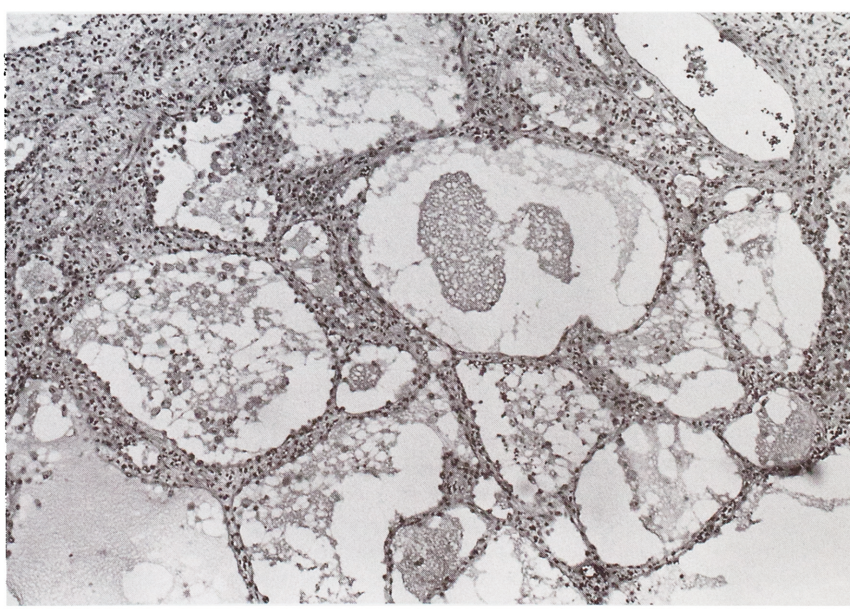

FIGURE 47-15. In the characteristic histologic picture of alveolar adenoma, formerly designated lymphangioma of lung, dilated alveolar spaces contain flocculent eosinophilic material. The intervening septa are thickened by chronic inflammation and fibrosis. (H & E stain; low magnification.)

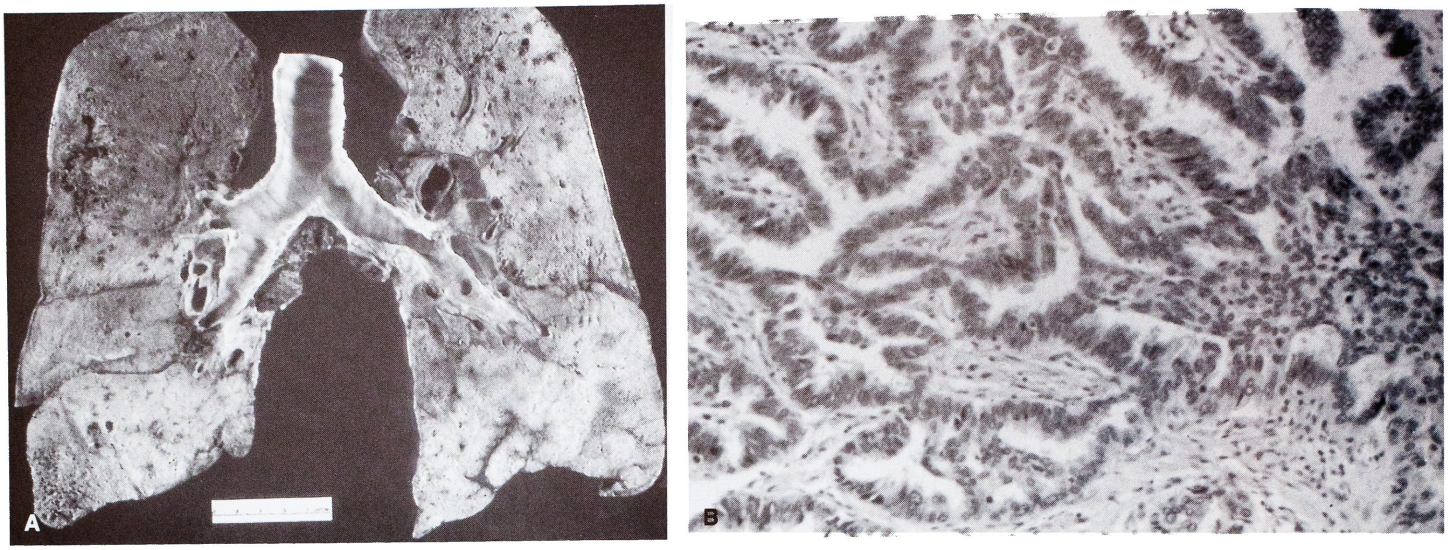

FIGURE 47-16. (**A**) Postmortem lungs from a man who had idiopathic pulmonary fibrosis; emphysema is also present at the apices. (**B**) The histologic section shows adenocarcinoma, which was interpreted as bronchioloalveolar carcinoma arising in diffuse interstitial fibrosis; the tumor was extensive and bilateral. (H & E stain; low magnification.)

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