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Squamous Cell Carcinoma

Mario J. Saldana
Joan M. Mones

Although the incidence of squamous cell carcinoma has been superseded by adenocarcinoma, it is still the most common histologic type of lung carcinoma associated with cigarette smoking, and the risk of developing squamous cell carcinoma increases in proportion to the number of cigarettes smoked.[1–4] In the lung, squamous cell carcinomas grow faster than adenocarcinomas but are less likely to form distant metastases.[1–4] The pathologic classification of this tumor is presented in Display 48-1.

PATHOLOGY

Gross Features

Approximately 90% of squamous cell carcinomas arise in lobar, segmental, and subsegmental bronchi. They usually present as fungating intrabronchial masses composed of friable, gray-white or yellowish tissue (Fig. 48-1). Blockage of the bronchi results in obstructive (*i.e.*, lipid) and organizing pneumonia distal to the main tumor mass (Fig. 48-2), and the resulting radiologic image is larger than the tumor itself. Although relatively rare, cancer of the trachea is usually squamous cell carcinoma; in Hadju's study, 30 (73%) of 45 carcinomas of the trachea were squamous cell varieties.[5,6] In Weber and Grillo's series of 30 malignant tracheal tumors, almost two thirds (19 patients) had this histology.[6]

Histologic Features

Histologically, keratinizing squamous cell carcinomas are classified as well, moderately, and poorly differentiated.[1–4] Well-differentiated squamous cell carcinoma exhibits keratin formation intracellularly and extracellularly, including the formation of keratin pearls (Fig. 48-3). Moderately differentiated squamous cell carcinoma shows less evidence of keratinization; for a tumor to be classified as such, about 20% of the tissue examined under the microscope should show evidence of keratinization, with the remaining 80% composed of undifferentiated cells.[3] Poorly differentiated forms are composed fundamentally of sheets of large, undifferentiated cells, and they are considered squamous cell carcinoma only because of foci of individual cell keratinization, layering, or stratification and a pavementlike appearance, as seen in the epidermis, including the presence of intercellular bridges (Fig. 48-4). Although these characteristics are relatively easy to ascertain in resected specimens, determination may be exceedingly difficult in small transbronchial biopsies. The concept of nonkeratinizing squamous cell carcinoma as used for uterine cervical cancer has not been applied to the lung; the pulmonary cases are better designated as large cell carcinomas.

Most squamous cell carcinomas of the lung are moderately or poorly differentiated; well-differentiated squamous cell carcinomas are relatively rare. The finding of a well-differentiated squamous cell carcinoma in a cervical lymph node or soft tissues suggests a metastasis from a primary tumor in the oropharynx,

DISPLAY 48-1. HISTOLOGIC CLASSIFICATION OF SQUAMOUS CELL CARCINOMAS OF THE LUNG

Keratinizing Subtypes (99%)

Well differentiated
Moderately differentiated
Poorly differentiated

Special Subtypes (1%)

Small cell squamous cell carcinoma (*i.e.*, basaloid)
Spindle cell squamous cell carcinoma (*i.e.*, pseudosarcomatous or sarcomatoid)
Lymphoepitheliomalike carcinoma

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

FIGURE 48-1. Squamous cell carcinoma grows as fungating masses that block bronchi and produce bronchiectasis and mucous plugging. The tumor has extended to an anthracotic hilar node (*bottom, right*).

larynx, or esophagus, rather than the lung.[1,2] This is probably because bronchial squamous cell carcinomas arise from a ciliated, pseudostratified, and mucinous epithelium undergoing squamous metaplasia and lack the intrinsic ability to generate large amounts of keratin, as cancers directly arising from squamous mucosa do.

Immunoperoxidase stains for keratin can help in the histologic diagnosis of squamous cell carcinoma.[7] Positive stains for antibodies to high-molecular-weight keratins (63 kd) are restricted to well-differentiated tumors, and the stains are negative for adenocarcinomas. More helpful are commercially available "cocktails" for several molecular species of cytokeratins, but they also stain adenocarcinomas. Methods for detection of the protein components of desmosomes and involucrin are also available.[7]

Stromal changes in squamous cell carcinoma are probably related to prognosis and include a rich desmoplastic response and eosinophilic leukocytic infiltration in patients with long-term survival.[8,9] Large numbers of plasma cells are a favorable feature, but the lack of macrophages in the infiltrate may indicate a poor prognosis.[8]

FIGURE 48-2. The squamous cell carcinoma arose in the medium-sized bronchus of the left lower lobe and produced blockage with secondary obstructive pneumonia. This phenomenon explains why the radiologic image is bigger than the tumor.

Peripheral Squamous Cell Carcinoma

About 16% of squamous cell carcinomas are peripherally located. In their study of 21 of these tumors, Tomashefski and colleagues found fewer associated symptoms at presentation and a better survival rate.[9] Morphologically, the tumors were smaller, had fewer mitosis, demonstrated less lymphatic invasion, and produced a more intense stromal reaction than central squamous cell carcinomas. These researchers concluded, however, that the better survival correlated with the more favorable stage at the time of resection. Invasion of the pleura elastica, best demonstrated by elastic tissue stains, confers an unfavorable prognosis in peripheral squamous cell carcinomas. Gallagher and Urbansky found that invasion of the internal elastic lamina was associated with significantly reduced survival; this was not the case for adenocarcinomas, large cell carcinomas, and small cell carcinomas.[10]

A large proportion of peripheral squamous cell carcinomas are well differentiated and have a tendency to cavitate (Fig. 48-5); one proposed explanation is their excessive keratin production and poor blood supply.[1,2] In his study of cavitation in pulmonary cancers, Chaudhuri found that 100 (16%) of 632 lung cancers were cavitary. There were 82 squamous cell carcinomas, 11 large cell undifferentiated carcinomas, and 7 adenocarcinomas. He proposed that cavities in patients with primary lung cancers can arise in one of three ways. The first is cavity necrosis due to breakdown of tumor itself after invasion of arteries and veins. The second is stenotic abscess due to infection and breakdown of lung tissue distal to bronchial obstruction by the tumor. A third mechanism of cavity formation was designated as "spillover abscess" from an infected primary growth, in which case the cavity may develop in a different lobe from the primary cancer or even in the opposite lung.[11]

UNUSUAL ASSOCIATIONS

For unknown reasons, superior pulmonary sulcus tumors producing the Pancoast syndrome are frequently squamous cell carcinomas (Fig. 48-6). Paulson observed that one half of 54 such tumor

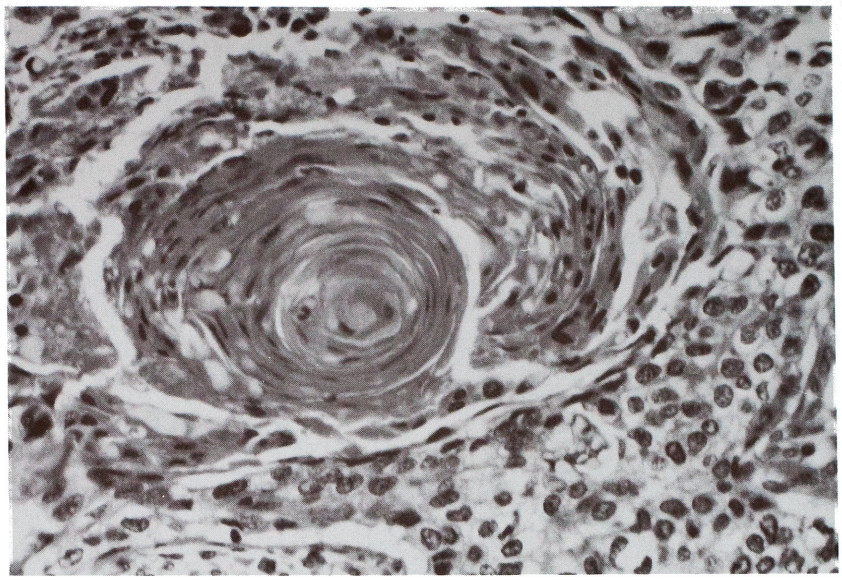

FIGURE 48-3. A well-differentiated bronchogenic squamous cell carcinoma producing large keratin pearls is relatively uncommon in the lung. (H & E stain; intermediate magnification.)

had squamous histologies.[12] Herbut and Watson, in their review of 104 patients with tumors of the thoracic inlet producing the Pancoast syndrome, found that most of them were pulmonary squamous cell carcinomas.[13]

Curious associations include the development of squamous cell carcinoma in bullae, squamous cell carcinoma arising in the wall of a congenital lung cyst, and a neoplastic origin in a bronchopulmonary sequestration.[14–16] A 63-year-old man with a large, well-differentiated squamous cell carcinoma of the left upper lobe had a concomitant plasmacytoma of the left hilar region that had IgA-κ–positive monotypic plasma cells.[17]

Squamous cell carcinoma has been associated with rapidly progressing systemic sclerosis (*i.e.*, scleroderma).[18] In another report, a 66-year-old man with clinical manifestations of systemic lupus erythematosus was found to have squamous cell carcinoma of the right middle lobe.[19] Remarkably, the manifestations of systemic lupus erythematosus largely regressed after excision of the tumor.

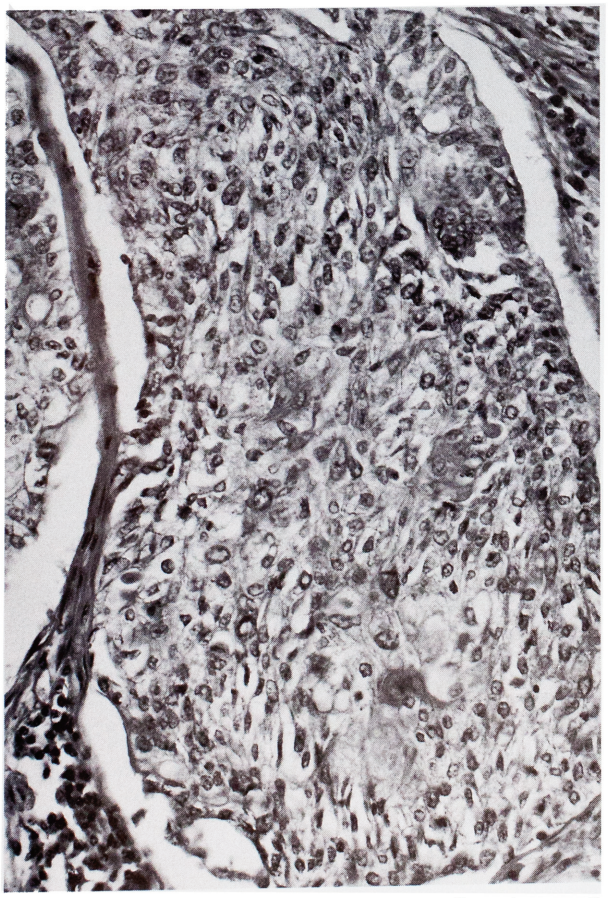

FIGURE 48-4. Poorly differentiated squamous cell carcinoma of the bronchus demonstrates stratification of cells and small foci of keratin production. (H & E stain; intermediate magnification; from Saldana MJ. Localized diseases of the bronchi and lung. In: Silverberg SG, ed. Principles and practice of surgical pathology. New York: Churchill-Livingstone, 1990:713.)

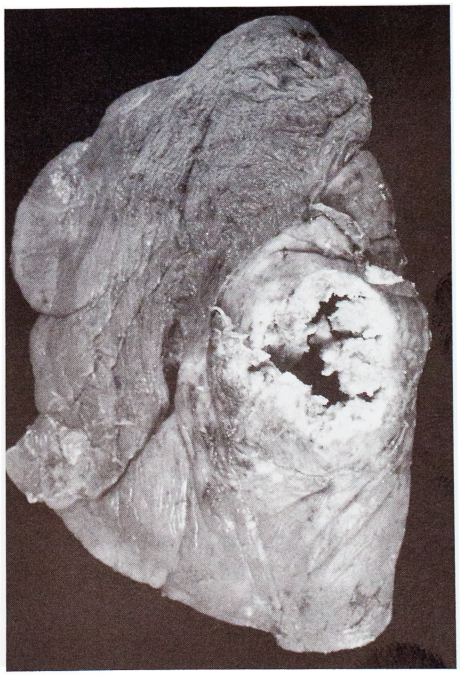

FIGURE 48-5. The characteristic appearance of a peripheral squamous cell carcinoma of lung includes cavitation, abundant keratinous debris, and perforation into the pleural space.

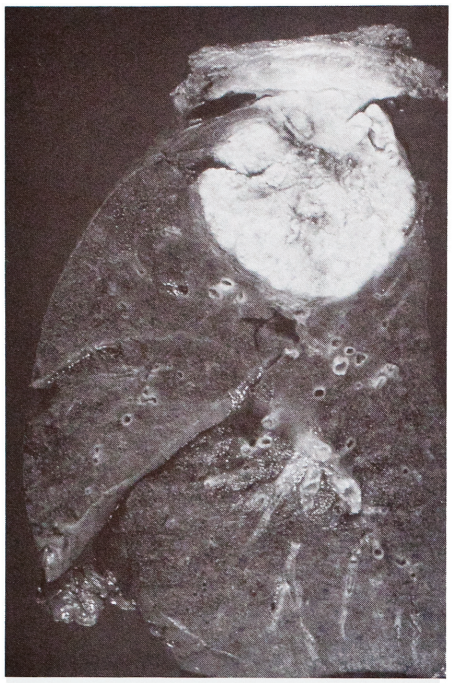

FIGURE 48-6. A Pancoast tumor infiltrates a segment of the rib (*left*). Histologically, the lung cancer was squamous cell carcinoma with necrosis and anthracotic pigment deposition.

Squamous cell carcinoma is a disease that preferentially affects older men.[1–3] However, the occurrence of these tumors in younger persons is well recognized.[20,22] In Niitu's study, a 15-year-old asymptomatic boy was found to have a 2.5-cm-diameter nodule in his upper right lobe.[22] The patient had never smoked, and his environmental exposure had not been unusual. The patient was reportedly doing well 3.5 years after lobectomy.

HISTOGENESIS

Squamous cell carcinoma is the one type of bronchogenic carcinoma for which premalignant and *in situ* stages have been well documented.[3,4] Grossly, the *in situ* lesion appears as red, granular plaques or gray, leukoplakic patches involving the bronchial mucosa and spreading from subsegmental or segmental bronchi to larger bronchi for distances up to several centimeters (Color Fig. 48-1). This *in situ* stage is frequently associated with infiltrating carcinoma. In our experience, the changes frequently reach the margin of resection of a lobectomy or pneumonectomy specimen.

The characteristic cytologic changes of human papillomavirus infection are identical to those in the uterine cervix in as many as 30% of bronchial squamous cell carcinomas.[23] Bejui-Thivolet detected human papillomavirus by *in situ* hybridization in the metaplastic bronchial epithelium of as many as 18% of the patients with squamous cell carcinoma.[24]

MULTIPLE PRIMARY CARCINOMAS OF THE LUNG

Cancer of the lung can arise at multiple sites, and these carcinomas are predominantly squamous types (Fig. 48-7).[25–29] They can be synchronous or metachronous growths; the prevalence of this phenomenon varies from 0.2% to 1.8% in different studies. Auerbach and associates found an incidence of 4% in their series of 225 patients who died of bronchogenic carcinoma and who had one or more additional, clinically unsuspected, primary, invasive carcinomas at necropsy.[25]

A 64-year-old Japanese man had three minute squamous cell carcinomas of the right lung.[27] Two years after bilobectomy, the patient died of squamous cell carcinoma of the esophagus. The researchers reviewed 12 comparable patients in the literature. Rohwedder and Weatherbee described five patients with bilateral

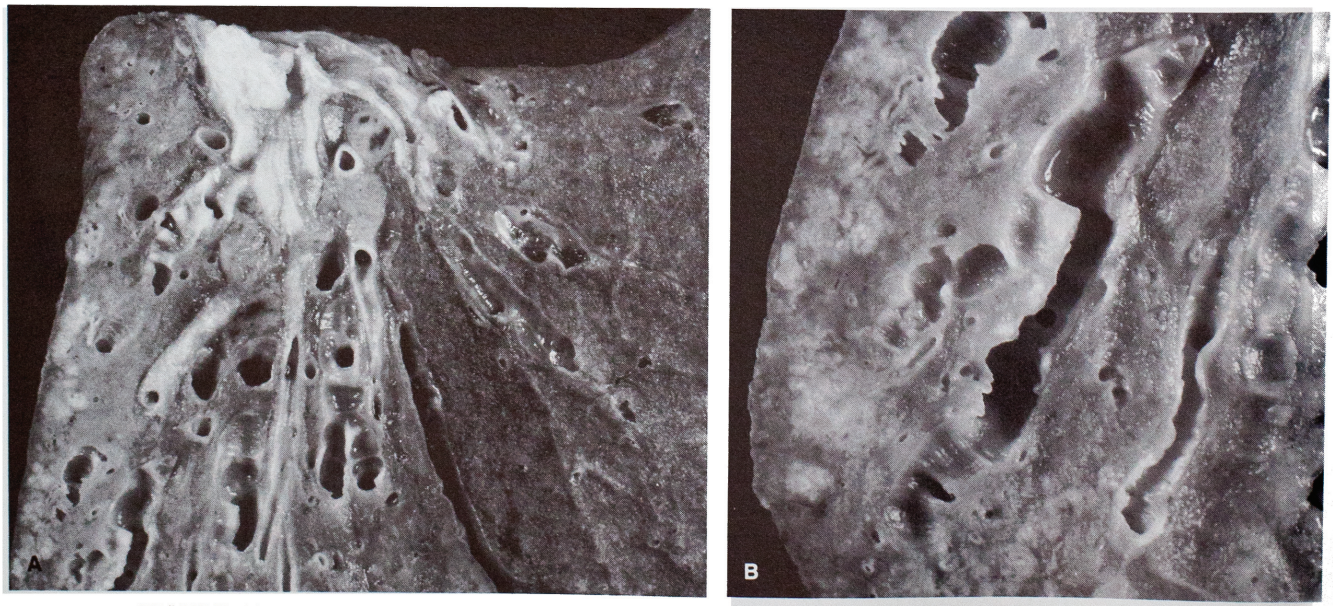

FIGURE 48-7. An unusual specimen shows a multifocal squamous cell carcinoma. (**A**) The largest lesion (*top*) is close to the margin of resection. There are extensive cylindric bronchiectases distal to the tumor. (**B**) A closer view shows bronchiectasis and whitish nodules of squamous cell carcinoma near the pleura. Because of the extensive areas of carcinoma *in situ* in the distal airways, a multicentric origin is favored over endobronchial metastases. (Courtesy of Christian Otrakji, M.D., Miami, FL.)

primary bronchogenic carcinomas, four of which were of the squamous cell variety, and reviewed the literature consisting of 155 examples of such occurrence.[28] Martini and Melamed presented data for 50 patients with multiple, separate bronchogenic carcinomas.[29] Eighteen had synchronous tumors, and 32 had metachronous tumors. The interval between the first and second tumor diagnoses was 5 months to 16 years. The histologic patterns of the two independent carcinomas were the same, most commonly squamous cell carcinoma, in 31 patients, but the patterns were different in 19 patients.

TREATMENT AND FOLLOW-UP

The treatment of choice for squamous cell carcinoma is surgery, and the prognosis depends on the clinical stage and the degree of histologic differentiation of the tumor. In the preclinical stage, there is a high resectability rate (81%), and the 5-year survival rate is approximately 75%.[3,4] A disturbing feature in this group of patients is the development of a second primary tumor in as many as 25%. Patients with stage I disease have a 54% 5-year survival rate; those with stage II disease have a 36% survival rate; and those with stage III disease have a 22% survival rate. The overall 5-year survival rate for squamous cell carcinoma is 37%, the highest among all lung cancer types.[1–4]

Huwer and colleagues presented their follow-up data on 435 patients who had been operated for bronchogenic squamous cell carcinoma.[30] The mean survival time after potentially curative surgery was 7.15 years for those with stage I disease, and the 5-year actuarial survival rate was 60.8%. The corresponding values were 2.68 years and 31.6% for stage II and 1.14 years and 13.4% for stage IIIA. The differences between tumor stages were statistically significant. The degree of keratinization and features such as necrosis or lymphangitic and vascular invasion in the resected specimen had no prognostic significance in Huwer's study. The researchers also analyzed to what degree tumor size and lymph node involvement influenced the prognosis after potentially curative surgery. Without hilar lymph node involvement, the prognosis of patients with T1 and T2 tumors was significantly better than for those with T3 tumors. However, if there were hilar node metastases (N1), the prognosis for patients with T1, T2, and T3 tumors no longer differed significantly from each other. If mediastinal lymph nodes were involved (N2), patients with T1 tumors had a better survival than those with T2 and T3 tumors.

Although the treatment of choice for squamous cell carcinoma is surgery, chemotherapy in some patients has remarkable effects (Fig. 48-8).

PROGNOSIS

Flow Cytometry

Flow cytometry provides interesting prognostic insights into the evolution of squamous cell carcinoma. Leoncini and associates studied the DNA index and percent S-phase fraction in squamous cell carcinomas from paraffin-embedded material.[31] Only 3 of 45 patients were diploid. The DNA index was significantly lower in grade 1 than in grade 2 and 3 tumors. No correlations were found between DNA index and lymph node metastasis, but the S-phase fraction was significantly higher in lymph node–positive tumors. In the study of Volin and colleagues, the cytometric DNA content analysis of 105 examples of squamous cell carcinoma had important prognostic implications.[32] Patients with aneuploid tumors died significantly sooner than those who had tumors with DNA diploidy. Patients whose tumors had high proliferative activity died significantly earlier than patients with tumors of lower proliferative activity. Comparisons between homogeneous groups of patients with respect to clinical parameters showed identical results. The researchers concluded that there are two sets of independent prognostic factors for the survival of patients with squamous cell carcinoma: clinical factors (*e.g.*, stage) and flow cytometric values.

Unusual Behavior

Squamous cell carcinoma usually has a predictable pattern of spread from a primary tumor in the lung to hilar nodes, followed by mediastinal nodes and later spread to distant sites. Even at postmortem analysis, the tumor is confined to the chest in one half of the patients.[1,2] However, rare patients may have early metastatic disease to distant places, a feature more characteristic of adenocarcinomas. For example, in one patient reported by Davies-Payne and associates, a primary squamous cell carcinoma of the lung presented as a metastasis in the tongue.[33] In the patient reported by Schwesinger and Braune, a squamous cell carcinoma had metastasized to the penis.[34]

Another remarkable feature is spontaneous regression of squamous cell carcinoma of the lung, which has been observed in a handful of patients. Geraads and Bonnamour described a small squamous cell carcinoma that was discovered by chance in an elderly man undergoing fiberoptic bronchoscopy for another reason.[35] A controlled endoscopy performed 4 years later confirmed normal tissue although the patient had received no treatment.

SPECIAL SUBTYPES

Small Cell Squamous Cell Carcinoma

The concept of small cell squamous cell carcinoma (SCSCC), also called basaloid squamous cell carcinoma, is well established for many organs, such as uterine cervix, upper airways, oropharynx, and esophagus. In the lung, the existence of such tumors is obscured by the occurrence of small cell carcinoma, a major form of lung cancer that closely resembles it (Fig. 48-9). Deciding whether a tumor represents small cell carcinoma, atypical (*i.e.*, malignant) carcinoid, or SCSCC is fraught with difficulties, particularly if dealing with small, artifactually altered transbronchial specimens or scant cytologic material. The use of the electron microscope and immunohistochemistry with conventional histologic methods has given legitimacy to the concept of SCSCC, but the information is incomplete.[36–38]

In practice, the diagnosis of SCSCC is based on the finding of relatively small cells with a tight epithelial arrangement and sharp cytoplasmic borders. Distinct stratification with larger squamoid cells also helps in their recognition, as does a basaloid disposition of the cells at the edges of the tumor lobules or masses. Foci of coagulative eosinophilic necrosis of individual cells or at the center of the tumor lobules closely resembles that seen in small cell carcinoma. Using immunohistochemistry and electron microscopy, the presence of markers of squamous differentiation and the absence or rarity of neuroendocrine differentiation is to be expected.

(*text continues on page 552*)

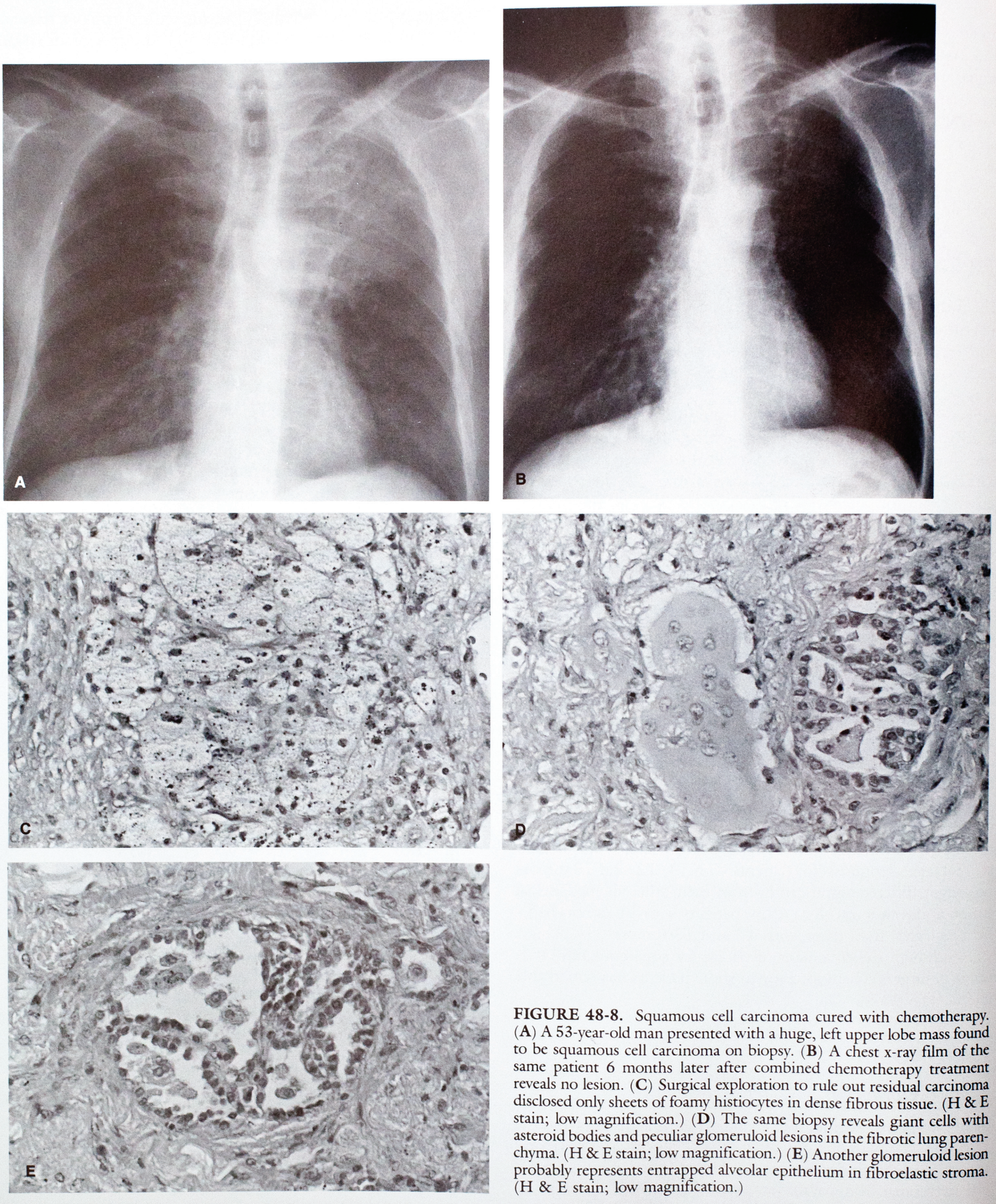

FIGURE 48-8. Squamous cell carcinoma cured with chemotherapy. (**A**) A 53-year-old man presented with a huge, left upper lobe mass found to be squamous cell carcinoma on biopsy. (**B**) A chest x-ray film of the same patient 6 months later after combined chemotherapy treatment reveals no lesion. (**C**) Surgical exploration to rule out residual carcinoma disclosed only sheets of foamy histiocytes in dense fibrous tissue. (H & E stain; low magnification.) (**D**) The same biopsy reveals giant cells with asteroid bodies and peculiar glomeruloid lesions in the fibrotic lung parenchyma. (H & E stain; low magnification.) (**E**) Another glomeruloid lesion probably represents entrapped alveolar epithelium in fibroelastic stroma. (H & E stain; low magnification.)

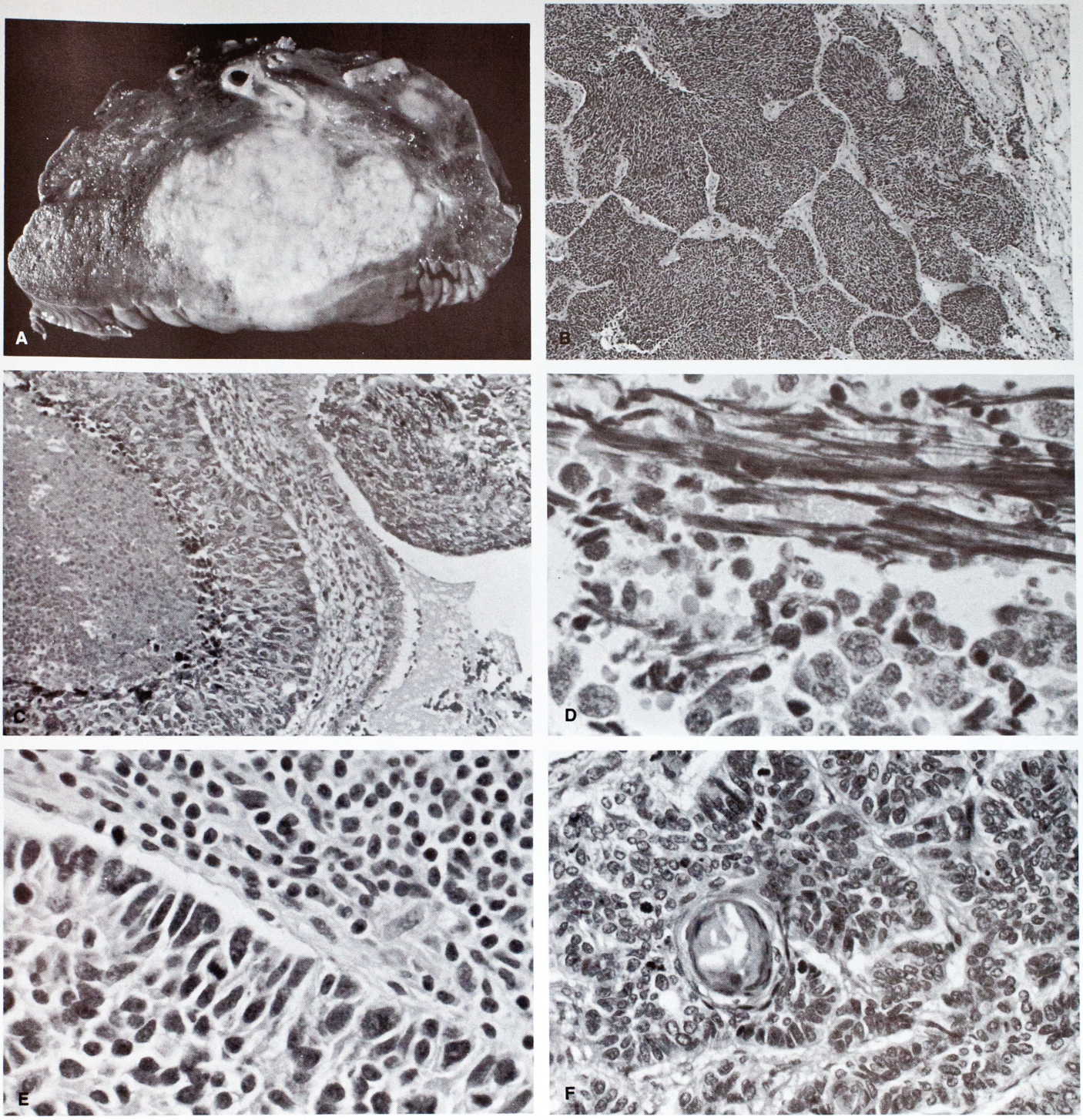

FIGURE 48-9. (**A**) A basaloid variant of squamous cell carcinoma presents as a large intraparenchymal mass. (**B**) The characteristic lobular distribution of basaloid carcinoma resembles basal cell carcinoma of the skin. (H & E stain; low magnification.) (**C**) The tumor is composed of small cells with extensive eosinophilic coagulative necrosis. (H & E stain; low magnification.) (**D**) The crush artifact in basaloid carcinoma closely resembles small cell carcinoma. (H & E stain; high magnification.) (**E**) Another detail of basaloid carcinoma is the palisading of cells at the periphery of the lobules. (H & E stain; intermediate magnification.) (**F**) In basaloid carcinoma, the cells tend to form lobules separated by fibrous trabeculae and some foci of keratin. (H & E stain; intermediate magnification.)

In the study by Churg and colleagues, there were five patients with histologic findings indicative of small cell carcinoma, but desmosomes and tonofilaments were seen using electron microscopy.[36] No neurosecretory granules were identified in four patients. Only one tumor had some neurosecretory granules in addition to tonofilaments. Because of the electron microscopic findings, the researchers concluded that the tumors represented SCSCC rather than small cell carcinoma. The average age of the five patients was 63 years. The four men and one woman were all smokers. One patient had a 3.0-cm coin lesion, and another patient had bilateral peripheral nodules. In the other three patients, the tumors were quite large.

Abe and associates described nine men and one woman with SCSCC.[37] The ages ranged from 52 to 82 years (mean, 66 years). They were all heavy smokers. At presentation, four had stage II and six had stage III disease. Clinically, all patients had a more aggressive growth and tendency to early regional metastasis than is common for usual squamous cell carcinomas. Using immunohistochemical techniques, three tumors were positive for neuron-specific enolase (NSE) and keratin; three were NSE-positive and keratin-negative; and four were NSE-negative and keratin-positive. Tumors with neuroendocrine differentiation had a worse prognosis than those without this feature. The researchers recognized two DNA histogram patterns, type I and type II, depending on the dispersion of values. The only correlation they observed was with the clinical course: patients with type II histograms (*i.e.*, those with a wide dispersion of values) had significantly shorter tumor volume doubling times than patients with type I histograms.

Brambilla and colleagues presented their observations on 38 cases of basaloid carcinoma found among 115 poorly or undifferentiated lung cancers.[38] The tumor was found in pure form in 19 cases, and the other 19 tumors were mixed types with associated keratinizing squamous cell carcinoma, large cell carcinoma, or adenocarcinoma. The results of staining for neuroendocrine markers were infrequently positive and often inconsistent. Ultrastructural study showed an absence of neurosecretory granules with squamous or glandular differentiation. The researchers think that the tumor arises from a pluripotent reserve stem cell. This is a tumor of unique histology and poor prognosis, with a median survival of 22 months for patients with stage I or II disease.

For localized tumors (*i.e.*, stage I), the patient should be given the benefit of intended curative surgery. In our experience, chemotherapy, as for small cell carcinoma, has been given to some of these patients, but it failed to significantly reduce the size of the mass. Palliative radiation probably has a place in the treatment of some of these lesions. In two examples of SCSCC of the lung known to us, the pulmonary lesion was associated with brain metastases alone; one of the patients was studied postmortem.

Spindle Cell Squamous Cell Carcinoma

Another unusual variant of squamous cell carcinoma of the lung is spindle cell squamous cell carcinoma (Color Fig. 48-2; Fig. 48-10). The designation of pseudosarcomatous or sarcomatoid seems appropriate for these tumors.[39–42] The tumors tend to be

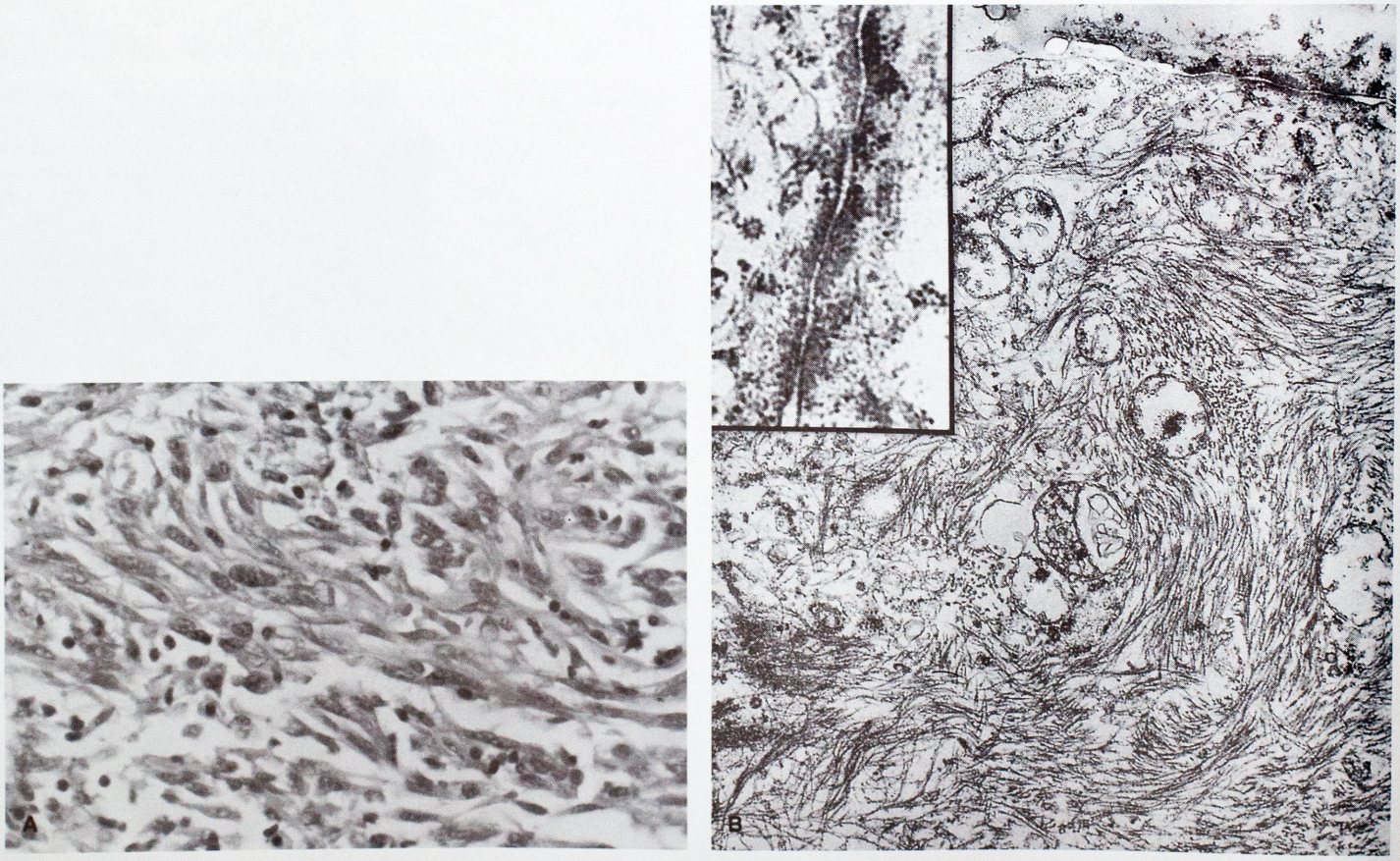

FIGURE 48-10. (**A**) A microscopic view of a squamous cell carcinoma reveals the spindle cell or pseudosarcomatous features (see Color Fig. 48-2). (H & E stain; intermediate magnification.) (**B**) An electron microscopic view of the tumor shows abundant cytoplasmic tonofilaments and desmosomal attachments (*inset*). (Original magnification × 20,000; inset: original magnification × 25,000.)

bulky and have extensive necrosis and inflammatory changes. The spindle cells of the tumor mimic malignant fibrous histiocytoma, but foci of squamous differentiation frequently aids in their recognition and should be sought diligently.

These are highly aggressive lesions, and the prognosis is usually poor. In a patient described by Love and Daroca, a huge spindle cell squamous cell carcinoma replaced the right lower lobe.[39] Extensive spindle cell areas with anaplastic giant cells were found in the tumor. There was extensive cavitation, and the sarcomatouslike areas eventually metastasized widely to skin, skull, abdomen, thyroid, heart, adrenals, and lymph nodes. Humphrey and associates described eight primary carcinomas of the lung with prominent spindle cell sarcomatoid components that were studied by immunocytochemistry and electron microscopy.[41] The eight tumors were indistinguishable by conventional light microscopy, with the exception of one unusual neoplasm that followed multiple pathways of differentiation with elements of squamous cell carcinoma, rhabdomyosarcoma, chondrosarcoma, and undifferentiated spindle cell population. The researchers proposed that pulmonary carcinomas exhibiting evidence of epithelial differentiation into a sarcomatoid component should be called spindle cell carcinomas and that those tumors exhibiting mesenchymal differentiation into neoplastic bone, cartilage, or striated muscle should be classified as carcinosarcomas. They concluded that the distinction may be ultimately unnecessary, because these two prototypes may represent different points along a morphologic and biologic continuum (see Chap. 54).[41]

Matsui and colleagues described 16 cases of lung carcinoma with spindle cell components studied by conventional histologic and immunohistochemical methods.[42] The epithelial components were squamous cell carcinoma in six patients, adenocarcinoma in four patients, adenosquamous carcinoma in five patients, and large cell carcinoma in one patient. In every case, sarcomatous areas proliferated in proximity to the epithelial elements. Using immunohistochemical techniques, the epithelial elements were found positive for keratin, epithelial membrane antigen, or carcinoembryonic antigen, depending on the histologic types. The spindle cell elements were positive for keratin in all but one case. Vimentin was demonstrated in the sarcomatous areas of five cases, although the results for desmin, actin, and myosin were negative. The researchers concluded that the spindle cell component of the 16 cases may represent mesenchymal differentiation with partial or complete loss of epithelial features.

Lymphoepithelial Carcinoma

Lymphoepithelial carcinoma, a tumor common in the upper respiratory passages, has been associated in the lung with Epstein-Barr virus infection.[43–46] Begin and associates reported a 40-year-old Asian woman with a mass involving the lingula and left lower lobe and extending to the pleura.[43] The histology was identical to that of a nasopharyngeal lymphoepithelial carcinoma (Fig. 48-11); electron microscopy confirmed squamous features in the large cell component of the lesion. Positive serologic proof of Epstein-Barr virus infection was obtained. Two years after surgical excision of the mass, the patient developed metastasis to paravertebral and retroperitoneal regions and died of disseminated disease 2 years later. Butler and colleagues reported four more patients with this tumor.[44] Of the three women and one man between the ages of 56 and 72 years, only one patient had a recurrence in the pleura 18 months after resection of the lung lesion. The other three patients were alive and well 18 months, 3.5 years, and 9 years after surgical resection. A patient with lymphoepitheliomalike carcinoma of the lung was reported by Miller and associates in 1991.[45] The patient was a 65-year-old, obese, Caucasian woman with a history of heavy smoking. The lesion consisted of a 4-cm cavitary lesion in the lingula. Thirteen months after resection of the lesion, a metastasis was found in the head of the right humerus.

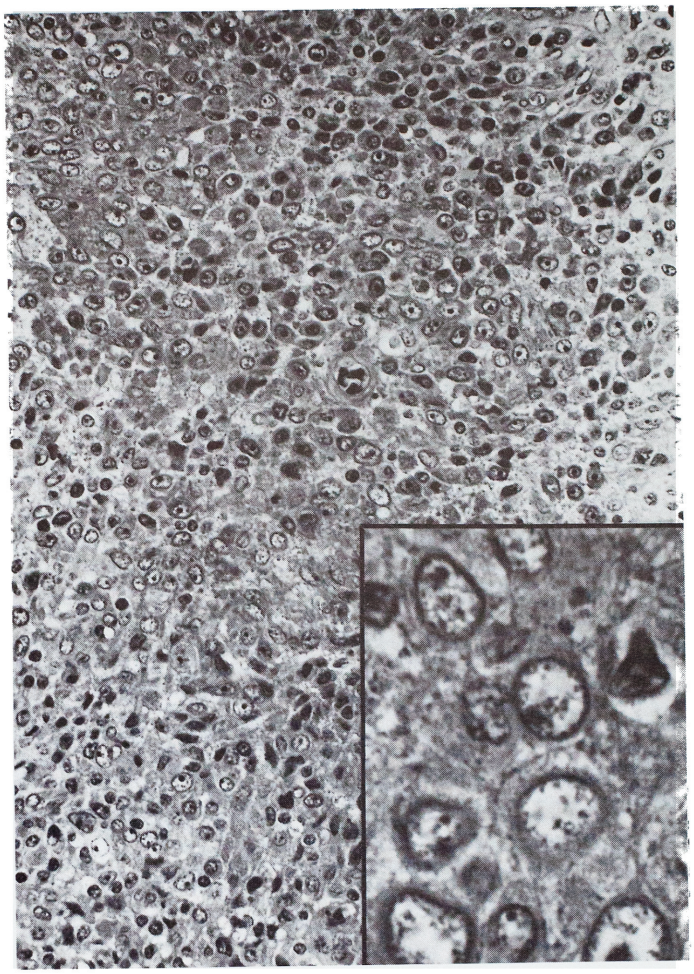

FIGURE 48-11. A lymphoepithelial carcinoma presents as a large intraparenchymal mass in an elderly Asian man. There is a bimodal population of cells consisting of large squamoid elements (*inset*) admixed with numerous lymphocytes. The tumor pursued a highly malignant course and resulted in the death of the patient due to metastases to the liver and other abdominal organs. (H & E stain; intermediate magnification; *inset:* oil immersion.)

In the report by Pittaluga and associates, *in situ* hybridization revealed the presence of Epstein-Barr virus in five cases of lymphoepithelial carcinoma of the lung.[46] Epstein-Barr virus was located in the epithelial cells only; the authors concluded that Epstein-Barr virus infection had preceded the clonal expansion of the tumor.

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