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Carcinoid and Other Neuroendocrine Tumors

William D. Travis

For many years, the carcinoid tumor and small cell lung carcinoma (SCLC) were the only two recognized categories of pulmonary neuroendocrine tumors. In 1972, Arrigoni and colleagues proposed that bronchial carcinoids be separated into typical and atypical variants, with the latter having more malignant histologic characteristics and clinical behavior.[1] Since then, several studies have confirmed that atypical carcinoid is a distinct entity.[2–9] However, careful review of the literature reveals that Arrigoni defined a histologically low-grade neuroendocrine neoplasm, and many of the subsequent studies included histologically higher-grade tumors in the category of atypical carcinoid. As a result, a heterogeneous spectrum of tumors have been called atypical carcinoid.[2–4,6–9]

Although Arrigoni and his colleagues did not specifically propose a three-category system, many pathologists who have embraced the concept of typical and atypical carcinoid have included them with SCLC to reflect the spectrum of neuroendocrine neoplasia in the lung.[10]

During the past two decades, various new terms have been proposed for atypical carcinoid, including malignant carcinoid, well-differentiated neuroendocrine carcinoma, Kulchitsky cell carcinoma II, and peripheral SCLC resembling carcinoid tumor.[11] With each newly proposed term, slightly different diagnostic criteria have been used.[12] Several investigators thought that the three-category classification system was inadequate and proposed several additional categories, including large cell neuroendocrine carcinoma (LCNEC), neuroendocrine carcinoma of intermediate differentiation, and non-small cell carcinoma (NSCC) with neuroendocrine features.[4,7–9,13,14] Although several groups have proposed a four-category scheme, the use of this concept has been limited.[4,7–9,15] The diversity of terminology and inconsistent histopathologic criteria has made it difficult for pathologists to classify neuroendocrine tumors, especially the more malignant forms.

Based on a review of a series of pulmonary neuroendocrine tumors at the National Cancer Institute, Travis and associates proposed a four-category classification scheme for neuroendocrine lung tumors (Display 51-1).[12] According to this scheme, neuroendocrine lung tumors were divided into high and low histologic grades. The three categories and terms of typical and atypical carcinoid and SCLC, used in the World Health Organization (WHO) classification were preserved.[16] However, it was decided to adhere to Arrigoni's original criteria for atypical carcinoid, which defined a histologically low-grade neoplasm, and LCNEC was introduced as a fourth category, representing a non-small cell neuroendocrine carcinoma with a high histologic grade.[12]

HISTOLOGICALLY LOW-GRADE NEUROENDOCRINE TUMORS: TYPICAL AND ATYPICAL CARCINOID TUMORS

Clinical Features

The mean age of patients with carcinoid tumors of the lung is 55 years (range, 12–82 years).[2] Carcinoid tumors are also one of the most common bronchial lung tumors in children.[17–22] There is no gender predominance.[2,23–25]

As many as 50% of carcinoid patients are asymptomatic at presentation. Patients with central carcinoids typically present with cough, hemoptysis, obstructive pneumonia, and dyspnea.[26] Carcinoids in the peripheral lung are more likely to present as incidental chest x-ray findings.[27]

Cushing syndrome can occur in typical and atypical carcinoids because of ectopic production of ACTH or corticotropin releasing factor.[12,28–33] Bronchial carcinoids can be associated with the carcinoid syndrome in 2% to 7% of patients, usually in the setting of liver metastases.[2,34] Infrequently, bronchial carcinoids secrete growth hormone and cause acromegaly.[35,36] Rarely, bronchial carcinoids may be a manifestation of multiple endocrine neoplasia type I.[37,38]

DISPLAY 51-1. CLASSIFICATION OF COMMON NEUROENDOCRINE TUMORS OF THE LUNG

Tumors With a Light Microscopic Neuroendocrine Appearance

Histologically low grade
- Typical carcinoid
- Atypical carcinoid

Histologically high grade
- Large cell neuroendocrine carcinoma
- Small cell carcinoma

Non–Small Cell Carcinoma With Neuroendocrine Features*

Squamous cell carcinoma

Adenocarcinoma

Large cell carcinoma

**Neuroendocrine granules by electron microscopy or positive immunohistochemical neuroendocrine markers.*

Patients with typical carcinoid have an excellent prognosis and rarely die of tumor. Metastases to regional lymph nodes occur in 5% to 20% of patients. Distant metastases of typical carcinoids at the time of presentation are rare; sometimes they occur many years after the initial diagnosis.[12]

Atypical carcinoids account for 10% to 25% of pulmonary carcinoid tumors.[1,2] Atypical carcinoids have a larger tumor size, a higher rate of metastases, and significantly reduced survival compared with typical carcinoids. The mortality rate reported in most series is approximately 30%, ranging from 27% to 47%.[1–4,6–9] For patients with atypical carcinoid who die, the mean survival is slightly longer than 2 years, with a range up to 10 years. According to one study, the 5- and 10-year disease-free survival rate for typical carcinoid is 100% and 87%, and for atypical carcinoid, it is 69% and 52%, respectively.[39] Tumor size (≥3 cm), lymph node fmetastases, and vascular invasion have correlated with adverse outcomes.[2,24]

Pathologic Features

Carcinoid tumors can be regarded as central or peripheral tumors. Between 16% and 40% of carcinoids are in the peripheral lung parenchyma and away from the bronchi.[2,23,40–42] Central carcinoids often appear grossly as a smooth, tan, polypoid endobronchial mass (Fig. 51-1). Central carcinoids tend to be larger than peripheral tumors, with a mean diameter of 3.1 cm (range, 0.5–10 cm) and 2.4 cm (range, 0.5–6 cm), respectively.[2]

Histologically, carcinoid tumors have an organoid growth pattern and uniform cytologic features (Fig. 51-2 and 51-3). The tumor cells have moderate amounts of eosinophilic, finely granular cytoplasm and nuclei with a finely granular chromatin pattern (see Fig. 51-2*B*). A variety of histologic patterns may occur in carcinoid tumors, including spindle cell, trabecular, palisading, papillary, glandular, follicular, and diffusely infiltrative patterns.[12,43–45] The tumor cells of pulmonary carcinoid tumors may have oncocytic, acinic cell–like, signet-ring, or melanocytic features.[46–54,56] Ultrastructurally, they may appear ciliated or have type II pneumocyte features.[57] Pulmonary carcinoids can have stromal deposition of amyloid, bone, or calcification.[58–61]

Atypical carcinoids are larger than typical carcinoids, with a mean diameter of 3.6 cm compared with 2.3 cm for a typical carcinoid.[2] The cut surface of typical carcinoids may show necrosis or hemorrhage. Arrigoni and colleagues proposed the following criteria for separation of atypical carcinoid from typical carcinoid: increased mitotic activity with one mitotic figure per one to two high-power fields (*i.e.*, 5–10 mitoses/10 HPF); nuclear pleomorphism, hyperchromatism, and an abnormal nuclear-cytoplasmic ratio; areas of increased cellularity with disorganization of the architecture; and tumor necrosis (Fig. 51-4).[1] Atypical carcinoid tumors may have infiltrative growth patterns, and the tumor cells may be spindle shaped. Typical carcinoids do not show necrosis, and mitotic figures are absent or rare.[1,12]

Differential Diagnosis

A variety of criteria should be considered in the separation of typical carcinoids from atypical carcinoids (Table 51-1). A small, crushed specimen may make recognition of these criteria difficult.

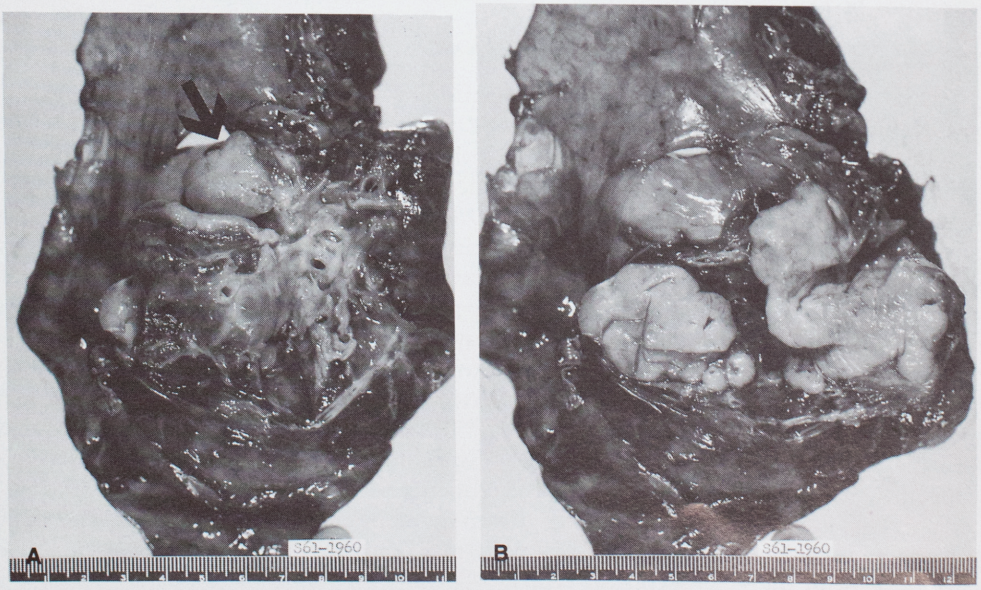

FIGURE 51-1. (**A**) A carcinoid tumor is situated centrally and has a polypoid endobronchial component (*arrow*). (**B**) A cross section of the same tumor reveals a tan-white mass 6 cm in its largest dimension.

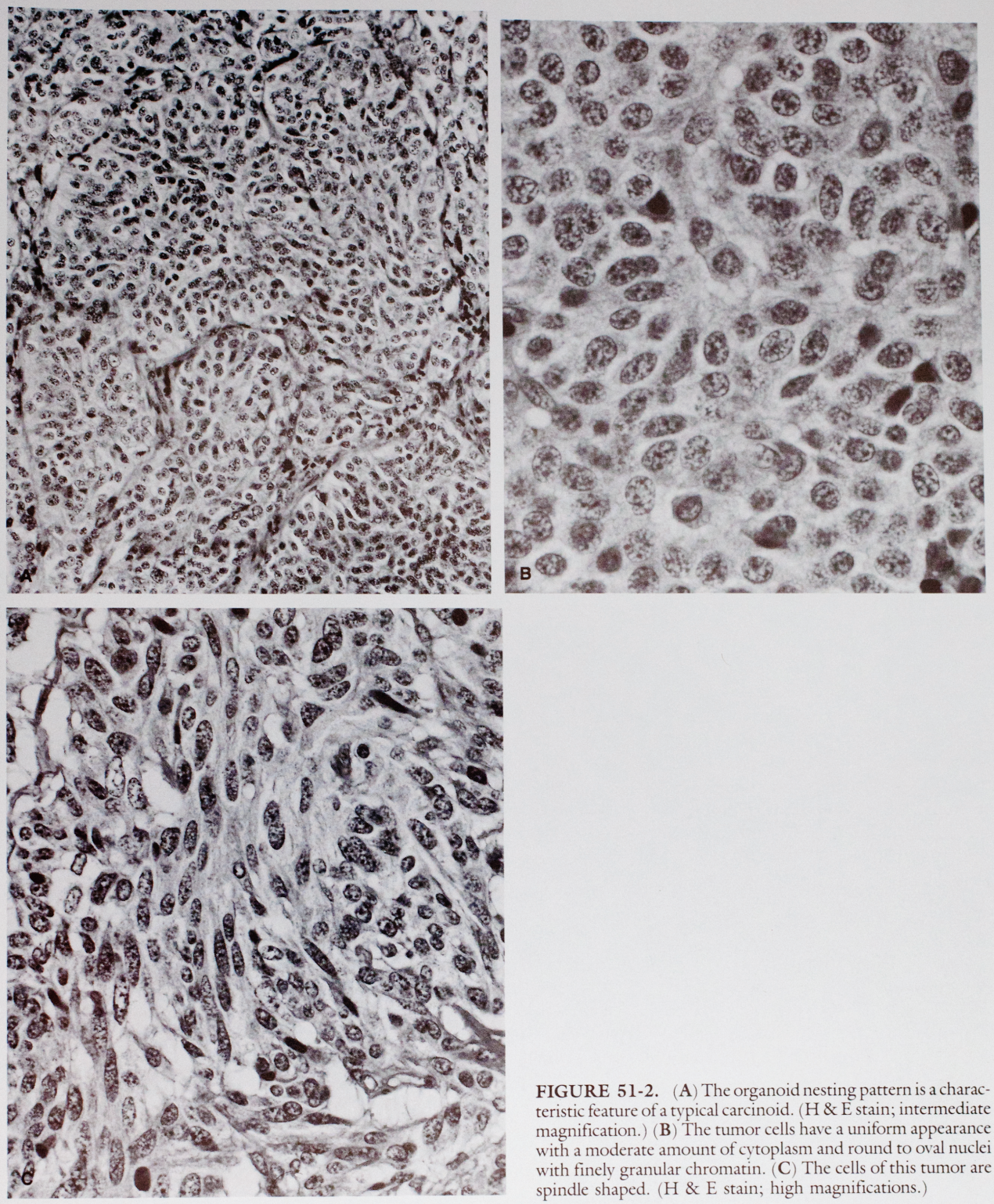

FIGURE 51-2. (**A**) The organoid nesting pattern is a characteristic feature of a typical carcinoid. (H & E stain; intermediate magnification.) (**B**) The tumor cells have a uniform appearance with a moderate amount of cytoplasm and round to oval nuclei with finely granular chromatin. (**C**) The cells of this tumor are spindle shaped. (H & E stain; high magnifications.)

The presence or extent of necrosis and mitotic activity are key features for separating these tumors.

The differential diagnosis of carcinoid tumors depends on the histologic features. For example, spindle cell carcinoids can be confused with smooth muscle tumors (*e.g.*, leiomyoma, leiomyosarcoma), schwannoma, fibrous mesothelioma, spindle cell carcinoma, and metastatic carcinoma, sarcoma, or melanoma. However, spindle cell carcinoids have an organoid pattern, characteristic finely granular nuclear chromatin, neuroendocrine markers by immunohistochemical methods, and dense-core granules by electron microscopy.

Carcinoids with oxyphilic tumor cells raise the possibility of oncocytoma. Both show numerous mitochondria by electron microscopy, but only carcinoids show neuroendocrine immunohistochemical markers and neuroendocrine granules by electron mi-

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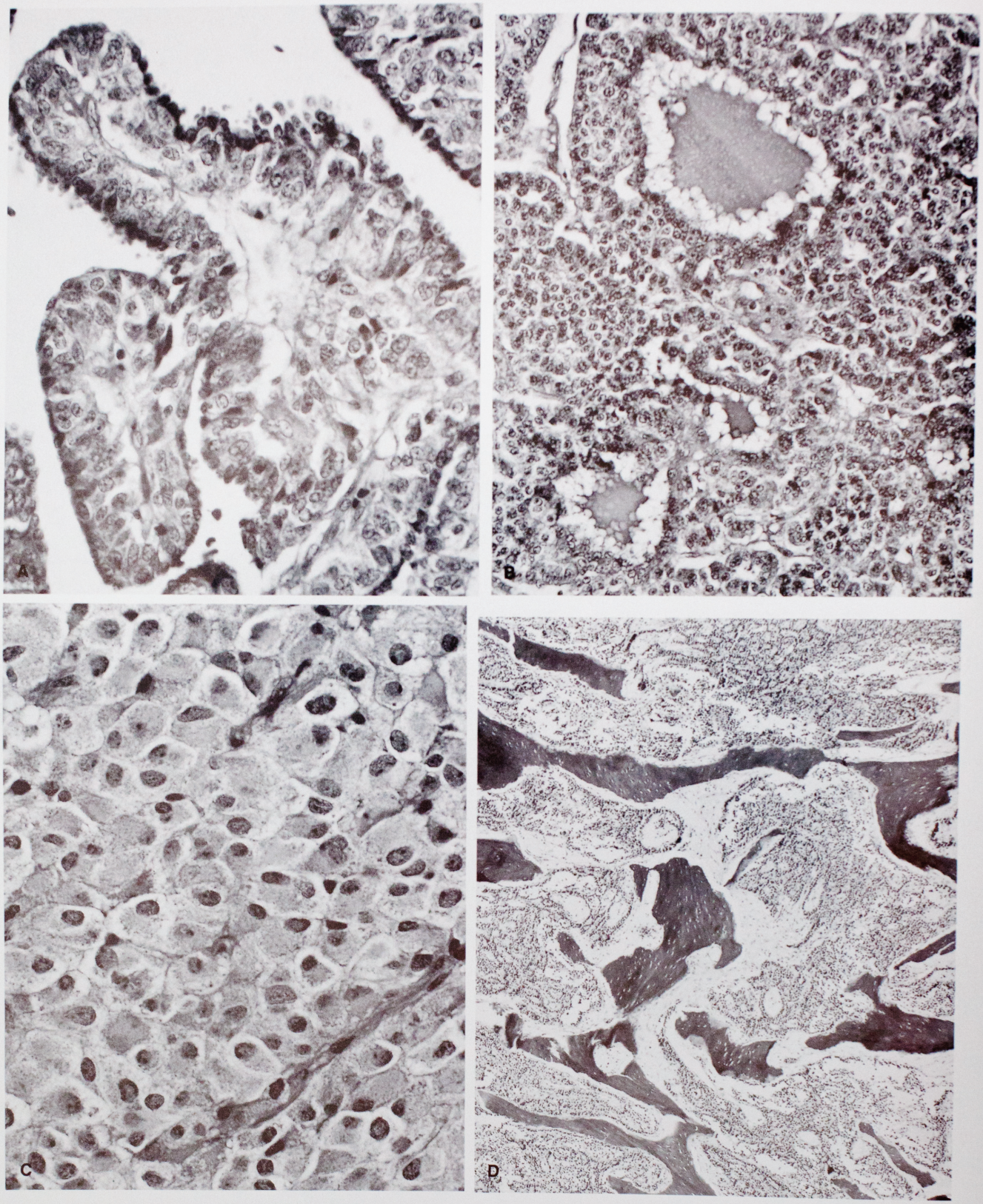

FIGURE 51-3. (**A**) This typical carcinoid is growing in a papillary pattern. (H & E stain; intermediate magnification.) (**B**) This carcinoid has a follicular pattern with glandlike spaces filled with eosinophilic colloidlike material that is scalloped around the edges. (H & E stain; low magnification; from Travis WD, Linnoila RI, Tsokos MG, et al. Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. Am J Surg Pathol 1991;15:529.) (**C**) The cells of this tumor are oxyphilic with abundant eosinophilic cytoplasm. (H & E stain; high magnification.) (**D**) This ossified carcinoid has extensive bone in the stroma. (H & E stain; low magnification.)

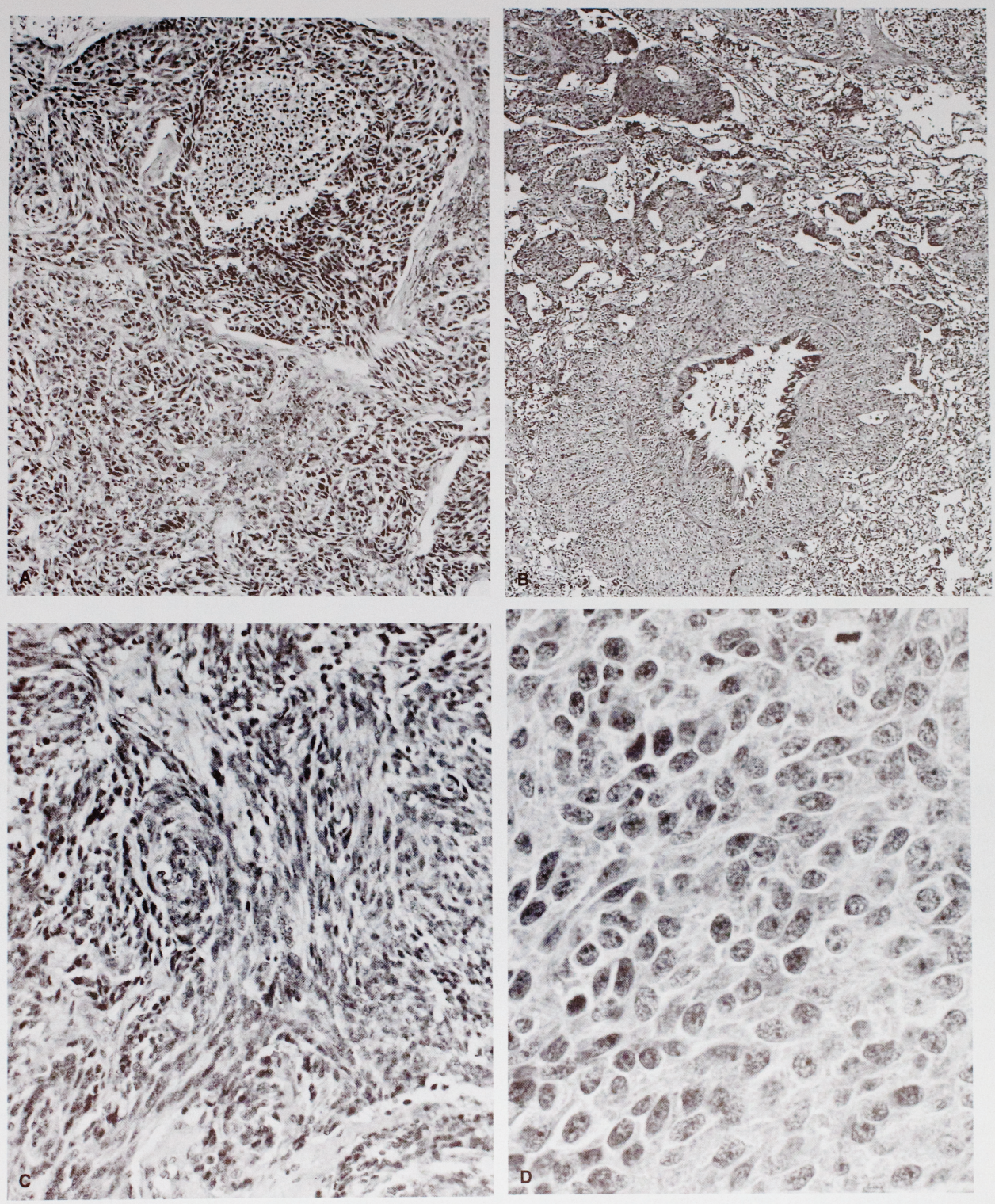

FIGURE 51-4. (**A**) An atypical carcinoid shows an organoid nesting pattern with necrosis within the center of a large nest of cells. (H & E stain; low magnification.) (**B**) This tumor shows prominent peribronchiolar infiltration and extension into the interstitium of the surrounding alveolar septa. (H & E stain; low magnification.) (**C**) This atypical carcinoid consists primarily of spindle-shaped tumor cells. (H & E stain; intermediate magnification.) (**D**) The tumor cells of this atypical carcinoid have a moderate amount of cytoplasm with round-to-oval nuclei showing finely granular chromatin; a single mitotic figure is apparent (*top right*). (H & E stain; high magnification; A, C, and D from Travis WD, Linnoila RI, Tsokos MG, et al. Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. Am J Surg Pathol 1991;15:529.)

TABLE 51-1
Distinguishing Features of Typical and Atypical Carcinoids

Histologic or Clinical Feature	Typical Carcinoid	Atypical Carcinoid
Histologic patterns: organoid, trabecular, palisading, and spindle cell	Characteristic	Characteristic
Mitoses	Absent or rare	Increased, up to 10 per 10 high-power fields
Necrosis	Uncharacteristic	Characteristic, usually focal or punctate
Nuclear pleomorphism, hyperchromatism	Usually absent, not sufficient by itself for diagnosis of atypical carcinoid	Often present
Regional lymph node metastases at presentation	5%–15%	40%–48%
Distant metastases at presentation	Rare	20%
Disease-free survival at 5 years	100%	69%
Disease-free survival at 10 years	87%	52%

croscopy.[46–51] Melanocytic carcinoids can be confused with malignant melanoma, but melanomas are not reactive with chromogranin and do not possess neuroendocrine granules.[54–56] Papillary carcinoids may be confused with a variety of neoplasms, particularly with sclerosing hemangioma.[12]

Carcinoid tumors must be differentiated from carcinoid tumorlets, which are incidental findings and usually are smaller than 0.5 cm in diameter.[62] Histologically, carcinoid tumorlets are identical to typical carcinoid tumors, because they consist of nodular proliferations of the same neuroendocrine cells. Carcinoid tumorlets are frequently associated with interstitial fibrosis or bronchiectasis (see Chap. 31).[63–67] It has been suggested that carcinoid tumorlets associated with bronchioles may cause a condition called idiopathic diffuse hyperplasia of pulmonary neuroendocrine cells and airway disease.[67a]

Histochemistry, Immunohistochemistry Electron Microscopy, and Flow Cytometry

The tumor cells of carcinoid tumors frequently show a granular cytoplasmic staining with argyrophilic techniques, such as the Gremelius stain (Fig. 51-5*A*). Argyrophilia is found more frequently in typical carcinoids than atypical carcinoids. Typical carcinoids have a higher percentage, distribution, and intensity of immunohistochemical staining for neuroendocrine and hormonal markers than atypical carcinoid tumors. The most useful neuroendocrine immunohistochemical marker is chromogranin (Fig. 51-5*B*), followed by synaptophysin and Leu-7.[12]

Compared with typical carcinoids, atypical carcinoids demonstrate slightly less overall percentage, distribution, and intensity of immunohistochemical staining for neuroendocrine and hormonal markers. By electron microscopy, typical carcinoids have numerous dense-core granules, which vary considerably in shape and size. Atypical carcinoids have fewer dense-core granules than typical carcinoids, and the granules are slightly smaller and show less variation in size.

Atypical carcinoid tumors are aneuploid more frequently than typical carcinoids.[24,39] Aneuploidy in carcinoid tumors correlates with poor prognosis.[39] However, all aneuploid carcinoid tumors do not behave aggressively; in one study, 58% of patients with aneuploid carcinoid tumors survived 5 years.[39] Most typical carcinoids are diploid, but aneuploidy can be seen in as many as 32% of preparations.[39] Aneuploidy is seen more often in carcinoid tumors with undifferentiated growth patterns, pleomorphic nuclei, lymph node metastases, vascular invasion, and necrosis.[5,24,39]

HIGH-GRADE NEUROENDOCRINE CARCINOMAS

High grade neuroendocrine carcinomas include LCNEC and SCLC. These tumors have a neuroendocrine appearance on light microscopy, exhibit a high mitotic rate, and frequently have extensive areas of necrosis. After a lung tumor with a neuroendocrine appearance is identified as a histologically high-grade neoplasm, the major question is whether it is SCLC or LCNEC.

Large Cell Neuroendocrine Carcinoma

CLINICAL FEATURES

The median age of patients with LCNEC is 64 years (range, 35–75 years). Although some patients are asymptomatic and have a solitary coin lesion discovered on a routine chest radiograph, most patients have manifestations related to bronchial obstruction, such as cough, obstructive pneumonia, and chest pain. Most patients are cigarette smokers, usually with more than a 50 pack-year smoking history.[12]

Most patients with LCNEC follow a malignant clinical course with widespread metastases and death within 16 months of initial diagnosis. However, a small percentage of patients with stage I or II tumors may have good prognoses. Some patients with advanced-stage disease who were initially considered to have SCLC have responded to chemotherapy. The category of LCNEC corresponds most closely with those tumors classified as intermediate cell neuroendocrine carcinoma by Gould and colleagues.[4] The rarity of LCNEC is reflected by the fact that only 15 cases were collected by one group over a 20-year period, and only 5 cases could be retrieved from the files of the National Cancer Institute for a 35-year period.[8,12,68]

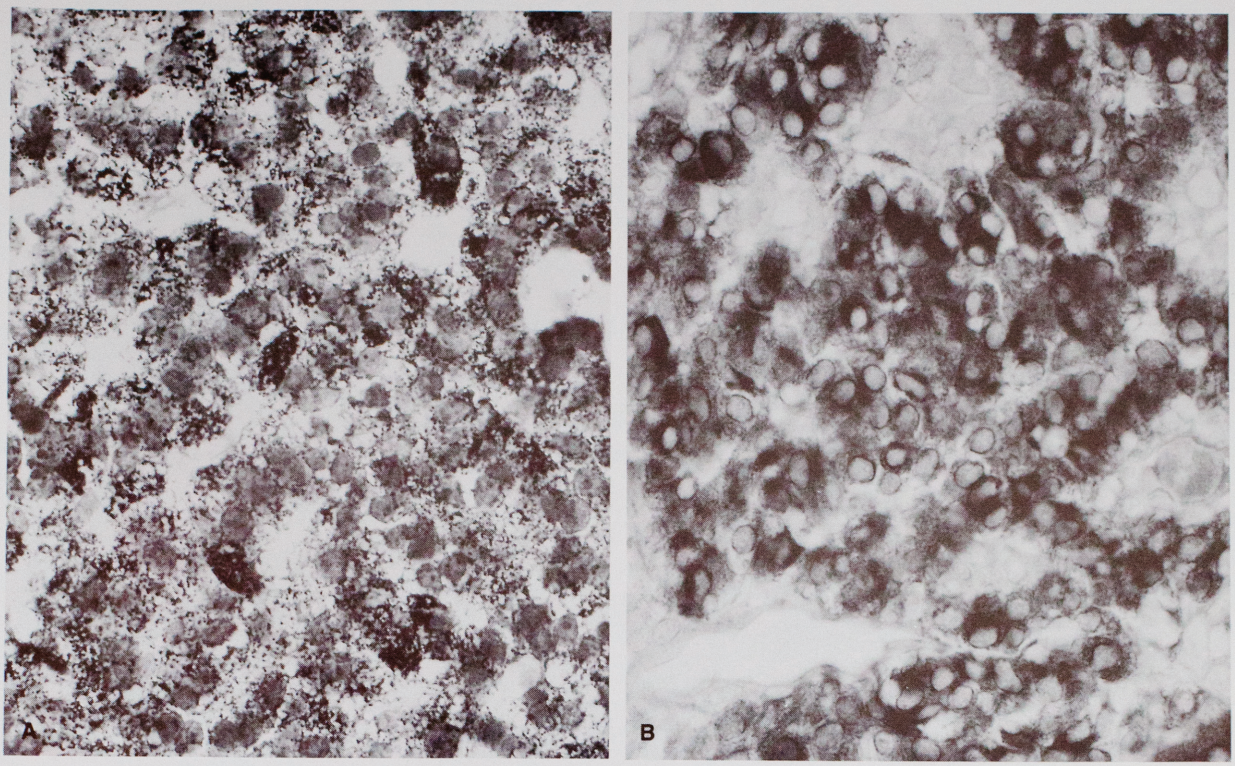

FIGURE 51-5. (**A**) The tumor cells in a typical carcinoid show finely granular staining with the Gremelius stain, which detects argyrophilia. (Gremelius stain; high magnification.) (**B**) These tumor cells stain positively with chromogranin. (Chromogranin by immunoperoxidase stain; high magnification.)

PATHOLOGIC FEATURES

The gross appearance of LCNEC is that of a mass averaging 3.0 cm in diameter (range, 1.3–8 cm). The tumor can develop centrally or peripherally. They are usually circumscribed, unencapsulated nodular masses with a tan-red cut surface that frequently shows necrosis.

LCNEC is defined by the following histologic criteria: a light-microscopic neuroendocrine appearance characterized by organoid, palisading, rosettelike, or trabecular growth patterns; tumor cells with a large size, polygonal shape, low nuclear-cytoplasmic ratio, and coarse or vesicular nuclear chromatin with frequent nucleoli; high mitotic rate (>10/10 HPF) and frequent necrosis; and neuroendocrine features demonstrated by immunohistochemistry or electron microscopy (Fig. 51-6).[12]

The differential diagnosis of LCNEC includes atypical carcinoid, SCLC, and large cell carcinoma (LCC) with or without neuroendocrine differentiation. LCNEC is histologically high grade, unlike atypical carcinoid, which is low grade. Atypical carcinoids by definition have mitotic rates of less than 10 per 10 HPF, and most LCNEC have mitotic rates over 30 and often up to 100 per 10 HPF.[12]

LCNEC is best differentiated from SCLC based on multiple criteria (Table 51-2) rather than a single feature. The examiner should be careful in suggesting the diagnosis of LCNEC on the basis of a small transbronchial biopsy and cytology specimens, because it can be difficult in small specimens to differentiate a light microscopic neuroendocrine pattern and to interpret immunohistochemical stains.

LCNEC is differentiated from LCC based on the presence or absence of a neuroendocrine pattern when viewed under light microscopy. If no light microscopic features suggest neuroendocrine differentiation, but immunohistochemistry or electron microscopy demonstrates neuroendocrine features, the tumor is called large cell carcinoma with neuroendocrine differentiation (LCC-NE). Such cases correspond to the 10% to 15% of NSCC of the lung in which neuroendocrine differentiation can be found by electron microscopy or immunohistochemistry but no neuroendocrine features are seen by light microscopy (see Display 51-1).[13,14,69–75]

According to the four-category classification scheme proposed by Travis and associates, the term LCNEC should be restricted to the NSCCs with a neuroendocrine appearance by light microscopy.[12] LCCs with immunohistochemical or electron microscopic evidence of neuroendocrine differentiation can be separated into those that have neuroendocrine features by light microscopy (*i.e.*, LCNEC) and those that do not (*i.e.*, LCC-NE).[12] It remains to be determined whether there are significant differences in survival and response to therapy in patients with LCNEC, LCC, LCC-NE, and SCLC. Because of the rarity of LCNEC, definitive studies to answer these questions must await accumulation of substantial numbers of patients.

LCNEC is more difficult to recognize than the other neuroendocrine lung tumors, because it requires immunohistochemical or ultrastructural support to establish the diagnosis; the terminology and criteria described in the literature is confusing and inconsistent.

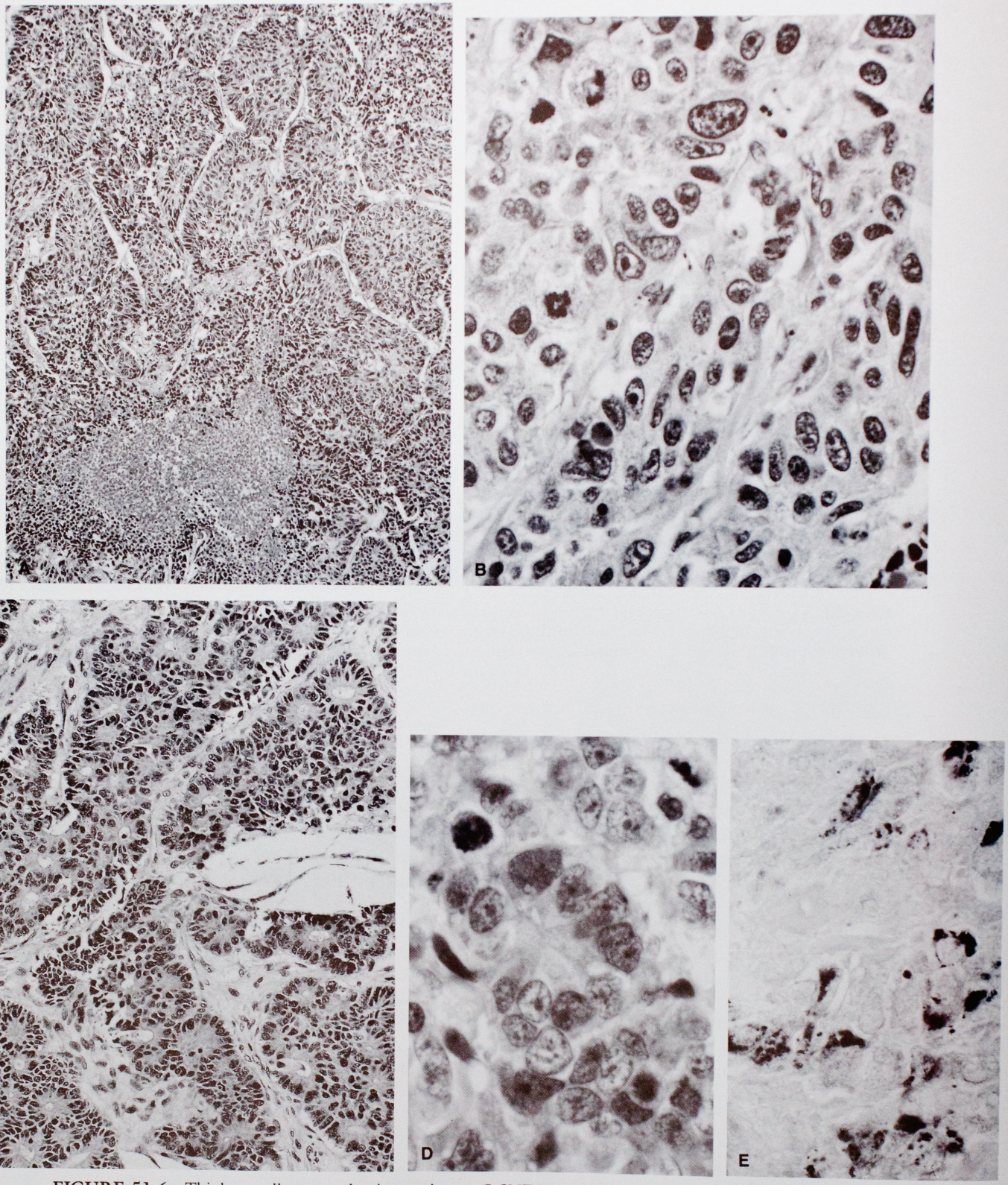

FIGURE 51-6. This large cell neuroendocrine carcinoma (LCNEC) consists of organoid nests of tumor cells with some palisading of nuclei at the periphery of the nests. (H & E stain; low magnification.) (**B**) The tumor cells show marked nuclear pleomorphism, abundant cytoplasm, coarse nuclear chromatin, prominent nucleoli, and several mitotic figures. (H & E stain; high magnification.) (**C**) The tumor cells of this LCNEC have a prominent rosettelike arrangement. (H & E stain; intermediate magnification.) (**D**) A rosettelike arrangement is seen; the tumor cells show vesicular chromatin or prominent nucleoli. (H & E stain; intermediate magnification.) (**E**) This LCNEC stains positively for chromogranin. (Chromogranin stain by immunoperoxidase at high magnification.)

TABLE 51-2
Light Microscopic Features for Differentiating Small Cell Carcinoma From Large Cell Neuroendocrine Carcinoma

Histologic Feature	Small Cell Carcinoma	Large Cell Neuroendocrine Carcinoma
Cell Size	Small (< diameter of 3 lymphocytes)	Large
Nuclear–cytoplasmic ratio	High	Low
Nuclear chromatin	Finely granular, uniform	Coarsely granular or vesicular; less uniform
Nucleoli	Absent or faint	Often present; may be either prominent or faint
Nuclear molding	Characteristic	Uncharacteristic
Fusiform shape	Common	Uncommon
Polygonal shape with ample pink cytoplasm	Uncharacteristic	Characteristic
Nuclear smear (*i.e.*, crush)	Frequent	Uncommon
Basophilic staining of vessels and stroma	Occasional	Rare

ELECTRON MICROSCOPY, IMMUNOHISTOCHEMISTRY, AND FLOW CYTOMETRY

The neuroendocrine granules seen by electron microscopy in LCNEC are often focal and less conspicuous than those seen in atypical carcinoids.[12] Well-developed cytoplasmic lumina suggesting glandular differentiation and prominent desmosomal intercellular attachments suggesting squamous differentiation may be seen in LCNEC specimens.[12]

Immunohistochemical stains of LCNEC are positive for neuron-specific enolase (NSE; 100%), chromogranin (80%), Leu-7 (40%), synaptophysin (40%), bombesin (40%), carcinoembryonic antigen (100%), and keratin (100%).[12] Immunoreactivity is often focal. Because NSE stains up to 60% of NSCC, it is not a useful neuroendocrine marker.[76] A small percentage of LCNEC stain positive for neuroendocrine and hormonal markers compared with typical and atypical carcinoid. Similar to SCLC, as many as 75% of LCNEC are aneuploid.[12]

Small Cell Lung Carcinoma

CLINICAL FEATURES

Approximately 20% to 25% of all bronchogenic carcinomas are SCLCs. The median age for patients with SCLC is 60 years (range, 32–79 years). Men predominate, but the percentage of affected women is increasing; the male-female ratio used to be 10:1, but it is now closer to 2:1. There is a strong association with smoking (see Chap. 49).[77]

The most common symptoms are cough, dyspnea, wheezing, hemoptysis, chest pain, or postobstructive pneumonitis.[77] Ten percent of patients present with superior vena cava syndrome.[77] Associated paraneoplastic syndromes include the inappropriate secretion of antidiuretic hormone, Cushing syndrome due to secretion of ectopic ACTH, and the Eaton-Lambert or myasthenia gravis–like syndrome.[77] Metastases to extrapulmonary locations such as the central nervous system, bone, and liver are common.

SCLC can be staged according to the TNM system or according to a limited and extensive staging system.[78,79] Limited-stage disease is found at initial diagnosis in about 30% of patients, and 70% have extensive stage disease.[77] SCLC presents as a solitary pulmonary nodule, or limited stage I disease according to the TNM staging system, in fewer than 5% of patients.[80] Without therapy, patients with limited-stage SCLC have a median survival of 3 months, in contrast to 1.5 months for those with extensive-stage disease. The median survival increases to 10 to 16 months for patients with limited-stage disease and 6 to 11 months for patients with extensive-stage disease after combination chemotherapy and chest radiotherapy. SCLC is responsive to combination chemotherapy, and great emphasis is therefore placed on the separation of SCLC and NSCC.[81]

PATHOLOGIC FEATURES

The most common gross presentation of SCLC is as a perihilar and peribronchial mass with extensive lymph node metastases. The cross-sectioned surface is white-tan, soft, and friable and frequently shows extensive necrosis. SCLC presents as a peripheral coin lesion in fewer than 5% of patients.[80,82]

In 1981, the WHO proposed the classification of SCLC into oat cell, intermediate, and combined types.[16] In 1988, the International Association for the Study of Lung Cancer proposed that the classification of SCLC be modified to drop the oat cell and intermediate subtypes and include the following three categories: SCLC, mixed small cell and large cell carcinoma, and combined SCLC with components of squamous cell or adenocarcinoma.[83]

Histologically, SCLC is composed of small, round-to-fusiform tumor cells with scant cytoplasm, finely granular nuclear chromatin, and absent or inconspicuous nucleoli (Fig. 51-7*A, B*).[83,84] Nuclear molding may be seen. The tumor cells grow in nests, ribbons, rosettes, and rarely in tubules or ductules.[84] Necrosis occurs frequently and is often extensive. Mitoses are frequent, and the mitotic rate is often as high as 50 to 100 per 10 HPF. Blood vessel walls often show hematoxyphilic encrustation by DNA from necrotic tumor cells, a phenomenon called the Azzopardi effect (Fig. 51-7*C*).[84]

Tumor cell size varies in SCLC and includes larger cells approaching the size of LCC. According to the 1981 WHO classification, cases of SCLC with larger tumor cell size were called the intermediate subtype.[16] However, a continuous spectrum of cell size shown by morphometry ranges from the smallest SCLC to LCC.[85] It has been suggested that the tumor cells of SCLC should be approximately the diameter of two to three small resting lymphocytes.[10] The tumor cells of SCLC appear larger in larger biopsy

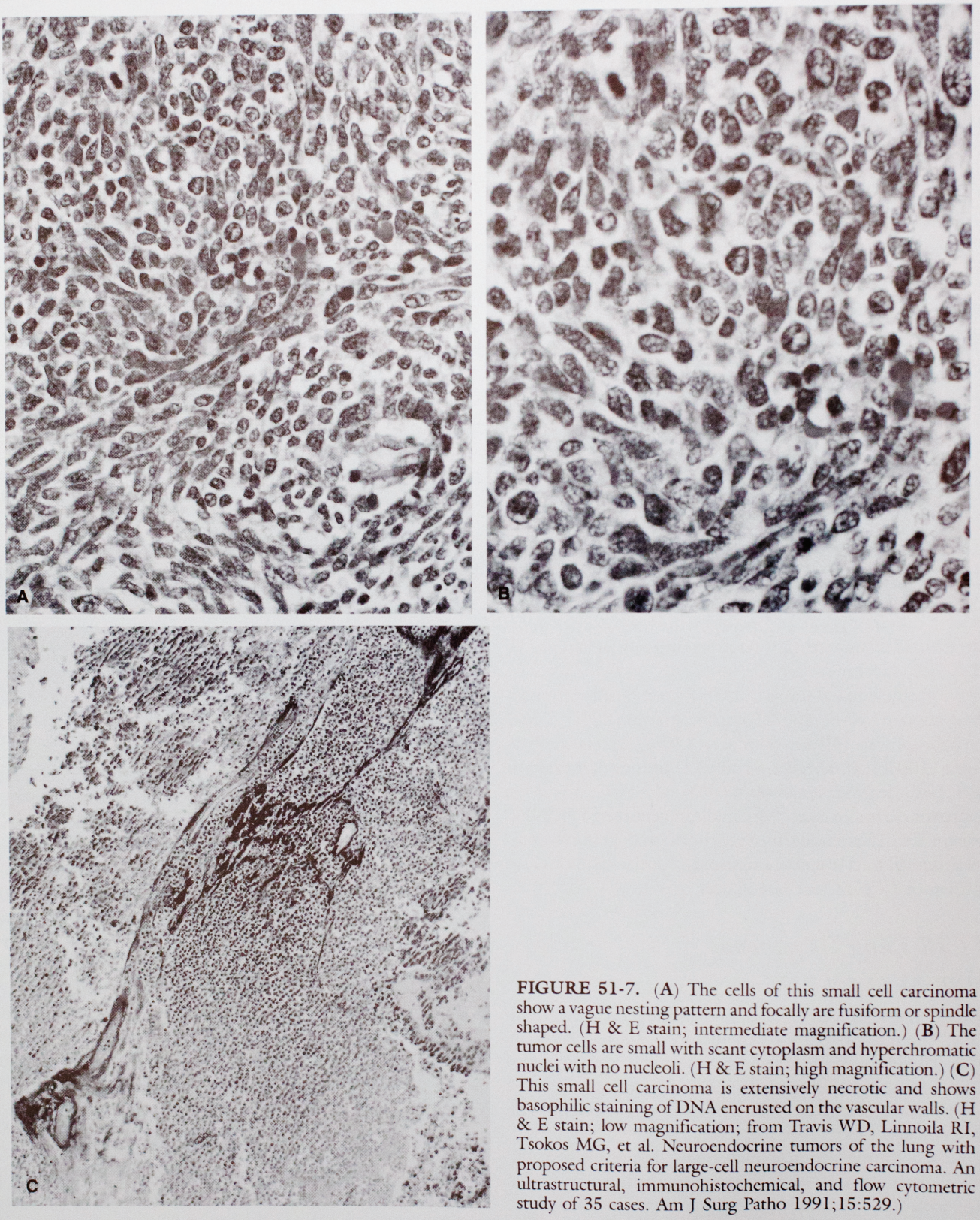

FIGURE 51-7. (**A**) The cells of this small cell carcinoma show a vague nesting pattern and focally are fusiform or spindle shaped. (H & E stain; intermediate magnification.) (**B**) The tumor cells are small with scant cytoplasm and hyperchromatic nuclei with no nucleoli. (H & E stain; high magnification.) (**C**) This small cell carcinoma is extensively necrotic and shows basophilic staining of DNA encrusted on the vascular walls. (H & E stain; low magnification; from Travis WD, Linnoila RI, Tsokos MG, et al. Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. Am J Surg Patho 1991;15:529.)

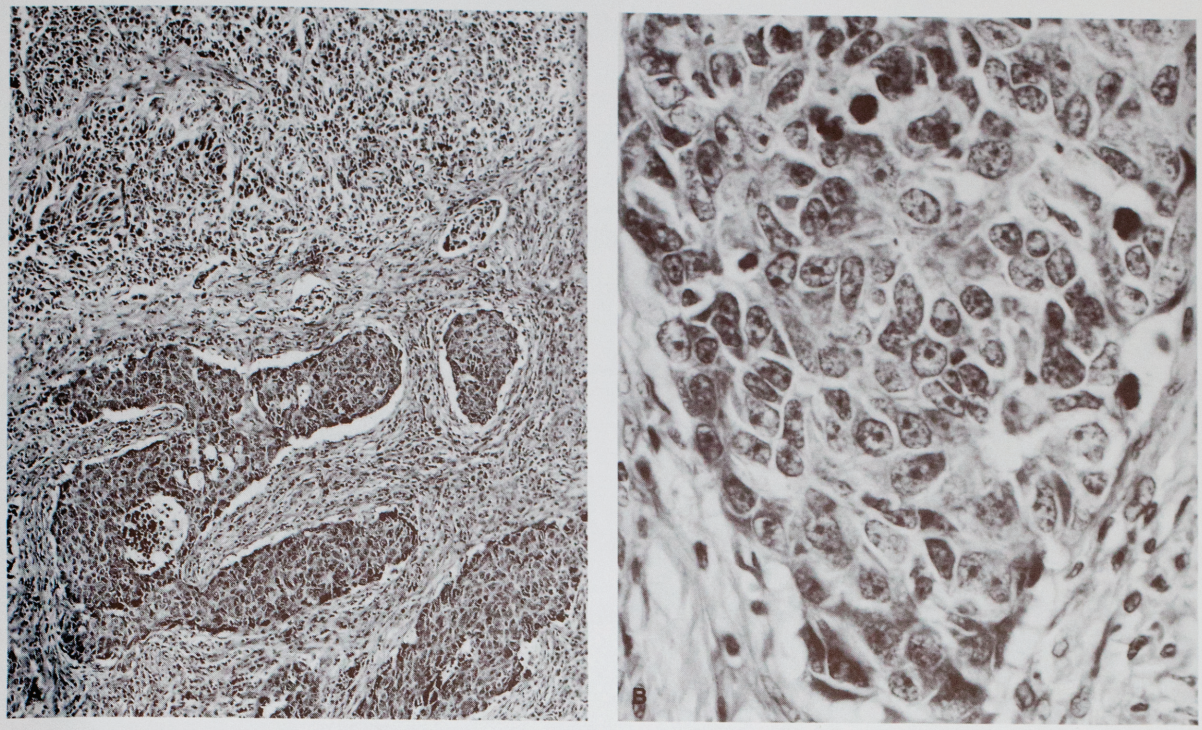

FIGURE 51-8. (**A**) Mixed small cell (*top*) and large cell carcinoma (*bottom*). (H & E stain; low magnification.) (**B**) The large cell component has tumor cells with a moderate amount of cytoplasm and prominent nucleoli. (H & E stain; high magnification.)

specimens; in well-fixed open biopsies, SCLC cells are larger than in transbronchial biopsy specimens.[85]

Mixed small cell and large cell carcinoma consists of a mixture of SCLC and LCC. Histologically, the two cell types may show a sharp separation (Fig. 51-8), or there may be a close intermixture of small and large cells. It was originally suggested that this subtype comprised 12% to 14% of SCLC, but later studies indicated a figure of about 4% to 5%.[83,86–90] A significantly worse survival was found in initial studies of patients with mixed small cell and large cell carcinoma compared with pure SCLC.[86,87] However, subsequent studies indicated that these patients had a better prognosis or no significant difference in survival.[88,89]

Combined SCLC is the least common of the subtypes, occurring in 1% to 3% of patients.[83,89,91–93] Squamous cell (Fig. 51-9*A–C*) and adenocarcinoma (Fig. 51-9*D,E*) are the most common histologic types encountered, but combinations can also occur with spindle cell carcinoma (Fig. 51-10) and giant cell carcinoma.[94]

After therapy, biopsy specimens from 13% to 45% of patients with pure SCLC may demonstrate a different morphology with mixed small cell and large cell carcinoma or SCLC combined with squamous cell carcinoma, adenocarcinoma, or giant cell carcinoma.[88,93,95–97] Most SCLCs have cytoplasmic dense-core granules by electron microscopy. These neuroendocrine granules are typically few and small (*i.e.*, 10–130 nm) and may be located in small dendritic cytoplasmic processes.[98,99] Ten percent to 35% of SCLCs may be regarded as nonneuroendocrine, because dense-core granules are absent.[99–103]

ELECTRON MICROSCOPY AND IMMUNOHISTOCHEMISTRY

As seen by electron microscopy, most SCLCs have scant cytoplasm, few organelles, and nuclei with moderately and uniformly dense chromatin. Nucleoli are small or absent, although they are more apparent than by light microscopy.[99,104] Ultrastructural examination of one SCLC revealed evidence of squamous cell carcinoma, adenocarcinoma, and SCLC differentiation within a single cell.[105]

An extensive number of antibodies can be used to immunohistochemically stain SCLCs; these include neuroendocrine, hormonal, and other markers. For formalin-fixed, paraffin-embedded tissue sections, chromogranin A, synaptophysin, and Leu-7 are the most useful neuroendocrine markers.[12] Many monoclonal antibodies for neuroendocrine differentiation have been tried, but none has proven useful in routine formalin-fixed, paraffin-embedded section.[106–110] Because NSE stains as many as 60% of NSCC, it is not a specific marker for neuroendocrine differentiation.[12,76] If the differential diagnosis of malignant lymphoma is a problem, keratin and leukocytic common antigen staining can be helpful.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of SCLC includes NSCC, malignant lymphoma, chronic inflammation, and other neuroendocrine lung tumors, including carcinoids and LCNEC. One of the most common problems in diagnosing SCLC is crush artifact,

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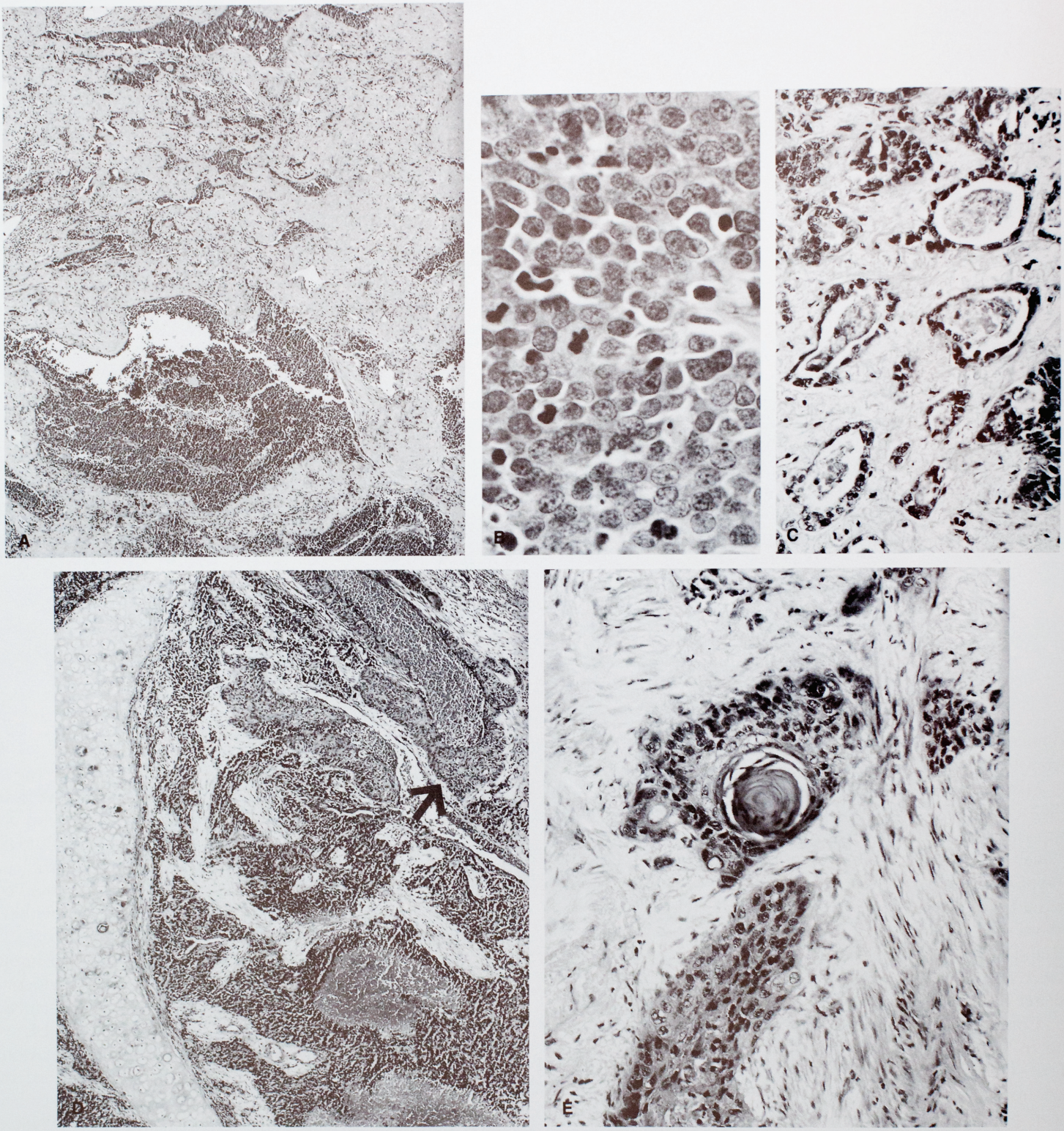

FIGURE 51-9. (**A**) A combined small cell carcinoma consists of a moderately differentiated adenocarcinoma (*top*) and a small cell carcinoma (*bottom*). (H & E stain; low magnification.) (**B**) The small cell carcinoma component shows hyperchromatic cells with scant cytoplasm, finely granular nuclear chromatin, and absent or faint nucleoli. (H & E stain; high magnification.) (**C**) High-power of the adenocarcinoma component reveals acinar structures. (H & E stain; low magnification.) (**D**) Most of this tumor consists of small cell carcinoma, but several foci represent squamous cell carcinoma (*arrows*). (H & E stain; low magnification.) (**E**) Keratinizing squamous cell carcinoma. (H & E stain; intermediate magnification.)

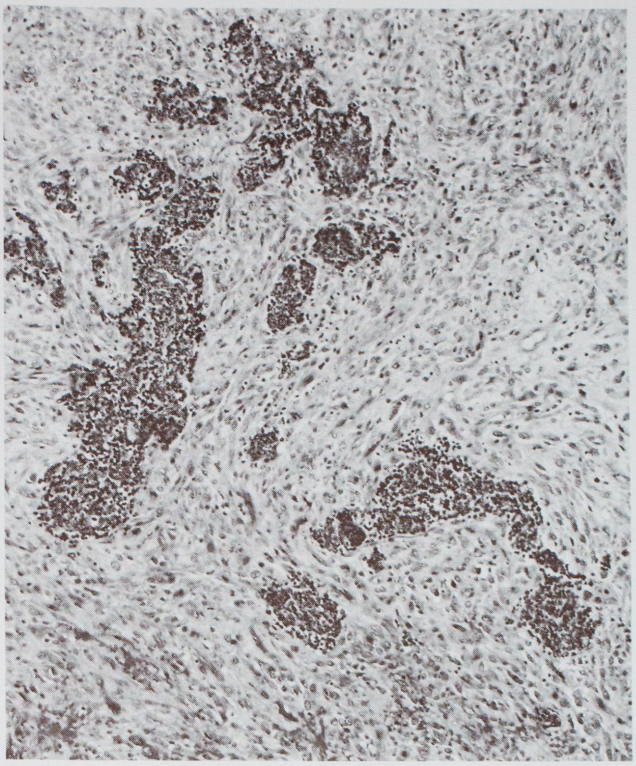

FIGURE 51-10. This tumor is composed of a mixture of small cell carcinoma and spindle cell carcinoma. (H & E stain; low magnification.)

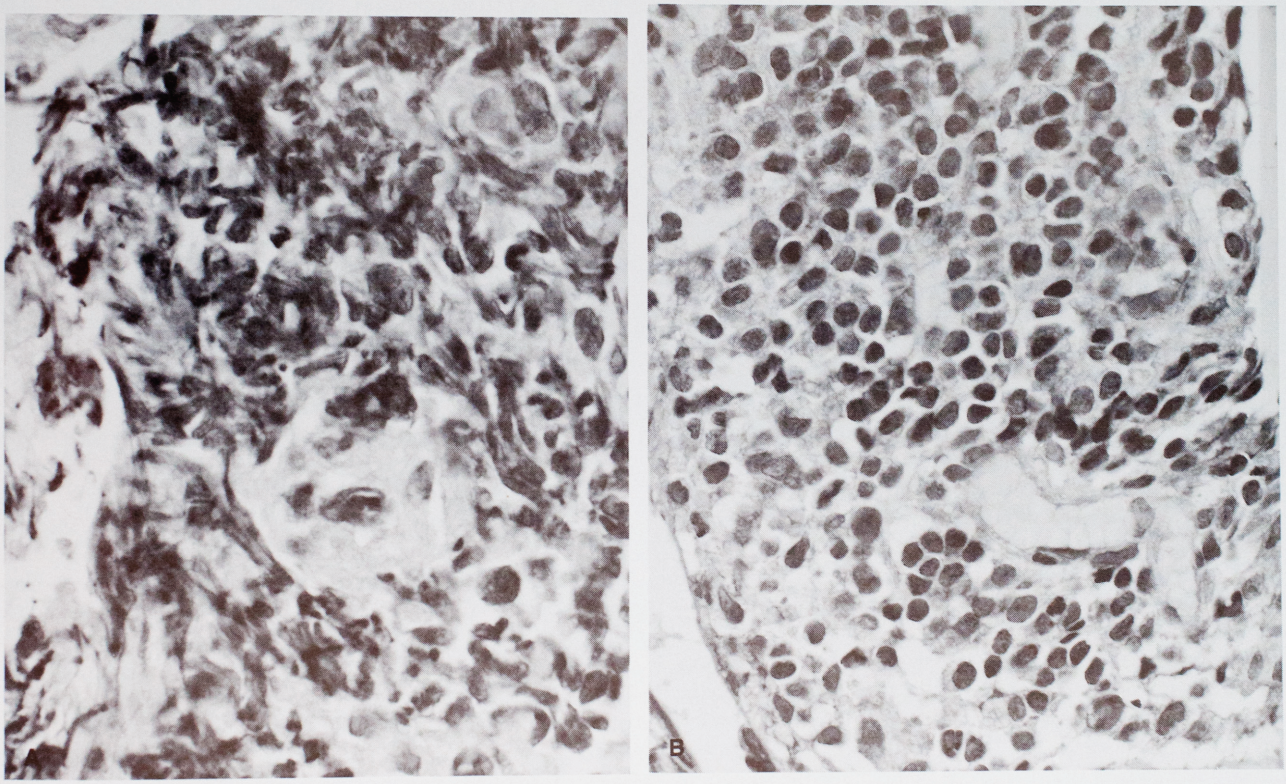

FIGURE 51-11. This biopsy was originally interpreted as a small cell carcinoma, but a subsequent resection revealed bronchiolitis obliterans with organizing pneumonia. (**A**) The crush artifact was initially thought to be small cell carcinoma. (**B**) In retrospect, other areas in the transbronchial biopsy showed these chronic inflammatory cells; the crushed cells were lymphocytes. (H & E stain; high magnifications.)

especially in small transbronchial or mediastinal biopsy specimens. However, similar crush artifact can be seen with lymphoma, NSCC, and chronic inflammation (Fig. 51-11).

Criteria useful in the separation of SCLC from LCC and LCNEC are listed in Table 51-2. These distinctions are best made using a group of criteria rather than a single histologic feature such as cell size.[12] Both typical and atypical carcinoid tumors are histologically much lower grade tumors than SCLC. Mitotic rates are high in SCLC, and necrosis tends to be extensive, but in atypical carcinoids, the rates are low, with up to 10 mitoses per 10 HPF, and necrosis tends to be focal. In a small, crushed specimen, it may be difficult to identifying mitoses. In SCLC, the tumor cells tend to have less cytoplasm than those of atypical carcinoid, and the tumor appears more hyperchromatic.

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