

# The Spectrum of Pulmonary Neuroendocrine Carcinomas: Radiologic and Pathologic Findings<sup>1</sup>

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Pulmonary neuroendocrine carcinoma constitutes a spectrum of malignancies and histopathologically, is classified into four distinct subtypes. At one end of this spectrum are typical carcinoids, low grade carcinomas with a low incidence of metastasis and excellent prognosis following surgical resection. At the other end is small cell carcinoma which typically metastasize early in their course, and for which surgery is rarely curative. Atypical carcinoids have an intermediate grade of malignancy, and their prognosis is somewhere between that of typical carcinoids and small cell carcinoma. Large cell neuroendocrine carcinoma is a high grade tumor that morphologically and biologically is between atypical carcinoids and small cell carcinoma. A knowledge of the radiologic findings of these tumors allows an appropriate differential diagnosis and can help avoid diagnostic pitfalls.

**Index words :** Lung neoplasms

Lung neoplasms, CT

Lung neoplasms, diagnosis

Pulmonary neuroendocrine carcinoma originate from neuroendocrine cells(Kulchitzky cells) normally found in the bronchial and bronchiolar epithelium and mucous glands, and are characterized by neuroendocrine features including an organoid growth pattern, argyrophilia, dense-core neurosecretory granules, and the production of hormones and/or neuropeptides.

The classification of pulmonary neuroendocrine carcinoma is a complex and controversial problem, though it has evolved substantially over the past two decades. In 1991, Travis et al. (1) proposed a four-category scheme for the classification of neuroendocrine tumors includ-

ing typical carcinoids, atypical carcinoids, large cell neuroendocrine carcinoma, and small cell carcinoma. Due to overlapping of clinical features, radiologic findings, and pathologic features, the classification of an individual neuroendocrine tumor into one of these categories is often difficult and misleading (2, 3). Because their prognosis and treatment of these tumors differ, classification and accurate preoperative diagnosis of these tumors are, however, important

The aim of this paper is to illustrate the radiologic and pathologic findings of the spectrum of pulmonary neuroendocrine carcinomas, based on a review of pathologically proven cases.

## Typical Carcinoids

Typical carcinoids are low-grade malignant tumors showing remarkably good prognosis and with a low incidence of metastasis. Typical carcinoids have been referred to as low-grade neuroendocrine tumors and

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Kulchitzky cell carcinomas grades I (2, 4), and there is a roughly equal male/female distribution (2). Age at diagnosis ranges from childhood to the ninth decade (average, 50 years), and this is the most frequently diagnosed primary neoplasm of the lung in children and adolescents (2). There is no association with cigarette smoking. Approximately 80% of these tumors occur centrally in the main, lobar or segmental bronchi, and about 20% in the periphery beyond the segmental bronchi (2). Central carcinoids may present as a sessile mass, an iceberg pattern, or an intraluminal polypoid mass (Fig. 1, 2) (2). Despite the production of peptide hormones, the carcinoid syndrome is uncommonly seen and is found only when extensive liver metastases are present. Other rare paraneoplastic syndromes including Cushing's syndrome, acromegaly, and inappropriate antidiuretic hormone secretion may be associated (2, 5). Bronchoscopy demonstrates that typical carcinoids are polypoid lesions that bleed easily; because of the potential risk of hemorrhage, bronchoscopic biopsy is not usually performed (2, 5). Prognosis following surgical resection is

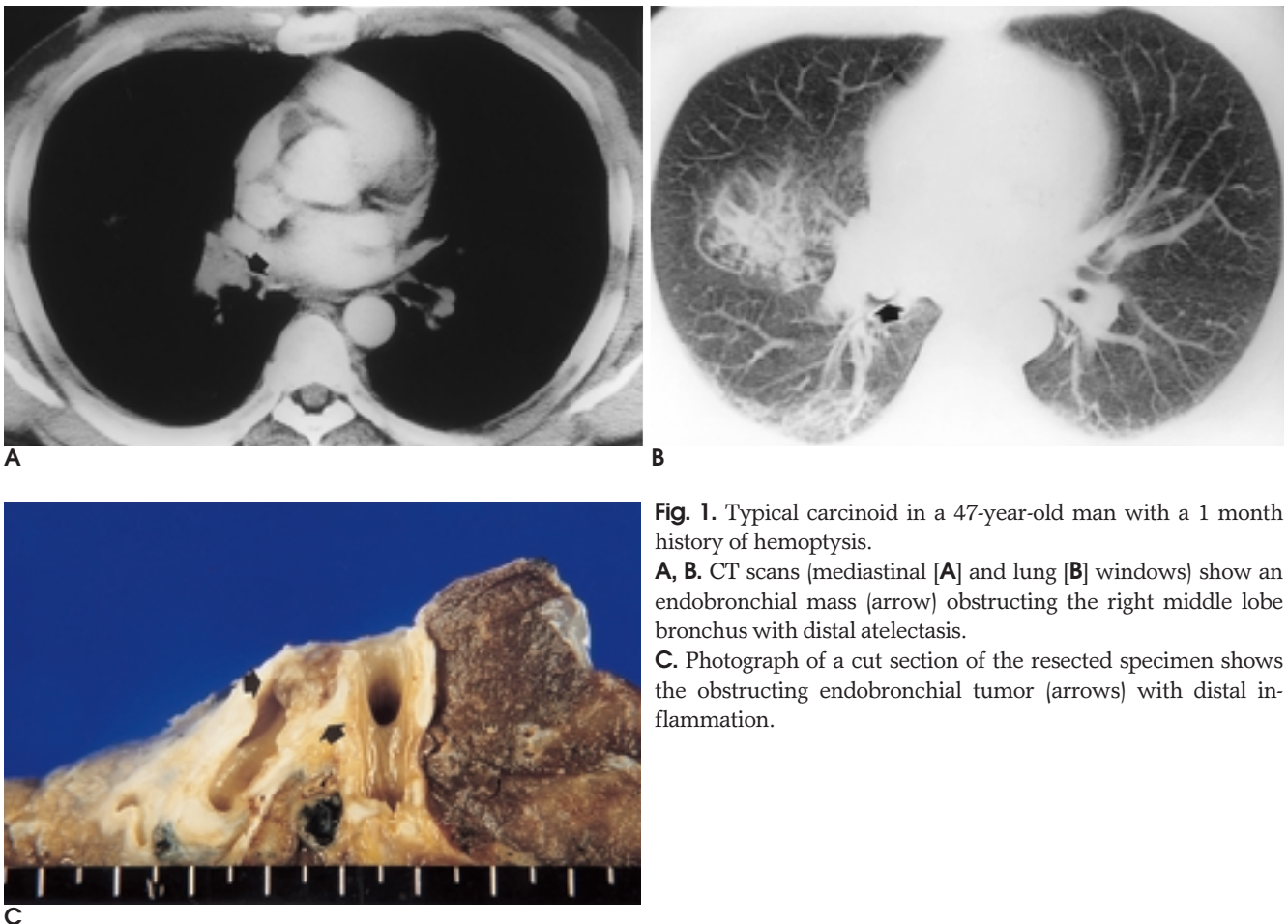
excellent, and the five-year survival rate is greater than 90% (1, 2, 5).

### Pathologic Findings

Typical carcinoids are characterized by an organoid growth pattern; solid, glandular, palisading, papillary, and follicular growth patterns have been observed (Fig. 2E). Rosette-like formations are rarely seen, and the absence of pleomorphism, mitotic figures, and tumor necrosis separates typical carcinoids from higher grade neuroendocrine carcinomas. Typical carcinoids have 0 to 1 mitoses per 10 high power fields, and features of neuroendocrine differentiation are seen with great regularity. Immunohistochemistry shows that carcinoids are typically positive for S-100 protein and Leu-7, as well as for neuroendocrine markers such as chromogranin (Fig. 2F), neuron-specific enolase, and synaptophysin,

### Radiologic Findings

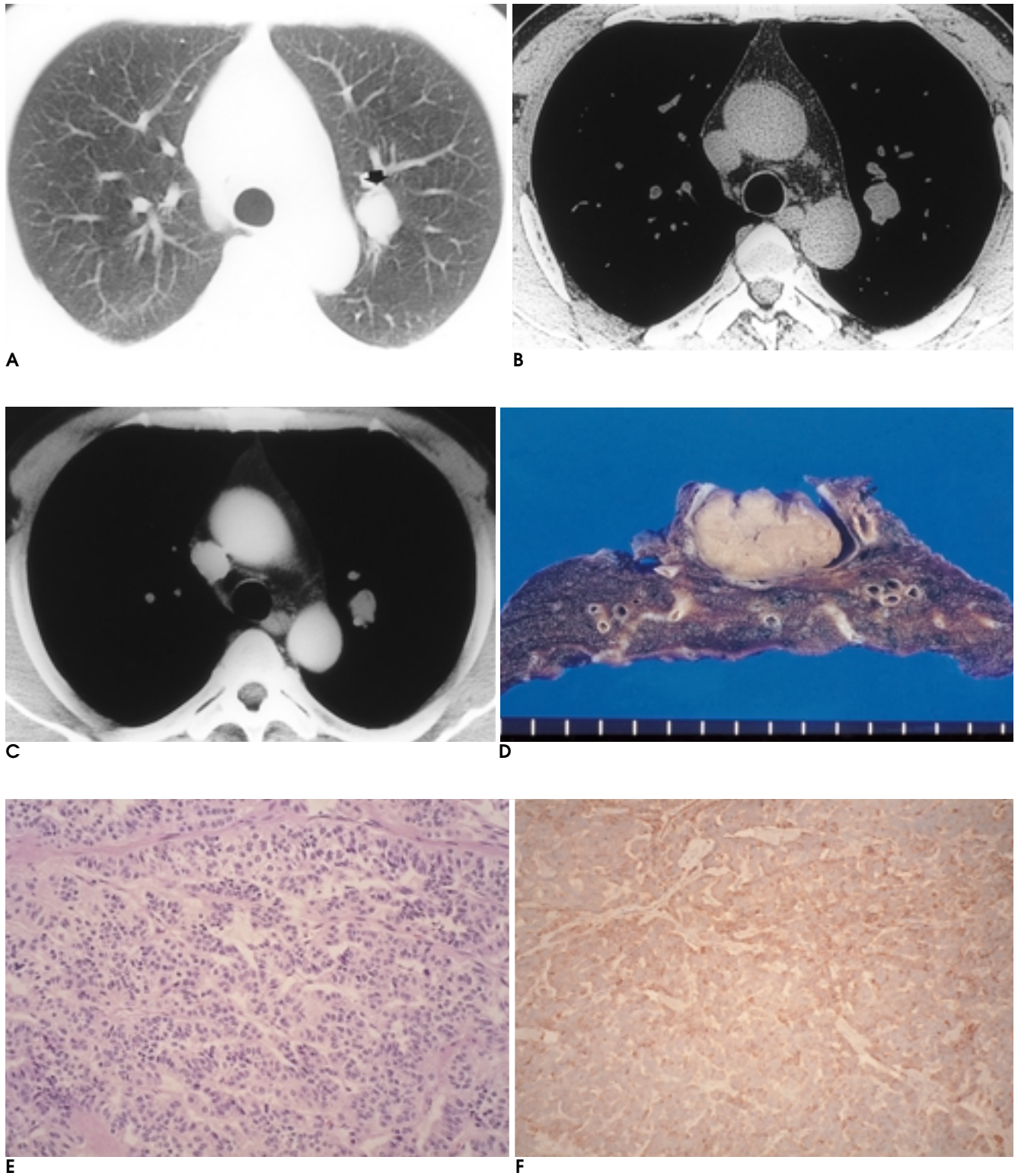
Radiologic manifestations depend on the location of the tumor. In central carcinoids, evidence of bronchial



**Fig. 1.** Typical carcinoid in a 47-year-old man with a 1 month history of hemoptysis.

**A, B.** CT scans (mediastinal [A] and lung [B] windows) show an endobronchial mass (arrow) obstructing the right middle lobe bronchus with distal atelectasis.

**C.** Photograph of a cut section of the resected specimen shows the obstructing endobronchial tumor (arrows) with distal inflammation.



**Fig. 2.** Typical carcinoid in a asymptomatic 52-year-old man

**A, B, C.** CT scans (lung **[A]**, non-enhanced mediastinal **[B]**, and enhanced mediastinal **[C]** windows) of left upper lobe shows a well-defined, 2 × 1.5 cm sized, well enhancing, soft tissue mass with peripheral air crescent (arrow) which is suggestive of relation with bronchus.

**D.** Photograph of a cut section of the resected left upper lobe demonstrates a well-circumscribed mass within a bronchus.

**E.** Photomicrograph shows uniform cells with organoid nesting pattern (H&E, × 100).

**F.** Immunohistochemical stain for chromogranin A shows cytoplasmic staining (× 100).



obstruction including atelectasis, recurrent pneumonia, and obstructive pneumonitis are common radiographic findings (Fig. 1) (5). Peripheral carcinoids appear as solitary pulmonary nodules which are usually homogeneous, sharply defined, round or oval, slightly lobulated, and measure less than 3 cm in diameter (Fig. 2). Typical carcinoids are smaller than atypical carcinoids (1, 6), and because the former are very vascular, marked enhancement of the lesion following intravenous administration of contrast medium is demonstrated by CT and MRI (Fig. 2C). Although calcification or ossification within carcinoids is a common pathologic finding, these features are seldom visible on chest radiographs. CT scan reveals calcification in approximately 30% of cases, however. Lymphadenopathy is uncommon.

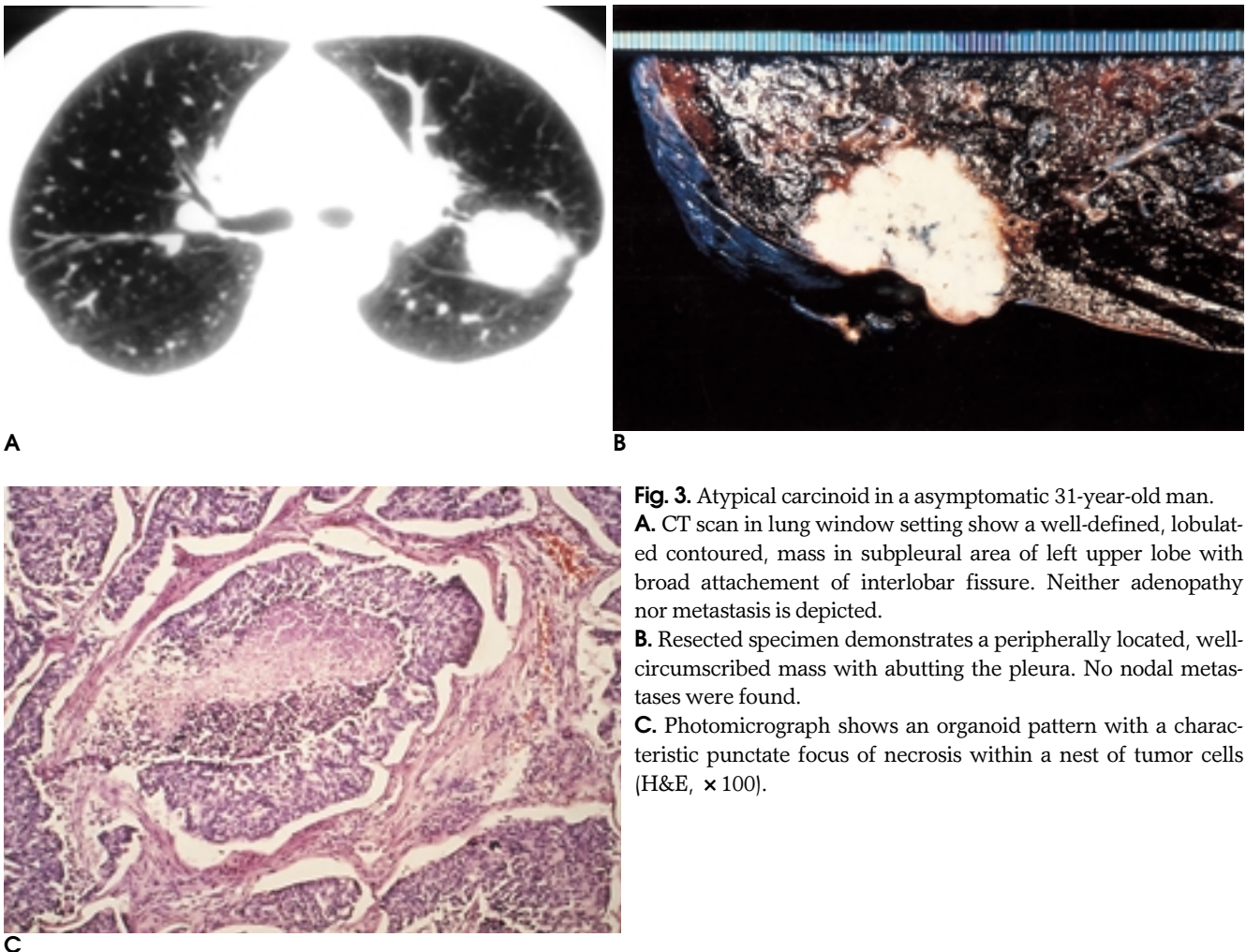
### Atypical Carcinoids

The clinicopathologic features of atypical carcinoids are intermediate between those of typical carcinoids and

small cell carcinoma. Atypical carcinoids have been referred to as intermediate-grade neuroendocrine tumors, well-differentiated neuroendocrine carcinoma, high-grade carcinoids, and Kulchitzky cell carcinoma grade II (2, 4). The majority are peripheral in location and are associated with a history of cigarette smoking (2). They occur more often in men and tend to be found in a slightly older age group (mean age, fifties to sixties) (2). Approximately 50% to 70% of patients have lymph node metastases at the time of initial evaluation. Distant metastasis may be present in 20 to 30% of patients at diagnosis and in up to 52% of patients there may be recurrence (2). The five-year survival rate is 55% (3). Treatment consists of surgery and adjuvant chemotherapy.

### Pathologic Findings

Overall, atypical carcinoids have an organoid pattern in which pseudorosettes may be present, as well as argyrophilia, dense-core granules, and positive immunostaining for neuroendocrine markers; the latter three fea-



**Fig. 3.** Atypical carcinoid in a asymptomatic 31-year-old man.  
**A.** CT scan in lung window setting show a well-defined, lobulated contoured, mass in subpleural area of left upper lobe with broad attachment of interlobar fissure. Neither adenopathy nor metastasis is depicted.  
**B.** Resected specimen demonstrates a peripherally located, well-circumscribed mass with abutting the pleura. No nodal metastases were found.  
**C.** Photomicrograph shows an organoid pattern with a characteristic punctate focus of necrosis within a nest of tumor cells (H&E,  $\times 100$ ).

tures may, though, be less frequent than in typical carcinoids (2). Compared with typical carcinoids, atypical carcinoids show greater mitotic activity (not more than 10 mitoses per 10 high power fields), greater cytological pleomorphism with larger, vesicular nuclei, larger more frequent nucleoli and higher nuclear to cytoplasmic ratios, increased cellularity and architectural irregularity, and a higher degree of tumor necrosis (Fig. 3D) (2, 4).

#### Radiologic Findings

A round or oval lobulated peripheral mass is the most frequent finding of atypical carcinoids (Fig. 3). They tend to be larger than typical carcinoids and are more commonly associated with hilar and mediastinal lymphadenopathy (5). In a study by Forster et al. (6), the mean tumor size of ten atypical carcinoids was 3.9 cm, none showed evidence of endobronchial tumor growth, and in four cases, hilar or mediastinal lymphadenopathy was noted. With regard to typical carcinoids, mean tumor size was 1.8 cm, 30% showed endobronchial tumor

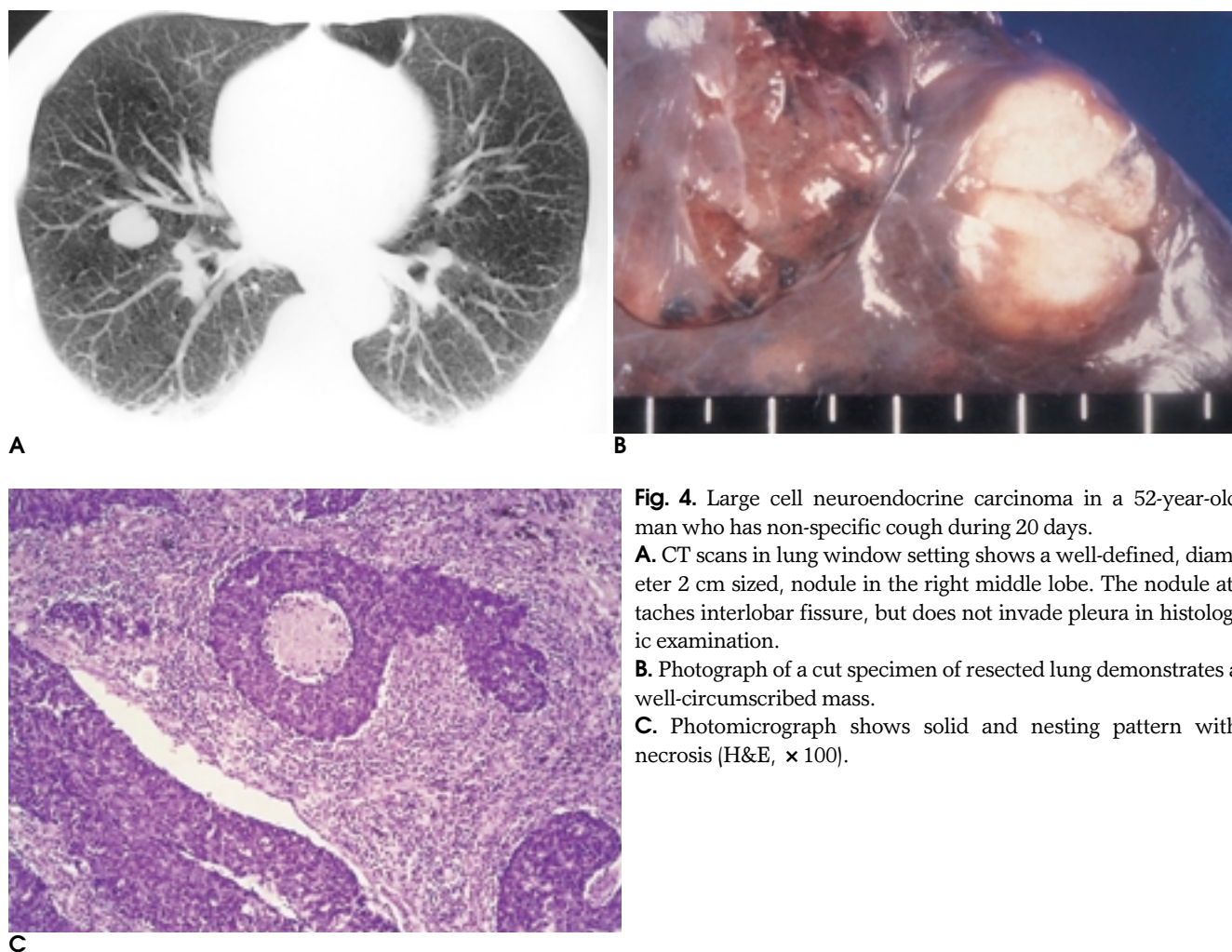
growth with associated atelectasis, and lymphadenopathy was seen in 10%.

#### Large Cell Neuroendocrine Carcinoma

Large cell neuroendocrine carcinoma is defined as a poorly differentiated, high-grade neuroendocrine tumor that morphologically and biologically is between atypical carcinoids and small cell carcinoma. Large cell neuroendocrine carcinoma, which may be peripheral or central (2), occurs more often in men. They are associated with cigarette smoking and present at an average age of 59 (range, 35 to 75) years (2); the five-year survival rate is 27% (3). Ectopic hormone production is, apparently, not a feature of these tumors (2).

#### Pathologic Finding

Large cell neuroendocrine carcinoma has neuroendocrine features including organoid, trabecular, pseudorosette and palisading growth patterns. Tumor



**Fig. 4.** Large cell neuroendocrine carcinoma in a 52-year-old man who has non-specific cough during 20 days.

**A.** CT scans in lung window setting shows a well-defined, diameter 2 cm sized, nodule in the right middle lobe. The nodule attaches interlobar fissure, but does not invade pleura in histologic examination.

**B.** Photograph of a cut specimen of resected lung demonstrates a well-circumscribed mass.

**C.** Photomicrograph shows solid and nesting pattern with necrosis (H&E, ×100).

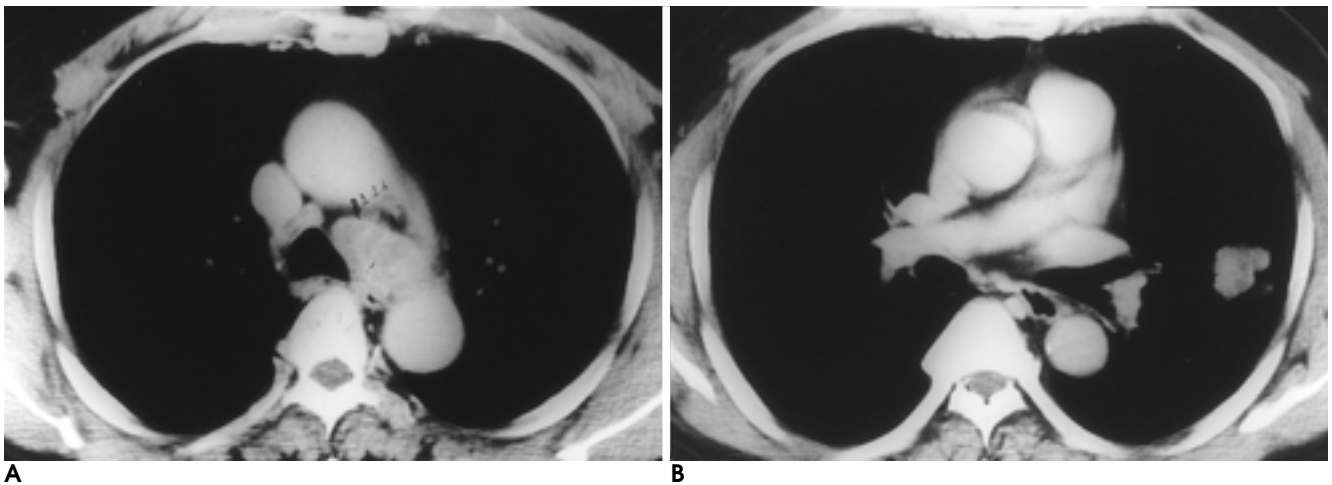


cells are polygonal and moderately pleomorphic with moderate to abundant eosinophilic cytoplasm, coarse nuclear chromatin, and frequent nucleoli, which are often prominent (2). Necrosis is typically present and the mitotic rate is high (2). Compared with atypical carcinoids, large cell neuroendocrine carcinoma has more frequent nucleoli, more extensive necrosis, more cytological atypia, a higher mitotic rate, and fewer dense-core granules (Fig. 4C).

### Radiologic Findings

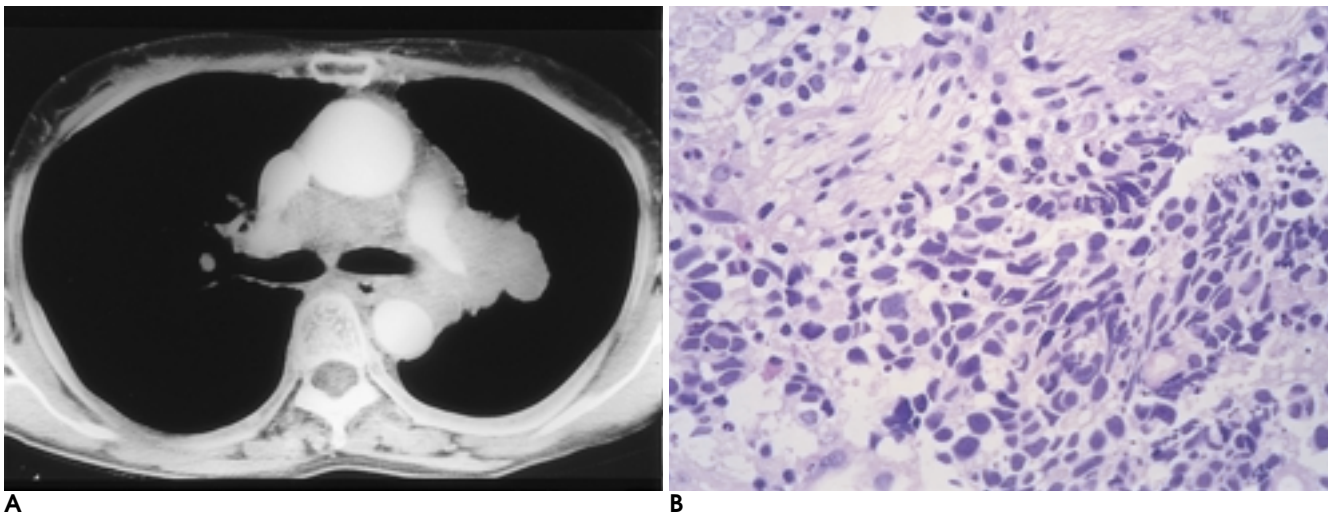
In a study by Shin *et al* (7), all five large cell neuroen-

docrine carcinomas showed a peripherally located nodule or mass without atelectasis (Fig. 4, 5). Mediastinal lymphadenopathy was noted in three (Fig. 5) and in one case there was distant metastasis to the liver. Although the epidemiology of large cell neuroendocrine carcinoma is more similar to that of small cell carcinoma than to atypical carcinoids in its strong association with smoking, rapid progression, and poor prognosis, large cell neuroendocrine carcinomas show pulmonary nodules with or without regional lymphadenopathy, which are findings similar to atypical carcinoids than to small cell carcinoma (7).



**Fig. 5.** Large cell neuroendocrine carcinoma in a 64-year-old man.

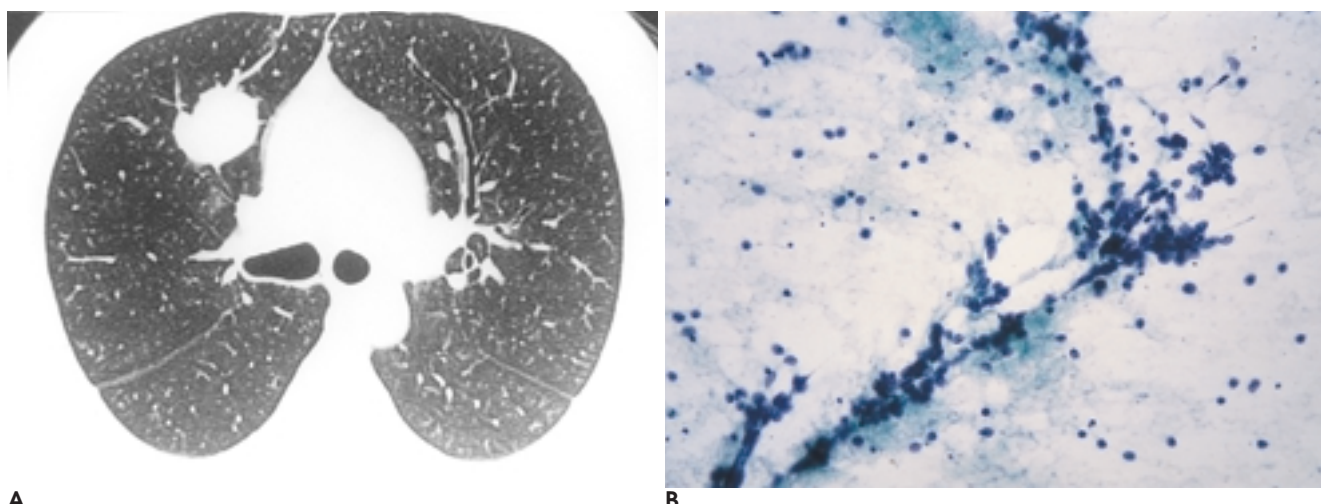
**A, B.** CT scans (mediastinal window, B obtained at a lower level than A) show a lobulated contoured, enhancing mass in left upper lobe with a large left lower paratracheal lymph node contained metastatic large cell neuroendocrine carcinoma at surgery.



**Fig. 6.** Small cell carcinoma in a 73 year old man.

**A.** Contrast-enhanced CT scan shows massive mediastinal and hilar lymphadenopathies and encasement of the left pulmonary artery and bronchus.

**B.** Histologic section obtained from bronchoscopic biopsy demonstrates small hyperchromatic cells, little cytoplasm, and molding (H&E,  $\times 400$ ).



**Fig. 7.** Small cell carcinoma in a asymptomatic 44-year-old man.  
**A.** CT scan in lung window setting shows a well-defined, lobulated, 2.5cm in diameter, soft tissue mass in anterior segment of right upper lobe. This mass is enhanced and a ipsilateral hilar lymphadenopathy is depicted in other sections. These lesions are completely improved after chemotherapy.  
**B.** Cytology obtained from fine needle aspiration of the peripheral lung mass demonstrates small tumor cells with scant cytoplasm (Papanicolaou stain,  $\times 400$ ).

### Small Cell Carcinoma

Small cell carcinoma is an extremely malignant tumor with early metastases, and accounts for 20% to 25% of all bronchogenic carcinoma (5). It has been referred to as Kulchitzky cell carcinoma grade III (4). These tumors are more common in men, and a patient's age is usually at least 40 (average, 60 to 70) years. Small cell carcinoma is strongly associated with cigarette smoking and the patients with small cell carcinoma are the heaviest smokers. The vast majority of small cell carcinomas occur in the central region of the lungs, typically in association with mainstem or lobar bronchi. Local lymphatic spread and metastases to the brain, liver, or adrenals are common at presentation. Ectopic hormone production is common and includes inappropriate antidiuretic hormone secretion, Cushing's syndrome, and the Eaton-Lambert syndrome (5). Small cell carcinoma is usually regarded as unsuitable for surgical resection, and the prognosis is poor. Even in a patient with localized disease and initial response to therapy, the median survival period is only 14 months (5).

### Pathologic Findings

Small cell carcinoma is composed of small, round to fusiform cells with a high nuclear to cytoplasmic ratio, hyperchromatic nuclei with finely granular chromatin, and absent or inconspicuous nucleoli. Nesting, solid,

and palisading histologic patterns have been observed, and necrosis is present in all tumors. The mitotic rates are high (Figs. 6B, 7B).

### Radiologic Findings

Small cell carcinomas show extensive hilar and mediastinal lymphadenopathy at presentation (Fig. 6), sometimes without a primary pulmonary tumor being recognizable on a radiograph or CT scan. In 14% of cases they present as a peripheral mass (Fig. 7), and accompanying hilar and mediastinal adenopathy is frequently noted.

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