Spectrum of Pulmonary Neuroendocrine Cell Proliferation: Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia, Tumorlet, and Carcinoids

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OBJECTIVE. The objectives of this article are to review the radiologic, pathologic, and clinical features of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, tumorlet, and carcinoids and to discuss the possible role of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia and tumorlet in the development of carcinoids.

CONCLUSION. Given the potential significant morbidity of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia and its neoplastic counterparts, it is important to understand and recognize these disease entities. A conceptual continuum of these neuroendocrine entities is suggested.

Keywords: carcinoids, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, lung neoplasms, oncologic imaging, tumorlet

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Normal adult lung tissue contains few neuroendocrine cells within the bronchial and bronchiolar epithelium. Despite their scarcity, neuroendocrine cell hyperplasia can be observed as a reaction to chronic airway inflammation [1, 2]. In patients with carcinoid tumors, neuroendocrine cell hyperplasia has been considered a preneoplastic lesion [3]. Diffuse neuroendocrine cell hyperplasia may occur without an identified cause and is designated diffuse idiopathic pulmonary neuroendocrine cell hyperplasia when neuroendocrine cell growth is confined to the bronchial or bronchiolar epithelial basement membrane. Extension beyond the basement membrane is termed "tumorlet" if the collection of cells is smaller than 5 mm and "carcinoid" when 5 mm or larger [4].

Current literature regarding these three entities focuses little on their radiologic appearances. We will discuss the radiologic features of these entities in relation to their pathologic characteristics and clinical presentations (Table 1). Additionally, we suggest a conceptual construct of viewing these three entities as stages along a continuum of neuroendocrine cell proliferation.

Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia

Patients with diffuse neuroendocrine cell hyperplasia are typically in their fifth or sixth decade; most are asymptomatic, but some may present with insidious cough or slowly progressive dyspnea. Women are more commonly affected than men. Pulmonary function testing often shows an obstructive pattern caused by protrusion of proliferating cells into multiple small airway lumens (Figs. 1A and 1B). Progressive fibrosis, possibly due to neuropeptide release from proliferating neuroendocrine cells, may further narrow airways and may eventually cause luminal obliteration [3, 5] (Fig. 2B).

Radiologic findings reflect these pathophysiologic changes. On high-resolution CT, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia is typically characterized by mosaic perfusion due to air trapping, bronchial wall thickening, and bronchiectasis (Figs. 1B, 1C, 2C, and 2D), although a normal appearance has been reported [4]. Mucus plugging is also seen (Figs. 2C and 2D) because of airway obstruction. Nodular bronchial wall thickening is the most direct radiologic–pathologic correlation of submucosal neuroendocrine cell proliferation and correlates well with the histologic findings of intraluminal protrusion of the proliferative cells.

Tumorlet

Clinically, there is a female preponderance [6] and pulmonary tumorlets are generally encountered in patients between 60 and 70 years old [6–8]. Like individuals with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, individuals with tumorlets are typically asymptomatic.

Unlike diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, the prolifer-

TABLE 1: Salient Clinical, Pathologic, and Radiographic Features of Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia, Tumorlet, and Carcinoids

Characteristics and Findings	Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia	Tumorlet	Typical Carcinoid	Atypical Carcinoid
Demographics				
Age range (y)	50–60	60–70	40–50	50–60
Male–female ratio (no.)	1:4	1:> 4	1:1	2:1
Histopathologic findings				
Basement membrane preserved	Yes	No	No	No
Nest formation	No	Yes	Yes	Yes
≥ 5 mm	Not applicable	No	Yes	Yes
Mitoses per 10 high power fields	No	No	< 2	2–10
Necrosis	No	No	No	Yes
Clinical presentation				
	Asymptomatic	Asymptomatic	Recurrent pneumonia	Same as typical carcinoid
	Cough and dyspnea of long duration		Wheezing or "recent asthma"	Paraneoplastic syndromes
	Irreversible airflow obstruction		Hemoptysis	
Radiographic				
	Mosaic attenuation due to air trapping	Subcentimeter nodules	Well-circumscribed nodule or mass	Same as typical carcinoid
	Nodular bronchial wall thickening		Postobstructive atelectasis	Positive octreotide scan for adrenocorticotropic hormone–secreting tumors
	Bronchiectasis		Postobstructive pneumonia	
			Calcification or ossification	
			Marked enhancement	

ation of neuroendocrine cells in tumorlets extends beyond the basement membrane. Additionally, as opposed to scattered proliferation of cells in diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, hyperplastic cells organize to form nests of less than 5 mm in tumorlets (Fig. 3A), thus differentiating tumorlets from carcinoids. Previously interpreted as early carcinoid, tumorlets are now accepted as benign [9], although extremely rare cases of tumorlets with atypia and regional lymph node metastases have been reported [6, 7].

These nests of hyperplastic cells manifest as nodules on CT. Tumorlets are also associated with areas of scarring, bronchiectasis, and emphysema (Fig. 3B) and are often associated with carcinoid and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia [8] (Fig. 2). Therefore, tumorlets should be included in the differential diagnosis when small nodules are identified alongside carcinoids.

Carcinoids

Unlike diffuse idiopathic pulmonary neuroendocrine cell hyperplasia and tumorlets, carcinoids affect more men than women [10] and typically present at a younger age than bronchogenic carcinoma (mean age, 46 years). Because most carcinoids are centrally located, patients often present with obstructive symptoms such as cough, dyspnea, wheezing, and recurrent infection.

Atypical carcinoids are distinguished from typical carcinoids histologically by having 2–10 mitotic figures per 10 high power fields and/or areas of necrosis [11]. Radiologically, typical and atypical carcinoids are indistinguishable and will collectively be referred to as "carcinoids" herein unless otherwise noted. Usually spheric or ovoid with well-defined and slightly lobulated borders (Fig. 2F), carcinoids are often located near bronchial bifurcations (Fig. 4). Approximately 30% of bronchial carcinoids exhibit calcification histologically that may manifest on CT (Figs. 5A and 5B). Thus, when one observes a central tumor that narrows, deforms, or obstructs a bronchus and that displays diffuse or punctate calcification, a diagnosis of bronchial carcinoid should be considered [12, 13]. Because carcinoids have a rich vascular stroma, some may show marked and homogeneous enhancement (Fig. 6). A small number of carcinoids manifest as a focal mass or nodule located entirely within a bronchial lumen (Fig. 6). Carcinoids may be associated with hilar or mediastinal lymphadenopathy. Atypical carcinoids have a higher tendency to metastasize [14] and are more likely to secrete adrenocorticotropic hormone than typical carcinoids. Carcinoid tumors producing adrenocorticotropic hormone have high numbers of somatostatin receptors, thus enabling detection with octreotide scanning (Fig. 7). Alternatively, carcinoids may show no or very little FDG avidity on PET (Fig. 5C).

Although diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, tumorlet, and carcinoids have distinguishing histologic features, they clearly show a common link of neuroendocrine cell proliferation (Fig. 8). One can conceptualize the three entities along a continuum with diffuse neuroendocrine cell hyperplasia as the initial event. Once hyperplasia organizes and progresses beyond the basement membrane, these neuroendocrine cells aggregate to form tumorlets.

When tumorlets grow larger, possibly because of an inciting critical genetic alteration, carcinoid tumors are generated. At least one report has alluded to this concept previously [4], and this concept is supported by the many shared common histologic and clinical features as well as the frequent coexistence of all three entities on radiographic examinations and pathologic specimens (Figs. 1, 2, and 4). Although this theoretic model is useful, it is important to note that carcinoids can be seen without any precursor lesions in the same biopsy specimen. Thus, additional study is essential in further defining the relationship among these entities.

Conclusion

We have illustrated the radiologic, pathologic, and clinical features of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, tumorlet, and carcinoids. In addition, we have discussed the potential role of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia and tumorlet in the development of carcinoids and have proposed a conceptual construct of viewing these three entities as stages along a continuum of neuroendocrine cell proliferation. Given their potential significant morbidity, additional study is essential in further defining the relationship among these entities.

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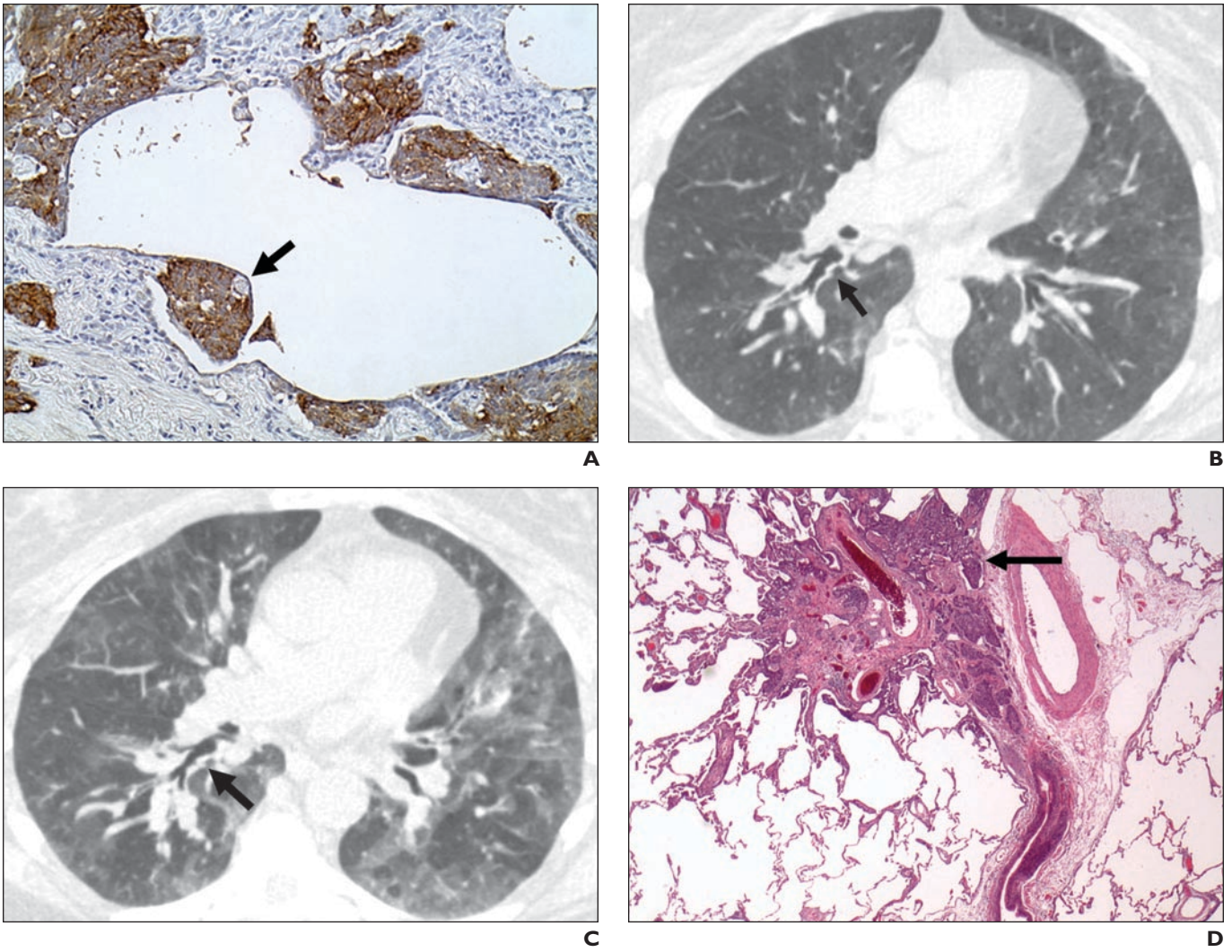


Fig. 1—Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia in 49-year-old woman with concomitant tumorlet.
A, High-power photomicrograph. Immunohistochemical stain for neurosecretory granules highlights nodular proliferation of neuroendocrine cells surrounding bronchiole (*arrow*). Note how intraluminal bulging of hyperplastic neuroendocrine cells corresponds to peribronchiolar nodularity seen on CT. (chromogranin stain, ×20)
B and **C,** Axial high-resolution CT scans obtained during inspiration (**B**) and expiration (**C**) show air trapping. Also, note nodular wall thickening (*arrow*).
D, Photomicrograph shows islands of neuroendocrine cells (*arrow*), which represent tumorlet, separated by fibrous bands adjacent to bronchovascular bundle. (H and E, ×2.5)

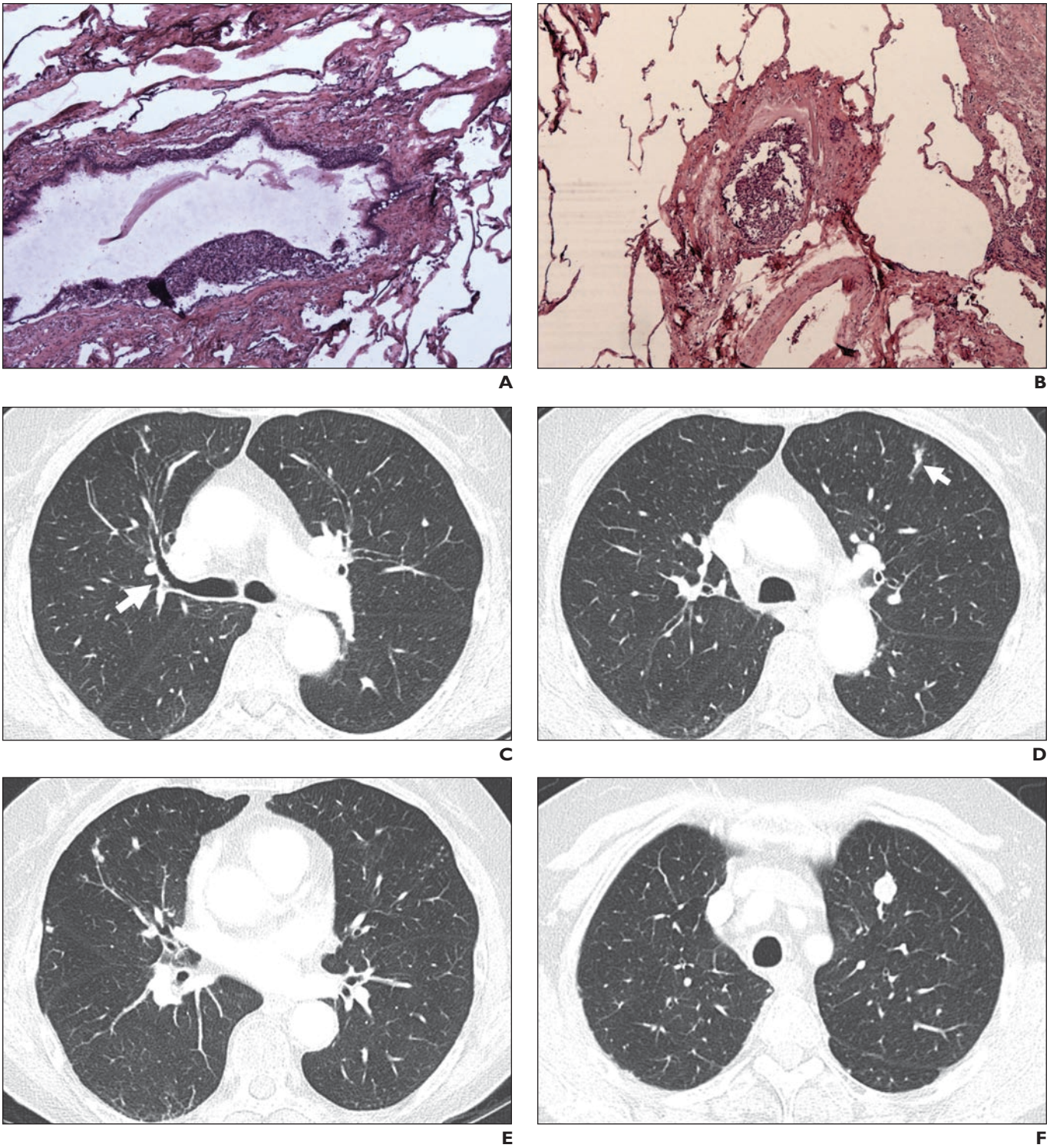


Fig. 2—Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia in 70-year-old woman with concomitant tumorlets and typical carcinoid.
A, Photomicrograph shows linear proliferation of neuroendocrine cells within confines of basement membrane. Note occasional bulging into lumen. (H and E, ×20)
B, Photomicrograph from different region reveals marked intraluminal proliferation of neuroendocrine cells. (H and E, ×2.5)
C, Axial chest CT image in lung window at level of carina shows mild bronchiectasis and minimal nodular thickening of right upper lobe bronchus (*arrow*) that corresponds to mild nodular thickening seen histologically.
D, Axial CT image obtained superior to **C** shows curvilinear opacity (*arrow*) in periphery representing mucoid-impacted airway that is likely secondary to obstruction from underlying diffuse idiopathic pulmonary neuroendocrine cell hyperplasia.
E, Several scattered nodules in right middle and inferior upper lobes correspond to histologically proven tumorlets.
F, Well-circumscribed lobulated nodule in left upper lobe corresponds to known typical carcinoid.

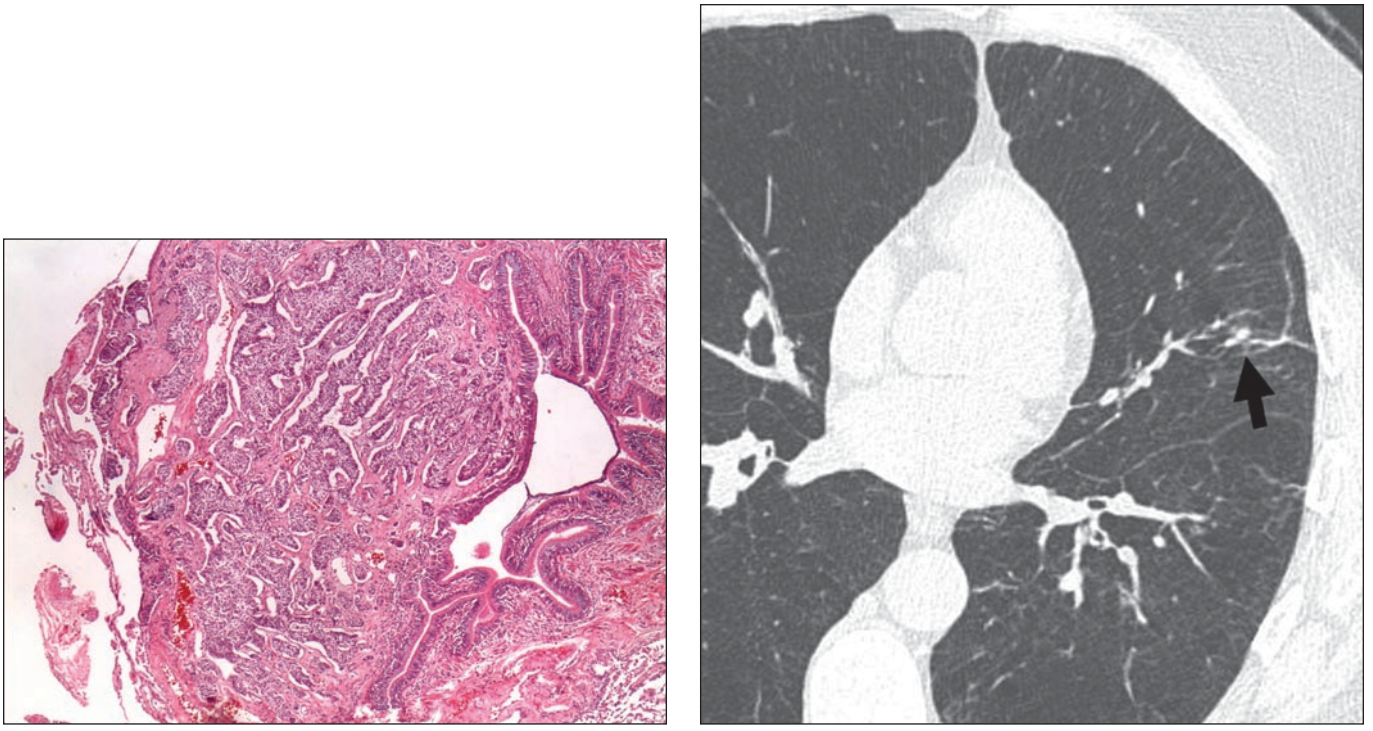


Fig. 3—Tumorlet in 58-year-old man with emphysema.
A, Photomicrograph shows trabecular and organoid proliferation of neuroendocrine cells beyond basement membrane separated by fibrous bands adjacent to airway. Proliferation measures 2 mm in greatest dimension. There is airway impingement with associated mild bronchiolitis. (H and E, ×5)
B, Axial chest CT scan in lung window shows small nodules in lingula (*arrow*) representing tumorlets in region of scarring. Patient also has centrilobular emphysema.

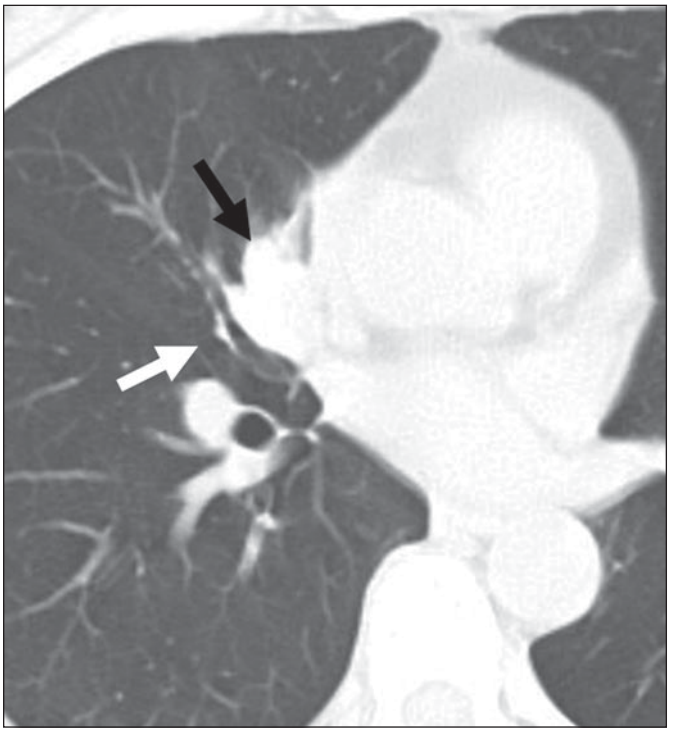
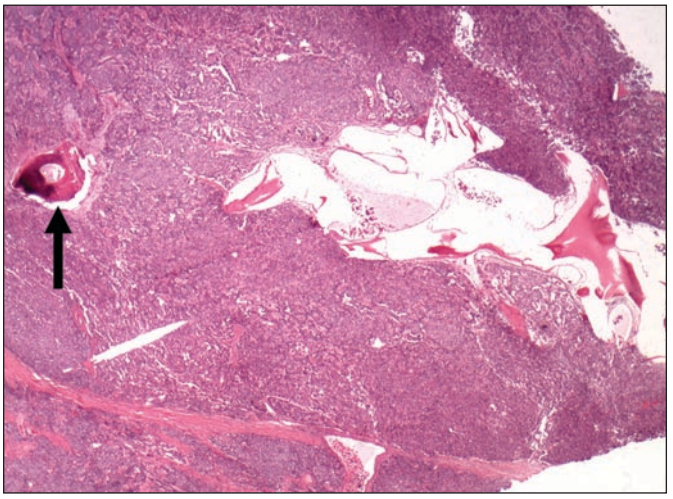


Fig. 4—Typical carcinoid in 46-year-old woman who has concomitant pathologically proven diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. Axial CT image in lung window shows splaying of airways by carcinoid (*black arrow*). Note adjacent bronchus has mild nodular thickening (*white arrow*) from concomitant diffuse idiopathic pulmonary neuroendocrine cell hyperplasia.



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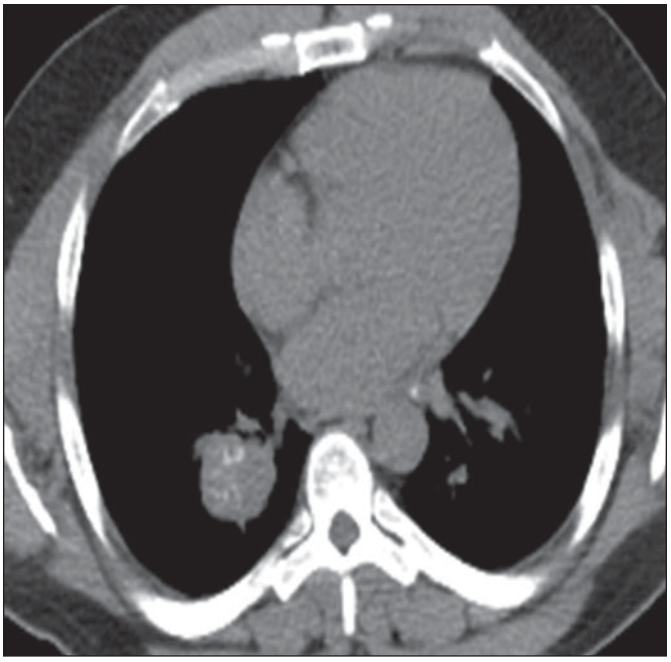

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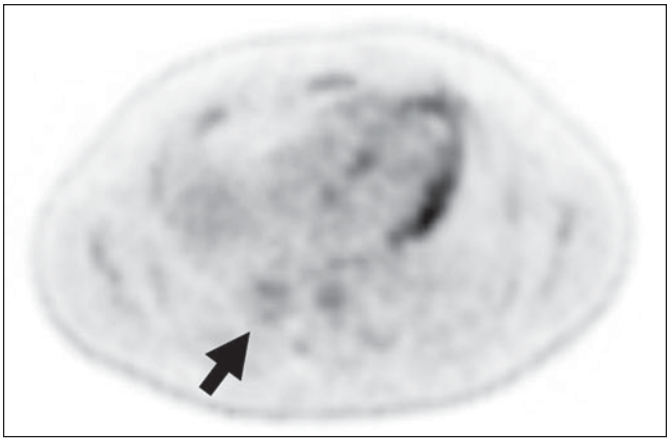

C

Fig. 5—Typical carcinoid in 39-year-old man.
A, Photomicrograph shows central ossification (*arrow*) within nests of neuroendocrine cells. No mitoses or necrosis is seen. (H and E, ×2.5)
B, Axial unenhanced CT scan in mediastinal window shows high attenuation within carcinoid tumor corresponding to histopathologic finding of ossification.
C, FDG PET image shows mild FDG uptake (*arrow*).

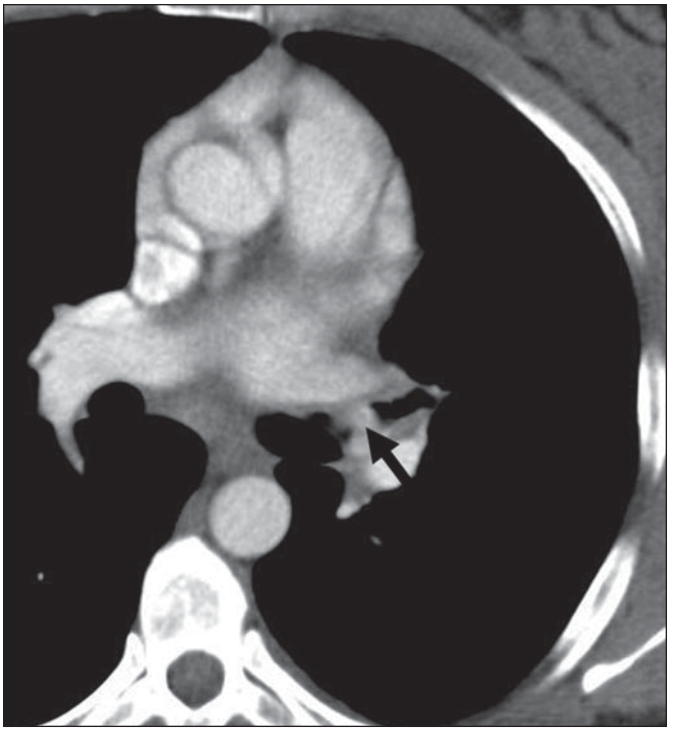

Fig. 6—Pathologically proven typical carcinoid in 45-year-old woman. Axial contrast-enhanced CT image in mediastinal window shows endobronchial homogeneously enhancing nodule (*arrow*).

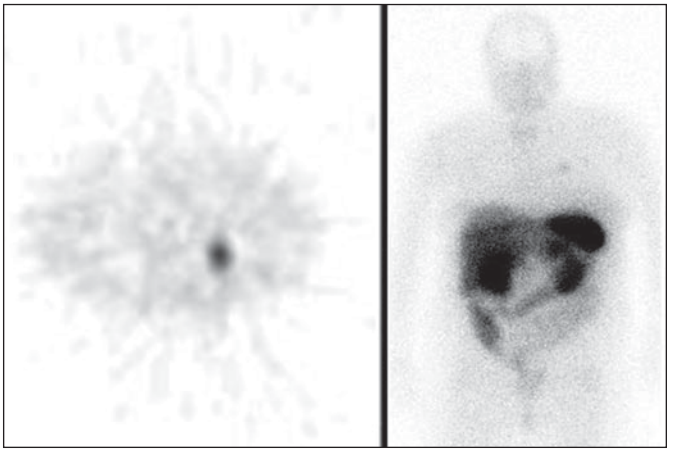

Fig. 7—Pathologically proven atypical carcinoid in 41-year-old woman. Transverse (*left*) and coronal (*right*) octreotide scans show radiotracer uptake by adrenocorticotropic hormone–secreting atypical carcinoid.

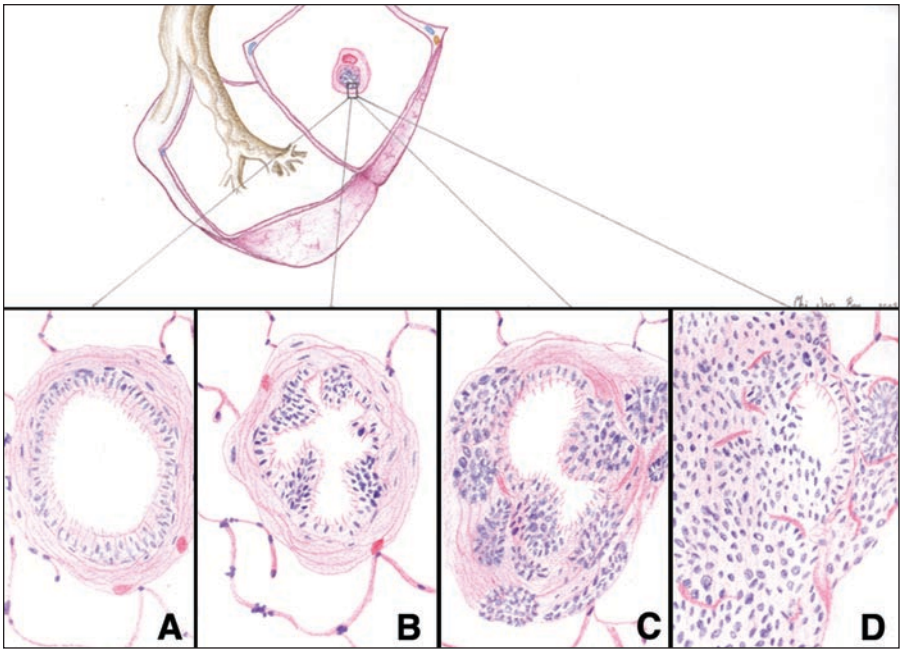

Fig. 8—Illustrations of airways seen in cross section depict neuroendocrine cell hyperplasia continuum.
A, Normal airway.
B, Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. Neuroendocrine cells have increased in number but do not breech basement membrane.
C, Tumorlet. Neuroendocrine cells have further increased in number with expansion beyond basement membrane. Note uniform polygonal cells have started to form nests. Aggregate size of these cellular islands is smaller than 5 mm.
D, Typical carcinoid. Further neuroendocrine cell growth has led to formation of mass that is 5 mm or larger.

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