Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia and a typical carcinoid tumor

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Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is regarded as a precursor to the development of carcinoid tumorlet and carcinoid tumor. It is confined to the neuroendocrine cell hyperplasia of the airway mucosa without penetration through the basement membrane and appears in a diffuse pattern, typically in association with obliterative bronchiolar fibrosis. DIPNECH belongs to the preinvasive lesions defined by the 1999 World Health Organization classification, including atypical adenomatous hyperplasia and squamous dysplasia–carcinoma in situ.

Clinical Summary

A 73-year-old female nonsmoker was known to have intermittent hemoptysis for several years. The family history and past medical history were noncontributory beside a chronic dry cough in part accompanied by mucous expectoration and a higher frequency of pulmonary infections in the past years.

Previous chest radiography showed no underlying causes of the clinical symptoms anamnestically. Contrast-enhanced spiral chest computed tomographic examination revealed no apparent tumor mass. Although bronchiectasis was multisegmental, the middle lobe appeared to be most affected (Figure 1). During an acute episode of hemoptysis, bronchoscopy revealed the superior segmental bronchus (B6) of the right lobe to be the source of bleeding.

Spirometry revealed a forced expiratory volume in 1 second of 69.1% of predicted value, a forced vital capacity of 78.5% of predicted value, and a forced expiratory volume in 1 second/forced vital capacity ratio of 0.73. Because of the severe episodes of hemorrhages and recurrent chest infections, the patient was scheduled to undergo thoracotomy.

No endobronchial lesion or bleeding was seen at repeated bronchoscopy before intubation for pulmonary resection. Subtotal obstruction of the right middle lobe was caused by mucus. For a more limited resection, the patient underwent a right middle lobectomy and systematic mediastinal and hilar lymph node dissection.

Figure 1. Computed tomographic scan showing noncharacteristic infiltrates and bronchiectasis of the middle lobe.

Pathology revealed diffuse neuroendocrine cell hyperplasia, especially in the peribronchial region (Figure 2), as well as tumorlet formation and a 1.2-cm typical carcinoid tumor. The resected hilar and mediastinal lymph nodes were negative for metastatic disease and had normal lymph node architecture. The postoperative recovery was uneventful, and 3 months after surgical intervention, she is stable with no pulmonary nodules on chest radiography.

Discussion

DIPNECH is a rarely described lesion. The term *diffuse idiopathic pulmonary neuroendocrine cell hyperplasia* refers to collections of scattered single cells, small nodules, or linear proliferations of neuroendocrine cells confined to the airway mucosa. It is reserved only for cases in which the hyperplasia is diffuse and primary in nature. It is regarded as a precursor to the development of carcinoid tumorlet (diameter <5 mm) or carcinoid tumor (diameter >5 mm). The diagnosis requires the presence of hyperplasia of the airway neuroendocrine cells without invasion beyond the basement membrane. It occurs in association with chronic inflammation or fibrosis.¹

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Figure 2. Microscopic appearance of DIPNECH: small groups and nodular aggregates of tumor cells associated with the bronchiolar epithelium. (Original magnification 40×; hematoxylin and eosin staining.)

Clinical symptoms, specific pathologic features, and the reported predilection for middle-aged or older nonsmoking women matched with the finding of DIPNECH.^{3,4} This is consistent with publications by Ruffini and associates² and Swigris and colleagues.³

The role of hormonal modulation in this disease has been suggested by Swigris and colleagues,³ but further studies are pending.

In our case the serum neuron-specific enolase level was within the normal values; nevertheless, the results of the immunohistochemical examination of the tissue was positive for neuron-specific enolase. The clinical picture of obliterative bronchiolitis and airway hyper-reactivity is thought to be correlated to peptide secretory substances. Because hyperplastic neuroendocrine cells contain a va-

riety of neuropeptides, including bombesin-like peptides, these are likely to be important in the pathogenesis.⁴

Although there are few reported cases, the prevalence of DIPNECH might be higher than it is supposed to be because there were no definition criteria until very recently, and the issue remains controversial.² A high index of suspicion is required to recognize this entity.³

Little is known of the clinical evolution and treatment options for DIPNECH. Therefore Swigris and colleagues³ presented 4 patients with 2- to 14-year follow-up and found an excellent long-term prognosis.

The management of patients with DIPNECH is predominantly close surveillance; the role of surgical intervention is not clearly defined. Worsening of obstructive symptoms (or in our case recurrent pulmonary hemorrhage) can be dealt with by means of palliative resection. In patients with carcinoid tumor formation, complete resection of the carcinoid tumor with lung preservation surgery, accompanied by a systematic mediastinal and hilar lymph node dissection, forms the basic treatment opinion.

In patients in whom DIPNECH continues to progress to carcinoid tumors and in whom surgical options run out, somatostatin analogs and interferon α might have a role as tumorostatic agents.⁵

In conclusion, long-term follow up is mandatory to detect the formation of early carcinoid tumors.

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