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ORIGINAL PAPER

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: 7-year follow-up of a rare clinicopathologic syndrome

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Abstract
Background Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare clinical pathological syndrome. There have been only 49 cases of DIPNECH reported in the literature so far. We report a case of a 69-year-old nonsmoking man with a 7-year follow-up.
Methods The initial CT scan from December 2003 showed persistent nonspecific bilateral reticulonodular infiltrates. In January 2004, the patient underwent a video-assisted thoracoscopic wedge resection of his right lower lobe for further diagnostic workup. Pathology of the resected wedge of the right lower lobe revealed a diffuse idiopathic pulmonary cell hyperplasia (DIPNECH) highlighted by staining for the neuroendocrine typical carcinoid markers, such as marker CD 56.
Results All the performed CT scans over a 7-year period showed no progression of the bilateral pulmonary lesion. The bilateral pulmonary nodules were stable in terms of size, number and form. The yearly control with chest CT scans will be continued.
Conclusions The neuroendocrine cell hyperplasia is confined to the airway mucosa without penetration through the basement membrane and appears in a diffuse pattern, generally in close association with obliterative bronchiolar fibrosis. DIPNECH is characterized by a mixed obstructive and/or restrictive ventilation pattern with bilateral reticulonodular infiltrates and a predilection for middle-aged women. Little is known about the clinical course and treatment for DIPNECH.

Keywords Neuroendocrine · Hyperplasia · Obstructive · Pulmonary nodules

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Introduction

A 69-year-old nonsmoking man was referred to our center for the evaluation of recurrent pneumonia since March 2003. A CT scan at the referring hospital showed persistent pulmonary infiltrations with bilateral lung nodules. The initial examination of the lung function had revealed a mild restrictive pattern with TLC 4.5 L (62% pred) at the referring hospital. His respiratory history included persistent dry cough combined with wheezing and dyspnoea. The past medical history was noncontributory. His initial physical examination and laboratory tests were unremarkable. C-reactive protein serum levels were within normal limits

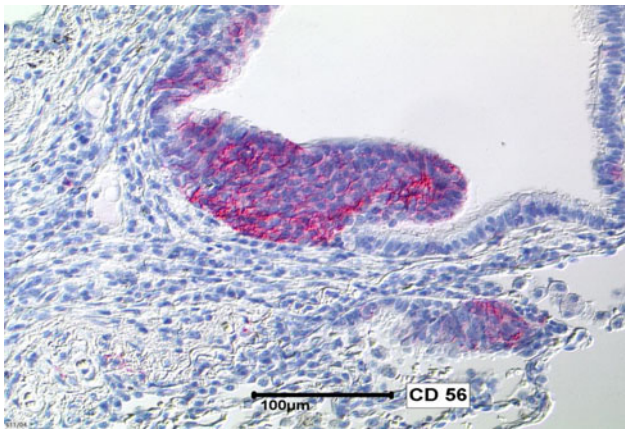

Fig. 1 Diffuse idiopathic pulmonary cell hyperplasia (DIPNECH), highlighted by staining for the neuroendocrine marker CD 56 (×400)

in repeated controls. At our center, the initial spirometry revealed a persistent mild combined obstructive/restrictive ventilation pattern with TLC 4.53 L (62% pred) and FEV1/VC 64%. The initial CT scan from December 2003 (Fig. 2a) showed persistent nonspecific bilateral reticulonodular infiltrates. In January 2004, the patient underwent a video-assisted thoracoscopic wedge resection of his right lower lobe for further diagnostic workup.

Histology

The pathology of the resected wedge of the right lower lobe revealed a diffuse idiopathic pulmonary cell hyperplasia (DIPNECH) highlighted by staining for the neuroendocrine typical carcinoid markers, such as marker CD 56 (×400) (see Fig. 1). There was no involvement of the visceral pleura, vascular spaces, mediastinal or hilar lymph nodes.

The histological specimen showed histological neuroendocrine cell hyperplasia involving the bronchioles and affecting the respiratory bronchioles. The neuroendocrine cells bulged into the lumen of the bronchioles (see Fig. 1) but were not penetrating the basement membrane. Further histological evidence of bronchiolitis, focal bronchiolectasis with mild chronic inflammatory and focal fibrosis of the involved airway could be seen. The pathological examinations also revealed a pulmonary lymph node with central scarring and focal necrosis.

The histopathology of the syndrome represents a spectrum of cellular hyperplasia consisting of neuroendocrine cell proliferations confined to the airway mucosa and cell clusters that invade beyond the base membrane forming tumorlets. The DIPNECH is localized superficially on the basement membrane of bronchial or bronchiolar epithelium with larger lesions bulging into the lumen. Only the pathologic evaluation of lung tissue allowed a definitive diagnosis of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia.

Clinical course

From 2004 to 2008, the patient was treated repeatedly with varying doses of oral steroids because of frequent wheezing, coughing and dyspnea. The oral steroid therapy was reduced to a daily dose of 5 mg during a 5-year period and was finally replaced by inhaled steroids. A follow-up by 7 years after initial evaluation revealed a persistent obstructive pattern (FEV 1 of 79%, FEV 1/FVC 73%).

The initial chest CT scan from December 2003 showed nonspecific bilateral pulmonary infiltration with bilateral pulmonary nodules (see Fig. 2a). Over a 7-year period, multiple follow-up CT scans have been performed in order to control any changes in the initial bilateral pulmonary nodules as a typical radiological manifestation of DIPNECH.

All the performed CT scans over a 7-year period showed no progression of the bilateral pulmonary lesion. The bilateral pulmonary nodules were stable in terms of size, number and form (see Fig. 2a–d).

Due to inhaled steroid medication, the patient was capable of dealing with the requirements of daily life. The yearly control with chest CT scans will be continued.

Discussion

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia is a rare clinicopathologic syndrome with only 49 cases reported in literature. DIPNECH is classified to be a primary proliferation of unknown etiology and is a precursor lesion of pulmonary carcinoid tumors. The term DIPNECH refers to collections of scattered single cells, small nodules or linear proliferations of neuroendocrine cells confined to the airway mucosa. The term is reserved for cases in which the hyperplasia is diffuse. The diagnosis requires the presence of hyperplasia of the airway neuroendocrine cells without invasion beyond the basement membrane. DIPNECH are frequently associated extra- and intraluminal fibrosis of the involved airways (Kerr 2001; Johney et al. 2006; Travis et al. 1999). Other generalized pathologies, e.g., inflammatory or fibrous lesions that can cause secondary pulmonary neuroendocrine cells hyperplasia, are not seen. Foci of neuroendocrine cell hyperplasia in association with other primary diseases (chronic lung abscess or chronic bronchiectasis) are considered to be reactive (Travis et al. 1999). DINECH are primary proliferations and can occasionally combine with obliterative bronchiolitis. DIPNECH that break through the basement

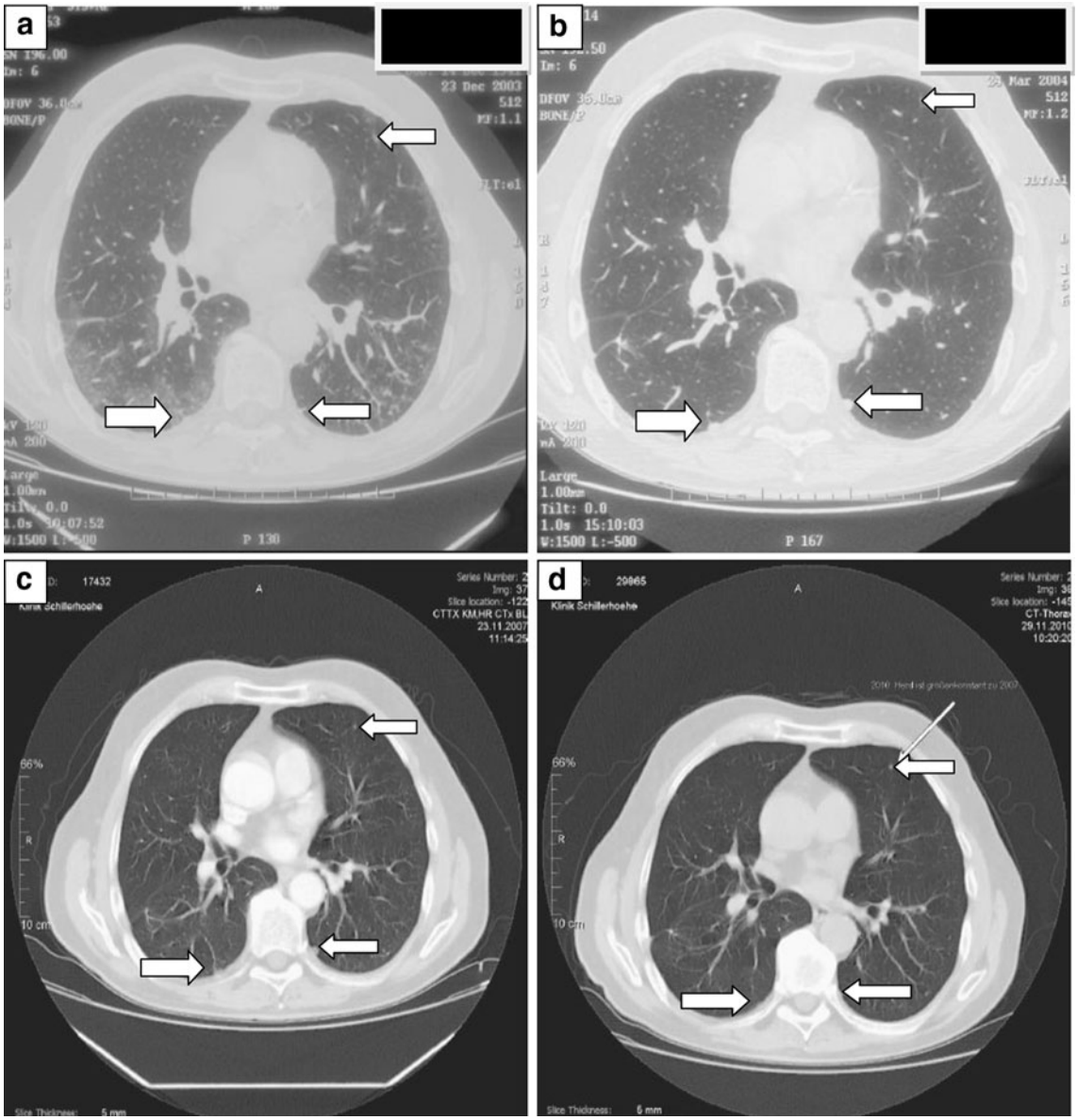

Fig. 2 **a**–**d** From December 2003 to November 2010, all the performed CT scans over a 7-year period showed no progression of the bilateral pulmonary lesion. The bilateral pulmonary nodules were stable in terms of size, number and form

membrane and invade locally are called tumorlets, and nodules >5 mm in diameter are classified as carcinoid tumors. Histopathological DIPNECH must be distinguished from neuroendocrine proliferations accompanying chronic inflammatory disease such as bronchiectasis or chronic lung abscess (Davis et al. 2006; Miller and Muller 1995).

The clinical picture of obliterative bronchiolitis and airway hyperreactivity with asthma-like symptoms is thought to be correlated with peptide secretory substances. Because a hyperplastic neuroendocrine cell contains a variety of neuropeptides, including bombesin-like peptides, these are likely to be important in the pathogenesis (Cohen et al. 1998). Most cases remain stable over many years independent of the mode of presentation, although a few patients progress to severe airflow obstruction (Davis et al. 2006). The normal human lung contains only few neuroendocrine cells, commonly found as a singular entity in close association with airways. A proliferation of the neuroendocrine cells or neuroendocrine cell hyperplasia can occur in 3 different settings: firstly, a nonspecific secondary reaction to airway or interstitial inflammation and/or fibrosis; secondly, in the mucosa of bronchi or bronchioles adjacent to carcinoid tumors; and thirdly, as a diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH). The latter is a very rare syndrome, which can cause an obstructive pulmonary disease (Swigris et al. 2005; Gould et al. 1983; Travis et al. 1999). As in our case, the patient suffered from asthma-like symptoms as coughing, wheezing and dyspnea.

The management of patients with DIPNECH requires long-term close monitoring. Inhaled bronchodilators and steroids palliate the symptoms of obstructive airway disease. The role of surgical interventions in these patients still remains unclear. In operable cases, complete removal of carcinoid tumors with lung preservation surgery accompanied by mediastinal lymph node sampling are the options of treatment (Swigris et al. 2005; Ginsberg 2000). If DIPNECH leads to inoperable carcinoid tumors, somatostatin analogs such as octreotide along with interferon alpha have been used successfully for the treatment for malignant carcinoid syndrome (Johney et al. 2006; Saltz 1993; Oberg 1991).

In conclusion, we present a 7-year follow-up of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). This is a rare clinicopathologic syndrome, and little is known about its clinical course and treatment options. Long-term follow-up is required to detect progress to carcinoid tumors.

Conflict of interest The author(s) indicated no potential conflicts of interest.

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