A female patient with multiple pulmonary nodules

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A 63-year-old female who was an ex-smoker (15 pack-years) with a 30-year history of a dry cough diagnosed as bronchial asthma, but who was in good general condition, was admitted to our hospital because of multiple lung nodules evident in a chest X-ray. A computed tomography (CT) of the chest (Fig. 1A,B) revealed multiple, small, randomly distributed, bilateral nodules and a diffuse, mosaic lung pattern featuring air-trapping and bronchial wall thickening but without enlargement of the hilar or mediastinal lymph nodes. Routine laboratory data, serum concentrations of carcinoembryonic antigens Ca72-4 and Ca19-9, and neuron-specific enolase levels were within normal limits. Pulmonary function tests demonstrated mild reversible obturation. Bronchoscopy revealed a normal bronchial tree. Microbiological cultures of bronchial washings were negative, and no Mycobacterium tuberculosis DNA was found. Cytological assessments were also negative. Transbronchial lung biopsy was not performed because of her continual cough. She underwent video-assisted thoracoscopy. Histological examination of lung samples revealed multiple foci of neuroendocrine cell hyperplasia, tumorlets, and typical carcinoid nodules of up to 8 mm in diameter, but these lacked necrosis and exhibited a low mitotic rate (2 FP/10 high-power fields) (Fig. 1C,D). Immunohistochemical staining revealed focally positive areas of cytokeratin, and diffuse synaptophysin (Fig. 1E,F), chromogranin A, and TTF-1 positivities. The Ki-67 antigen index was 2%. We diagnosed diffuse, idiopathic, pulmonary neuroendocrine cell hyperplasia (DIPNECH). Inhaler therapy featuring long-acting beta-stimulators and steroids was recommended. No disease progression has been observed during 3 years of follow-up.

DIPNECH is extremely rare [1–5]. Pulmonary neuroendocrine cell hyperplasia can be either primary or reactive. The reactive form is a non-neoplastic condition caused by chronic hypoxia-associated disorders such as chronic obstructive pulmonary disease and interstitial pulmonary fibrosis. DIPNECH refers to diffuse pulmonary neuroendocrine cell hyperplasia.
evident with the absence of any underlying disease. The World Health Organization defines DIPNECH as a generalized proliferation of pulmonary neuroendocrine cells confined to the airway epithelium or invading beyond the basement membrane, with formation of tumorlets (diameter < 5 mm) or carcinoid tumors (diameter > 5 mm); it is a pre-invasive neoplastic lesion [1]. Two types of clinical presentations have been described [2]. The first encompasses incidental pathologic findings in asymptomatic patients undergoing lobectomy or wedge lung resection, especially those with peripheral carcinoid tumors. The second is DIPNECH syndrome [3]; patients are symptomatic, usually over 50 years of age, commonly female (~90%), and usually nonsmokers (~70%) with a chronic non-productive cough and dyspnea and (less commonly) wheezing, a productive cough, hemoptysis, and chest pain [4]. Pulmonary function tests reveal mild or moderate airflow obstruction. Chest CTs reveal multiple nodules that vary in size and that exhibit a random or centrilobular distribution, a diffuse mosaic lung pattern with air-trapping, and (less commonly) bronchiectases, bronchial wall thickening, and atelectasis [4]. Lung biopsy remains the gold standard for DIPNECH diagnosis. No evidence-based management guidelines are available. Oral and inhaled steroids, azithromycin, somatostatin analogs, inhibitors of the mechanistic target of rapamycin, surgical lung resection, and lung transplantation have all been employed [5].
References:


Figure 1A. Chest computed tomography: axial maximum intensity projection image revealing numerous, small, randomly distributed nodules (arrows).

Figure 1B. Chest computed tomography: axial image revealing a mosaic lung pattern with air-trapping (white arrows) and bronchial wall thickening (black arrow).
Figure 1C. The bronchiolar epithelium is partially replaced by proliferating neuroendocrine cells - arrow (hematoxylin-and-eosin staining, ×200).

Figure 1D. The lung parenchyma contains irregular foci of proliferating neuroendocrine cells; these are termed tumorlets - arrows (hematoxylin-and-eosin staining, ×100).
Figure 1E. Immunostaining with an anti-synaptophysin antibody reveals that the cell cytoplasm is strongly positive (×200).

Figure 1F. The carcinoids stain positively for synaptophysin (×100).