CLINICAL VIGNETTE

Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia

[1]Margaret Wei, MD and [2]Mehri Manouchehr-Pour

[1]UCLA Department of Medicine
[2]UC Riverside Department of Cell, Molecular, and Developmental Biology

Case Presentation

A 55-year-old female with remote history of papillary thyroid cancer over 35 years ago presented with chronic dry cough of unclear etiology. The cough started 20 years ago and was initially thought to be secondary to gastric reflux. However, the symptoms did not resolve after gastric fundoplication surgery.

Review of systems was noteworthy only for cough. The cough, although a nuisance, was fairly well controlled and did not significantly affect her quality of life. She had no shortness of breath, hemoptysis, or tachycardia. She did not have any symptoms of flushing, diarrhea, or excessive sweating. Physical exam including lung auscultation was normal. Complete blood count and complete metabolic panel were unremarkable. 24-hour urine 5-HIAA levels and serum chromogranin A levels were normal.

She underwent extensive negative allergy and pulmonology testing including normal pulmonary function testing (PFT) and a negative methacholine challenge. Infectious work-up was also negative. She had tried steroid and albuterol inhalers without symptom alleviation. A computed tomography (CT) scan of the sinuses was normal. Serial chest radiographs spanning over several years were normal.

After three years of investigation, a CT of her chest was performed that demonstrated numerous bilateral subcentimeter pulmonary nodules, with the largest measuring 7 mm in the left lower lobe (Figures 1 and 2).

The pulmonary nodules were initially suspicious for metastatic disease, given her history of thyroid cancer. However, since a recurrence of thyroid cancer 35 years after the initial presentation was deemed highly unlikely, the patient underwent pulmonary wedge resection of the left lower lobe to determine the etiology of the numerous pulmonary nodules. The tissue stained positive for chromogranin A and synaptophysin identifying these nodules as carcinoid tumorlets – neuroendocrine cell proliferations less than 5mm in diameter. Two bronchioles within the samples stained positive for chromogranin A and synaptophysin, but not the three that is necessary for the definitive diagnosis of diffuse idiopathic pulmonary neuroendocrine hyperplasia (DIPNECH). Therefore, the diagnosis was determined to be suspicious for, not diagnostic of DIPNECH.

Clinical Follow-Up

Since bronchodilators and steroids had not improved her symptoms in the past, these were not continued after diagnosis. She was managed conservatively with serial chest CT scans, which have thus far shown no interval growth in size or increase in number of pulmonary nodules over the past 5 years. Her symptoms continue to remain well controlled.

Discussion

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare pulmonary disorder that was first described by *Aguayo et al* in 1992.[1,2] It is caused by proliferation of single pulmonary neuroendocrine cells (PNEC), nodular collection of cells (neuroendocrine bodies), or linear proliferations of PNEC, which are confined to the bronchial epithelium.[1,3] More advanced lesions are often seen as well where the neuroendocrine cell aggregates extend past the basement membrane forming tumorlets with diameter <5mm or carcinoid tumors with diameter >5mm.[3]

PNECs secrete bombesin and gastrin-releasing peptides, which can lead to inflammation and fibrosis of the airways.[4,5] This process can lead to constrictive obliterative bronchiolitis, a histological hallmark of DIPNECH, and rarely can progress to bronchiolitis obliterans syndrome.[3,5,6]

Clinical Presentation

Patients with DIPNECH have a female to male ratio of 10:1.[3,7] They often present in their fifth or sixth decade of life and with no smoking history.[4,7] In contrast, carcinoid tumors tend to occur equally in men and women and more commonly in younger patients.[3] Importantly, reactive neuroendocrine cell hyperplasia is a distinctly different clinical entity that occurs as a result of airway inflammation and irritation and is often associated with underlying lung disease or prior smoking history.[3]

Patient can present with chronic dry cough or dyspnea, which slowly progresses over several years.[4] These symptoms are often erroneously attributed to asthma, chronic obstructive pulmonary disease (COPD), or gastro-esophageal reflux disease (GERD).[5] Patients can rarely present with hemoptysis.[7] Some patients are asymptomatic but may be diagnosed

following an incidental finding of pulmonary nodules on a CT scan.[4] Physical examination is usually nonspecific.[1] PFTs can demonstrate an obstructive or mixed obstructive and restrictive pattern.[1,3] Less commonly, some patients may have a normal or a purely restrictive pattern on PFTs.[3]

Imaging

Plain chest radiographs are usually reported as normal, but may show nodules.[1,3,5] Pulmonary nodules corresponding to tumorlets or carcinoid tumors on CT scan are the most common radiographic finding.[4,6] Lung nodules tend to be distributed in the mid- to lower-lung fields.[8] More than 60% of patients with DIPNECH have multiple nodules.[3,6] These nodules may initially be confused for metastatic disease, but are typically noncalcified, well-defined, and rounded.[8]

Mosaic attenuation and air trapping are also common findings.[5,6,8] One review reported air trapping in 26% of patients and mosaic attenuations in 25% patients.[6] These findings reflect small airway obstruction and are best visualized on expiratory high resolution CT images.[3] Thickened bronchial and bronchiolar walls, bronchiectasis, and ground-glass attenuation have also been described.[4,8]

Pathology

The gold standard for diagnosis of DIPNECH is surgical lung biopsy. However, if there is a high clinical suspicion for the diagnosis of DIPNECH, a transbronchial biopsy may be sufficient to make the diagnosis.

To date, there are no consensus diagnostic guidelines for radiologic or pathologic criteria for DIPNECH.[3] However, *Marchevsky et al* reported the following histologic criteria can be used to consistently diagnose DIPNECH: (1) The patient must have five or more neuroendocrine cells, either singly or in clusters, confined to the bronchiolar epithelial basement membrane in three or more bronchioles. (2) The patient must additionally have three or more carcinoid tumorlets.[9]

On microscopy, neuroendocrine cells are typically identified with round or oval nuclei, “salt and pepper” chromatin, and eosinophilic cytoplasm.[4] The neuroendocrine cells in DIPNECH stain positive for the following neuroendocrine markers: synaptophysin, chromogranin, and CD56.[8] CD10 is often stained in neuroendocrine cells. Bombesin, bcl-2, retinoblastoma protein, p27, or calcitonin expression in these cells is variable.[8]

Lab testing

The diagnosis of DIPNECH is primarily made by histology. There are no clinical or radiological criteria for diagnosis.[8] However, serum chromogranin A, which is synthesized by pulmonary neuroendocrine cells, can occasionally be elevated in patients with DIPNECH. 5-hydroxyindoleacetic acid levels in a 24-hour urine collection may also be elevated.[8]

Clinical Course

DIPNECH is considered to be pre-neoplastic condition.[1,3] However, there is limited evidence to support this classification.[6] Patients typically have a slowly progressive decline or stable clinical course. One systematic review found atypical features (2%) and extrapulmonary metastatic disease (2%) to be quite rare.[6] There is no current evidence to suggest DIPNECH patients are at risk for developing high-grade neuroendocrine carcinomas such as large cell or small cell neuroendocrine carcinomas.[4,9] Rapid progression or life-threatening disease is very rare, affecting <10% of patients.[3]

Treatment

Most DIPNECH patients have a benign course spanning over several years and can be managed conservatively. Patients should be followed every 12 months to assess for progression of symptoms or pulmonary nodules on CT scan.[8] There is no clear evidence to support any specific treatment.[6] Regardless, many patients are treated with either oral or inhaled corticosteroids.[3] It is thought that steroids may reduce the inflammatory response to the cytokines and peptides secreted by the pulmonary neuroendocrine cells of DIPNECH.[3] Somatostatin analogs, such as octreotide, have been used as well with some success in improving cough symptoms.[3,8] Patients with progressive constrictive bronchiolitis may develop respiratory failure and require lung transplantation.[4,5]

Conclusion

DIPNECH is a rare condition that is becoming increasingly recognized. Patients with DIPNECH often have a long clinical course prior to diagnosis. This case highlights the clinical, histological, radiological characteristics of DIPNECH. We hope that this can increase awareness of this condition among clinicians. As patients may otherwise be misdiagnosed with asthma, COPD, or GERD and may undergo unnecessary treatments or procedures.

Figures

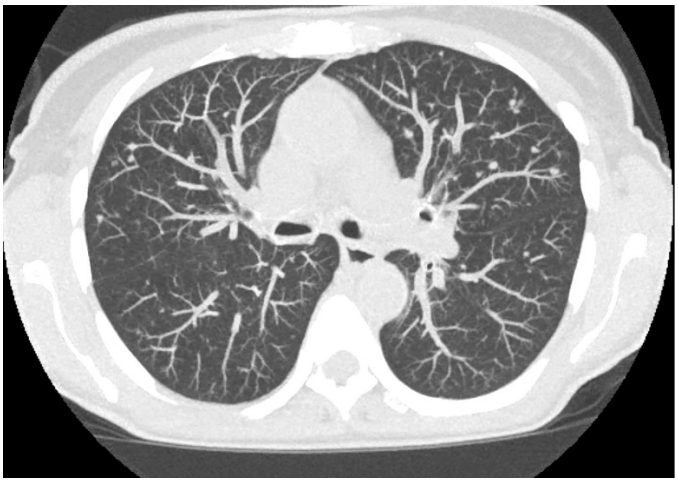

Figure 1. Maximum intensity projection axial CT through the lungs in lung windows demonstrates multiple bilateral subcentimeter pulmonary nodules.

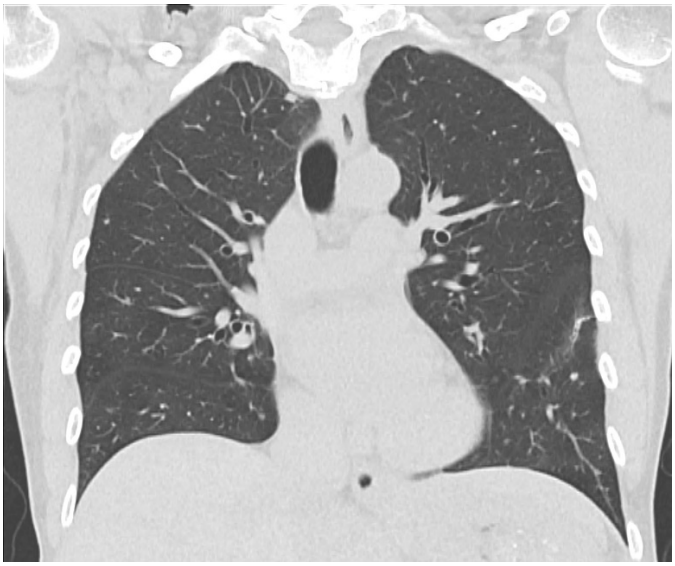

Figure 2. Coronal CT through the lungs in lung windows demonstrates multiple bilateral subcentimeter pulmonary nodules. There is a suture line from left lower lobe pulmonary wedge resection.

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