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Case Report

Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia: A Blanked Out Pulmonary Neuroendocrine Tumor

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Keywords

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia · Lung neuroendocrine tumor · Somatostatin analogs · Octreotide

Abstract

Introduction: Lung neuroendocrine tumors (NETs) are a rare type of pulmonary tumor and represent approximately 2% of all lung cancers. The prevalence of lung NETs is increasing, which may be due to improved diagnostic techniques for asymptomatic tumors. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare and underdiagnosed disease that falls under the spectrum of NETs. ***Case Presentation:*** We presented a case of a 59-year-old male who presented with severe coughing spells, flushing, and diarrhea. His computed tomography scan showed innumerable pulmonary nodules and irregular nodular opacities throughout the lungs. He underwent a left upper lobe wedge resection and was eventually diagnosed with neuroendocrine tumorlets via immunohistochemical stains. He was started on a trial of octreotide and reported significant improvement in symptoms after 1 month. ***Conclusion:*** DIPNECH is a rare preinvasive lesion characterized by the abnormal proliferation of pulmonary neuroendocrine cells. Patients with DIPNECH can present initially with respiratory symptoms, while other cases are discovered incidentally during the workup of different conditions. Definitive diagnosis of DIPNECH requires histopathological examination of lung tissue. There is limited evidence on DIPNECH management, and an individualized approach is currently advised.

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Introduction

Lung neuroendocrine tumors (NETs) account for only 2% of all lung cancers and 25% of all NETs [1]. The increasing use of imaging and increased awareness have contributed significantly to the rise in pulmonary NETs [1]. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare pulmonary disease that is not well understood, with less than 200 documented cases [2]. The World Health Organization (WHO) defines DIPNECH as a condition with multifocal hyperplasia of neuroendocrine cells in the bronchiolar epithelium associated with multiple neuroendocrine tumorlets, generally less than 5 mm, with or without obliterative bronchiolitis and a NET. Patients with DIPNECH typically experience respiratory symptoms, such as chronic cough, wheezing, or breathlessness [3]. DIPNECH can also be discovered incidentally during the workup of a different diagnosis. There is limited information regarding the natural history and management of DIPNECH, which can pose challenges in clinical practice since it is an under-recognized entity and is considered a pre-invasive lung lesion, according to the WHO [4]. Here, we report a rare case of a patient with DIPNECH who presented initially with severe cough, diarrhea, and flushing. The CARE Checklist, attached as an online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538796), has been completed by the authors for this case report.

Case Report

A 59-year-old Caucasian male with a medical history of asthma and gastroesophageal reflux disease, who is never a smoker, presented to the oncology clinic for evaluation and management of recently diagnosed neuroendocrine tumorlets after a left upper lobe wedge resection. Approximately 1 year before this visit, a chest computed tomography (CT) scan was done for the workup of severe coughing spells, flushing, and diarrhea that were interfering with his daily activities and work. The CT scan showed innumerable pulmonary nodules and irregular nodular opacities throughout the lungs, and the majority were stable from prior imaging, but one of which was new in the medial left upper lobe, measuring up to 15 mm (Fig. 1). The patient eventually underwent a positron emission tomography scan, which showed multiple nodules in the left lung exhibiting variable degrees of abnormally increased tracer activity, including the new nodule in the medial left upper lobe on the recent CT scan (Fig. 2). The patient was eventually seen by cardiothoracic surgery, and they decided to do a left upper lobe wedge resection for diagnosis. Immunohistochemical stain for AE1/AE3 performed on block A3 suggested entrapped benign acini/glands within the granulomatous inflammation with no evidence of malignancy. Special staining for acid-fast bacillus and Grocott's methenamine silver performed on block A3 were negatives for acid-fast bacilli and fungal organisms, respectively. Immunohistochemical stains for chromogranin and synaptophysin performed on blocks A5 and A6 were positive within the lesional cells of interest, consistent with neuroendocrine hyperplasia/tumorlets (Fig. 3). The granulomatous inflammation appeared to be causing most of the lesion. In addition, neuroendocrine proliferations were small (2 mm or less) and most likely an incidental finding. The patient got referred to an infectious disease service that worked up fungal infections, and all the workup was negative. After that, he got referred to the oncology clinic for further evaluation and management of the neuroendocrine tumorlets. Positron emission tomography scan was repeated and showed bilateral pulmonary nodules overall similar in size. Many of these pulmonary nodules had an uptake similar to or slightly higher than the blood pool. The nodule with the most avid radiotracer uptake was located within the

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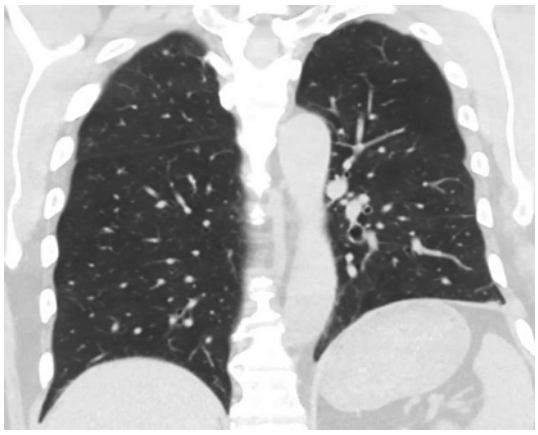

Fig. 1. CT scan showing innumerable pulmonary nodules and irregular nodular opacities throughout the lungs. CT, computed tomography.

superior and medial left lower lobe, measuring up to 15 mm (Fig. 4). Brain magnetic resonance imaging was done and showed no signs of metastasis. All biochemical testing, including VIP, insulin, cortisol, somatostatin, and 5-hydroxy indole acetic acid, showed normal levels, but the glucagon levels were mildly elevated. The case was discussed in a multidisciplinary thoracic tumor board setting, and a decision was made to start a trial of octreotide according to the National Comprehensive Cancer Network (NCCN) guidelines. One month after treatment, the patient came for a follow-up and reported significant improvement in his symptoms of diarrhea and cough after taking octreotide. He also felt an improvement in his quality of life.

Discussion

Pulmonary neuroendocrine cells are an important component of airway epithelial cells in adult human beings. These cells are mainly located in the bronchial walls and bronchioles. The function of these cells is unknown, but these cells respond to noxious stimuli, physiologic stressors, and chronic lung disease, which can lead to abnormal proliferation of the cells, resulting in neuroendocrine cell hyperplasia. In 2001, the WHO named this entity as diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH).

DIPNECH is a rare lung condition characterized by the abnormal proliferation of pulmonary neuroendocrine cells. It primarily affects older individuals, especially women. The underlying cause of DIPNECH is still not fully understood, but it is believed to involve a combination of genetic and environmental factors. The diagnosis of DIPNECH is made through a combination of clinical presentation, radiological findings, and histopathological examination of lung tissue. Patients with DIPNECH typically present with symptoms such as chronic cough, dyspnea, wheezing, and decreased exercise tolerance, as in our case. These symptoms arise due to the narrowing of the airways caused by the abnormal proliferation of neuroendocrine cells and subsequent constrictive bronchiolitis. Although our patient had very small DIPNECH nodules, he was very symptomatic with significant impairment in his quality of life. Imaging studies, such as high-resolution CT of the chest, can reveal characteristic findings in DIPNECH. These findings may include thickening of the bronchial walls, nodular lesions, and air trapping. However, these findings are not specific to DIPNECH and can be seen in other lung conditions as well. Definitive diagnosis of DIPNECH requires histopathological examination of lung tissue obtained through a biopsy or surgical resection. In DIPNECH, there is diffuse hyperplasia of neuroendocrine cells throughout the bronchial walls and bronchioles. These cells can be identified using

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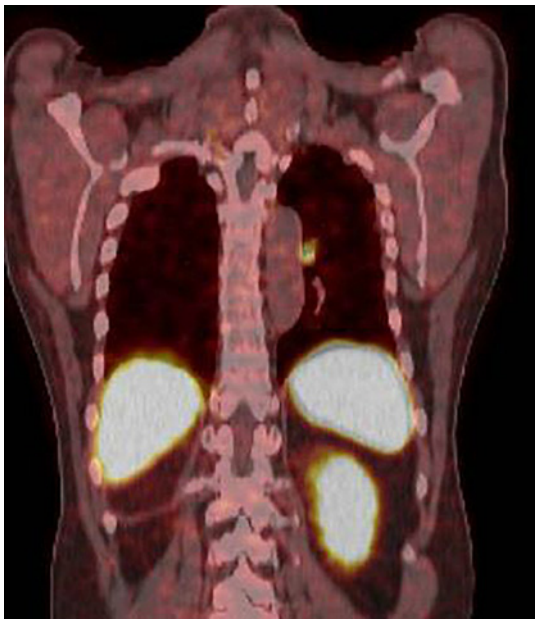

Fig. 2. PET scan showing multiple nodules in the left lung exhibiting variable degrees of abnormally increased tracer activity. PET, positron emission tomography.

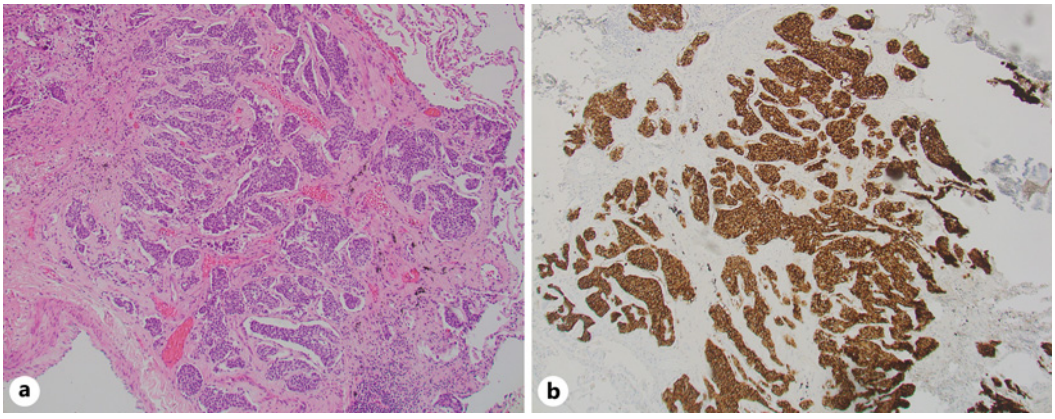

Fig. 3. a Hematoxylin and eosin stain showing pulmonary neuroendocrine cell hyperplasia (×100 magnification). **b** Immunohistochemical staining showing lesional cells positive for chromogranin.

specific immunohistochemical markers such as chromogranin A and synaptophysin, as seen in our case. It is important to note that DIPNECH is considered a preinvasive lesion or a precursor to carcinoid tumors. Carcinoid tumors are low-grade NETs that can develop from DIPNECH over time, although not all cases progress to malignancy. Regular follow-up and monitoring of patients with DIPNECH are necessary to detect any progression to carcinoid tumors or the development of other complications. Treatment options for DIPNECH are limited and primarily aimed at managing symptoms and preventing complications. Inhaled bronchodilators and corticosteroids may be used to alleviate airway obstruction and reduce inflammation. Inhaled bronchodilators and inhaled steroids can be used to alleviate airway obstruction and reduce inflammation in the lungs. Systemic steroids may be considered in cases of more severe symptoms or exacerbations. Somatostatin analogs, such as octreotide or lanreotide, have been used in some cases to control symptoms and potentially inhibit the growth of neuroendocrine cells. In our case,

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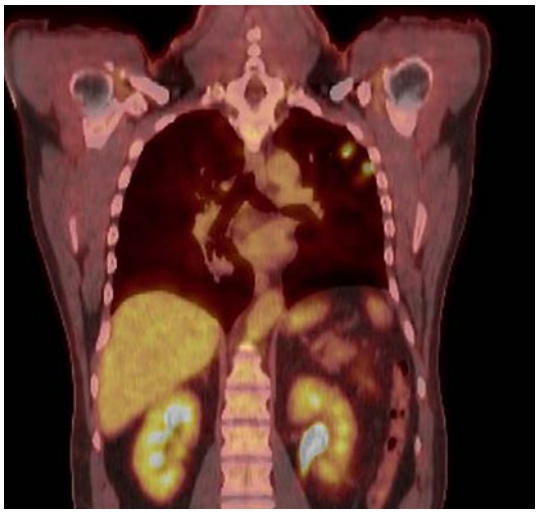

Fig. 4. PET scan showing bilateral pulmonary nodules overall similar in size with an uptake similar to or slightly higher than the blood pool. The nodule with the most avid radiotracer is within the superior and medial left lower lobe, measuring up to 15 mm. PET, positron emission tomography.

the patient's symptoms improved significantly with octreotide. Additionally, mTOR inhibitors, such as everolimus, have shown promise in the treatment of NETs and may be considered in select cases of DIPNECH. It is important for patients with DIPNECH to receive multidisciplinary care involving both pulmonologists and oncologists. This allows for a comprehensive approach to managing the disease, addressing symptoms, and monitoring for potential progression to carcinoid tumors or other complications. Regular follow-up visits, imaging studies, and pulmonary function tests are typically recommended to monitor disease progression and response to treatment [5, 6]. The available evidence for the management of DIPNECH is limited to case reports, case series, and retrospective studies. This highlights the need for further research and larger clinical trials to better understand the optimal treatment strategies for this condition. Overall, the management of DIPNECH requires an individualized approach based on the patient's symptoms, disease progression, and response to treatment. The coordination of care between pulmonologists and oncologists is crucial in providing comprehensive and effective management for patients with DIPNECH. Long-term monitoring is essential to detect any progression to carcinoid tumors or other complications.

Conclusion

DIPNECH is an under-recognized disease of the lungs which is often mislabeled as chronic obstructive pulmonary disease or asthma and does not get appropriate treatment. It is important to educate medical professionals about this entity and should be considered in patients not responding very well to standard treatment for asthma and chronic obstructive pulmonary disease. The use of somatostatin analogs and mTOR inhibitors has shown improvement in DIPNECH patients' clinical symptoms.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

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Author Contributions

M.Y.S. wrote the introduction and case and edited the final version of the manuscript after receiving input from the other authors. W.A. wrote the discussion and conclusion and edited the final draft of the manuscript. A.A. wrote the abstract and reviewed the final draft of the manuscript. F.Z. reviewed and approved the final draft of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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