



Case report

A 68-year-old woman with a diagnosis of asthma and multiple fleeting pulmonary nodules- a case report



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ABSTRACT

Diffuse idiopathic pulmonary neuroendocrine cell (DIPNECH syndrome) remains unfamiliar to most clinicians even though it was first described almost 30 years ago. Diagnosis is usually confirmed histopathologically after lung biopsy, but often, a diagnosis or suspected diagnosis can be made radiographically.

In this paper, we present a case report of a 68-year-old female with shortness of breath and fleeting pulmonary nodules observed on chest CT scan. She was initially misdiagnosed with asthma based on an abnormal pulmonary function test which revealed an obstructive ventilatory defect. The classic radiographic findings of DIPNECH syndrome and the typical patient demographics that should arouse suspicion of a DIPNECH diagnosis were also illustrated.

DIPNECH syndrome is a clinicopathological syndrome whereas focal NECH is a pathological diagnosis that is often made incidentally on histological examination and is encountered in a variety of settings, including in resected carcinoid tumors, in the context of reactive changes concomitant with infection, in metastatic cancer, radiation pneumonitis, intra-lobar sequestration, smokers, interstitial lung disease, and lung adenocarcinoma.

There are no proven treatments for DIPNECH syndrome. In patients with obstructive ventilatory symptoms, bronchodilators with inhaled steroids are usually prescribed. Some severe cases may require parenteral steroids. Somatostatin analogs (SSA) have also been used in some cases with mixed results. Rapamycin has been used in several cases based on the purported activation of the mammalian target of rapamycin (mTOR) in DIPNECH. Some patients with large carcinoid tumors may benefit from resection.

1. Case presentation

A 68-year-old woman with a history significant for hyperlipidemia and asthma diagnosed 4 years ago came for a second opinion regarding the findings of multiple pulmonary nodules. She was evaluated 4 years ago by a different pulmonologist for shortness of breath. She had a PFT at the time that showed an obstructive ventilatory defect. A CT scan of the chest showed air-trapping, multiple pulmonary nodules, and post-obstructive pneumonia or atelectasis. She underwent a PET scan, which did not show any significant uptake, and a diagnostic bronchoscopy was not informative. She was placed on Symbicort for asthma and

watchful observation of the lung nodules with CT scan of the chest was recommended. She was told that over the 4-year period most of the nodules remained unchanged and some had disappeared while a few had gotten slightly larger. She decided to seek a second opinion regarding her diagnosis. She had a smoking history of four pack-years but quit in 1972. She had no history of connective tissue disease and no family history of pulmonary disease. She had no history of allergies. She is a retired school teacher without any history of exposure to any noxious chemicals or inhalants. The review of her other systems yielded no positive information except as above.

Vital signs on presentation were as follows: axillary temperature, 37.1 °C; pulse, 63 beats/min; respiratory rate, 16 breaths/min; BP, 121/

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Abbreviation list

PFT	Pulmonary function test
CT	Computed Tomography
PET	Positron Emission Tomography
SUV	Standardized Uptake Value
DIPNECH	Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
NECH	Neuroendocrine cell hyperplasia
COPD	Chronic obstructive pulmonary disease
HRCT	High resolution computed tomography
SSA	Somatostatin analogs
SSR	Somatostatin receptor
ICS	Inhaled corticosteroids
LAMA	Long-acting muscarinic antagonists

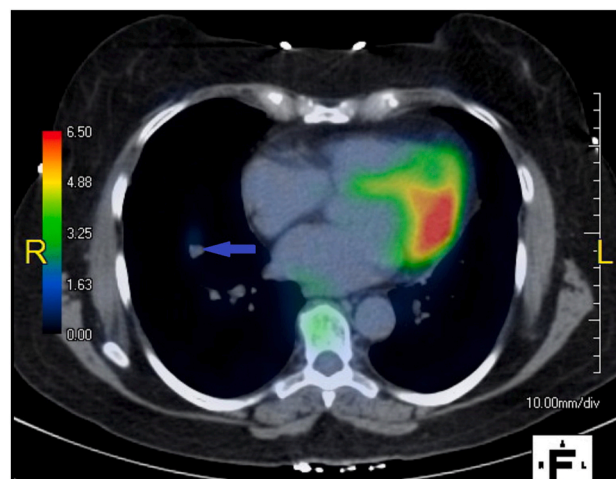


Fig. 2. PET Scan from 2016 showing mild uptake of 2.1 SUV in the right-lower lobe 1.2-cm nodule (indicated by arrow).

Table 1

Spirometry result of the patient showing evidence of mild obstructive ventilatory defect with air-trapping and normal diffusion capacity.

Parameter	Best	Predicted	% Predicted	% Predicted (Post-bronchodilator therapy)
FVC (Liters)	2.11	2.51	84	85
FEV ₁ (Liters)	1.40	1.97	71	73
FEV ₁ /FVC %	66	79	84	86
TLC (Liters)	4.49	4.24	106	-
DLCO (mL/min/mmHg)	14.52	16.96	86	-

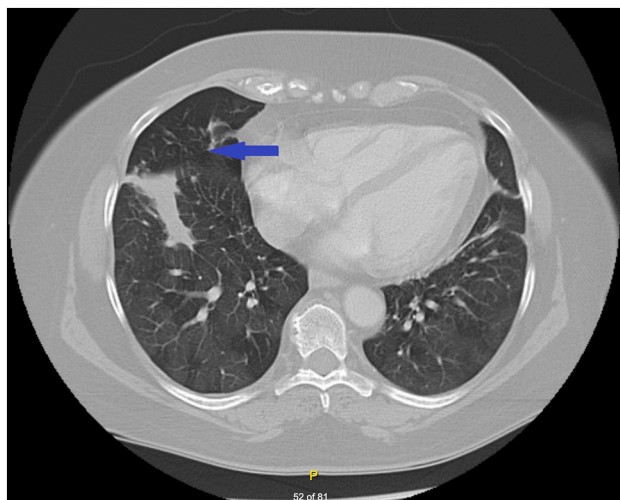


Fig. 1. Chest CT scan from 2016 showing evidence of mosaic attenuation, numerous pulmonary nodules, airway wall thickening, and post-obstructive atelectasis.

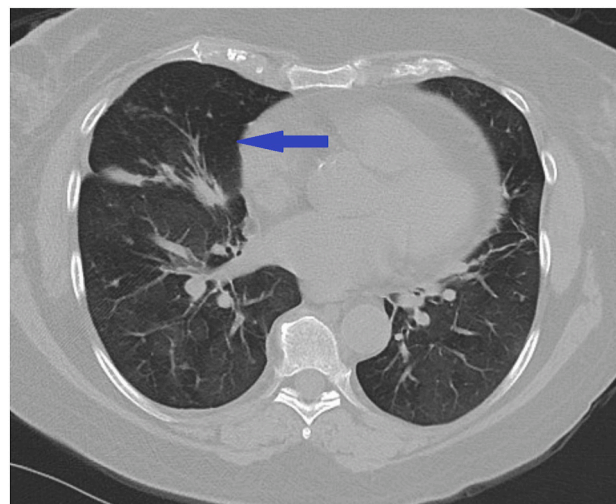


Fig. 3. Chest CT scan from 2020 again showing mosaic attenuation, numerous nodules, right-middle node and lingula infiltrates with increased right-lower lobe post-

lobes 1.2-cm nodule. A CT scan of the chest (Fig. 3) from 2020 again showed mosaic attenuation, numerous nodules, and right-middle node and lingula infiltrates with increased right-lower lobe post-obstructive atelectasis. The patient underwent a video-assisted thoracoscopic surgical lung biopsy.

66 mmHg; O₂ sat, 98% on ambient air. Her chest moved with respiration, no surface mass was observed, no tenderness was detected, and chest auscultation yielded vesicular breath sounds with no wheezing, rhonchi, or added sounds and had a resonant percussion note.

PFT (Table 1) showed evidence of a mild obstructive ventilatory defect with air-trapping and normal diffusion capacity. A review of the CT scan of the chest from 2016 (Fig. 1) showed evidence of mosaic attenuation, numerous pulmonary nodules, airway wall thickening, and post-obstructive atelectasis. The PET scan (Fig. 2) from 2016 showed mild uptake of 2.1 standardized uptake value (SUV) in the right-lower

2. What is the diagnosis?

2.1. Diagnosis

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) syndrome or DIPNECH with airway involvement.

3. Discussion

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) syndrome is a rare disorder that is characterized by the presence of respiratory symptoms, airflow obstruction, and constrictive bronchiolitis with nodular proliferation of the neuroendocrine cells with or without tumorlets/carcinoid tumors on histology. It was first recognized in 2015 by the World Health Organization (WHO) classification of

lung tumors as a premalignant lesion. In 1953, Felton et al. reported several cases of patients with bronchial and peripheral adenoma, which most likely represented neuroendocrine cell hyperplasia (NECH) with possible carcinoid [1]. It was not until 1992 that Aguayo et al. described and coined the entity now known as DIPNECH [2].

DIPNECH syndrome is a clinicopathological syndrome whereas focal NECH is a pathological diagnosis that can be found incidentally on histological examination or encountered in a variety of settings such as incidental findings in resected carcinoid tumors, reactive changes adjacent to infection, metastatic cancer, radiation pneumonitis, intra-lobe sequestration, smokers, and interstitial lung disease. There are more published cases of NECH than DIPNECH and the two entities, despite being different, are often confused. Patients with DIPNECH usually have clinical symptoms of airflow limitation secondary to peribronchiolar fibrosis and obliterative bronchiolitis and the presence of mosaic attenuation on high-resolution CT scan. A review of this subject in 2016 by Rossi et al. described the difference between these two entities and made a compelling case for why the entities should be formally separated [3]. The demographic characteristics of DIPNECH are different from those with reactive NECH. DIPNECH occurs in non-smokers and predominantly females in their late 50s. On the other hand, NECH, like carcinoids, has no sex predilection and occurs mostly in younger adults.

The symptoms of DIPNECH are insidious and usually take years before a definitive diagnosis can be made. Most patients with DIPNECH are erroneously diagnosed with asthma, COPD, or occasionally idiopathic bronchiolitis obliterans. There are radiographic findings on HRCT of the chest, such as mosaic attenuation, small nodules, and bronchial obstruction, that should arouse the suspicion for DIPNECH in patients evaluated for shortness of breath with the presence of obstructive physiology on spirometry. Mosaic attenuation is not seen in all patients with DIPNECH, which may contribute to a delay in diagnosis in some cases. Marchevsky et al. reported findings of constrictive bronchiolitis in 24% of patients with DIPNECH in their case series, which unfortunately was a mixed bag of both NECH and DIPNECH, resulting in the underestimation of the true prevalence of constrictive obliterans in DIPNECH [4]. The prevalence of DIPNECH will also depend on whether the diagnosis was made histopathologically or simply based on findings of mosaic attenuation on HRCT of the chest. There are reported cases of bronchiolitis obliterans on lung biopsy without any symptoms of obstructive lung disease. Nevertheless, symptomatic patients with DIPNECH tend to almost always have mosaic attenuation on HRCT scans [5].

The pulmonary nodules in DIPNECH correspond to proliferations of neuroendocrine cells, which may be confined to bronchiolar mucosa and can progress into tumorlets or carcinoid tumors. According to the WHO classification, tumors smaller than 5 mm are classified as tumorlets. Those 5 mm or larger are classified as carcinoid tumors, which are further separated into typical and atypical carcinoids based on mitotic activity and the presence or absence of necrosis. Carcinoid tumors can be found in 53% of patients with DIPNECH. It remains contentious whether all focal NECH findings can progress into full-blown carcinoid tumors. The morphology and gene expression were found to be different between reactive NECH and preneoplastic DIPNECH [6]. The distinction between carcinoid tumors with NECH and DIPNECH can sometimes be difficult. Even in those patients with no symptoms and without radiographic evidence of DIPNECH, there is overlap between each diagnosis in about 40% of cases when only a histological definition of DIPNECH was applied [7]. Although there are also many reported cases of adenocarcinoma of the lungs in patients with DIPNECH/NECH, it is still unclear if these findings were happenstance or if an unknown causal relationship exists [8]. A case of metastatic carcinoid tumor has also been reported with DIPNECH syndrome [9].

The natural history of DIPNECH syndrome is favorable. It tends to be stable without evidence of progression in the majority of patients. A subset of the cases will progress into carcinoid tumors that may need

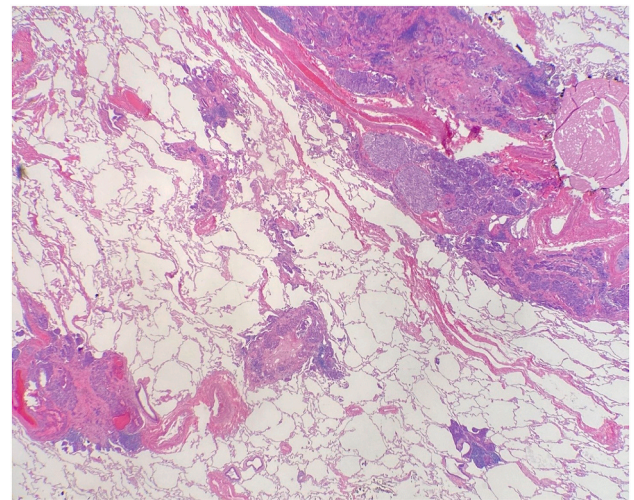


Fig. 4. H&E, showing alveolated lung parenchyma with several carcinoid tumorlets (original magnification x 40).

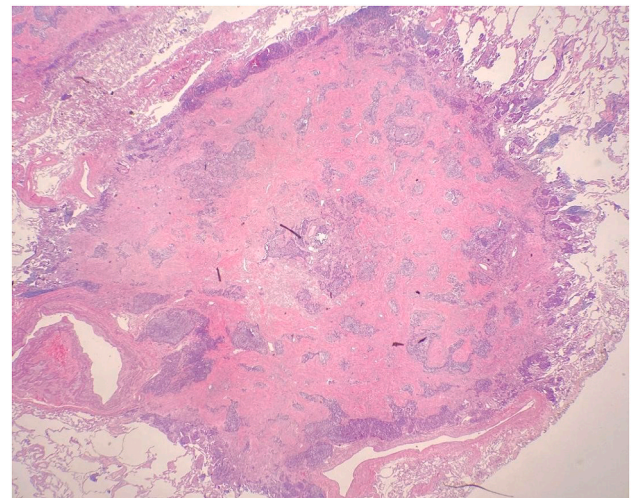


Fig. 5. H&E, showing one carcinoid tumor (original magnification x 40).

resection. Mortality directly associated with DIPNECH is uncommon but has been reported. Some patients with DIPNECH may also require lung transplantation due to progression to end-stage constrictive bronchiolitis.

There are no proven treatments for DIPNECH syndrome. In patients with obstructive ventilatory symptoms, bronchodilators with inhaled steroids are usually deployed. Some severe cases may require parenteral steroids. Somatostatin analogs (SSA) have also been used in some cases with mixed results. The use of an octreotide scan has been advocated by some groups to identify the patients with a high level of expression of somatostatin receptor (SSR) to predict the therapeutic response to SSA. Rapamycin has also been used in a few cases based on the purported activation of the mammalian target of rapamycin (mTOR) in DIPNECH. Carcinoid tumors can also be surgically resected in some cases.

4. Clinical course

The patient underwent video-assisted thoracoscopic surgery with wedge resections of the middle and right-lower lobes. Histologic examination demonstrated evidence of DIPNECH with multiple tumorlets (Fig. 4) and typical carcinoid tumors up to 1.1 cm (Fig. 5) involving pulmonary parenchyma and present at the stapled margin. There was

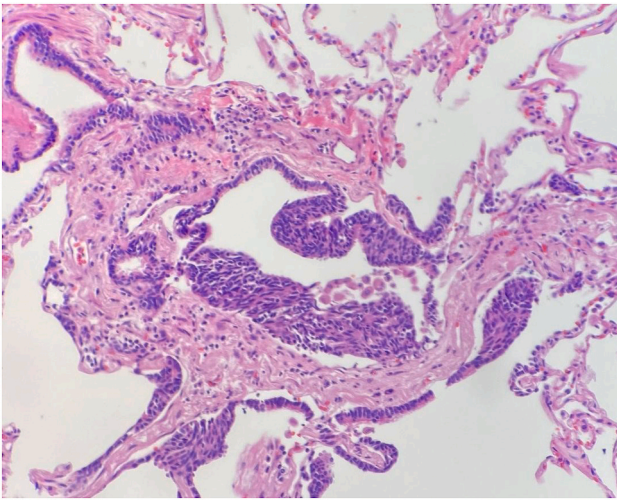


Fig. 6. H&E, showing distinct proliferation of neuroendocrine cells associated with luminal narrowing and involving the bronchiolar mucosa (original magnification x 200).

also evidence of constrictive bronchiolitis (Fig. 6) characterized by a proliferation of neuroendocrine cells involving the bronchiolar mucosa and associated with luminal narrowing. No additional treatment was recommended secondary to stability in the CT scan findings over the years coupled with improved symptoms of obstructive ventilatory defect with combined ICS/LAMA.

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CRedit authorship contribution statement

Fortune O. Alabi: Conceptualization, Data curation, Writing - original draft. **Christopher O. Alabi:** Writing - original draft. **Hadaya A. Alkhateeb:** Writing - original draft. **Naim K. Fanaian:** Visualization, Investigation, Investigation, Writing - review & editing. **Ashkan Gha-neie:** Validation, Visualization, Investigation, Writing - review &

editing.

Declaration of competing interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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