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Case Report

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Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) in a 50-Year-Old Woman

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ABSTRACT

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare pulmonary disorder characterized by hyperplasia of pulmonary neuroendocrine cells. It is frequently asymptomatic and can be challenging to differentiate from other forms of reactive pulmonary neuroendocrine cell hyperplasia (NECH). Presented is a case report of DIPNECH along with a review of the diagnosis and management. A 50-year-old female patient with a history of airway disease presented to the pulmonary ward with complaints of Functional Class III dyspnea and productive cough. The HRCT revealed the presence of multiple bilateral nodules in both lungs. The histopathology report from the nodule resection confirmed the presence of a carcinoid tumor, specifically identified as DIPNECH. As many similar cases have favorable treatment responses and satisfactory prognoses due to multidisciplinary treatment methods, the necessity of evidence-based management guidelines for DIPNECH and the accuracy of the disease definition is emphasized.

Introduction

Neuroendocrine tumors (NETs) encompass a diverse spectrum of malignancies originating from neuroendocrine cells in various organs, predominantly the lungs and gastrointestinal tract [1]. The histological characteristics and clinical behavior of NETs categorize them into four distinct groups: intermediate-grade atypical carcinoids (AC), well-differentiated (low-grade) typical carcinoids (TC) with a frequency of 10 times more than the atypical subtype, large-cell neuroendocrine carcinomas (LCNCs) in 3% of lung cancers, and poorly differentiated or high-grade large cell neuroendocrine carcinoma (SCLCs) in 15% of lung cancers [2-6]. Apart from isolated pulmonary manifestations, there have been documented occurrences of two or more carcinoid tumors in the lung, gastrointestinal tract, and pancreas. Uncommon localizations include the breast, ovary, testicle, endometrium, vulva, cervix, kidney, extrahepatic bile tract, thymus, or nasal sinuses [7]. Bronchial carcinoid tumors constitute 10% of all carcinoid tumors and 4% of total lung

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tumors [8]. Pulmonary carcinoids have an incidence of 0.2-2/100,000 cases both in the USA and the EU, illustrating an increase of up to 6% per year in LNETs [9, 10]. The classification of LNETs from low-grade to aggressive tumors was established based on the histopathological aspect, Ki-67 index, mitotic rate, and the presence of necrosis. Another LNET tumor is DIPNECH, specified by fibrosis and small neuroendocrine bodies [11]. DIPNECH syndrome, defined as a pre-neoplastic lesion to pulmonary neuroendocrine tumors by WHO [12], is symptomatic NEC proliferations and clinical constrictive bronchiolitis [13]. It is confirmed by pathology examination that DIPNECH occurs most often in women and patients with obliterative bronchiolitis [1]. Some characteristic CT findings in DIPNECH include multifocal pulmonary micronodules (< 3 mm) or nodules < 5 mm, mosaic attenuation, and bronchial wall thickening [14]. Moreover, diagnostic findings of HRCT include multifocal pulmonary micronodules (solid or ground-glass attenuation), multifocal expiratory air-trapping, mosaic attenuation on inspiratory imaging, and sometimes bronchiolocentric distribution [15, 16]. Owing to the 2015 WHO classification of lung tumors, DIPNECH is considered a preneoplastic condition with some microscopic features including generalized NEC proliferation, neuroendocrine bodies, and linear NEC proliferation. Immunohistochemistry expresses markers of NEC differentiation, including chromogranin A, synaptophysin, and CD56 among others. Although lung biopsy is the gold standard option for treatment, bronchoscopy has shown considerable effectiveness in disease diagnosis.

Case Presentation

A 50-year-old woman was referred for further evaluation of dyspnea. She reported having had airway disease for the last 10 years. She experienced dyspnea one month ago, which was classified as MMRC II. She also had a persistent cough and scant sputum production. She initially presented as an outpatient, but despite drug therapy, her symptoms worsened to MMRC III dyspnea, leading her to visit a pulmonologist for further evaluation. During this month, she did not experience weight loss or loss of appetite, and she did not exhibit symptoms of upper respiratory tract infection such as rhinorrhea, throat pain, or fever.

The patient is a non-smoker with no reported allergies or occupational/environmental exposures. Her medical history includes hypertension (treated with Bisoprolol 2.5 mg BD, Amlodipine/Valsartan 5/80 daily, and aspirin), hypothyroidism (treated with Levothyroxine 100 daily), hyperlipidemia (treated with Atorvastatin), and asthma (treated with Budesonide Formoterol inhaler BD and Montelukast 10 daily). Her review of systems was otherwise negative.

During the physical examination, her oxygen saturation was measured at 92%, with a normal temperature of 37°C. Other vital signs were within normal limits. Lung auscultation revealed expiratory wheezing, and there were no abnormalities in the cardiovascular examination. No clubbing or cyanosis was observed in her extremities.

In the primary workup, laboratory samples, oxygen therapy, nebulizer treatment, an electrocardiogram, chest X-ray (Figure 1), spiral lung CT scan, and PCR for coronavirus were performed. Laboratory tests revealed moderate leukocytosis with a white blood cell count of 15,000 (Table 1). An echocardiography was also performed, showing a normal ejection fraction rate of 50-55%. The bronchoscopy of the patient illustrated a normal appearance in the trachea, carina, right/left lung, and the BAL (broncho-alveolar lavage) specimen

Table 1. Laboratory findings.

WBC	12300	AST	30
Hb	13.6	ALT	32
MCV	89	ALK	162
RBC	3.2	Bill T	1.4
Platelet	238	Bill D	0.7
BUN	59	Na	137
Cr	1	K	3.9
ESR	30	Ca	8.5
CRP	2	P	3
TSH	3.8	Mg	2
LDH	360	PT	12
Uric Acid	4	PTT	24
		INR	1

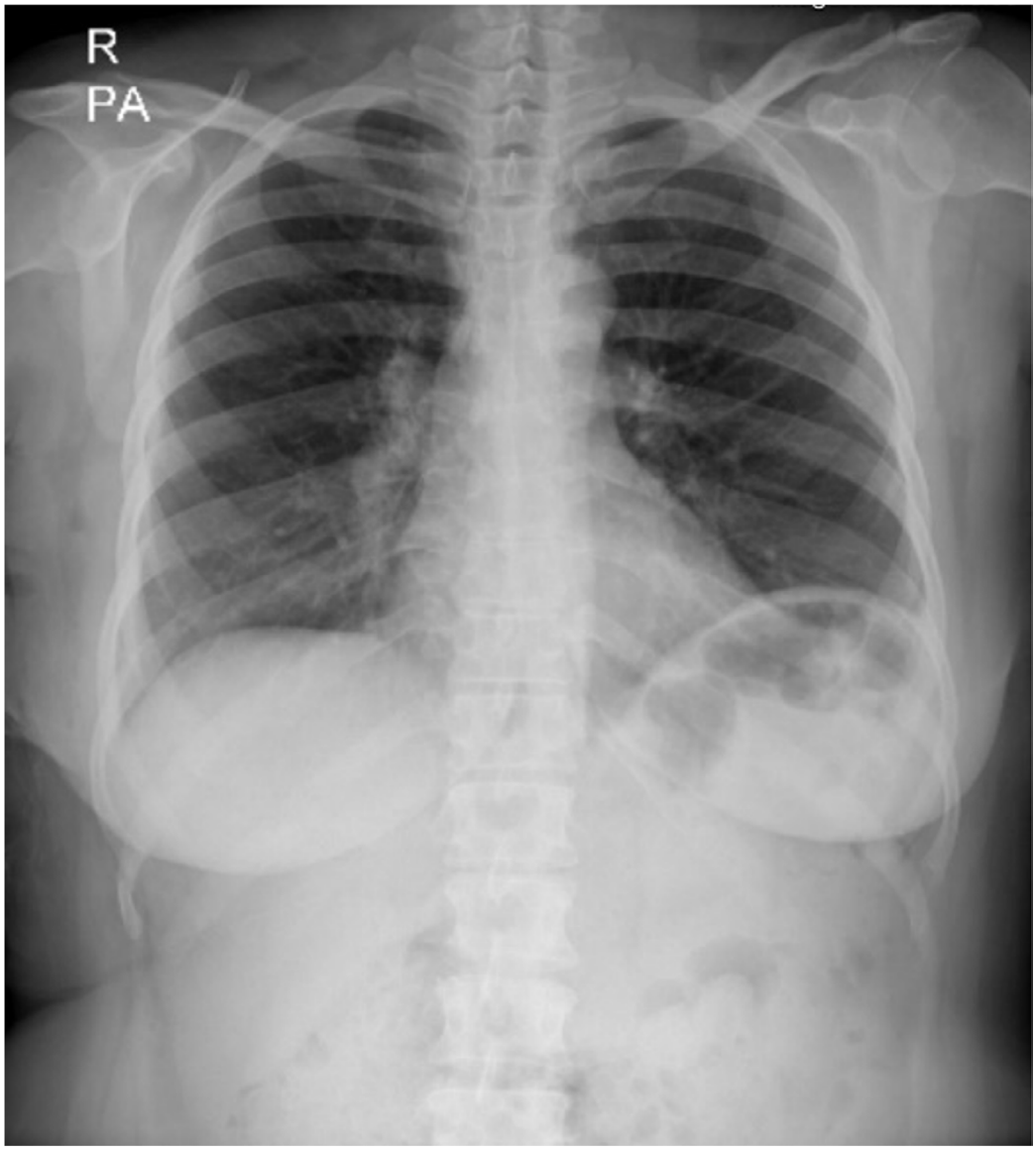

Fig. 1. Chest X-Ray of our patient's chest on admission to our hospital.

was performed (Figure 2). In the first BAL culture, growth of less than 100,000 of Enterobacter cloacae, and in the second culture, growth of less than 10,000 colonies of alpha-hemolytic Streptococcus was seen, and the sensitive antibiotics were prescribed as well. The CT scan showed a normal broncho-vascular lung pattern, with no evidence of lung fibrosis. Centrilobular nodules scattered in the field of both lungs were seen with a tree-in-bud view in the right middle lobe (RML), which suggests acute bronchiolitis. Moreover, nodules were observed in both lungs, with 15 solid nodules in the right lung with a maximum diameter of 9 mm visible in the anterior segment of the right upper lobe (RUL), and 7 solid nodules in the left lung with a maximum diameter of 5 mm in the antero-basal segment of the left lower lobe (LLL) (Figure 3).

Following the initial evaluation, the patient underwent video-assisted thoracoscopic surgery (VATS). The specimen of a "lung nodule" was resected during a thoracoscopy and wedge resection of the upper lobe of the right lung held by the surgical team. Subsequently, the specimen was examined histopathologically, and a bifocal carcinoid tumor, measuring 0.9 cm x 0.3 cm, was found with a mitotic count of less than 1 per 2 mm. There was no evidence of necrosis, and the resected parenchymal margin was tumor-free (Figure 4).

Immunohistochemistry (IHC) study showed AE1/AE3 positive, weakly positive synaptophysin on some tumoral cells, chromogranin positive, and Ki67 positive in less than 1% of tumoral cells.

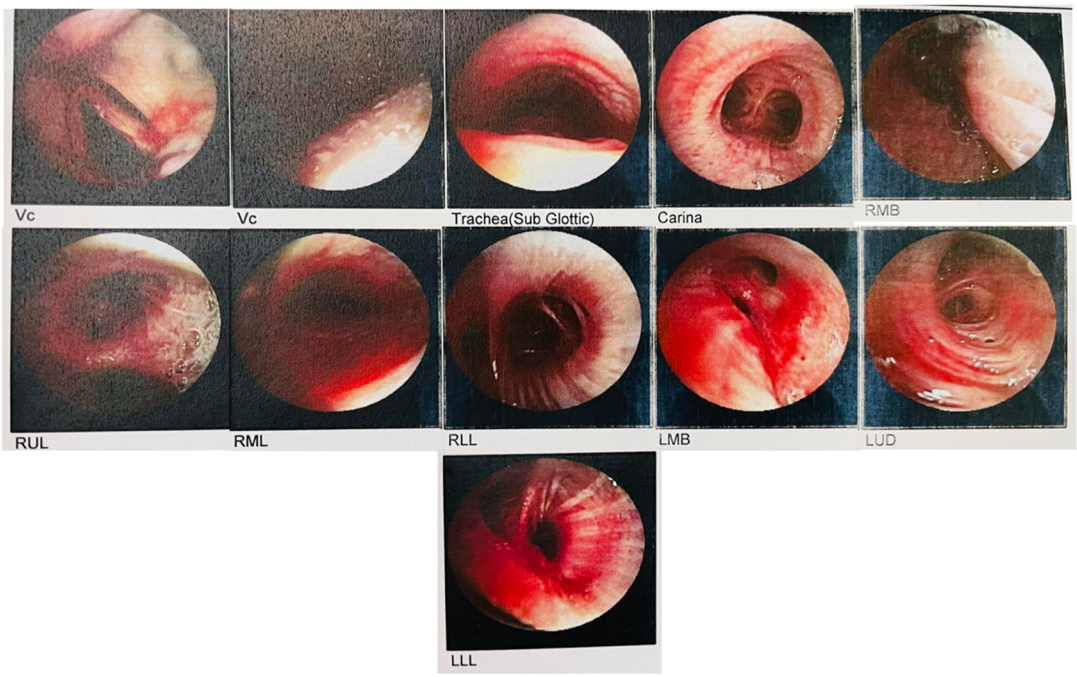

Fig. 2. The bronchoscopy didn't show any abnormality in the Trachea and both Lungs.

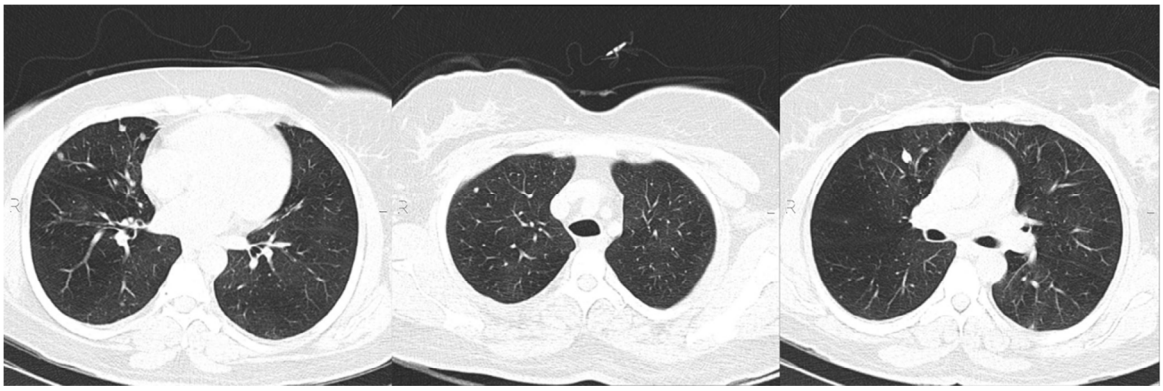

Fig. 3. Spiral lung CT scan illustrating the lung carcinoid tumor with multiple smaller carcinoid tumorlets in both lungs

Following the confirmation of the diagnosis by pathology, the patient was presented at a multidisciplinary chest tumor conference and was reported as a DIPNECH case.

Discussion

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) represents a rare pulmonary condition, defined as a pre-neoplastic lesion to pulmonary neuroendocrine tumors by WHO. This pathological entity triggers the proliferation of neuroendocrine cells, which may be confined to the lung mucosa, resulting in local invasion, or progress into invasive carcinoid tumors. It is predominantly diagnosed in middle-aged individuals who are non-smokers, with a discernible female predominance [17, 18].

It is noteworthy that as many as 50% of DIPNECH patients may exhibit no detectable symptoms. Those who do manifest symptoms typically present with a gradual onset of nonproductive cough, exertional dyspnea, and wheezing, which could mistakenly be attributed to asthma. Additional symptoms may encompass productive cough, hemoptysis, and chest pain, while pulmonary function tests may reveal obstructive or mixed restrictive/obstructive patterns. Due to the high incidence of misdiagnosis with asthma, the diagnosis will be delayed, as the average period

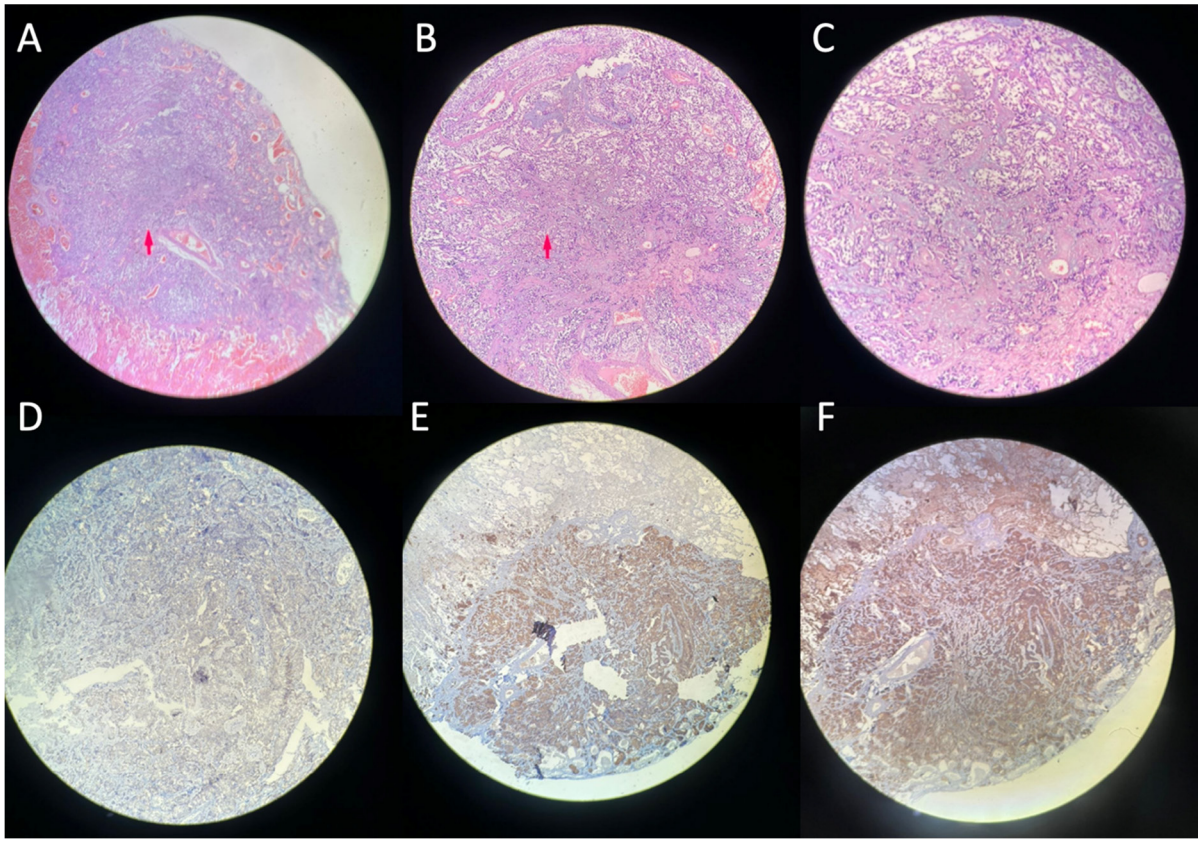

Fig. 4. Strong positivity in immunohistochemical analysis, sections show lung parenchyma involved by a neoplasm composed of nests of rather uniform cells with polygonal shape, round to oval nuclei with salt and pepper chromatin, inconspicuous nuclei, moderate clear cytoplasm. A.B.C. Diffuse proliferation of neuroendocrine cells with fascicles of plump spindle cells separated by thin fibrovascular septa.D.E.F. CD 56, synaptophysin, and Ki-67 positive stains for neuroendocrine cells

between symptom onset and diagnosis is between 9 and 16 years [19]. Similarly, our patient was under the treatment for asthma for some time before the referral to our ward.

From a demographic point of view, the prevalence of the disease in women surpasses that in men by a factor of ten, and it predominantly affects individuals aged 50-70, with an average age of 58 [15]. The radiologic findings of DIPNECH include multiple small nodules that are typically less than 5 mm in size and are scattered throughout the lungs, often appearing as a mosaic pattern on CT scans due to air-trapping [20, 21]. In our patient, the CT findings demonstrated multiple nodules, scattered in both lungs, with a maximum diameter of 5 mm in the left lower lobe (LLL) and a maximum diameter of 9 mm in the right upper lobe (RUL). Unlike metastases and hematogenous infections, which have a random distribution, DIPNECH nodules are centrilobular. The presence of air trapping, which leads to mosaic attenuation, is a characteristic feature of DIPNECH [22].

The findings from routine laboratory tests typically do not yield definitive results. Normally, the peripheral eosinophil count remains within the standard range in cases of DIPNECH, thereby aiding in the differentiation from severe asthma, which typically presents with an eosinophilic phenotype [23, 24]. Upon CT examination, DIPNECH consistently presents as bilateral, noncalcified, and noncavitary pulmonary nodules with well-defined borders, distributing throughout both lungs, with a preference for the middle and lower zones. The peribronchovascular distribution was identified as the most reliable CT feature for distinguishing DIPNECH nodules from other causes of pulmonary nodules in women, where a centrilobular distribution is typically observed [14, 25]. Another radiologic characteristic of DIPNECH is mosaic attenuation, which was observed in 80% of patients in a study conducted by Carr LL et al. [26]. Other features, including bronchial wall thickening and bronchiectasis, might be seen in radiologic tools.

Immunohistochemistry is another diagnostic tool. Chromogranin-A (CG-A) serves as a widely employed biomarker in patients with NETs and may exhibit elevated levels in individuals with DIPNECH. Notably,

in a study held by Hayes AR et al., elevated CG-A levels were observed in 45% of the DIPNECH patients [27]. Identically, this case had Chromogranin positive in IHC. AE1/AE3, Synaptophysin, and Ki67 were also positive to varying degrees.

Treatment modalities encompass the utilization of β2-agonists and inhaled or oral corticosteroids. Furthermore, the potential administration of octreotide for patients with somatostatin receptors, contemplation of lung transplantation for eligible patients, and surgical excision of coexistent carcinoid tumors as a viable option should be considered. It is proved by Hayes et al. that after the resection procedure, more than 75% of DIPNECH-carcinoids do not relapse in a 10-year period [27]. The condition referred to as DIPNECH currently lacks delineated risk factors, diagnostic criteria, treatment guidelines, and prognosis.

Conclusion

This creates numerous opportunities for future research to enhance our comprehension of this rare pulmonary disease, highlighting the imperative nature of considering DIPNECH in the differential diagnoses when a patient presents with dyspnea, chronic cough, and lung nodules. Furthermore, DIPNECH has the potential to advance into unresectable carcinoid tumors. Consequently, early detection may prove pivotal in the management and prognosis of this exceptionally rare pathology.

Ethical Considerations

Ethical Approval

The authors' institute provided ethical approval for this case study.

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Authors' contribution

R.M.A: did the procedure, managed the patient and led to the ultimate diagnosis and the current study. F.F: collected the data and write the manuscript. C.A: revised the manuscript.

Conflict of Interests

The authors state that this publication process does not involve any conflicts of interest. Research registration unique identifying number (UIN): None

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