

Let's Look further: "Not Everything is Asthma" Let's talk about DIPNECH: Case Report

Veamos más allá: "No todo es asma". Hablemos de DIPNECH: reporte de caso

Liseth Mora Crespo¹ , Fernando Saldarini , Nolkelys Nemer , Flavia Scibetta , Marcelo Echeverría , Loreley Toreysan 

¹ Hospital de Donación Francisco F. Santojanni, Buenos Aires-Argentina

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Correspondence

Liseth Mora Crespo mail:
lisethmoracrespo@gmail.com

ABSTRACT

Background: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare entity considered a pre-invasive lesion within the spectrum of neuroendocrine tumors. Its pathophysiology involves chronic inflammatory injury to the respiratory epithelium that leads to smooth muscle hypertrophy, and nodular cell proliferation.

Objective: This paper reviews the main characteristics of this pathology and highlights the importance of reconsidering the diagnosis in cases of treatment failure in severe asthma.

Case report: We present the case of a 61-year-old patient under follow-up for diagnosis of severe asthma, who, after six months of biological treatment with Mepolizumab and optimal inhaled therapy, remained symptomatic.

Results: In the diagnostic re-evaluation, the computed tomography of the chest revealed multiple nodules, which did not show pathological uptake on the 18F- FDG PET-TC. Following discussion in a multidisciplinary meeting, a confirmatory lung biopsy for DIPNECH was performed.

Key words: diffuse neuroendocrine cell hyperplasia asthma tomography histopathology

RESUMEN

Introducción: La hiperplasia idiopática difusa de células neuroendocrinas pulmonares (DIPNECH) es una entidad infrecuente considerada una lesión preinvasiva dentro del espectro de los tumores neuroendocrinos. Su fisiopatología involucra una lesión inflamatoria crónica del epitelio respiratorio que condiciona fibrosis, hipertrofia del músculo liso y proliferación celular nodular.

Objetivo: El presente trabajo revisa las principales características de esta patología y resalta la importancia de reconsiderar el diagnóstico ante el fracaso terapéutico en el asma grave.

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Presentación del caso: Se presenta el caso de una paciente de 61 años en seguimiento por diagnóstico de asma grave, que, tras seis meses de tratamiento biológico con mepolizumab y terapia inhalada óptima, persistió sintomática.

Resultados: En la reevaluación diagnóstica, la tomografía computarizada de tórax reveló múltiples nódulos pulmonares, que no presentaron captación patológica en la tomografía por emisión de positrones combinada con tomografía computarizada con ^{18}F -fluorodesoxi-glucosa. Tras la discusión en un ateneo multidisciplinario, se realizó una biopsia pulmonar confirmatoria de DIPNECH.

Palabras clave: hiperplasia difusa de células neuroendocrinas asma tomografía histopatología

INTRODUCTION

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia was first described in 1992 and was included in the World Health Organization (WHO) International Histological Classification of Tumors in 1999. Its estimated worldwide prevalence is approximately 1 case per 100,000 inhabitants. DIPNECH affects both children and adults, but predominantly occurs in women during the fifth and sixth decades of life, and is not associated with smoking.¹

Neuroendocrine cells are present in the bronchial wall lining, extending from the trachea to the terminal bronchioles, where they function as chemoreceptor sensors. In the setting of repetitive injury, these cells excrete excessive amounts of bombesin and serotonin, triggering the excessive migration of eosinophils and mast cells, with subsequent release of inflammatory substances. This process may contribute to a cycle of persistent inflammation. In addition, the release of growth factors contributes to bronchial smooth muscle hypertrophy, fibrosis, and the formation of nodules, which are classified as tumorlets or tumors depending on their size.^{2,3}

Respiratory symptoms such as bronchospasm and chronic cough are typically long-standing; however, some patients remain asymptomatic, leading to a delayed diagnosis. Chest CT is a key imaging modality for raising diagnostic suspicion, though in some cases the condition is discovered incidentally following the detection of nodules. Consequently, the definitive diagnosis relies on histopathological characteristics.

CASE REPORT

A 61-year-old nonsmoking woman with a history of high type 2 (T2) allergic asthma and elevated fractional exhaled nitric oxide (FeNO) was referred to our hospital's severe asthma clinic in 2022. Over the past year, she required multiple courses of oral corticosteroids for exacerbations and persistent dyspnea. Respiratory function testing revealed obstruction with a positive bronchodilator response. In 2023, following persistent exacerbations and despite the Step 5 Global Initiative for Asthma (GINA) therapy and the presence of a fixed obstructive pattern on spirometry, treatment with mepolizumab was decided; however, due to administrative delays, the patient did not begin therapy until 2024. After 12 months of mepolizumab therapy, she experienced mild symptomatic improvement and had four unscheduled visits to the severe asthma clinic for exacerbations. She continued to report cough and dyspnea, and audible wheezing was noted on physical examination. The case was reassessed, and laboratory testing and chest imaging were obtained.

Laboratory testing showed improvement in the absolute eosinophil count (186 cells/mm³). The rheumatologic workup was negative. Inflammatory markers remained elevated, including C-reactive protein (34.3 mg/dL) and erythrocyte sedimentation rate (40 mm/h). Pulmonary function testing showed a forced expiratory volume in 1 second (FEV₁) of 1.57 L (59% predicted), forced vital capacity (FVC) of 1.90 L (86% predicted), and diffusing capacity for carbon monoxide (DLCO)

of 25.69 mL/min/mm Hg (118% predicted). Total lung capacity (TLC) was 6.01 L (126% predicted); residual volume (RV) was 3.58 L (191% predicted), and the RV/TLC ratio was 59% (150% predicted), consistent with moderate airflow obstruction, air trapping, and hyperinflation. Chest CT showed bronchial wall thickening and diffuse mosaic attenuation of the lung parenchyma. Multiple well-defined, lobulated solid pulmonary nodules of varying sizes were identified in both lungs, with the largest measuring 16 mm in diameter.

Based on the chest imaging findings and the initial suspicion of an underlying malignancy, an 18F-FDG PET-CT scan was performed. It demonstrated bilateral nodular and pseudonodular opacities without abnormal FDG uptake, failing to clarify the etiology of the pulmonary nodules. A multidisciplinary case conference involving thoracic surgery, oncology, and pathology was subsequently held. Given the patient's favorable clinical and functional status, a left pulmonary segmentectomy was performed. Histopathological analysis revealed diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, with peribronchiolar fibrosis and chronic inflammation, as well as a typical carcinoid tumor (grade G1 neuroendocrine tumor). Immunohistochemical staining

was positive for CD56, chromogranin A, TTF-1, INSM1, CK18, and Ki-67, thereby establishing the diagnosis.

The patient is currently receiving monthly treatment with a somatostatin analog and remains under follow-up at the severe asthma clinic.

DISCUSSION

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, histologically defined by the World Health Organization as a preinvasive lesion within the spectrum of pulmonary neuroendocrine neoplasia, is characterized by repeated injury to neuroendocrine cells lining the bronchial epithelium, leading to fibrosis and tumorlet formation. First described in 1992 by Aguayo et al as a syndrome predominantly affecting non-smoking women in their fifth and sixth decades of life, presenting with characteristic thoracic imaging findings and a low global prevalence.⁴

Given its underlying pathophysiology, clinical manifestations directly correlate with bronchial tissue hyperplasia, manifesting as cough, bronchospasm, wheezing, and dyspnea. These broad, non-specific respiratory symptoms frequently mimic common pulmonary conditions –most no-

Figure 1. Chest CT scan: (A and C) Inspiratory images showing mosaic attenuation and air trapping. (B and D) Expiratory images showing persistent mosaic attenuation; multiple well-defined, lobulated solid pulmonary nodules of varying sizes, visible on both inspiratory and expiratory images. (E) FDG PET/CT: showing bilateral nodular and pseudonodular opacities without abnormal FDG uptake

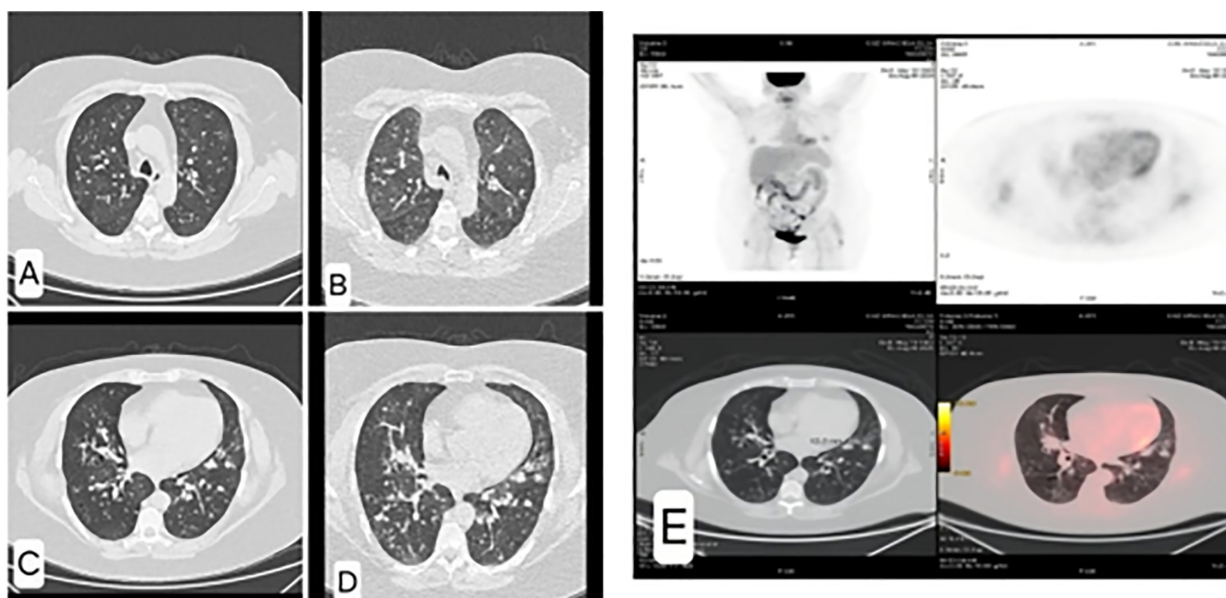
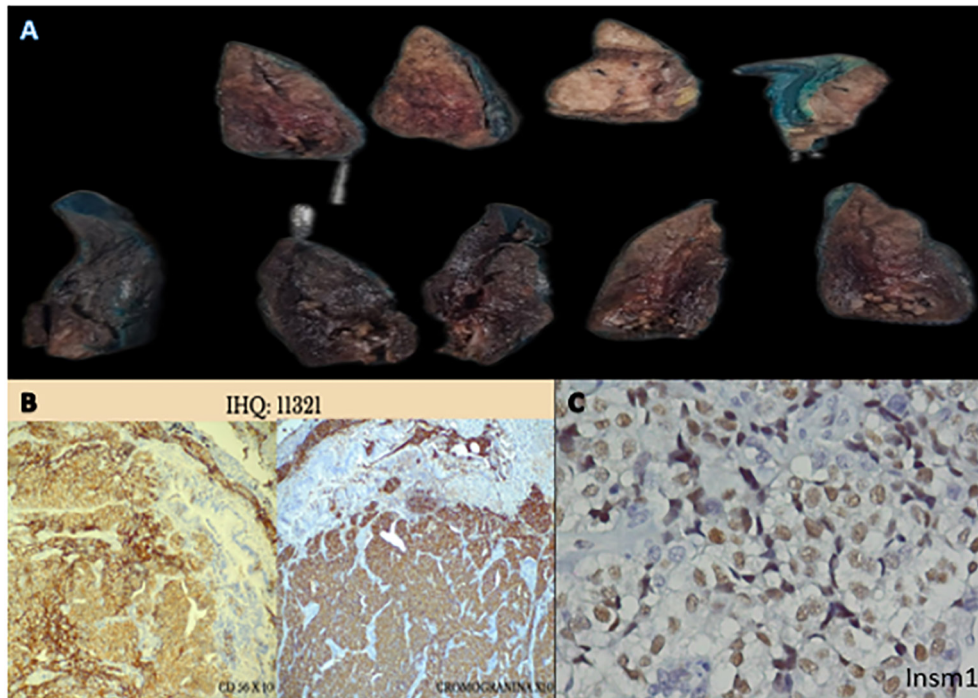


Figure 2. A. Left pulmonary segmentectomy. B. Immunohistochemistry CD56 (10x) and Chromogranin (10x): Cells within the area of bronchiolar neuroendocrine cell hyperplasia, as well as those comprising the grade 1 neuroendocrine tumor, demonstrate uniform, polygonal morphology with round-to-oval nuclei, finely stippled ("salt-and-pepper") chromatin, inconspicuous nucleoli, and eosinophilic cytoplasm. Fewer than 2 mitotic figures per 10 high-power fields (HPF) were observed, with no evidence of necrosis. C. INSM1 (insulinoma-associated protein 1) immunohistochemical stain: Demonstrates positive nuclear staining, confirming a nuclear marker of neuroendocrine differentiation.



tably asthma and chronic bronchitis— or prompt suspicion for malignant processes. Consequently, literature consistently highlights substantial diagnostic delays of up to three years, underscoring DIPNECH as a major diagnostic challenge.⁵

Regarding diagnostic workup, pulmonary function testing typically demonstrates a predominantly obstructive ventilatory defect accompanied by air trapping, which may occasionally exhibit a bronchodilator response. In laboratory studies, the eosinophil count may be within the normal range, which could provide limited assistance in distinguishing DIPNECH from severe asthma. However, this finding has limited discriminatory value, particularly in patients with coexisting conditions, in whom the eosinophil count may be altered. Other biomarkers, such as chromogranin A and the multigene blood mRNA transcriptomic assay (NETest), have also been investigated; however, their utility for both the diagnosis and monitoring of DIPNECH remains controversial.²

Chest CT scan is the primary imaging modality when DIPNECH is suspected. Characteristic findings include bronchial wall thickening, mild bronchiectasis, mucus impaction, and, most notably, a mosaic attenuation pattern. Mosaic attenuation patterns result from vasoconstriction in obstructed lung segments with neuroendocrine cell hyperplasia. Nodules are associated findings that enable differentiation between carcinoid tumors and tumorlets based on size; typically located distally in the lung periphery, these lesions may present as solitary or multiple nodules.^{1,5}

As noted previously, the diagnostic challenge posed by DIPNECH makes it easily susceptible to misdiagnosis. Consequently, clinicians must maintain a high index of suspicion and include it in the differential diagnosis of other conditions such as asthma, Sjögren's syndrome, rheumatoid arthritis, and transplant rejection, which can themselves cause constrictive bronchiolitis and lead to diagnostic confusion. A multidisciplinary

team approach is therefore essential to establish a reliable diagnostic pathway toward a definitive diagnosis.⁶

Given the clinical presentation, it is worth noting that DIPNECH and asthma, despite being distinct clinical entities, may coexist. This overlap can be explained by a cascade of events in which an allergic stimulus triggers an inflammatory response, activating downstream inflammatory cascades that ultimately drive neuroendocrine

cell hyperplasia. Clinically, this coexistence manifests as persistent asthma symptoms, elevated inflammatory biomarkers (such as eosinophils), and an increased frequency of exacerbations, significantly impairing the patient's quality of life while promoting neuroendocrine cellular hyperplasia.⁷

Conflict of interest

None to declare.

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