

CASE REPORTS

Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia. A Case Report.

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Abstract

Introduction: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a sporadic but underdiagnosed pulmonary disorder at the benign end of the neuroendocrine cell proliferation spectrum of preinvasive lesions of the lungs. This disease is characterized by hyperplasia of bronchiolar and bronchial pulmonary neuroendocrine cells. DIPNECH can be primary or reactive.

In the WHO - IASLP classification of lung tumors (1999, 2004, 2005, 2015), DIPNECH is considered a preneoplastic lesion in the spectrum of pulmonary tumors. According to the WHO classification, the definition of DIPNECH is purely histological.

The DIPNECH was initially described in 1992 by Aguayo et al., who reported six non-smoking patients with cough, exertional dyspnea, wheezing, less frequent hemoptysis, and a mixed obstructive/restrictive defect on pulmonary function tests. This disease has a predilection for non-smoking middle-aged women (female to male ratio is approximately 10:1)

In this article, we present a 62-year-old, non-smoker woman presented with respiratory symptoms ascribable to DIPNECH. After surgery, the morphological study of lung specimens confirmed the DIPNECH, multiple tumors, one peripheral carcinoid, and obliterative bronchiolitis in the right middle pulmonary lobe.

Conclusions: DIPNECH remains a rare pulmonary condition and is considered a preneoplastic lesion in the spectrum of pulmonary tumors. According to the WHO classification, the definition of DIPNECH is purely histological. While most patients experience a relatively uneventful clinical course, this condition may be associated with tumors, carcinoid tumors, and airway obstruction (Aguayo-Miller disease).

Keywords: DIPNECH, tumourlets, carcinoid, obliterative bronchiolitis.

Introduction

Neuroendocrine cells are components of the normal bronchiolar and bronchial epithelium, which comprise about 1 % of epithelial cells in an adult lung. These cells express

neuroendocrine markers (chromogranin A, synaptophysin, CD 56, etc.).

DIPNECH is a clinicopathological syndrome and an incidental finding on histological examination, although there are apparent differences between these two scenarios. [1 - 10]

When no other pathological pulmonary disease is detected, DIPNECH is idiopathic. Instead, reactive neuroendocrine hyperplasia is believed to be a response to hypoxia and chronic obstructive pulmonary disease, such as interstitial fibrosis, asthma, cystic fibrosis, bronchopulmonary dysplasia, bronchiectasis, chronic obstructive pulmonary disease, neuroendocrine pulmonary tumors, non-endocrine pulmonary tumors, chronic exposure to high altitude, exposure to tobacco smoke. [2, 3, 4, 5, 6.]

In the WHO classification of tumors of the lung (1999, 2004, 2005, 2015), the DIPNECH has been defined

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as a preneoplastic lesion because it is commonly found in patients with tumors and carcinoid tumors. [2, 3, 4, 5]

Histologically, the DIPNECH is characterized by diffuse idiopathic hyperplasia of scattered neuroendocrine cells in the distal bronchi and bronchioles, linear hyperplasia in alveolar ducts and alveoli associated with multiple tumors and peripheric carcinoid and peribronchiolar fibrosis obliterating small airways, and by mild chronic lymphocytic inflammation. These lesions which have continuity and correlation [1, 3, 4, 5, 6, 7]

More than 250 cases of this disease have been published since the initial description by Aguayo in 1992 in the form of case reports or small case series. However, the literature must establish a clear consensus about the radiological or pathological diagnostic criteria for managing this disease. [3, 6, 10]

Case Report.

A 62-year-old woman, non-smoking, presented with a respiratory tract infection, expressed with cough, exertional dyspnea, and wheezing. The chest's radiography and high-resolution computed tomography (HRCT) showed a mosaic attenuation due to interstitial fibrosis, some little nodules, and a nodule measuring 28 mm in the right middle pulmonary lobe.

The lung function tests show an obstructive ventilation defect. After the lobe resection, the microscopic examination (histopathology and immunohistochemistry) confirmed the diagnosis of diffuse idiopathic pulmonary neuroendocrine cells hyperplasia, multiple tumors, one carcinoid tumor, and obliterative bronchiolitis with peribronchiolar fibrosis obliterating small airways and interstitial chronic

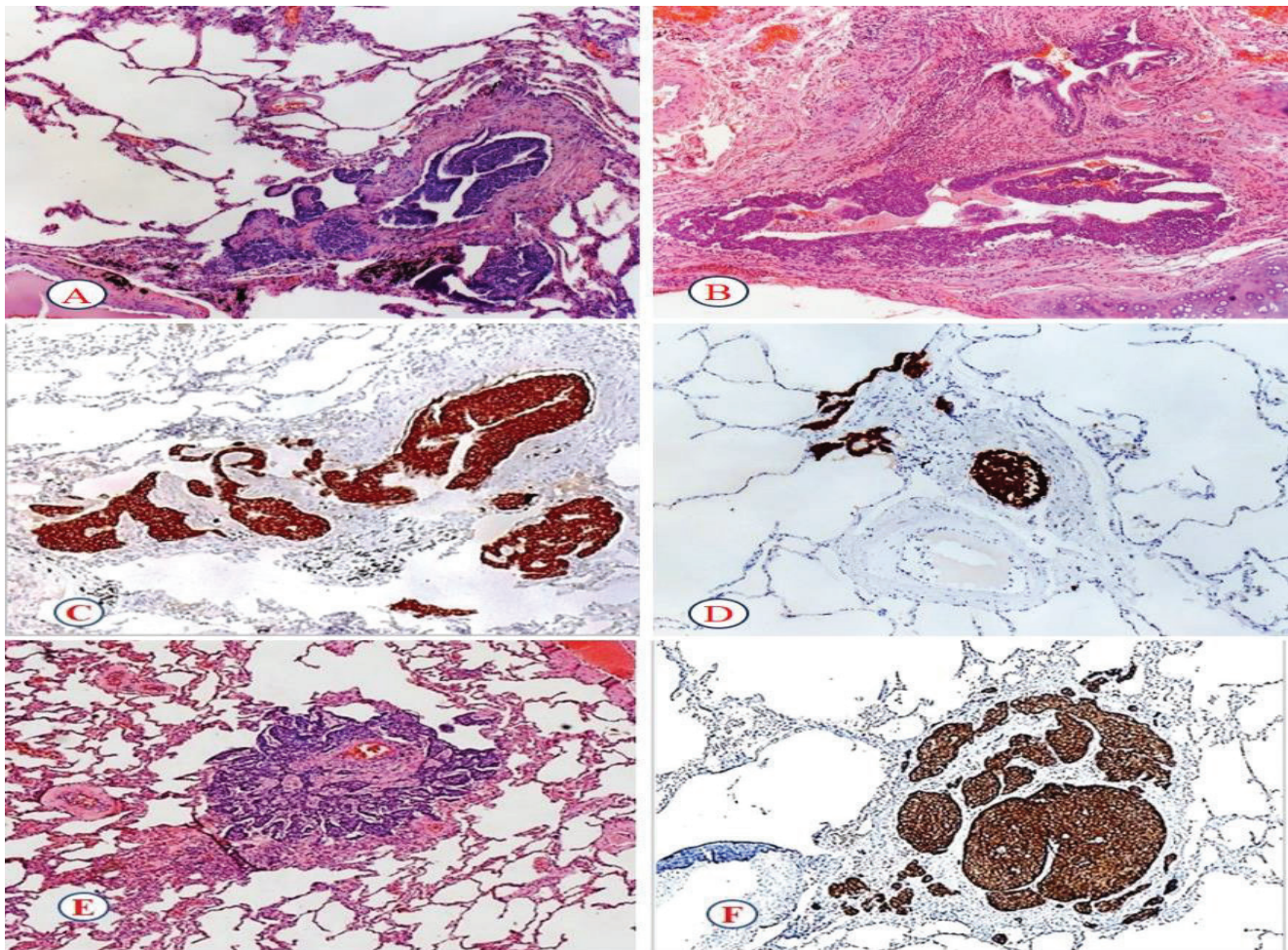


Figure 1A - (Eosin – Hematoxylin) Neuroendocrine cells involved bronchioles with numerous neuroepithelial bodies present within the mucosa, and two tumourlets.

Figure 1B - A nodular and circumferential arrangement of Neuro replaces the residual airway lumen-endocrine cells, associated peribronchiolar fibrosis, and interstitial chronic inflammation (eosin – hematoxylin).

Figure 1C - Immunohistochemical staining: Neuroendocrine pulmonary cells positive for Chromogranin A.

Figure 1D - Linear proliferation of NEP cells in the bronchioles, in the alveolar ducts and alveoli, positive for chromogranin A.

Figure 1E - Tumourlet neuroendocrine cells are embedded with a dense fibroblastic stroma (eosin –hematoxylin).

Figure 1F - Immunohistochemical staining: tumourlet neuroendocrine cells overexpression of CD 56.

inflammation. The patient was followed according to standard follow-up for patients after lobe resection. She is alive and well four years after surgery.

Pathologic Findings

In the histopathological examination (hematoxylin and eosin staining) of lung surgical specimens, we have revealed diffuse idiopathic hyperplasia of pulmonary neuroendocrine cells involved distal bronchi and bronchioles with numerous neuroepithelial bodies present within the mucosa. (Figure 1A).

The neuroendocrine cells are round or ovalin, monomorphic in size, with less cytoplasm, large nuclei deeply stained, or fine granular-like nucleoli that are unobvious. Neuroendocrine cells are scattered in individual

ones or at line-like or form small nests in the bronchiolar epithelium and even completely replace the bronchiolar epithelium, resulting in a narrow lumen but not penetrating basement membrane. This neuroendocrine cell hyperplasia is complicated with obliterative bronchiolitis. The residual airway lumen is replaced by a nodular and circumferential arrangement of neuroendocrine cells, expressed with peribronchiolar fibrosis obliterating small airways and associated with a small quantity of interstitial chronic inflammation. (Figure 1B) In some fields, we have seen the line of neuroendocrine cell hyperplasia in alveolar ducts and alveoli. No mitotic figures, no areas of necrosis, and no cell pleomorphism were detected in the proliferative neuroendocrine cells.

In the immunohistochemical staining, we have revealed the neuroendocrine cells involving distal bronchi

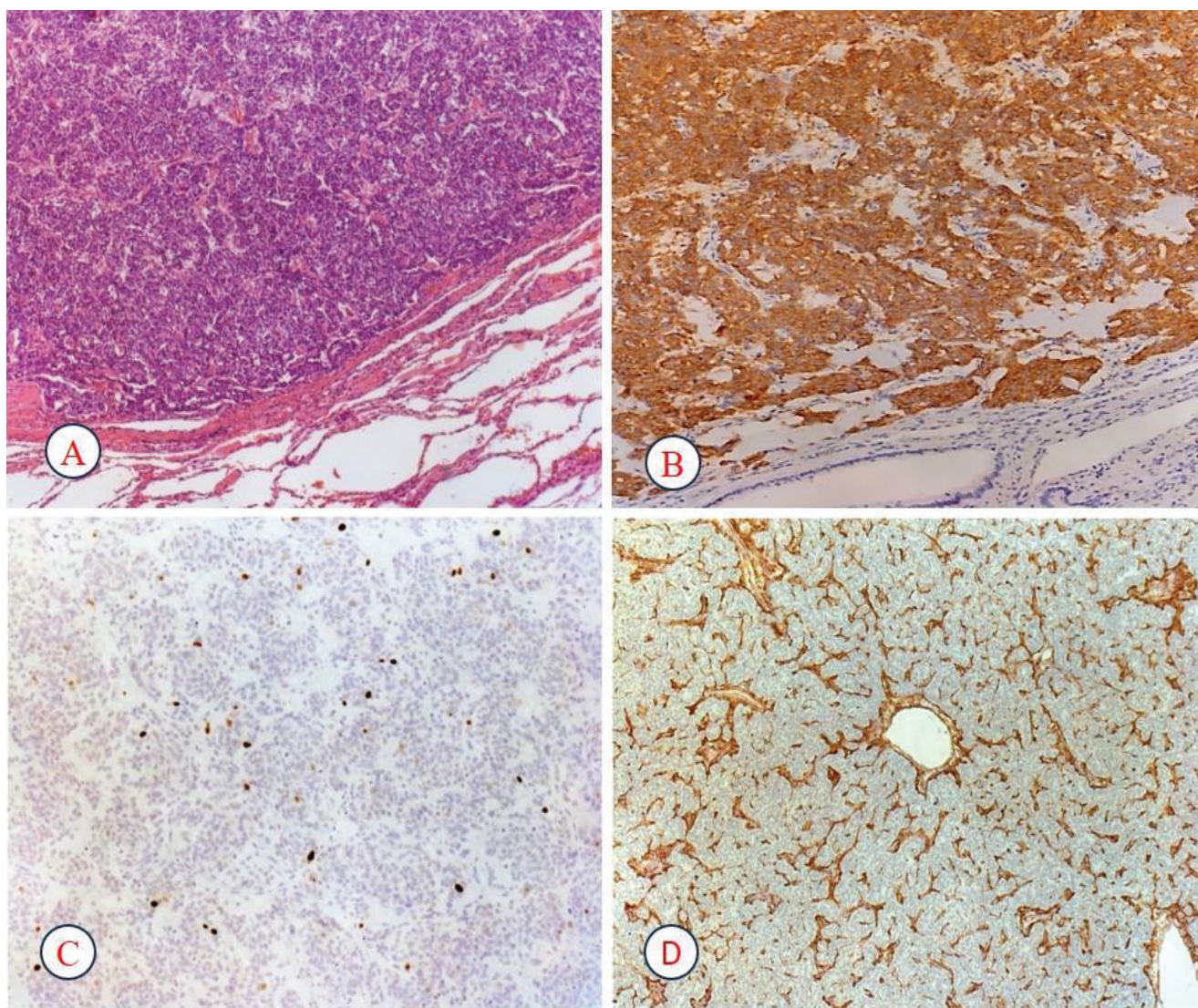


Figure 2 A. Typical carcinoid is circumscribed but not encapsulated (eosin – hematoxylin).

Figure 2 B. Immunohistochemical staining: diffuse expression of Synaptophysine.

Figure 2 C. Immunohistochemical staining Ki-67 (MIB-1) positivity < 5 %.

Figure 2 D. Microvascular component of typical carcinoid: Immunohistochemical staining positive with antibodies anti-actine.

and bronchioles (Figure 1C) and linear proliferation in the alveolar ducts and alveoli contain neurosecretory granules which are favorable for chromogranin A (Figure 1E), and for synaptophysin, and CD56 (Figure 1F), which is a marker of neuroendocrine cell differentiation.

At least nine tumors were found in the right middle pulmonary lobe's peribronchial region, varying size and morphologic features. The tumors are 2 – 4 mm-sized nodular hyperplasia of neuroendocrine cells embedded in dense fibroblastic connective tissue. (Figure 1E).

Movat's pentachrome staining demonstrated an abnormal deposition of disorganized collagen and elastic fibers in both the tumors and in the submucosa underlying areas of pulmonary neuroendocrine cells hyperplasia in small airways not obliterated by tumors.

In the immunohistochemical stains, the neuroendocrine cells of tumors present positivity for chromogranin A (Figure 1C), also positive for synaptophysin, Neuron Specific Enolase, CD56 (Figure 1F), and bombesin. The proliferative activity with Ki-67 < 1 % in the tumourlets.

We have detected a typical carcinoid with a 28 mm diameter in the parenchyma of the right middle pulmonary lobe. This carcinoid is circumscribed but not encapsulated and has nests of uniform cells covered in the elegant fibrovascular stroma. (Figure 2A)

The cytologic appearance of neuroendocrine cells of carcinoid is the same: monomorphic cell population with scarce eosinophilic cytoplasm, a monomorphic central nucleus with finely granular chromatin as "salt and pepper." Immunohistochemical staining: diffuse expression for chromogranine and Synaptophysine. (Figure 2 B) The neuroendocrine cells were arranged in delimiting nests, without necrosis and with 1 - 2 mitosis in 10 hpf, but without significant atypia. Immunohistochemical staining Ki-67 (MIB-1) positivity < 5 %. (Figure 2 C)

In the immunohistochemical staining, the neuroendocrine cells of typical carcinoid were positive for Neuron Specific Enolase, CD56. Also, we have seen EGF focal expression, VEGF modest expression, and Bax overexpression. The microvascular component contributes to the organoid structure, as confirmed by the activity distribution in the sinusoidal capillaries. Immunohistochemical staining with antibodies anti-acting was positive. (Figure 2 D)

Discussion

Pulmonary Neuroendocrine cells are part of the normal epithelium of bronchial and bronchiolar anatomy. They are thought to play an essential role in lung development, as they are frequently found

in the airways of fetal and neonatal lungs [1, 3]. Neuroendocrine cells of the lung decrease in number with age and are only present focally in adult airways, representing approximately 1 % of all epithelial cells in the adult lung. [2, 3]

Pulmonary neuroendocrine cell hyperplasia can be either primary or reactive. It is important to emphasize that the DIPNECH is defined as being idiopathic, so existing without any pre-existing chronic lung disease and in the absence of other lung diseases. However, reactive pulmonary neuroendocrine cell hyperplasia can occur as a result of a broad spectrum of chronic conditions that are expressed with hypoxia, including pulmonary interstitial fibrosis, asthma, cystic fibrosis, bronchopulmonary dysplasia, bronchiectasis, chronic obstructive pulmonary disease, neuroendocrine lung tumors, non neuroendocrine lung tumors, chronic exposure to high altitude, exposure to tobacco smoke, etc. [2, 3, 4, 5, 6, 7].

Aguayo et al. published the first series of six cases of DIPNECH in 1992 [1], describing a clinical condition with respiratory symptoms and specific radiological and histological characteristics.

The treatments of these patients included the lobe or the lung resection. [1, 2, 3, 5, 8, 9].

The WHO classification 2015 has considered the DIPNECH a precancerous lesion of lung neuroendocrine tumors. It is defined as within bronchial mucosal epithelium, where there is diffuse clustered, linear, or nodular neuroendocrine cell hyperplasia without basement membrane breakthrough [2, 3, 4, 6, 10, 11, 12].

The WHO's current definition of DIPNECH is exclusively histological [3, 6, 11, 12, 13, 14].

Since the initial description by Aguayo and Miller, more than 200 cases of DIPNECH have been described in case reports or small case series. However, no clear consensus has been established in the literature about the radiological or pathological diagnostic criteria or the management of this condition [6, 10, 11, 12].

DIPNECH has a predilection for nonsmoking middle-aged women and is associated with a predominantly obstructive ventilatory pattern on pulmonary function tests seen in obliterative bronchiolar fibrosis. [1, 3, 5, 6, 14]

The diagnosis of DIPNECH is often made several years after the onset of clinical symptoms, usually following the incidental discovery of a lung nodule on chest radiography or CT scan.

The condition progresses slowly, although there have been cases reported of a rapidly progressive and more aggressive clinical course, which has required lobectomy, pneumonectomy, and even lung transplantation. [6, 10, 11, 12, 14].

There are two different modes of DIPNECH clinical presentation. Onset is occult, there may be no clinical symptoms, or there is a long duration of dry cough and exertional dyspnea, expressed with an obstructive–restrictive lung function profile. These cases are commonly misdiagnosed as bronchial asthma or chronic bronchitis [5, 6, 9, 12, 13].

DIPNECH is often accompanied by chronic airway inflammation and diseases that can cause severe interstitial pulmonary fibrosis. [4, 6, 10, 11, 12, 15, 16].

Our case has clinical-morphological characteristics similar to those of the symptomatic form published. Under a light microscope, our case presents hyperplasia of pulmonary neuroendocrine cells confined within the bronchial mucosal epithelium and manifest as round or oval cells with relatively consistent size and shape showing hyperplasia, less cytoplasm, large nuclei deeply stained or chromatin fine granule-like, nucleoli are unobvious. Neuroendocrine cells are scattered in individual ones or form small nests at the base of the bronchiolar epithelium and even completely replace the bronchiolar epithelium, resulting in a narrow lumen but not penetrating the basement membrane.

This neuroendocrine cell hyperplasia is complicated with obliterative bronchiolitis. In some fields, we have seen the line of neuroendocrine cell hyperplasia in alveolar ducts and alveoli (Figure 1A and Figure 1D). The residual airway lumen is replaced by a nodular and circumferential arrangement of neuroendocrine cells, expressed with peribronchiolar fibrosis obliterating small airways and associated with interstitial fibrosis and chronic inflammation. (Figure 1B). No atypical mitotic figures, no areas of necrosis, and no cell pleomorphism were detected in the proliferative neuroendocrine cells. In other fields, the neuroendocrine cells penetrate the basement membrane to infiltrate the lung interstitium and show nodular growth and tumors.

In the immunohistochemical staining, we have revealed neuroendocrine cells involving distal bronchi and bronchioles (Figure 1C) and linear proliferation in the alveolar ducts and alveoli, which contain neurosecretory granules that are positive for chromogranin A (Figure 1D), synaptophysin, and CD56, which is a marker of neuroendocrine cell differentiation.

We have identified nine tumors in the peribronchial region. The tumors, 2 – 4 mm in size, present nodular hyperplasia of neuroendocrine cells embedded in dense fibroblastic connective tissue (Figure 1E). In the immunohistochemical stains, the neuroendocrine cells are positive for chromogranin A, synaptophysin, Neuron-Specific Enolase, CD56 (Figure 1F), and bombesin.

The nodular proliferation of neuroendocrine cells, formed lesions with a diameter < 5 mm, is considered to be tumors, but where the nodules are > 5 mm, they are classified as typical carcinoid tumors. [3, 5, 6, 7, 8, 9].

Also, we have diagnosed a typical carcinoid tumor (28 mm diameter) in the right middle pulmonary lobe. In the immunohistochemical study, the neuroendocrine cells of carcinoid are positive for chromogranin A, synaptophysin, Neuron Specific Enolase, and CD56, and also have EGF focal expression, VEGF modest expression, and Bax overexpression. Proliferative activity with Ki-67 < 3 %.

DIPNECH is regarded as a precursor lesion for tumors and carcinoid tumors. [3, 6, 10, 14, 15, 16]

The carcinoid is subdivided into typical carcinoid, which is a low-grade tumor, and atypical carcinoid, which is an intermediate-grade tumor. [3, 4, 6] In the series

by Davies [13], there were three cases associated with atypical carcinoid, one of whom had multiple endocrine neoplasia. This is the first case with a classic clinical picture of DIPNECH with metastatic carcinoid and multiple unrelated tumors. [6, 13]

The morphological diagnosis of our case is DIPNECH in the distal bronchial and bronchiolar wall, the linear proliferation confined to the alveolar duct and alveoli, presence of multiple tumors, one carcinoid tumor and obliterative bronchiolitis, interstitial fibrosis associated with chronic interstitial inflammation.

However, a recent paper by Marchevsky et al. [11] reported on 70 consecutive surgical lung biopsies showing multifocal neuroendocrine proliferations, which had neither histological features of obliterative bronchiolitis nor had they been diagnosed with DIPNECH before histological examination, indicating that the condition can be asymptomatic [13]. This study suggested that the presence of multifocal PNECH combined with more than three tumors is the minimum pathological criteria for the diagnosis of DIPNECH, limiting the condition to a pathological entity. [7]

A pathology-based approach by Marchevsky aimed at distinguishing DIPNECH from reactive neuroendocrine cell hyperplasia suggested that multifocal NECH associated with more than three tumors could represent a pathological criterion for diagnosing DIPNECH.

Wirtschafter et al. [12] evaluated 30 DIPNECH cases, systematically reviewing 169 cases reported in the English literature, and concluded that only 55 (28 %) had obliterative or constrictive bronchiolitis. This same conclusion has been drawn by Davies et al. [11, 13], who suggest that most patients did not have clinically meaningful airflow obstruction, even in cases with histological evidence of airway wall thickening, chronic inflammation, and constrictive obliterative bronchiolitis. [10, 11, 12, 13]

About symptomatic cases of DIPNECH, as in the case we have presented, the condition typically presents with a chronic cough, exertional dyspnea, and frequent wheezing, with a clinical presentation predominantly in non-smoking middle-aged women.

A transbronchial biopsy may be sufficient to diagnose DIPNECH in the appropriate clinical and radiological setting, although open surgical lung biopsy is considered optimum [10, 12, 13, 14, 16].

The histological features of DIPNECH include constrictive/obliterative bronchiolitis characterized by chronic inflammation, bronchial wall thickening, and fibrosis, which is believed to be the reason for progressive narrowing and complete obliteration of the bronchiolar lumen in severe cases [12, 13, 14, 16, 17, 18, 19, 20].

Chromogranin A, synaptophysin, and CD56 are the most commonly expressed immunohistochemical markers, while p53, Ki-67, and p16 may distinguish DIPNECH from reactive pulmonary neuroendocrine cell hyperplasia [3, 19, 21, 22].

The patient profile and presentation in this case report fit the typical DIPNECH profile, that of a middle-aged, non-smoking female presenting with exertional dyspnea, in association with the discovery of a lung nodule on chest CT [3, 8].

The biopsy findings are those of the histological criteria for DIPNECH diagnosis as defined by the WHO and cited by Marchevsky et al. [11, 16, 21, 22, 23]

The treatment for our case was surgery (lobectomy), but some authors use somatostatin analogs (SSA) in DIPNECH. [17, 18, 23]. Gorshtein et al., in their review of 11 DIPNECH patients, suggested the affirmative role of SSA in the symptom management of DIPNECH. In the American single-center experience, most of their patients responded to treatment with SSA and significantly improved their presenting symptoms. [18]

Conclusions

DIPNECH remains a rare pulmonary condition and is considered a preneoplastic lesion in the spectrum of pulmonary tumors. According to the WHO classification, the definition of DIPNECH is purely histological. While most patients experience a relatively uneventful clinical course, this condition may be associated with tumors, carcinoid tumors, and airway obstruction (Aguayo-Miller disease). Awareness of the condition, imaging, and histopathology are required to make the definitive diagnosis, and close follow-up is essential in the more aggressive cases of DIPNECH.

DIPNECH may be an under-diagnosed pulmonary condition because it is rarely associated with symptoms. This case report has highlighted this rare but potentially progressive condition and the need for evidence-based management guidelines for DIPNECH.

COI Statement:

This paper has not been submitted in parallel, presented fully or partially at a meeting, podium, or congress, published, or submitted for consideration beforehand.

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