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Constrictive Bronchiolitis in Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia

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Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is an under-recognized cause of obstructive lung disease in women. Constrictive bronchiolitis associated with DIPNECH manifests limited response to currently employed therapies.

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Abbreviation list

5-HIAA: 5-Hydroxyinoleacetic acid

AAH: Atypical adenomatous hyperplasia

ACOS: Asthma COPD overlap syndrome

B₂: Beta-2

CB: Constrictive bronchiolitis

COPD: Chronic obstructive pulmonary disease

DIPNECH: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

DLCO: Diffusing capacity for carbon monoxide

FEV₁: Forced expiratory volume in 1 second

FVC: Forced vital capacity

Ga: Gallium

ICS: Inhaled corticosteroid

IQR: Interquartile range

IRB: Institutional review board

LLN: Lower limit of normal

MIP: Maximum intensity projection
mTOR: Mammalian target of rapamycin

NET: Neuroendocrine tumor

NSIP: Nonspecific interstitial pneumonia

PD-L1: Programmed death-ligand 1

PFT: Pulmonary function testing

PNECs: Pulmonary neuroendocrine cells

RV: Residual volume

SSA: Somatostatin analog

SSTR: Somatostatin receptor

TLC: Total lung capacity

UACS: Upper airway cough syndrome

WHO: World Health Organization
Abstract: (word count = 247)

Background: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is characterized by multifocal proliferation of neuroendocrine cells and belongs in the spectrum of pulmonary neuroendocrine tumors. Some patients with DIPNECH develop airflow obstruction but the relationship between the two entities remains unclear.

Methods: We performed a computer-assisted search of the Mayo Clinic’s electronic medical records for biopsy-proven cases of DIPNECH. We extracted clinical, pulmonary function, imaging and histopathologic data along with treatments and outcomes.

Results: Among 44 patients with DIPNECH 91% were female and median age was 65 years (IQR: 56–69 years); 73% were never smokers. 38 patients (86%) had respiratory symptoms including cough (68%) and dyspnea (30%); 45% were previously diagnosed to have asthma or COPD. Pulmonary function testing showed an obstructive pattern in 52%, restrictive pattern 11%, mixed pattern 9%, nonspecific pattern 23%, and normal 5%. On chest CT scan, 95% manifested diffuse nodules and 77% manifested mosaic attenuation. For management, 25% of patients were observed without pharmacologic therapy, 55% received an inhaled bronchodilator, 41% received an inhaled corticosteroid, 32% received octreotide; systemic steroids, azithromycin, or combination chemotherapy was employed in 4 patients (9%). Of 24 patients with follow-up PFT available, 50% remained stable, 33% worsened and 17% improved over a median interval of 21.3 months (IQR: 9.7–46.9 months).

Conclusion: DIPNECH occurs mostly in women and manifests diffuse pulmonary nodules and mosaic attenuation on imaging. It is commonly associated with airflow obstruction due to constrictive bronchiolitis, which manifests limited response to current pharmacologic therapy.
Introduction:

Pulmonary neuroendocrine cells (PNECs) are dispersed throughout the lungs and constitute <1% of the cells in adult human lungs.[1] The majority of PNECs are located in the bronchi, while others are situated in terminal bronchioles and alveolar ducts.[2] The function of PNECs is not entirely clear but studies have suggested that they play a role in detecting hypoxemia,[3] immunomodulation,[4] and regeneration of lung epithelial cells.[5] Hyperplasia of PNECs can occur secondary to various forms of injuries (e.g. chronic hypoxia associated with living at high altitudes and chronic obstructive pulmonary disease [COPD]) or can be idiopathic.[6, 7]

In 1992, Aguayo et al described six patients exhibiting multifocal hyperplasia of PNECs with associated peribronchiolar fibrosis on histological examination combined with clinical and radiological features suggestive of small airway disease.[8] This disease entity was referred to as “idiopathic diffuse hyperplasia of pulmonary neuroendocrine cells and airways disease”. In the 2001 World Health Organization (WHO) classification of lung tumors, this entity was termed “diffuse idiopathic pulmonary neuroendocrine cell hyperplasia” (DIPNECH).[9]

Additional studies followed describing the association of DIPNECH with obstructive small airways disease (constrictive bronchiolitis [CB]) through mechanisms that will be discussed later in this paper.[8, 10, 11] Thus, patients with DIPNECH may manifest respiratory symptoms, an obstructive pattern on pulmonary function testing (PFT), and mosaic pattern (i.e. “patchwork regions of differing attenuation”)[12] with patchy air trapping on chest CT.[10, 13] The term “DIPNECH syndrome” has been proposed for the combination of these features occurring with histological DIPNECH.[14]
Because of the rarity of this recently described entity, we aimed to further characterize the relationship between small airways disease (constrictive bronchiolitis) and DIPNECH including clinical, physiologic, and radiologic correlates.

Methods:

We conducted a search of Mayo Clinic electronic medical records for cases of biopsy-proven DIPNECH seen at the three Mayo Clinic campuses in Minnesota, Florida and Arizona. We manually extracted demographic, clinical, laboratory, pulmonary function, and imaging data from electronic medical records including review of radiologic studies. The pathological diagnosis of DIPNECH was confirmed by the finding on lung biopsy of multifocal proliferation of PNECs involving the bronchial or bronchiolar epithelium (Figure 1).[15]

PFT results were classified as normal, obstructive, restrictive, mixed or nonspecific pattern. Obstructive pattern was defined as FEV1/FVC<LLN.[16] Restrictive pattern was defined by TLC<LLN.[16] Mixed pattern (obstructive and restrictive) was diagnosed when FEV1/FVC<LLN and TLC<LLN.[16] Nonspecific pattern was defined as FEV1 and/or FVC<LLN, with normal FEV1/FVC ratio and a TLC value that was >LLN or not obtained.[17] Positive bronchodilator response was defined as an increase of >12% and >200 ml in FEV1 and/or FVC following the inhalation of a β2-agonist.[16] Air trapping was defined as residual volume (RV) >120% predicted. Per the American Thoracic Society/European Respiratory Society guidelines, the severity of obstructive, restrictive and mixed PFT patterns was graded based on the FEV1, expressed as a percentage of the predicted value: 1) mild: FEV1 ≥70%, 2) moderate: FEV1 60-69%, 3) moderately severe: FEV1 50%-59%, 4) severe: FEV1 35-49% and
5) very severe: FEV1 <35%.[16][18] Reduced diffusing capacity of carbon monoxide (DLCO) was defined as DLCO <LLN. A significant change on follow-up PFT was defined as a change of ≥15% for FEV1 and/or FVC, and ≥10% for DLCO.[16]

Counts and percentages were used for descriptive statistics. Median and interquartile range (IQR) 25-75 were used to describe central tendency measures. Chi-square test was used for analyzing correlations between categorical variables. A p<0.05 was used for determination of statistical significance.

This study was approved by Mayo Clinic’s Institutional Review Board (IRB) (IRB# 17-000885).

**Results:**

We identified 44 patients with biopsy-proven DIPNECH; 91% were women and 73% were never smokers (Table 1). Most patients (89%) were Caucasian. Median age at diagnosis was 65 years (IQR 56–69). Past medical history included cancer in 6 patients (14%); skin cancer in 3, breast cancer in 1, lung adenocarcinoma in 1, and a combination of papillary thyroid cancer, retroperitoneal sarcoma and melanoma in 1.

Most patients (86%) presented for evaluation of respiratory symptoms, most commonly cough (Table 1). Symptoms were present for a median duration of 120 months (IQR: 24-240) prior to diagnosis. Six patients (14%) had no respiratory symptoms but presented for evaluation of pulmonary nodules incidentally identified on a chest CT scan performed for another indication. On lung auscultation, wheezes or crackles were described in 14%, distant breath sounds or prolonged expiratory phase in 11%, but normal breath sounds in the remaining 75%. 5-
hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin, was measured in 6 patients, and was elevated in one.

Chest CT scans were available for all patients (Table 2). Nearly all patients (95%) manifested numerous small bilateral pulmonary nodules (Figure 2A), while 2 patients did not; 1 patient manifested subtle regions of ground-glass attenuation, and 1 patient manifested an enlarging single nodule (1.7 cm in size) that was found to represent a carcinoid tumor with the resected specimen revealing a background of DIPNECH and CB. Mosaic attenuation with air-trapping (Figure 2B) was present in 77% of patients, all of whom also manifested diffuse pulmonary nodules.

One or more PFT results were available for all patients and demonstrated obstructive pattern in 23 patients (52%), restrictive pattern in 5 (11%), mixed pattern in 4 (9%), nonspecific pattern in 10 (23%) and normal in 2 (5%). The PFT data are illustrated in Table 3 and Supplementary Table 1. Since the focus of this study is the characterization of the small airway disease associated with DIPNECH, we divided patients into two groups based on the presence (isolated obstructive or mixed obstructive-restrictive pattern) or absence of obstructive ventilatory defect on PFT. Approximately one-half (52%) of 27 patients with an obstructive component had severe to very severe impairment. DLCO value was available for all patients, and was reduced in 48% of patients.

Patients with obstruction manifested mosaic attenuation on chest CT scan with a higher frequency than patients without obstruction (82% vs. 65%, respectively, p=0.21), but manifested constrictive bronchiolitis on biopsy with a comparable frequency to patients without obstruction (44% vs. 53%, respectively, p=0.58) (Table 4 and Supplementary table 2).
Diagnostic lung specimens were obtained surgically in 95% of patients, while 5% were obtained through transbronchial biopsy. Histopathologic findings are summarized in Table 4. Aside from DIPNECH, carcinoid tumorlets (focal collection of PNECs < 5 mm in size) were identified in 34 patients (77%) and carcinoid tumors in 16 (36%).

Among the 16 patients who underwent carcinoid tumor resection, 5 patients (31%) reported symptomatic improvement following surgery, 9 (56%) reported no change and 2 (13%) had no respiratory symptoms before or after surgery. 10 patients had a follow-up PFT; 5 (50%) declined, 2 (20%) improved and 3 (30%) remained stable.

Monitoring (clinical, radiological and with serial PFTs) without pharmacologic therapy was recommended for 11 patients (25%), while pharmacotherapy was recommended for 33 (75%) (Supplementary table 3). An inhaled bronchodilator (B₂-agonist and/or an antimuscarinic agent) was prescribed in 24 patients (55%); 18 (75%) of whom manifested an obstructive component on PFT. Of all patients prescribed a bronchodilator, only four (17%) reported symptomatic improvement, 2 of whom manifested a positive bronchodilator response on PFT. It is worth noting that a positive bronchodilator response on PFT was not consistently associated with symptomatic response to inhaled B₂-agonists; 7 patients with a positive bronchodilator response received a B₂-agonist without improvement.

An inhaled corticosteroid (ICS) was prescribed in 18 patients (41%); 4 (22%) experienced subjective improvement, and 3 (25%) of 12 patients with available follow-up PFT data demonstrated improvement on PFT. One patient received a systemic steroid (prednisone) and reported stable symptoms.
Octreotide, a somatostatin analog (SSA), was prescribed in 14 patients (32%); 4 (29%) experienced symptomatic improvement, but only 1 (13%) of 8 patients with available follow-up PFT data demonstrated an improvement on PFT. It is worth noting that 57% of the patients prescribed a SSA did not have a carcinoid tumor. Everolimus, in combination with cabozatinib and a programmed death-ligand 1 inhibitor was prescribed in one patient with metastatic pulmonary carcinoid tumor. This patient reported stable respiratory symptoms but manifested radiological progression of extra-pulmonary metastases despite treatment.

One patient in our study underwent bilateral lung transplantation for progressive, multifactorial respiratory failure. This patient had surfactant protein C deficiency, with chronic bronchiolitis, bronchiolectasis, follicular bronchiolitis and interstitial fibrosis diagnosed by lung biopsy at 5 years of age. He underwent bilateral lung transplantation at the age of 21, and DIPNECH was diagnosed upon examination of the explanted lungs. The most recent PFT prior to transplantation had revealed a very severe mixed abnormality (FEV1 14% predicted) and air trapping (RV 272%).

In the overall cohort, 35 patients (80%) had at least one follow-up appointment at our institution, with a median follow-up interval of 30 months (IQR: 14–52). Symptoms remained stable in 77% (27/35), worsened in 3% (1/35) and improved in 20% (7/35) (Table 5). Among the 24 patients (55%) with available follow-up PFT data, 50% remained stable, 33% worsened and 17% improved over a median follow-up interval of 21.3 months (IQR 9.7–46.9) (Table 6).

**Discussion:**

DIPNECH is a rare disorder first described in 1992.[8] According to the WHO’s definition, DIPNECH diagnosis is solely made on pathology, irrespective of clinical, physiological or
radiological parameters.[15] To the best of our knowledge, this study includes the largest single cohort of patients with DIPNECH evaluated for airway disease, i.e., “DIPNECH syndrome”. Among our patients, 61% manifested airflow obstruction on PFTs and only a minority manifested symptomatic or objective response to bronchodilators, SSAs or other pharmacotherapies.

Similar to others, our cohort was predominantly comprised of middle-aged and older women, with a female:male ratio of 10:1.[10, 11, 13, 19] The most common presenting symptoms were chronic cough and dyspnea, with a median symptomatic duration of 10 years prior to DIPNECH diagnosis. 45% of our cohort, 50% and 63% of two other cohorts had been given a diagnosis of another obstructive lung disease prior to DIPNECH diagnosis.[10, 19] Given its rarity, DIPNECH is under-recognized as a potential cause for obstructive lung disease, particularly in women, and the diagnosis is often delayed.

On PFT, our cohort demonstrated obstruction with a frequency similar to that reported by Nassar et al (52% vs. 54%, respectively).[13] Conversely, the cohort studied by Carr et al manifested obstruction markedly more than ours (87% vs. 52%, respectively).[10] This notable difference might be related to: 1) all 30 patients reported by Carr et al manifested respiratory symptoms compared to 86% in our cohort, and/or 2) definition of obstruction used by Carr et al was not clearly stated and may have differed from the definition we used.[10] Defining obstruction as FEV₁/FVC<0.7 rather than the definition we used can over-diagnose obstruction in older individuals.[20]

The presumed etiology of airflow obstruction in DIPNECH is narrowing of the bronchiolar lumen (i.e., constrictive bronchiolitis) owing to intraluminal growth of PNECs, and/or mucosal
and peribronchiolar fibrosis. It is surprising, however, that only 53% of our patients with airflow obstruction demonstrated CB on histological examination. Similarly, in a study of 30 patients with DIPNECH, 86% of whom manifested airflow obstruction, CB was observed in only 8 (44%) of the 18 examined biopsies. This finding can be explained by the patchy nature of CB, which may have limited its identification upon histological examination. However, the comparable frequency of CB among patients with and without airflow obstruction in our study (53% vs. 44%, respectively; p=0.58), and the bronchodilator responsiveness, an unusual finding in CB, in some patients suggest that pathophysiologic mechanisms other than CB contribute to airflow obstruction in DIPNECH.

Among patients who underwent bronchodilator responsiveness testing, 23% in this study, 33% and 10% in two other studies manifested a positive bronchodilator response. This finding suggests that bronchospasm contributes to airflow obstruction in some patients with DIPNECH. Bronchospasm may simply be due to a comorbid reactive airway disease like asthma, or, theoretically, may be related to increased amounts of bioactive substances (e.g., histamine and 5-hydroxytryptamine) secreted by the hyperplastic PNECs and carcinoid cells, and exerting their effect locally, on adjacent airways, rather than systemically. 33 patients in this study and two others had 5-HIAA measured; only one patient had 5-HIAA elevation.

Although incompletely understood, tissue fibrosis (e.g., in mesenteric tissue and cardiac valves) is a well-known complication of neuroendocrine tumors (NETs). Serotonin and several growth factors have been implicated in its pathogenesis. The most widely accepted pathophysiologic mechanism underlying the development of peribronchiolar fibrosis and constrictive bronchiolitis in DIPNECH is that bioactive substances (e.g., bombesin) secreted in larger-than-normal amount by the hyperplastic PNECs exert pro-fibrotic and pro-inflammatory effects on the adjacent
This hypothesis triggered some physicians to propose two plausible therapeutic approaches to DIPNECH: 1) using SSAs to decrease the secretion of bioactive substances from the hyperplastic PNECs,[10, 28] and 2) using steroids (inhaled and/or systemic) to control inflammation and prevent further parenchymal and airway damage.[13]

Nassar et al summarized 25 cases of DIPNECH reported in the literature. Seven patients received systemic steroids; 4 improved (“clinically”), 2 remained stable and 1 worsened. One patient received ICS without systemic steroids and experienced respiratory decline.[13] 46% and 67% of the patients studied by Carr et al received systemic and inhaled steroids, respectively. Although it is unclear how patients responded specifically to steroids, it is worth noting that 33% of their entire cohort continued to have respiratory decline.[10] In our study, one patient received systemic steroids and remained stable. 18 patients received ICS; 25% experienced subjective improvement, and 17% manifested improvement on PFT.

The WHO considers DIPNECH as the precursor of other pulmonary NETs.[15] Studies have shown that pulmonary carcinoid tumors express somatostatin receptors (SSTR) in a large percentage of patients,[29] and the more differentiated a tumor is, the higher the likelihood of SSTR expression becomes.[30] SSTR expression in tumors can be detected noninvasively via different imaging modalities such as Octreoscan and the more sensitive, $^{68}$Gallium (Ga) DOTATATE scan.[31, 32] Gorshtein et al reported that Octreoscan was positive in 10/11 patients with DIPNECH, but the uptake was exclusively found in the dominant lesion.[28] Al-Toubah et al reported that some level of uptake on SSTR imaging (Octreoscan and $^{68}$Ga-DOTATATE) was noted in 12/19 patients with DIPNECH. However, it is unclear whether the uptake was exclusively in the dominant lesion as reported by Gorstein et al, or more diffuse.[19, 28] The small size of the lesions found in DIPNECH negatively impacts the sensitivity of SSTR
imaging modalities; hence, a negative study does not rule out the possibility of SSTR expression by those lesions.[33, 34] Therefore, using SSAs in the treatment of DIPNECH, irrespective of the findings on SSTR imaging, is plausible.

SSA use has been reported in patients with DIPNECH.[10, 19, 28, 35] Al-Toubah et al. studied a cohort of 42 patients with DIPNECH, all of whom received a SSA; 11 patients (26%) received a SSA alone, and 31 (74%) received a SSA in combination with other therapies, including inhalers, steroids, and benzonatate. Thirty-two patients (76%) reported symptomatic improvement, and 14/15 patients with available pre and post-treatment PFT data had an increase in FEV1, the magnitude of which was not specified. In another study, 6 patients with progressive DIPNECH received a SSA; 4 demonstrated improvement in FEV1, and 2 demonstrated stability.[28] In another study, 11 patients with DIPNECH received a SSA; 3 patients reported improvement of their cough, and all nine follow-up PFTs demonstrated stability.[10] A small case series reported drastic improvement of cough in all 4 patients treated with SSA.[35] In a small case series, one patient with DIPNECH received a SSA, with temporary improvement in her cough.[36] In our study, 14 patients received a SSA; 4 (29%) experienced improvement in their cough. Among the 8 patients with follow-up PFTs, 1 (12.5%) improved, 3 (37.5%) worsened and 4 (50%) remained stable.

Some NETs demonstrate aberrant activation of the mechanistic target of rapamycin (mTOR) pathway, which led to the successful use of everolimus, an mTOR inhibitor, in improving outcomes in patients with NETs of different origins.[37] This activation of mTOR pathway was also demonstrated in DIPNECH.[38] This led to the use of sirolimus, another mTOR inhibitor, in the management of 3 patients with progressive DIPNECH and presumed carcinoid tumors. Two patients had radiological improvement, 1 patient had radiological progression, and all 3 patients
demonstrated improvement in FEV1 over time.[39] In our study, one patient received everolimus for metastatic pulmonary carcinoid. This patient reported stable symptoms, but manifested radiological progression on follow-up.

In a study of 55 patients with resected carcinoid tumors, 3 patients (5%) were found to have DIPNECH on histopathology. Those 3 patients did not behave differently than the 52 patients without DIPNECH during a 37-month follow-up. Although the sample size is too small and no statistical testing was feasible, the authors concluded that co-existing DIPNECH is probably of no clinical consequence following the resection of the carcinoid tumor.[40] In Al-Touba et al, 37/42 patients (88%) underwent surgical resection of at least one tumor. However, the outcomes for the group that underwent resection were not reported separately.[19] In another study, 9/11 patients with DIPNECH and carcinoid tumor underwent surgical resection of the dominant lesion. In this study, 5/11 patients remained stable, while 6 progressed requiring treatment with SSA.[28] In our study, 5/12 patients (42%) with follow-up data, reported improved respiratory symptoms following resection of the dominant carcinoid lesion.

Similar to others, our study demonstrates that DIPNECH remains stable or progresses very slowly in most patients, but can result in severe airflow limitation and respiratory impairment.[8, 10, 13, 26, 28, 35, 36]

Our study has limitations inherent to the retrospective single-center design and the rarity of the disease under study. The number of subjects in this study is modest and the features described within may reflect the more severe end of the disease spectrum due to referral bias. Some data were missing, and several patients were lost to follow-up at our institution.

**Conclusion:**
DIPNECH syndrome is likely an under-recognized form of obstructive lung disease in middle-aged and older women, often misdiagnosed as asthma or COPD. DIPNECH typically manifests diffuse pulmonary nodules on chest CT scan, often associated with mosaic attenuation. DIPNECH syndrome can progress slowly and sometimes lead to respiratory failure. Response to currently employed therapies seems limited and optimal management strategies need to be identified, ideally in the context of well-designed prospective trials.
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Table 1. Demographic and clinical characteristics (n = 44)

| Characteristic                  | Value                  |
|---------------------------------|------------------------|
| Female sex, n (%)               | 40 (91)                |
| Age at diagnosis, years        |                        |
| Median (IQR)                    | 65 (56-69)             |
| Smoking status, n (%)           |                        |
| Never                           | 31 (73)                |
| Previous                        | 11 (25)                |
| Current                         | 1 (2)                  |
| Presenting symptoms, n (%)     |                        |
| Cough                           | 30 (68)                |
| Dyspnea                         | 13 (30)                |
| Wheezing                        | 5 (11)                 |
| Dysphonia                       | 1 (2)                  |
| None                            | 6 (14)                 |
| Lung biopsy method, n (%)       |                        |
| Surgical                        | 42 (95)                |
| Bronchoscopic                   | 2 (5)                  |

Abbreviations. IQR: interquartile range.
Table 2. Chest CT scan features at the time of DIPNECH diagnosis (n = 44).

| Chest CT scan features, n (%)                      |        |
|---------------------------------------------------|--------|
| Bilateral nodules                                 | 42 (95)|
| Mosaic attenuation                                | 34 (77)|
| Lymphadenopathy                                  | 4 (9)  |
| Interstitial fibrosis                             | 4 (9)  |
| Emphysema                                         | 2 (5)  |
| Pleural effusion                                  | 1 (2)  |

| Nodule size on follow-up chest CT when performed (36 patients), n (%) |
|---------------------------------------------------------------------|
| Follow-up interval in months, median (IQR)                          | 31.5 (12.5-52.4) |
| Enlarged                                                            | 24 (67) |
| Stable                                                              | 12 (33) |

| Size (mm) of largest nodule/mass on chest CT based on presence/absence of carcinoid tumor on biopsy |
|-------------------------------------------------------------------------------------------------|
| Carcinoid tumor found on biopsy, median (IQR)                                                  | 17 (11-22) |
| No carcinoid tumor on biopsy, median (IQR)                                                      | 5 (5-7) |

**Abbreviations.** CT: Computed tomography, IQR: interquartile range.
Table 3. Pulmonary function characteristics of patients with or without an obstructive component

|                                | Obstruction | No obstruction | Overall |
|--------------------------------|-------------|----------------|---------|
| Number of patients (%)         | 27 (61)     | 17 (39)        | 44      |
| Severity of disease graded by FEV1 (n = 44), n (%) |             |                |         |
| ≥70% predicted                 | 3 (11)      | 5 (29)         | 8 (18)  |
| 60-69% predicted               | 2 (7)       | 5 (29)         | 7 (16)  |
| 50-59% predicted               | 8 (30)      | 3 (18)         | 11 (25) |
| 35-49% predicted               | 7 (26)      | 4 (24)         | 11 (25) |
| <35% predicted                 | 7 (26)      | 0 (0)          | 7 (16)  |
| Bronchodilator responsiveness when tested (n = 37), n (%) |             |                |         |
| Present                        | 12 (52)     | 1 (7)          | 13 (35) |
| Absent                         | 11 (48)     | 13 (93)        | 24 (65) |
| Air trapping among patients with RV measurement (n = 43), n (%) |             |                |         |
| Present                        | 22 (85)     | 2 (12)         | 24 (56) |
| Absent                         | 4 (15)      | 15 (88)        | 19 (44) |
| Diffusing capacity of carbon monoxide (n=44) |             |                |         |
| Reduced DLCO, n (%)            | 13 (48)     | 8 (47)         | 21 (48) |
| DLCO %predicted, median (IQR)  | 77 (66-86)  | 77 (65-99)     | 76 (65-92) |

**Abbreviations.** PFT: pulmonary function test, FEV1: Forced expiratory volume in 1 second, RV: residual volume. DLCO: Diffusing capacity of carbon monoxide.
Table 4. Chest CT scan and pathology findings for patients with and without obstruction on PFT.

|                                | Obstruction | No obstruction | Overall |
|--------------------------------|-------------|----------------|---------|
| **Number of patients (%)**     |             |                |         |
| **Chest CT scan findings, n (%)** |             |                |         |
| Diffuse nodules                | 26 (96)     | 16 (94)        | 42 (95) |
| Mosaic attenuation             | 22 (82)     | 11 (65)        | 33 (75) |
| Emphysema                      | 2 (7)       | 0 (0)          | 2 (5)   |
| Interstitial fibrosis          | 3 (11)      | 1 (6)          | 4 (9)   |
| **Biopsy findings (42 patients), n (%)** |             |                |         |
| Carcinoid tumorlets            | 22 (81)     | 12 (75)        | 34 (77%)|
| Constrictive bronchiolitis     | 12 (44)     | 9 (53)         | 21 (50) |
| Carcinoid tumor                | 7 (26)      | 9 (53)         | 16 (36) |
| Granuloma                      | 2 (7)       | 5 (29)         | 7 (16)  |
| Emphysema                      | 5 (19)      | 1 (6)          | 6 (14)  |
| Organizing pneumonia           | 0 (0)       | 3 (18)         | 3 (7)   |
| NSIP                           | 1 (4)       | 0 (0)          | 1 (2)   |
| Respiratory bronchiolitis | 1 (4) | 0 (0) | 1 (2) |

**Abbreviations.** CT: computed tomography, n: number of patients, NSIP: Nonspecific interstitial pneumonitis.
Table 5. Characteristics of patients with clinical follow-up data.

| Symptom change                      | Improved | Worsened | Stable |
|-------------------------------------|----------|----------|--------|
| n (%)                               | 7 (20)   | 1 (3)    | 27 (77)|
| History of an obstructive lung disease; n (%) | 4 (57)   | 1 (100)  | 11 (41)|
| PFT pattern; n (%)                  |          |          |        |
| Normal                              | 0 (0)    | 0 (0)    | 2 (7)  |
| Obstructive                         | 4 (57)   | 1 (100)  | 15 (56)|
| Restrictive                         | 1 (14)   | 0 (0)    | 3 (11)|
| Mixed                               | 0 (0)    | 0 (0)    | 1 (4)|
| Nonspecific                         | 2 (29)   | 0 (0)    | 6 (22)|
| Positive bronchodilator response; n (%) | 1 (14)   | 1 (100)  | 7 (26)|
| Constrictive bronchiolitis on biopsy; n (%) | 3 (43)   | 1 (100)  | 11 (41)|
| Treatment given; n (%)              |          |          |        |
| Observation                         | 1 (14)   | 0 (0)    | 7 (26)|
| Inhaled B₂ agonist                  | 5 (71)   | 1 (100)  | 9 (33)|
| Inhaled antimuscarinic              | 2 (29)   | 0 (0)    | 6 (22)|
| ICS                                 | 4 (57)   | 0 (0)    | 10 (37)|
| Octreotide                          | 4 (57)   | 0 (0)    | 10 (37)|

Abbreviations: PFT: Pulmonary function test. ICS: Inhaled corticosteroid.
Table 6. Characteristics of patients with follow-up PFT data.

| PFT change                      | Improved | Declined | Stable |
|---------------------------------|----------|----------|--------|
| n (%),                         |          |          |        |
| **PFT change**                  |          |          |        |
| **History of an obstructive lung disease; n (%)** |          |          |        |
| Normal                          | 0 (0)    | 1 (13)   | 1 (8)  |
| Obstructive                     | 2 (50)   | 5 (63)   | 7 (58) |
| Restrictive                     | 1 (25)   | 1 (13)   | 2 (17) |
| Mixed                           | 0 (0)    | 1 (13)   | 1 (8)  |
| Nonspecific                     | 1 (25)   | 0 (0)    | 1 (8)  |
| **Carcinoid tumor on biopsy; n (%)** |          |          |        |
| **Constrictive bronchiolitis on biopsy; n (%)** |          |          |        |
| **Treatment given; n (%)**      |          |          |        |
| Observation                     | 1 (25)   | 1 (13)   | 2 (17) |
| Inhaled B_2 agonist             | 3 (75)   | 4 (50)   | 7 (58) |
| Inhaled antimuscarinic          | 2 (50)   | 4 (50)   | 6 (50) |
| ICS                             | 3 (75)   | 3 (38)   | 6 (50) |
| Octreotide                      | 1 (25)   | 3 (38)   | 4 (33) |
| **Mean FEV1 % predicted (initial → follow-up)** | 46 → 59  | 55 → 50  | 52 → 52 |

**Abbreviations.** PFT: Pulmonary function test. ICS: Inhaled corticosteroid. FEV1: Forced expiratory volume in 1 second
Figure legends:

**Figure 1.** A. Normal appearing alveolar parenchyma with multiple small airways involved by neuroendocrine cell hyperplasia (hematoxylin and eosin, 40x original magnification); **B.** Proliferating neuroendocrine cells highlighted by chromogranin immunostaining (anti-chromogranin antibody, 40x); **C.** Partial or complete obliteration of the bronchiolar lumens by proliferating neuroendocrine cells and mucosal fibrosis (Verhoeff-Van Gieson, 40x); **D.** Carcinoid tumor arising in a background of diffuse neuroendocrine cell hyperplasia (hematoxylin and eosin, 20x)

**Figure 2.** Chest CT images of a 60-year-old female patient with DIPNECH. Image **A** is a maximum intensity projection (MIP) image demonstrating multiple bilateral micronodules. Image **B** demonstrates mosaic attenuation.
Supplementary table 1. PFT characteristics for each PFT pattern

|                           | Normal | Obstructive | Restrictive | Mixed | Nonspecific | All groups |
|---------------------------|--------|-------------|-------------|-------|-------------|------------|
| Number of patients        | 2      | 23          | 5           | 4     | 10          | 44         |
| Severity based on FEV1 % predicted |        |             |             |       |             |            |
| FEV1 ≥70%                 | 2      | 3           | 0           | 0     | 3           | 18% (8/44) |
| FEV1 60-69%               | 0      | 2           | 0           | 0     | 5           | 16% (7/44) |
| FEV1 50-59%               | 0      | 7           | 1           | 1     | 2           | 25% (11/44)|
| FEV1 35-49%               | 0      | 6           | 4           | 1     | 0           | 25% (11/44)|
| FEV1 <35%                 | 0      | 5           | 0           | 2     | 0           | 16% (7/44) |
| Number of patients who had BD response assessed | 0    | 21          | 5           | 2     | 9           | 37         |
| BD response               |        |             |             |       |             |            |
| Positive                  | 0      | 11          | 0           | 1     | 1           | 35% (13/37) |
| Negative                  | 0      | 10          | 5           | 1     | 8           | 65% (24/37) |
| Number of patients with RV measurement | 2     | 22          | 5           | 4     | 10          | 43         |
| Air trapping              |        |             |             |       |             |            |
| Present                   | 0      | 20          | 0           | 2     | 2           | 56% (24/43) |
| Absent                    | 2      | 2           | 5           | 2     | 8           | 44% (19/43) |

**Abbreviations.** PFT: pulmonary function test. FEV1: Forced expiratory volume in the first second. BD: Bronchodilator. RV: residual volume.
### Supplementary table 2. Patient characteristics, chest CT and biopsy findings based on the pulmonary function pattern

|                          | Normal (n=2) | Obstructive (n=23) | Restrictive (n=5) | Mixed (n=4) | Nonspecific (n=10) | Overall (n=44) |
|--------------------------|--------------|--------------------|------------------|------------|-------------------|----------------|
| **Smoking history**      |              |                    |                  |            |                   |                |
| Never                    | 1            | 15                 | 4                | 4          | 8                 | 32 (73%)       |
| Ex-smoker                | 1            | 7                  | 1                | 0          | 2                 | 11 (25%)       |
| Current                  | 0            | 1                  | 0                | 0          | 0                 | 1 (2%)         |
| **History of asthma or COPD** |              |                    |                  |            |                   |                |
| Yes                      | 0            | 15                 | 1                | 2          | 2                 | 20 (45%)       |
| No                       | 2            | 8                  | 4                | 2          | 8                 | 24 (55%)       |
| **Presenting symptoms**  |              |                    |                  |            |                   |                |
| Cough                    | 1            | 17                 | 4                | 2          | 6                 | 30 (68%)       |
| Dyspnea                  | 0            | 7                  | 1                | 3          | 2                 | 13 (30%)       |
| Wheezing                 | 0            | 4                  | 0                | 1          | 0                 | 5 (11%)        |
| Incidental chest CT finding | 1            | 1                  | 0                | 0          | 4                 | 6 (14%)        |
| Dysphonia                | 0            | 0                  | 1                | 0          | 0                 | 1 (2%)         |
| **Chest CT findings**    |              |                    |                  |            |                   |                |
| Mosaic                   | 0            | 18                 | 4                | 4          | 7                 | 33 (75%)       |
|                      | Absent |  2 |  5 |  1 |  0 |  3 | 11 (25%) |
|----------------------|--------|----|----|----|----|----|---------|
| **attenuation**      |        |    |    |    |    |    |         |
| **Emphysema**        | Present|  0 |  1 |  0 |  1 |  0 |  2 (5%) |
|                      | Absent |  2 | 22 |  5 |  3 | 10 |  42 (95%) |
| **Interstitial**     | Present|  0 |  2 |  1 |  1 |  0 |  4 (9%) |
| **fibrosis**         | Absent |  2 | 21 |  4 |  3 | 10 |  40 (91%) |
| **Biopsy findings**  |        |    |    |    |    |    |         |
| **Constrictive**     | Present|  1 | 10 |  1 |  2 |  7 |  21 (48%) |
| **bronchiolitis**    | Absent |  1 | 12 |  4 |  2 |  2 |  21 (48%) |
|                      | NA     |  0 |  1 |  0 |  0 |  1 |  2 (4%) |
| **Carcinoid tumor**  | Present|  2 |  6 |  3 |  1 |  4 |  16 (36%) |
|                      | Absent |  0 | 16 |  2 |  3 |  5 |  26 (59%) |
|                      | NA     |  0 |  1 |  0 |  0 |  1 |  2 (5%) |
| **Other biopsy**     | Emphysema|  1 |  5 |  0 |  0 |  0 |  6 (14%) |
| **findings**         | Organizing pneumonia|  0 |  0 |  2 |  0 |  1 |  3 (7%) |
|                      | NSIP   |  0 |  0 |  0 |  1 |  0 |  1 (2%) |
|                  | 0  | 1  | 0  | 0  | 0  | 1 (2%) |
|------------------|----|----|----|----|----|--------|
| Respiratory bronchiolitis |    |    |    |    |    |        |
| Granulomas       | 1  | 2  | 1  | 0  | 3  | 7 (16%) |

**Abbreviations.** COPD: Chronic obstructive pulmonary disease, NA: Not applicable, CT: Computed tomography, NSIP: Nonspecific interstitial pneumonia
**Supplementary table 3.** Treatments prescribed in our study population.

| Treatments prescribed | N (%) |
|-----------------------|-------|
| Inhaled B\textsubscript{2} agonist | 21 (48) |
| Inhaled corticosteroids | 18 (41) |
| Octreotide | 14 (32) |
| Inhaled antimuscarinic agent | 10 (23) |
| Systemic steroids | 1 (2) |
| Combination therapy with PD-L1 inhibitor, everolimus + cabozatinib | 1 (2) |
| Combination therapy with capecitabine + temozolamide | 1 (2) |
| Azithromycin | 1 (2) |

**Abbreviations.** B\textsubscript{2}: Beta-2. PD-L1: Programmed death–Ligand 1.