



Constrictive bronchiolitis in diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

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ABSTRACT

Background: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is characterised by multifocal proliferation of neuroendocrine cells and belongs in the spectrum of pulmonary neuroendocrine tumours. 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 histopathological data along with treatments and outcomes.

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



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Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is an under-recognised cause of obstructive lung disease in women. Constrictive bronchiolitis associated with DIPNECH manifests limited response to currently employed therapies. <https://bit.ly/3c3RZoe>

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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, whereas 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 hypoxaemia [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 COPD) or can be idiopathic [6, 7].

In 1992, AGUAYO *et al.* [8] 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. 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 tumours, 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 computed tomography (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 characterise the relationship between small airways disease (CB) and DIPNECH including clinical, physiological and radiological 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 in the United States. We manually extracted demographic, clinical, laboratory, pulmonary function and imaging data from electronic medical records, including review of radiological 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].

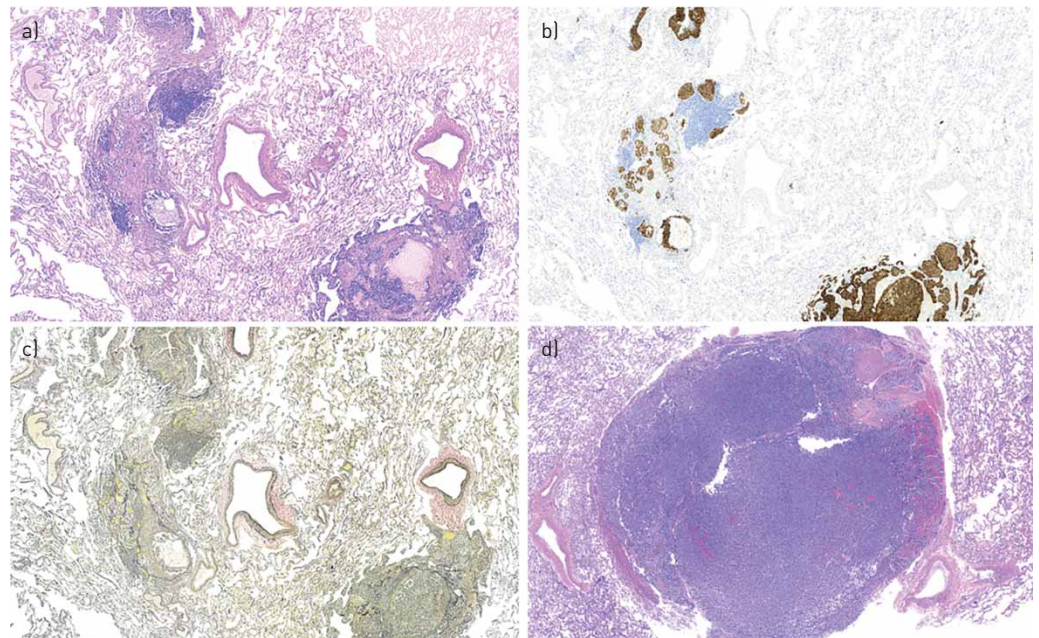


FIGURE 1 a) Normal-appearing alveolar parenchyma with multiple small airways involved by neuroendocrine cell hyperplasia (haematoxylin and eosin, $\times 40$ original magnification). b) Proliferating neuroendocrine cells highlighted by chromogranin immunostaining (anti-chromogranin antibody, $\times 40$). c) Partial or complete obliteration of the bronchiolar lumens by proliferating neuroendocrine cells and mucosal fibrosis (Verhoeff–Van Gieson, $\times 40$). d) Carcinoid tumour arising in a background of diffuse neuroendocrine cell hyperplasia (haematoxylin and eosin, $\times 20$).

PFT results were classified as normal, obstructive, restrictive, mixed or nonspecific patterns. An obstructive pattern was defined as forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC)<lower limit of normal (LLN) [16]. The restrictive pattern was defined by total lung capacity (TLC)<LLN [16]. The mixed pattern (obstructive and restrictive) was diagnosed when $FEV_1/FVC < LLN$ and $TLC < LLN$ [16]. The nonspecific pattern was defined as FEV_1 and/or $FVC < LLN$, with a normal FEV_1/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 FEV_1 and/or FVC following the inhalation of a β_2 -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 FEV_1 , expressed as a percentage of the predicted value: 1) mild: $FEV_1 \geq 70\%$; 2) moderate: FEV_1 60–69%; 3) moderately severe: FEV_1 50–59%; 4) severe: FEV_1 35–49%; and 5) very severe: $FEV_1 < 35\%$ [16, 18]. Reduced diffusing capacity of carbon monoxide (D_{LCO}) was defined as $D_{LCO} < LLN$. A significant change on follow-up PFT was defined as a change of $\geq 15\%$ for FEV_1 and/or FVC, and $\geq 10\%$ for D_{LCO} [16].

Counts and percentages were used for descriptive statistics. Median and interquartile range (IQR) 25–75 were used to describe central tendency measures. A Chi-squared test was used for analysing 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 (no. 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 white. Median age at diagnosis was 65 years (IQR 56–69). Past medical history included cancer in six patients (14%), skin cancer in three, breast cancer in one, lung adenocarcinoma in one and a combination of papillary thyroid cancer, retroperitoneal sarcoma and melanoma in one.

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%. The major metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), was measured in six 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 two patients did not; one patient manifested subtle regions of ground-glass attenuation and one patient manifested an enlarging single nodule (1.7 cm in size) that was found to represent a carcinoid tumour, 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.

TABLE 1 Demographic and clinical characteristics (n=44)

Female sex	40 (91)
Age at diagnosis years median (interquartile range)	65 (56–69)
Smoking status	
Never	31 (73)
Previous	11 (25)
Current	1 (2)
Presenting symptoms	
Cough	30 (68)
Dyspnoea	13 (30)
Wheezing	5 (11)
Dysphonia	1 (2)
None	6 (14)
Lung biopsy method	
Surgical	42 (95)
Bronchoscopic	2 (5)

Data are presented as n (%) unless otherwise stated.

TABLE 2 Chest computed tomography (CT) scan features at the time of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia diagnosis (n=44)

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 (n=36)	
Follow-up interval months	31.5 (12.5–52.4)
Enlarged	24 (67)
Stable	12 (33)
Size of largest nodule/mass on chest CT based on presence/absence of carcinoid tumour on biopsy mm	
Carcinoid tumour found on biopsy	17 (11–22)
No carcinoid tumour on biopsy	5 (5–7)

Data are presented as n (%) or median (interquartile range).

One or more PFT results were available for all patients and demonstrated an 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. As the focus of this study is the characterisation 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. The D_{LCO} 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% *versus* 65%, respectively, $p=0.21$), but manifested CB on biopsy with a comparable frequency to patients without obstruction (44% *versus* 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. Histopathological findings are summarised in table 4. Aside from DIPNECH, carcinoid “tumourlets” (focal collection of PNECs <5 mm in size) [15] were identified in 34 patients (77%) and carcinoid tumours in 16 (36%).

Among the 16 patients who underwent carcinoid tumour 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. Overall, 10 patients had a follow-up PFT; 5 (50%) declined, 2 (20%) improved and 3 (30%) remained stable.

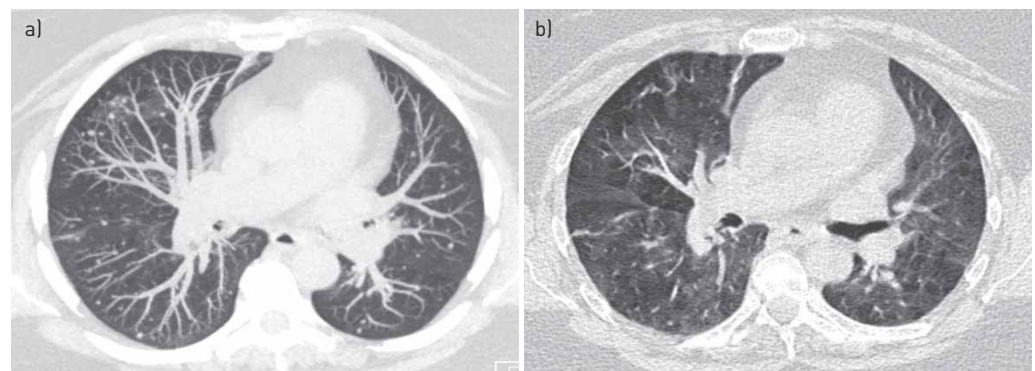


FIGURE 2 Chest computed tomography images of a 60-year-old female patient with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. a) Maximum intensity projection image demonstrating multiple bilateral micronodules. b) Mosaic attenuation.

TABLE 3 Pulmonary function characteristics of patients with or without an obstructive component

	Obstruction	No obstruction	Overall
Patients	27 (61)	17 (39)	44
Severity of disease graded by FEV₁ (n=44)			
≥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)			
Present	12 (52)	1 (7)	13 (35)
Absent	11 (48)	13 (93)	24 (65)
Air trapping among patients with RV measurement (n=43)			
Present	22 (85)	2 (12)	24 (56)
Absent	4 (15)	15 (88)	19 (44)
D_{LCO} (n=44)			
Reduced D _{LCO}	13 (48)	8 (47)	21 (48)
D _{LCO} % predicted median (interquartile range)	77 (66–86)	77 (65–99)	76 (65–92)

Data are presented as n (%) unless otherwise stated. FEV₁: forced expiratory volume in 1 s; RV: residual volume; D_{LCO}: diffusing capacity of carbon monoxide.

Monitoring (clinical, radiological and with serial PFTs) without pharmacological therapy was recommended for 11 patients (25%), whereas pharmacotherapy was recommended for 33 (75%) (supplementary table 3). An inhaled bronchodilator (β_2 -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, two 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 β_2 -agonists; seven patients with a positive bronchodilator response received a β_2 -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.

TABLE 4 Chest computed tomography (CT) scan and pathology findings for patients with and without obstruction on pulmonary function testing

	Obstruction	No obstruction	Overall
Patients	27 (61)	17 (39)	44 (100)
Chest CT scan findings			
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 (n=42)			
Carcinoid tumourlets	22 (81)	12 (75)	34 (77)
Constrictive bronchiolitis	12 (44)	9 (53)	21 (50)
Carcinoid tumour	7 (26)	9 (53)	16 (36)
Granuloma	2 (7)	5 (29)	7 (16)
Emphysema	5 (19)	1 (6)	6 (14)
Organising pneumonia	0 (0)	3 (18)	3 (7)
NSIP	1 (4)	0 (0)	1 (2)
Respiratory bronchiolitis	1 (4)	0 (0)	1 (2)

Data are presented as n (%). NSIP: nonspecific interstitial pneumonitis.

Octreotide, a somatostatin analogue (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 an SSA did not have a carcinoid tumour. Everolimus, in combination with cabozantinib and a programmed death ligand-1 inhibitor was prescribed in one patient with a metastatic pulmonary carcinoid tumour. This patient reported stable respiratory symptoms but manifested radiological progression of extrapulmonary 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 out of 35), worsened in 3% (1 out of 35) and improved in 20% (7 out of 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 to male ratio of 10:1 [10, 11, 13, 19]. The most common presenting symptoms were chronic cough and dyspnoea, with a median symptomatic duration of 10 years prior to DIPNECH diagnosis. Overall, 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-recognised 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.* [13] (52% *versus* 54%, respectively). Conversely, the cohort studied by CARR *et al.* [10] manifested obstruction markedly more than ours (87% *versus* 52%, respectively). This notable difference might be related to: 1) all 30 patients reported by CARR *et al.* [10] manifested respiratory symptoms compared to

TABLE 5 Characteristics of patients with clinical follow-up data

Symptom change	Improved	Worsened	Stable
Patients	7 [20]	1 [3]	27 [77]
History of an obstructive lung disease	4 [57]	1 [100]	11 [41]
PFT pattern			
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	1 [14]	1 [100]	7 [26]
Constrictive bronchiolitis on biopsy	3 [43]	1 [100]	11 [41]
Treatment given			
Observation	1 [14]	0 [0]	7 [26]
Inhaled β_2 -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]

Data are presented as n (%). PFT: pulmonary function test; ICS: inhaled corticosteroid.

TABLE 6 Characteristics of patients with follow-up pulmonary function test (PFT) data

PFT change	Improved	Declined	Stable
Patients	4 (17)	8 (33)	12 (50)
History of an obstructive lung disease	2 (50)	3 (38)	5 (42)
PFT pattern			
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 tumour on biopsy	2 (50)	5 (63)	7 (58)
Constrictive bronchiolitis on biopsy	0 (0)	3 (38)	3 (25)
Treatment given			
Observation	1 (25)	1 (13)	2 (17)
Inhaled β_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

Data are presented as n (%) unless otherwise stated. ICS: inhaled corticosteroid; FEV₁: forced expiratory volume in 1 s.

86% in our cohort, and/or 2) the definition of obstruction used by CARR *et al.* [10] was not clearly stated and may have differed from the definition we used. Defining obstruction as FEV₁/FVC<0.7 rather than the definition we used can over-diagnose obstruction in older individuals [20].

The presumed aetiology of airflow obstruction in DIPNECH is narrowing of the bronchiolar lumen (*i.e.* CB) owing to intra-luminal 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 [10]. This finding can be explained by the patchy nature of CB, which may have limited its identification upon histological examination [21]. However, the comparable frequency of CB among patients with and without airflow obstruction in our study (53% *versus* 44%, respectively; $p=0.58$), and the bronchodilator responsiveness, an unusual finding in CB [22], in some patients suggest that pathophysiological 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 [10, 13]. 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 such as 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 [23, 24]; 33 patients in this study and 2 others had 5-HIAA measured; only one patient had 5-HIAA elevation [10, 19].

Although incompletely understood, tissue fibrosis (*e.g.* in mesenteric tissue and cardiac valves) is a well-known complication of neuroendocrine tumours (NETs). Serotonin and several growth factors have been implicated in its pathogenesis [25]. The most widely accepted pathophysiologic mechanism underlying the development of peribronchiolar fibrosis and CB in DIPNECH is that bioactive substances (*e.g.* bombesin) secreted in a larger-than-normal amount by the hyperplastic PNECs exert pro-fibrotic and pro-inflammatory effects on the adjacent airways [8, 26, 27]. 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.* [13] summarised 25 cases of DIPNECH reported in the literature. Seven patients received systemic steroids; four improved (“clinically”), two remained stable and one worsened. One patient received ICS without systemic steroids and experienced respiratory decline. Overall, 46% and 67% of the patients studied by CARR *et al.* [10] 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. In our study, one patient received systemic steroids and remained stable. A total of 18 patients received ICSs; 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 tumours express somatostatin receptors (SSTRs) in a large percentage of patients [29], and the more differentiated a tumour is, the higher the likelihood of SSTR expression becomes [30]. SSTR expression in tumours can be detected noninvasively *via* different imaging modalities such as OctreoScan and the more sensitive, ⁶⁸Gallium (Ga) DOTATATE scan [31, 32]. GORSSTEIN *et al.* [28] reported that OctreoScan was positive in 10 out of 11 patients with DIPNECH, but the uptake was exclusively found in the dominant lesion. AL-TOUBAH *et al.* [19] reported that some level of uptake on SSTR imaging (OctreoScan and ⁶⁸Ga-DOTATATE) was noted in 12 of 19 patients with DIPNECH; however, it is unclear whether the uptake was exclusively in the dominant lesion as reported by GORSSTEIN *et al.* [28] or more diffuse. 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.* [19] studied a cohort of 42 patients with DIPNECH, all of whom received an SSA; 11 patients (26%) received an SSA alone, and 31 (74%) received an SSA in combination with other therapies, including inhalers, steroids and benzonatate. Thirty-two patients (76%) reported symptomatic improvement, and 14 of 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, six patients with progressive DIPNECH received an SSA; four demonstrated improvement in FEV₁, and two demonstrated stability [28]. In another study, 11 patients with DIPNECH received an SSA; 3 patients reported improvement of their cough, and all 9 follow-up PFTs demonstrated stability [10]. A small case series reported drastic improvement of cough in all four patients treated with SSA [35]. In a small case series, one patient with DIPNECH received an SSA, with temporary improvement in her cough [36]. In our study, 14 patients received an SSA; 4 (29%) experienced improvement in their cough. Among the eight patients with follow-up PFTs, one (12.5%) improved, three (37.5%) worsened and four (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 three patients with progressive DIPNECH and presumed carcinoid tumours. Two patients had radiological improvement, one patient had radiological progression, and all three 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 tumours, 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 coexisting DIPNECH is probably of no clinical consequence following the resection of the carcinoid tumour [40]. In the study by AL-TOUBAH *et al.* [19], 37 of 42 patients (88%) underwent surgical resection of at least one tumour. However, the outcomes for the group that underwent resection were not reported separately. In another study, 9 of 11 patients with DIPNECH and carcinoid tumour underwent surgical resection of the dominant lesion. In this study, 5 of 11 patients remained stable, while 6 progressed requiring treatment with SSA [28]. In our study, 5 of 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-centre 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 probably an under-recognised 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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