Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: clinical characteristics and progression to carcinoid tumour

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To the Editor:

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is considered a preinvasive lesion that may progress to carcinoid tumour [1]. Histologically, it is marked by a proliferation of neuroendocrine cells that is confined to the basement membrane (neuroendocrine cell hyperplasia; NECH), and/or has invaded past the basement membrane (carcinoid tumourlet) [2]. Tumourlets equal to or larger than 5 mm are classified as carcinoid tumours. Per the World Health Organization 2021 criteria, DIPNECH can be pathological (based solely on characteristic histological features) or clinical (diagnosed per characteristic symptoms and imaging findings, *e.g.* respiratory symptoms, bilateral pulmonary nodules, mosaic attenuation on computed tomography (CT)) [2]. In contrast to some lung diseases or neoplasms that can cause secondary, reactive NECH/tumourlets to form, DIPNECH is marked by such hyperplasia without an identifiable cause.

Given only ∼ 200 cases have been reported in the literature [3], DIPNECH is still poorly understood, and as a result is frequently under- or misdiagnosed, especially as asthma/COPD given the symptomatology of chronic cough and dyspnoea. Although a few retrospective cohort studies have been published more recently [3, 4], there is still more to be learned about this rare entity, including the clinical presentation, the population affected, differences from secondary NECH/tumourlets, treatment algorithms and, importantly, the rate and frequency of progression to malignant carcinoid tumour. Here, we present a descriptive retrospective single institution study of 78 patients with NECH/tumourlets, comparing patients with secondary NECH/tumourlets to those with DIPNECH.

A retrospective analysis of patients who were treated at Stanford Health Care from 1 January 2000 to 14 November 2020 was conducted, with institutional review board approval. Patients included had either pathological confirmation of NECH and/or carcinoid tumourlets, or were diagnosed with clinical DIPNECH after multidisciplinary review based on characteristic radiographic and clinical features [5]. NECH was defined pathologically as proliferation of neuroendocrine cells involving small airways without invasion through the basement membrane, while tumourlet was defined as nodular proliferation <5 mm with invasion beyond the membrane.

Pathological and clinical DIPNECH were defined based on the 2021 WHO classification of thoracic tumours [2]. Pathological DIPNECH required NECH and/or multifocal tumourlets. Clinical DIPNECH was defined by symptoms related to airway obstruction, mosaic attenuation on CT and/or bilateral pulmonary nodules, and pathological confirmation of NECH/tumourlets was optional. Secondary NECH/tumourlets were defined by the co-occurrence of an alternative non-carcinoid lung disease identified on the same pathological specimen, or unifocal tumourlet with co-existing carcinoid tumour.

An additional 145 patients with typical carcinoid, 34 patients with atypical carcinoid and 1771 patients with non-high grade, non-lung neuroendocrine tumours (NETs) were identified using the Stanford Neuroendocrine Tumor Database as comparison cohorts for demographics. Statistical analyses were performed using Fisher's exact test or Chi-squared analysis for categorical variables, or unpaired t-test for continuous variables.

Shareable abstract (@ERSpublications)
DIPNECH is a rare disease that is often misdiagnosed. In this study, it primarily affected elderly white women who were non-smokers. Lung nodules could slowly progress over years to carcinoid tumours. Average growth rate per nodule was 0.8 mm per year. https://bit.ly/3q1HD1k

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Progression to carcinoid tumour was defined radiographically as growth of a pulmonary nodule from <5 mm to ⩾5 mm in a patient with either pathological or clinical DIPNECH who had scans available for evaluation prior to the progression event. The definition of a progression event required pathological confirmation of an invasive carcinoid tumour and absence of any other malignancy. For each patient with progression, a median of three pulmonary nodules (range 2–3) with the most notable growth were measured as index lesions in their long axis and tracked over time.

A total of 78 patients were included, with their characteristics summarised in table 1. 33 patients had DIPNECH (24 pathological DIPNECH, nine clinical DIPNECH), while 45 patients had secondary NECH/tumourlets. Among the DIPNECH subgroup, patients were mostly elderly (median age 68 years, range 54–89 years), women (100%), white (87.9%), and overweight according to body mass index (median 29.1 $kg \cdot m^{-2}$, range 18–51 $kg \cdot m^{-2}$). Compared to patients with secondary NECH/tumourlets, patients with DIPNECH were more likely to be female (p=0.009), but racial distribution was not significantly different. When the demographics of patients with DIPNECH, secondary NECH/tumourlets, typical carcinoid tumours, atypical carcinoid tumours, and non-high grade extrapulmonary NETs were all compared, there was a significant difference observed in racial and gender distribution (p<0.0001). Patients with DIPNECH had the highest percentage of patients who were white (87.9%) and female (100%), while patients with non-lung NETs had the lowest (52.5% and 57.1%, respectively). In contrast to patients with secondary NECH/tumourlets, patients with DIPNECH were more like to have never smoked (75.8% *versus* 31.1%; p<0.0001).

The majority of patients with DIPNECH were symptomatic (78.8%), with cough and dyspnoea being the most common. Two patients (6.1%) who had no other lung disease required home oxygen. Three patients developed carcinoid syndrome, while none with secondary NECH/tumourlets did. Among patients with DIPNECH who had undergone pulmonary function testing (n=29), the results ranged from normal (44.8%) to obstructive (31.0%), restrictive (13.8%) and mixed (10.3%) patterns. The pattern of pulmonary function test abnormalities was not significantly different from those with secondary NECH/tumourlets (p=0.779).

For patients with DIPNECH, while CT was the preferred method for radiographic evaluation (90.9%), somatostatin receptor (SSTR)-based imaging (Octreoscan and/or DOTATATE-PET; 60.6%) and ^{18}F-fluorodeoxyglucose positron emission tomography/CT (48.5%) were also used. Only 65.0% of DIPNECH cases were positive when SSTR-based imaging had been performed, and all positive nodules had a subsequent pathological diagnosis of carcinoid tumour. Characteristic CT features included bilateral lung nodules (80.0%), mosaic attenuation (50.0%), air trapping (26.7%) and bronchial wall thickening (23.3%). Patients with DIPNECH had mosaic attenuation on CT more than twice as often when compared to patients with secondary NECH/tumourlets (50.0% *versus* 19.4%; p=0.016). There was a trend towards a higher proportion of bilateral nodules in patients with DIPNECH (80.0% *versus* 54.8%; p=0.056).

In contrast to the vast majority of patients with secondary NECH/tumourlets who had only tumourlets (88.9%), most patients with pathologically proven DIPNECH (87.5%) had more than one disease along the neuroendocrine spectrum. For instance, nearly half of the patients with pathologically proven DIPNECH (45.8%) had all three diseases of NECH, tumourlet and carcinoid tumour found in the same tissue sample. All carcinoid tumours found were exclusively low to intermediate grade: typical carcinoid (85%) and atypical carcinoid (15%). Among patients with secondary NECH/tumourlets, 51.1% of patients had a non-carcinoid lung malignancy (lung adenocarcinoma 87.0%, lung squamous cell carcinoma 26.1%, sarcoma 4.3%), while the remainder of patients had a benign lung disease, such as emphysema or interstitial lung disease co-identified in the same specimen.

Of the 33 patients with DIPNECH, nine patients (27.3%) had evidence of progression from DIPNECH to carcinoid tumour, all of which were typical carcinoids. The median time to radiographic progression was 3.3 years (range 1.0–7.6 years). Of the baseline index <5 mm nodules measured for each patient, the average rate of growth was 0.8 mm per year (range 0.2–2.0) assuming linear kinetics. None of these patients had or developed a non-NET malignancy, or carcinoid metastasis.

Management strategies for DIPNECH included beta-adrenergic and/or steroid inhalers (36.4%), somatostatin analogues (SSA; 24.2%), oral steroids (12.1%) and active imaging surveillance (12.1%). The majority of patients who were treated with any of the above treatments had symptomatic improvement (88.9%), including all eight patients who received SSA therapy. One patient was able to transition from continuous home oxygen to only at night and upon exertion after receiving SSA therapy. One patient who had recurrence of symptoms 3 weeks after monthly SSA injection had symptom improvement after the schedule was increased to every 3 weeks. Half of the patients experienced SSA side-effects, with diarrhoea

TABLE 1 Patient characteristics

	Cohort (n = 78)	DIPNECH (n = 33)	Secondary NECH/ tumourlet (n = 45)[#]	Typical carcinoid (n = 145)	Atypical carcinoid (n = 34)	Non-lung NETs[¶] (n = 1771)	p-value[+]
Age (years)	68 (44–89)	68 (54–89)	66 (44–86)				0.576
Sex							**0.009/ <0.0001**[§]
Female	69 (88.5%)	**33 (100%)**	**36 (80.0%)**	103 (71.0%)	27 (79.4%)	930 (52.5%)	
Male	9 (11.5%)	0 (0%)	9 (20.0%)	42 (29.0%)	7 (20.6%)	841 (47.5%)	
Race							0.196/ **<0.0001**[§]
White	61 (78.2%)	29 (87.9%)	32 (71.1%)	102 (70.3%)	22 (64.7%)	1011 (57.1%)	
Asian	10 (12.8%)	2 (6.1%)	8 (17.8%)	8 (5.5%)	1 (2.9%)	174 (9.8%)	
Black	1 (1.3%)	0 (0%)	1 (2.2%)	0 (0%)	0 (0%)	55 (3.1%)	
American Indian or Alaska Native	1 (1.3%)	0 (0%)	1 (2.2%)	1 (0.7%)	0 (0%)	2 (0.1%)	
Native Hawaiian or other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	9 (0.5%)	
Unknown	5 (6.4%)	2 (6.1%)	3 (6.7%)	33 (22.8%)	11 (32.4%)	520 (29.4%)	
BMI ($kg \cdot m^{-2}$)	28.2 (17.3–51.0)	29.1 (18.7–51.0)	27.4 (17.3–43.1)				0.081
Smoking history							**<0.0001**
Current or former	39 (50%)	8 (24.2%)	31 (68.9%)				
Never	39 (50%)	**25 (75.8%)**	**14 (31.1%)**				
Symptoms							0.232
Cough	50 (64.1%)	22 (66.7%)	28 (62.2%)				
Dyspnoea	42 (53.8%)	18 (54.5%)	24 (53.3%)				
Asymptomatic	14 (17.9%)	7 (21.2%)	7 (15.6%)				
Home oxygen	11 (14.1%)	2 (6.1%)	8 (17.8%)				
Wheezing	4 (5.1%)	2 (6.1%)	2 (4.4%)				
Haemoptysis	3 (3.8%)	0 (0%)	3 (6.7%)				
Carcinoid syndrome	3 (3.8%)	3 (9.1%)	0 (0%)				
Other[f]	9 (11.5%)	5 (15.2%)	4 (8.9%)				
Radiographic features[##]	(n = 61)	(n = 30)	(n = 31)				
Bilateral lung nodules	41 (67.2%)	24 (80.0%)	17 (54.8%)				0.056
Mosaic attenuation	21 (34.4%)	**15 (50.0%)**	**6 (19.4%)**				**0.016**
Bronchial wall thickening	14 (23.0%)	7 (23.3%)	7 (22.6%)				0.944
Air trapping	14 (23.0%)	8 (26.7%)	6 (19.4%)				0.497
Pulmonary function testing	(n = 69)	(n = 29)	(n = 40)				0.779
Normal	33 (47.8%)	13 (44.8%)	20 (50.0%)				
Obstructive	18 (26.1%)	9 (31.0%)	9 (22.5%)				
Restrictive	12 (17.4%)	4 (13.8%)	8 (20.0%)				
Mixed	6 (8.7%)	3 (10.3%)	3 (7.5%)				
Pathological diagnosis	(n = 69)	(n = 24)	(n = 45)				**<0.0001**
NECH	2 (2.9%)	2 (8.3%)	0 (0%)				
Tumourlet	41 (59.4%)	**1 (4.2%)**	**40 (88.9%)**				
NECH+tumourlet	3 (4.3%)	2 (8.3%)	1 (2.2%)				
NECH+carcinoid	3 (4.3%)	3 (12.5%)	0 (0%)				
Tumourlet+carcinoid	8 (11.6%)	5 (20.8%)	3 (6.7%)				
All of above	12 (17.4%)	**11 (45.8%)**	**1 (2.2%)**				
Clinical diagnosis[¶¶]	N/A	(n = 9)	N/A				

Data are presented as median (range) or n (%), unless otherwise stated. Bold indicates statistical significance. DIPNECH: diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; NECH: neuroendocrine cell hyperplasia; NET: neuroendocrine tumour; BMI: body mass index; N/A: not applicable. [#]: NECH/tumourlets secondary to conditions including chronic bronchitis/emphysema and interstitial lung disease (*e.g.* hypersensitivity pneumonitis). [¶]: G1-2 NETs from extrapulmonary sites. [+]: p-value either by unpaired t-test, Chi-squared analysis or Fisher's exact test; p-value tests comparison between the DIPNECH group and the secondary NECH/tumourlet group, unless marked by §, which indicates comparison with the additional groups of typical carcinoid, atypical carcinoid and non-lung NETs. [f]: other symptoms: diarrhoea, chest tightness, chest pain, dyspepsia. [##]: statistical comparison was made for each radiographic feature instead of as a whole group, as the features listed did not encompass all potential radiographic features. [¶¶]: diagnosis by clinical and radiographic data without pathological confirmation of NECH or tumourlet. 8/9 samples had pathological confirmation of carcinoid tumour.

being the most common. One patient ceased therapy due to refractory diarrhoea that was not secondary to carcinoid syndrome. The most common starting SSA treatment and dose was octreotide LAR 30 mg every 28 days. In terms of surveillance imaging, the most commonly employed interval was every 12 months.

DIPNECH remains a rare pulmonary disease that is hypothesised to exist along a neuroendocrine tumour spectrum consisting of NECH, tumourlets and carcinoid tumours. After the first case report in 1992 [6], a limited number of small case series have since been published [3, 4, 7–10]. To our knowledge, this study is one of the largest to report the characteristics of patients with pathological and clinical DIPNECH in comparison to those with secondary NECH/tumourlets, and one of the first to report the growth kinetics of these preinvasive lesions to guide surveillance planning.

Consistent with prior reports [5, 11], we found that patients with DIPNECH were predominantly white women in their sixties. In fact, in our cohort we found that all patients with DIPNECH were female, which was more than those with secondary NECH/tumourlets. Patients with a lung neuroendocrine spectrum disorder (DIPNECH, secondary NECH/tumourlets, carcinoid tumours) had a higher proportion of white female patients compared to patients with non-lung neuroendocrine tumours.

Compared to previous reports [3, 4], we also found that most patients had never smoked. The opposite was seen in patients with secondary NECH/tumourlets. In addition, we found that DIPNECH could be difficult to diagnose with SSTR-based imaging in most patients. SSTR-based imaging was able to detect carcinoid tumour concurrent with DIPNECH but not NECH/tumourlets, the size of which were likely below the limit of resolution. The presence of mosaic attenuation on CT, more so than bilateral lung nodules, was a distinguishing characteristic in DIPNECH patients, compared to those with secondary NECH/tumourlets.

In stark contrast to patients with secondary NECH/tumourlets, the majority of whom had tumourlets only, most patients with DIPNECH had multiple diseases along the neuroendocrine spectrum concurrently, suggesting that lesions can be at varying stages of progression. As patients with DIPNECH often have innumerable pulmonary nodules, this highlights the difficulty of surveillance and treatment. In our analysis, we found that 27.3% of patients with DIPNECH had progression to carcinoid tumour after a median time of 3.3 years. As patients at the time of diagnosis may have nodules at varying sizes, a more useful metric may be growth kinetics data. This showed that the fastest growing nodules grew at an average rate of 0.8 mm per year. As there has been scant data to guide monitoring of this disease, this benchmark may be helpful for the clinician in determining surveillance intervals, although we acknowledge the very limited sample size of only nine patients and inconsistent frequency of imaging. Given our experience, we generally perform surveillance CT scans every 12 months.

Of the patients with DIPNECH who did progress, all of the malignant tumours were identified as typical carcinoid tumours which were amenable to surgical resection. The absence of high-grade neuroendocrine tumours (small cell or large cell lung carcinoma) may suggest that DIPNECH/tumourlets and low-intermediate grade carcinoid tumours exist on one spectrum, and the higher-grade neuroendocrine tumours have a separate oncogenic profile.

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