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Early View

Research letter

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Caroline Hurabielle, Camille Taillé, Grégoire Prévot, Maud Russier, Alain Didier, Pierre-Olivier Girodet, Magali Colombat, Julien Mazières, Laurent Guilleminault

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De-labeling Severe Asthma Diagnosis: The Challenge of DIPNECH

Caroline Hurabielle[1], Camille Taillé[2], Grégoire Prévot[1], Maud Russier[3], Alain Didier[1,4], Pierre-Olivier Girodet[5], Magali Colombat[6], Julien Mazières[1], Laurent Guilleminault[1,4]

1. Department of respiratory medicine, Toulouse University Hospital Centre, Toulouse, France
2. Groupe Hospitalier Universitaire AP-HP Nord-Université de Paris, Hôpital Bichat, Service de Pneumologie et Centre de Référence constitutif des Maladies Pulmonaires Rares; Inserm UMR 1152; CRISALIS F-CRIN, Paris, France.
3. Centre Hospitalier Régional d'Orléans, Orléans, France
4. Center for pathophysiology of Toulouse Purpan, INSERM U1043, CNRS UMR 5282, Université Toulouse III ; CRISALIS F-CRIN, Toulouse, France
5. Université de Bordeaux, Pharmacologie, CIC1401, INSERM U1045, F-33000 ; CRISALIS F-CRIN, Bordeaux, France
6. Service d'anatomopathologie, CHU de Toulouse, Toulouse France

Corresponding author

Laurent Guilleminault

Pôle des voies respiratoires

CHU de Toulouse

24 chemin de Pouvourville

31059 Toulouse

Phone: 0033567771850

Fax: 003356771472

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Take home message: DIPNECH appears as a differential diagnosis of severe asthma with no specific biomarkers. Chronic cough and multiple nodules on CT-scan should prompt clinicians to consider this diagnosis. Differentiating DIPNECH and severe asthma remains crucial.

To the Editor,

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare pulmonary disease characterized by neuroendocrine cell hyperplasia within the bronchial epithelium[1]. The clinical presentation is characterized by non-specific respiratory symptoms such as chronic cough, dyspnea and bronchospasm. Given the rarity of the disease and the low specificity of symptoms, the diagnosis of DIPNECH is challenging and the time between symptom onset and diagnosis is long[1]. DIPNECH comprises a generalized proliferation of scattered neuroendocrine cells, small nodules (neuroendocrine bodies) or a linear proliferation of pulmonary neuroendocrine cells. It has been suggested that DIPNECH may mimick[2] or precede asthma[3]. The role of products of neuroendocrine cells, such as substance P, which contribute to eosinophil migration, has been suggested to explain asthma symptoms in DIPNECH[3]. However, the characteristics of patients with DIPNECH who have symptoms suggestive of asthma have never been described. The aim of our study was to determine whether patients diagnosed with DIPNECH and initially referred for severe asthma management had specific characteristics.

A retrospective study was conducted in the respiratory medicine departments of four hospitals in France. We reviewed all medical records of patients who were diagnosed with DIPNECH between January 2015 and June 2019. The inclusion criteria were: respiratory symptoms and a histological pattern of DIPNECH on surgical lung biopsy. We present here the characteristics of the patients who were referred for severe asthma management. The study was approved by the Institutional Review Board of the French Society of Respiratory Diseases (*Société de Pneumologie de Langue Française* - CEPRO 2019-031).

Among 21 patients included in the whole cohort, 20 (95.2%) were female with mean age of 62.4 ± 9.1 years. In the whole cohort of DIPNECH, all of them had cough and multiple nodules. Regarding the treatment, 15 (71.4%) were given inhaled steroids.

Ten patients (47.6%) out of 21 were initially referred for severe asthma management. Among those patients, only one patient was male. All the patients had chronic cough and the median duration of cough was 17 [10-30] years. The median [IQR] eosinophil count was 0.18 [0.09-0.33] 10^9/l (Table 1). Four patients out of 10 had an eosinophil count < 0.15 G/l. The median concentration of total IgE was 15 [30-98] kUI/l. The median forced expiratory volume in 1 second (FEV1) was 61% [35-79] of the predicted value. Regarding radiological features, CT scans showed multiple nodules in all patients and air trapping in 6 patients (54.5%) (Figure 1). The characteristics of our patients were similar to those reported in the literature in terms of gender (female predominance), age and respiratory symptoms[4-6]. In our study, the proportion of patients with DIPNECH who had a prior diagnosis of asthma was 47.6%. This is slightly higher than the previously described prevalence which ranges from 26 to 40%[5, 6]. The fact that our centres are specialist of severe asthma may explain the higher prevalence. Diagnosing asthma in patients with DIPNECH is very challenging. In fact, respiratory symptoms of DIPNECH are not specific and can mimic asthma. In our study, no specific symptoms were observed in patients with DIPNECH who were referred for severe asthma management compared to patients referred for another reason. Airflow limitation seemed a bit more severe but the difference was not statistically significant. Interestingly, none of the patients with DIPNECH and initially labelled as severe asthma had a history of atopy. Bronchodilator response was noted in only 3 patients. However, this criterion is not specific to asthma and a recent study in three large cohorts concluded that bronchodilator reversibility was at least as common in participants with COPD as those with asthma [7]. Moreover, in a recent study, it has also been shown that BHR is observed in one third of patients with DIPNECH[8]. In two other studies, 33% and 10% of patients with DIPNECH manifested a positive bronchodilator response[9, 10]. This means that BHR is not restricted to patients with asthma and is common in DIPNECH. Consequently, the presence of BHR in DIPNECH patients does not mean that

those patients also have asthma. In our study, no histological pattern of asthma was described on surgical lung biopsies.

Regarding biological markers, there are no specific features. The median blood eosinophil count seems to be low (0.18 G/l). However, only four patients out of 10 had an eosinophil count < 0.15 G/l indicative of non-type-2 inflammation. The median concentration of total IgE also seems to be low (15 kUI/l). In a recent study conducted in a global real-life severe asthma cohort, 1.6% of patients showed a non-eosinophilic phenotype[11]. This study emphasizes that a non-eosinophilic phenotype is likely to be uncommon in severe asthma patients. According to our study and the low eosinophil count observed in our patients with DIPNECH, the clinicians should be aware of considering differential diagnosis including DIPNECH in patients labelled as non-eosinophilic severe asthma.

Interestingly, some characteristics are indicative of DIPNECH. In our study, 100% of the patients with DIPNECH had a chronic non-productive cough. In other case series, the proportion of patients with cough ranges from 21% to 71%[4-6, 12]. In DIPNECH, cough is commonly refractory to standard treatments. In ERS guidelines published in 2020, it is not recommended to routinely perform chest CT scan in chronic cough[13]. In fact chest CT scan has a low impact on chronic cough management[14]. However, in patients with refractory chronic cough and airflow limitation experiencing long duration of cough (more than 10 years), chest CT scan seems to be an interesting tool for DIPNECH screening. Further studies are needed to better identify those patients.

In severe asthma, although that HRCT abnormalities are common in this disease[15], HRCT scan does not seem appropriate to differentiate subphenotypes of asthma[16]. However, according to GINA guide on difficult-to-treat & severe asthma, HRCT scan should be considered as a tool for screening of comorbidities and differential diagnoses. To the best of our knowledge, no biological or clinical characteristics have been available up to now for the

decision to perform HRCT in severe asthma. According to our study, persistent dry cough in patients labelled with severe asthma should prompt the clinicians to perform HRCT for the investigation of alternative diagnosis such as DIPNECH. A CT scan is an essential component of the investigation of DIPNECH. In fact, in our study, the presence of multiple pulmonary nodules on CT scan was a criterion and air trapping was observed in half of the patients. In the literature, multiple nodules are very common in patients with DIPNECH and this feature is described in as much as 100% of the patients in certain case series[12]. Mosaic perfusion has also been reported as the predominant finding in several studies. In a context of severe asthma, the combination of multiple nodules and mosaic perfusion on CT scan is highly evocative of DIPNECH. Histopathological confirmation is required. In clinical practice, the distinction of the two diseases is crucial, considering that the treatment for severe asthma and that for DIPNECH are different, in order to avoid inadequate use of biological therapies or continuous oral steroid therapy for example. In DIPNECH, it has been shown that somatostatin analogs improve respiratory symptoms. In a recent study conducted in 42 patients with DIPNECH treated with somatostain analogs, 15 (36%) reported mild improvement of symptoms, 6 (14%) reported moderate improvement, and 11 (26%) reported significant improvement [17]. Somatostatin analogs seem to also have beneficial effect on cough[18]. Cough and dyspnea improvement have also been described in 3 patients with the use of mTor inhibitor[19]. In our study, a small number of patients received somatostatin agonist or an mTor inhibitor and the response was equivocal.

Given the histopathological features and the patients' characteristics (low type 2 inflammation), a coexistence of 2 rare diseases (severe asthma and DIPNECH) seems to be unlikely. Very low FEV1 values appears in approximately half of our patients but this feature like low type 2 inflammation is uncommon in severe asthma. In patients with DIPNECH, low FEV1 values could be the expression of constrictive bronchiolitis. In a recent study, 52% of patients with

DIPNECH had airflow limitation[8]. However, only 53% of those patients demonstrated constrictive bronchiolitis on histological examination. The proportion of patients with constrictive bronchiolitis was similar between patients with and with no airflow limitation (53% vs 44%, respectively). The authors suggest that pathophysiological mechanisms other than constrictive bronchiolitis contribute to airflow obstruction in DIPNECH. Regarding FEV1 variability, included in asthma definition, this characteristic was not observed in our cohort. Our series does not support the hypothesis of DIPNECH-induced asthma, but rather highlights the fact that DIPNECH should be more considered as a differential diagnosis of severe asthma than a comorbid condition of severe asthma.

Our study has limitations. The number of patients is low but DIPNECH is a very rare disease and our cohort is among the largest in the literature. We show that patients with DIPNECH who were referred for uncontrolled asthma management have no specific usual biomarkers. However, we cannot exclude a recruitment bias related to the investigator's specific involvement in severe asthma care.

To conclude, DIPNECH clearly appears to be a differential diagnosis of severe asthma, particularly in women. The presence of chronic cough with a long duration and multiple nodules on the CT scan should prompt clinicians to consider this differential diagnosis. Given the difference in prognosis and treatment, differentiating DIPNECH and severe asthma remains crucial to improve patient outcomes.

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Table 1: Characteristics of patients with DIPNECH referred for asthma management. Cough was assessed at 6 months after therapy initiation. Cough improvement or no cough change was subjectively collected from patients' testimonies. Data are expressed as numbers (percentages) for categorical data and median and interquartile range [IQR] for continuous data.

Patients	1	2	3	4	5	6	7	8	9	10
Age (years)	68	77	76	56	50	71	65	66	55	62
Gender	F	F	F	F	F	F	F	M	F	F
BMI (kg/m^2)	29.4	23.1	22.8	32.3	24.8	26.2	27.6	25.0	25.9	22.7
History of smoking	No	No	No	Yes	No	No	No	No	No	Yes
Dry cough	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cough duration (year)	> 30	10	30	10	25	10	>30	12	14	20
≥ 2 Exacerbations within the last 12 months	Yes	No	Yes	No	No	No	Yes	No	No	No
Rhinitis	Yes	No	Yes	No	No	No	Yes	No	No	No
Dose inhaled steroid (µg/day of fluticasone equivalent dose)	2000	400	800	750	1000	800	2000	1000	800	1000
Oral steroids	No	No	No	No	Yes	No	No	No	No	No
FEV1/FVC (%)	68	64	41	79	33	58	57	91	63	73
BHR	Yes	Yes	No	No	No	No	No	No	Yes	No
FEV1 (L)	1.69	1.84	0.80	0.80	0.70	-	0.88	1.20	1.83	1.73
FEV1 (%)	71	92	36	33	26	70	52	40	74	103
TLC (%)	NA	108	119	64	121	111	96	64	107	102
RV (%)	NA	132	198	115	229	152	129	106	123	98
FENO (ppb)	6	NA	NA	NA	NA	NA	NA	NA	6	NA
Air trapping	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	No
Number of pulmonary nodules	> 10	2-5	> 10	2-5	5-10	2-5	2-5	2-5	2-5	>10
Blood eosinophils (10^9/l)	0.21	0.230	0.840	0.150	0.240	0.140	0.060	0.07	0.09	0.59
Total IgE (kUI/l)	15	NA	22	37	50	NA	15	NA	241	NA
Somatostatin analog **Effect on cough**	Yes Yes	No -	No -	No -	Yes No	No -	No -	No	No	No
mTor inhibitor **Effect on cough**	No -	No -	Yes Yes	No -	Yes No	No -	No -	No	No	No

BHR: Bronchial hyper-responsiveness; BMI: body mass index; FENO: Fractional exhaled nitric oxide; GERD: gastroesophageal reflux disease; GINA: Global initiative for asthma; PPIs: proton-pump inhibitors; FEV1: forced expiratory volume in one second; FVC: forces vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; neg: negative.

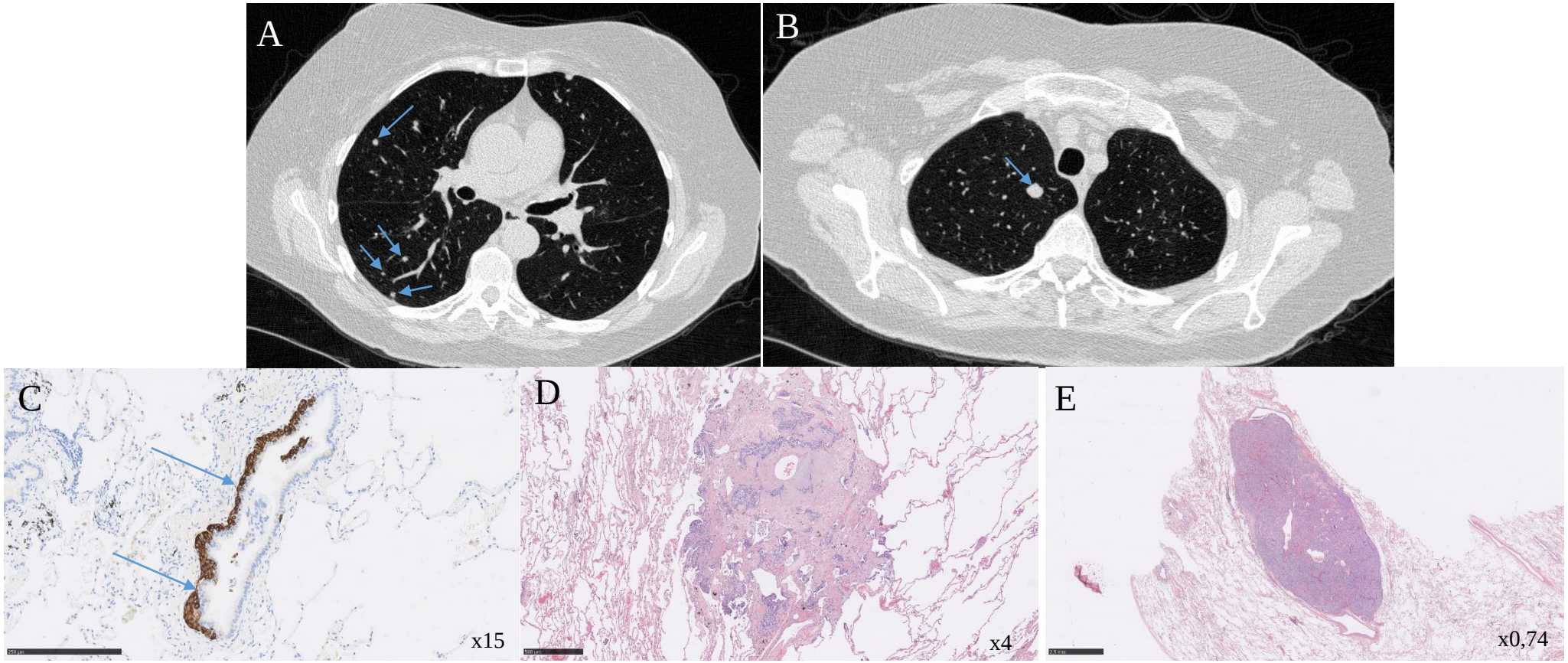

Figure 1: DIPNECH in a 68-year-old woman. Chest CT scan showed A) multiple nodules (arrows) and B) an 11-mm nodule in the right upper lobe (arrow). Wedge resection of the right upper lobe showed C) neuroendocrine cell hyperplasia beneath the bronchiolar epithelium (arrows) highlighted by chromogranin-A staining, D) a tumorlet and E) a carcinoid tumor (hematoxylin and eosin staining).