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Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia of the Lung (DIPNECH): Current Best Evidence

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Abstract Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is recognized as a preneoplastic condition by the World Health Organization. We reviewed our experience with 30 patients and performed a systematic review of the English literature to collect best evidence on the clinical features and disease course in 169 additional patients. Some patients presented with one or more carcinoid tumors associated with multiple small pulmonary nodules on imaging studies and showed DIPNECH as a somewhat unexpected pathologic finding. Others presented with multiple small pulmonary nodules that raised suspicion of metastatic disease on imaging. A third subset was presented with previously unexplained respiratory symptoms. In most patients, DIPNECH was associated with a good prognosis, with chronological progression into a subsequent carcinoid tumor noted in only one patient and death attributed directly to DIPNECH in only two patients. There is no best evidence to support the use of octreotide, steroids, or bronchodilators in DIPNECH patients.

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Introduction

Neuroendocrine cells (NEC) were first identified in the intestine and lung by Feyrter in the 1930s [1]. NEC occur in the small airways of the lung as individual cells or in aggregates known as neuroendocrine bodies. Although frequent in the airways of fetal and neonatal lung, NEC decrease in density with age and are found only focally in adult lung airways. Pulmonary NEC have paracrine functions and are thought to play an important role in lung development [2–4].

Pulmonary neuroendocrine cell hyperplasia (NECH) has been described in children as an idiopathic condition [5, 6] and in association with tobacco inhalation, chronic high altitude exposure, and a variety of pulmonary conditions including bronchiectasis and interstitial fibrosis in adults [7–9]. NECH is also thought to give rise to pulmonary tumors that are currently classified as carcinoid tumors (lesions >5 mm in diameter) or carcinoid tumorlets (lesions ≤5 mm in diameter).

In 1992, Aguayo et al. described six non-smoking patients with cough and exertional dyspnea who, on open lung biopsy, had "diffuse hyperplasia and dysplasia of pulmonary neuroendocrine cells, multiple carcinoid tumorlets, and peribronchiolar fibrosis obliterating small airways" [10]. In the absence of an apparent etiology, Aguayo et al. proposed that the condition was idiopathic and that secretion of serotonin by hyperplastic NEC led to the obliteration of small airways and development of peribronchiolar fibrosis. However, the study provided no

evidence to exclude the possibility that NECH was secondary to the obliterative bronchiolitis (OB). Additional reports of diffuse NECH with and without OB followed and, in 1999, the World Health Organization accepted diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) into its classification of lung neoplasms as a preneoplastic condition [11].

To date, DIPNECH has been reported in small case series with somewhat variable clinical, imaging, and histological features. The absence of long-term prospective trials and a lack of standardized clinico-pathologic criteria for diagnosis have impeded further definition and understanding of DIPNECH. We recently proposed a set of histologic criteria to diagnose DIPNECH in lung biopsies and resection specimens [12]. Here, we apply a best evidence approach to assess the clinical and imaging findings in 30 cases of DIPNECH from our institution and an additional 169 cases identified in a systematic review of the English literature.

Materials and Methods

This study was approved by the Cedars-Sinai Medical Center (CSMC) Institutional Review Board. The clinical and imaging findings of 30 patients diagnosed with DIPNECH at CSMC from 1993 through 2014 were reviewed. Pathologic findings and diagnostic criteria in 29 of these patients were recently reported [12]. NECH was diagnosed based on the presence of at least five NEC in a minimum of three separate airways (Fig. 1). DIPNECH was diagnosed pathologically in the presence of NECH associated with three or more carcinoid tumorlets (Table 1) (Fig. 2). We also conducted a systematic review of the English literature using PubMed (National Library of Medicine) and the following search terms: DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, and neuroendocrine cell hyperplasia + lung.

The following information was searched for in all cases: age at diagnosis, gender, initial symptoms, smoking status, imaging results, pulmonary function tests (PFTs), pathology findings, the presence or absence of a neuroendocrine tumor at DIPNECH diagnosis, treatment, response to treatment, and progression of disease. The level of evidence of each study was determined using Cochrane Collaboration criteria [13].

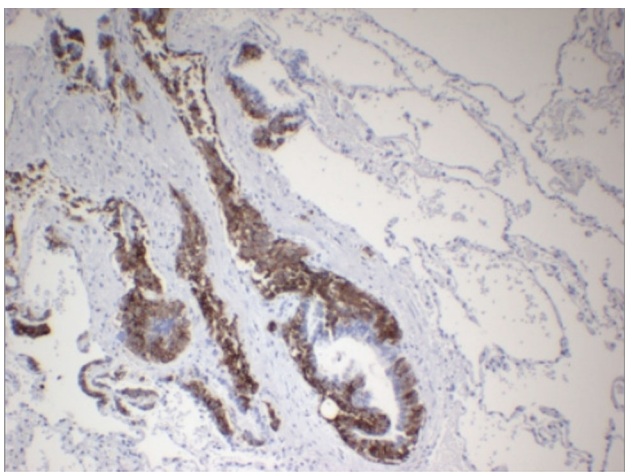

Fig. 1 Bronchioles showing numerous neuroendocrine cells (NEC), singly and in clusters present within the epithelial basement membrane (Chromogranin 40×). The presence of a minimum of five NEC in at least three separate bronchioles has been proposed in a previous study to define neuroendocrine cell hyperplasia [12]. These criteria are semi-arbitrary but provide consistency in diagnosis

Results

In addition to our 30 patients, 169 DIPNECH cases have been reported in the English literature in 39 clinico-pathologic studies. Twenty-two of these cases were single case reports; the others were in small case series of 2–30 patients each. In contrast to the DIPNECH cases reported from our institution, none of these 39 studies provided explicit pathologic criteria to define "diffuse", "NECH," and/or "idiopathic."

The 199 patients presented with a variety of clinical and imaging findings, which are summarized in Tables 2, 3, 4.

Demographic Data

Age at diagnosis ranged from 36 to 84 years with a median age of 66 (in some papers, only an average age was available; therefore, for each study, an average age was calculated, and the overall median was calculated from the aggregate averages). 184 (93 %) of the 199 patients were female.

Clinical Presentation

Initial symptoms were described in 171 (86 %) of the 199 patients and included cough in 78 (46 %), dyspnea in 77 (45 %), and others as shown in Table 2. Smoking data were available for 166 (83 %) of the 199 patients. Fifty-three (32 %) were described as current or former smokers (defined as at least one pack year where data were available) [14–24].

Imaging Findings

Imaging findings were reported in 159 (80 %) of the 199 patients. As shown in Table 3, the findings were variable.

Table 1 Criteria used in this study and past literature for the diagnosis of DIPNECH

Pathologic criteria used in current study
≥3 bronchioles with ≥5 neuroendocrine cells (neuroendocrine cell hyperplasia) and ≥3 carcinoid tumorlets
Clinico-pathologic criteria used in previous studies
Obliterative bronchiolitis diagnosed pathologically or on the basis of pulmonary function tests associated with neuroendocrine cell hyperplasia on histology, without the use of specific histopathologic criteria to define hyperplasia
Neuroendocrine cell hyperplasia diagnosed pathologically without the use of specific histopathologic criteria to define hyperplasia, associated with carcinoid tumorlets and/or single or multiple carcinoid tumors

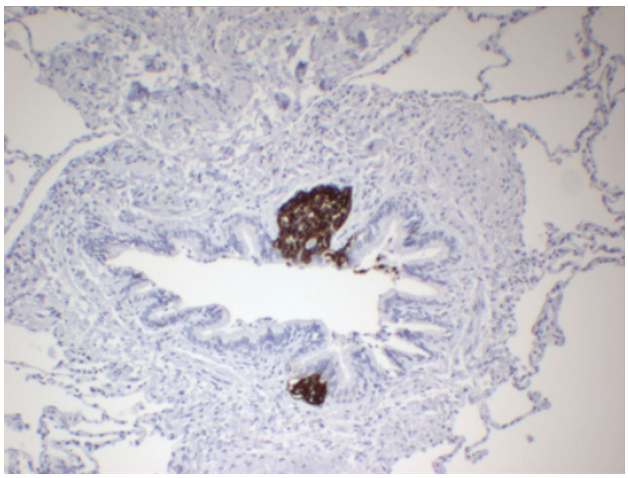

Fig. 2 Bronchiole showing two microscopic nodules composed of neuroendocrine cells that have proliferated beyond the epithelial basement membranes (Chromogranin 40×). These nodules are classified as carcinoid tumorlets when they measured up to 5 mm, the arbitrary size criterion to distinguish them from larger carcinoid tumors

Multiple (>1) pulmonary nodules (Fig. 3) and/or masses, seen in 129 or 81 % of patients, were the most frequent imaging findings and the most frequent indication for surgery, including in 82 % of the cases from our institution (Fig. 1, 2). Indeed, DIPNECH was an unexpected pathologic finding that had not been suspected clinically in any of the reported cases. Among the CSMC cases, the most common clinical diagnosis prior to surgery was primary lung cancer, less frequently metastatic cancer (breast, prostate, kidney, colon, melanoma), and only in a few cases idiopathic pulmonary fibrosis, coccidiomycosis, chronic obstructive pulmonary disease, asthma, bronchiectasis, GERD, anxiety, and cardiac disease. The second and third most common findings on imaging were air trapping and mosaic attenuation, which is seen in 42 (26 %) patients and 39 (25 %) patients, respectively.

Pulmonary Function Tests (PFTs)

Comprehensive PFT data were not provided in most of the published cases, although PFTs were variably described as restrictive [21], obstructive [14, 15, 18, 20, 22, 23, 25–30], mixed restrictive/obstructive [14, 31, 32], or normal [14, 16, 17, 22, 24, 33–36] for selected patients. PFTs at or near the time of diagnosis were available for only 13 of our 30 CSMC patients. PFTs were within normal limits in 7 (54 %) of these 13 patients. An obstructive defect (with a mean FEV1 of 42 % predicted) was observed in 4 (31 %) and restrictive defects were noted in two patients (15 %).

Pathologic Findings

At diagnosis of DIPNECH, pulmonary typical carcinoid tumor (Fig. 4) was present in 106 (53 %) patients, including 8 (4 %) patients with one or more regional lymph node metastases [8, 10, 14–16, 18, 20–22, 25, 27, 30, 34, 36–41]. Atypical carcinoid tumors were described in only 3 (2 %) patients [14]. OB, described as a key feature in Aguayo's initial report, was reported in only 48 (24 %) cases [10, 14, 16, 18, 22, 30, 36, 37, 39, 42]. A total of 7 (4 %) additional patients [21, 28, 31, 32, 38, 43, 44] were reported to have luminal "narrowing" or "compression," terminology that suggests a more mild degree of OB. Interestingly, from the available data, only one patient was diagnosed with a carcinoid tumor subsequent to (rather than synchronous with) an initial diagnosis of DIPNECH [16]. No patients with DIPNECH who evolved to high-grade neuroendocrine carcinomas (small-cell carcinoma, large-cell neuroendocrine carcinoma) have been described.

Treatment

Surgical processes used in the study are as follows: Detailed information regarding the surgical diagnosis/treatment of DIPNECH patients was available for 127 (64 %) of the 199 patients. These included 78 (61 %) biopsies (via video-assisted thoracoscopic surgery, open, CT-guided, transbronchial, and wedge) [16–19, 22, 23, 26, 27, 29, 32–35, 38, 39, 42, 45–49], 21 (17 %) wedge resections [8, 21, 31], 16 (13 %) lobectomies [8, 15, 16, 21, 24, 25, 36, 37, 40, 44], 8 (6 %) segmentectomies

Table 2 Most common presenting symptoms in patients with dipnech in the literature ($n = 141$) and in CSMC cohort ($n = 30$)

Study	Cough	Dyspnea	Asymptomatic	Hemoptysis	Wheezing	Endocrine syndrome[a]
Case reports ($n = 22$)	12	13	2	2	4	2
Aguayo et al. [10] ($n = 6$)	6	6				
Aubry et al. [16] ($n = 28$)	8	9	10			2
Carr et al. [18] ($n = 30$)	21	19				
Coletta et al. [39] ($n = 3$)	3	3				
Davies et al. [14] ($n = 19$)	4	6	9	2		
Gorshtein et al. [20][b] ($n = 11$)			5			
Gosney et al. [51] ($n = 7$)	2	2	3			
Lee et al. [47] ($n = 5$)	3	4				
Lim et al. [21] ($n = 2$)	1	1				
Mireskandari et al. [50] ($n = 2$)			2			
Reyes et al. [49] ($n = 2$)	2	1				
Rowan et al. [42] ($n = 2$)	2	1				
Zhou et al. [30] ($n = 2$)	2	2				
Total ($n = 141$)	66 (47 %)	67 (48 %)	31 (22 %)	4 (3 %)	4 (3 %)	4 (3 %)
Marchevsky et al. [12] ($n = 30$)	12 (40 %)	10 (33 %)	8 (27 %)	0	3 (10 %)	0

Case reports: [15, 17, 23–27, 29, 31–38, 40, 43–46, 48]

Did not directly address initial presence of absence of symptoms: [19, 22, 28, 41]

[a] Fessler et al.: patient presented with coarsened facial features and large hands. Nests of NECH were found by immunohistochemistry to be corticotropin and growth hormone releasing hormone positive. Cameron et al.: patient presented with proximal muscle weakness, moon facies, and easy bruising. Nests of NECH were found by immunohistochemistry to produce corticotropin. Aubry et al.: both patients presented with cushingoid syndrome

[b] Gorshtein et al. described five asymptomatic patients; the remaining six had respiratory symptoms, but the specific symptoms were not clearly delineated

[16, 18], and 4 (3 %) lung explants [30] (including two CSMC patients). The two CSMC patients who underwent single lung transplantation were being treated for emphysema, and DIPNECH was an incidental finding. One was clinically stable 1.5 years post transplantation, and the other was lost to follow-up. Five cases from the literature cohort also underwent lung transplantation (two double lung transplants, one single lung transplant, and two for whom the type of transplant was not specified). Two were described as doing well without recurrence of DIPNECH on re-biopsy at 12 and 24 months post transplant [30]. Deaths in the other three patients were described as transplant-associated complications [14, 16].

Medications used in this study are as follows: Twenty patients were treated with octreotide/somatostatin analogs (SSA). Of the three CSMC patients who were treated with long-acting release (LAR) octreotide (30 mg monthly intramuscular injection), one reported improvement in carcinoid syndrome-type symptoms (diarrhea and flushing), while the other two patients reported no improvement. Of the latter, one was subsequently treated with everolimus (10 mg daily) but was lost to follow-up, and the other was subsequently treated with pasireotide (120 mg intramuscularly per week) with no change in symptoms. Sixteen of the 17 patients in the literature who were treated with somatostatin analogs received octreotide LAR and one received lanreotide [18, 20]. Seven patients reported subjective improvement in respiratory symptoms with SSA therapy. Post-therapy improvement in FEV1 was documented in four patients but did not reach statistical significance [20].

Other medications used to treat DIPNECH included long- and short-acting beta agonists (nine patients, or 5 %) [10, 28, 39, 46, 49] and inhaled corticosteroids (27 patients, or 14 %) [14, 18, 28, 39, 43, 49]. None of these treatments were reported to be unequivocally beneficial or to improve overall outcome.

Long-Term Outcomes and Progression

Data on long-term outcomes and progression of respiratory symptoms and/or development of neuroendocrine malignancies following a diagnosis of DIPNECH are limited.

Table 3 Most common imaging findings near the time of diagnosis of dipnech for patients in the literatu RE ($n = 131$) and in CSMC cohort ($n = 28$)

Study	>1 nodule and/or >1 mass	1 nodule or 1 mass	Air trapping	Mosaic attenuation	Adenopathy (hilar or mediastinal)	PET-uptake[a]	Bronchiectasis	Cystic lung disease
Case reports ($n = 22$)	17	3	4	6	1	3	2	
Aguayo et al. [10] ($n = 6$)	5		1					
Aubry et al. [16] ($n = 28$)	18	8	1	1	2		1	
Carr et al. [18] ($n = 26$)	26		25	21				
Coletta et al. [39] ($n = 3$)	2		1					
Davies et al. [14] ($n = 15$)	12	3	5	5			2	
Gorshtein et al. [20] ($n = 11$)	11				2			
Gosney et al. [51] ($n = 7$)	6	1						
Lee et al. [47] ($n = 5$)	3		5	5				
Lim et al. [21] ($n = 2$)	2					1		
Reyes et al. [49] ($n = 2$)	2			1	1		2	
Rowan et al. [42] ($n = 2$)								2
Zhou et al. [30] ($n = 2$)	2							
Total ($n = 131$)	106 (81 %)	15 (11 %)	42 (32 %)	39 (30 %)	6 (5 %)	4 (3 %)	7 (5 %)	2 (2 %)
Marchevsky et al. [12] ($n = 28$)	23 (82 %)	5 (18 %)	0	0	1 (4 %)	4 (14 %)	2 (7 %)	0

Case reports: [15, 17, 23–27, 29, 31–38, 40, 43–46, 48]

Did not directly address radiographic findings: [19, 22, 28, 41, 50]

[a] PET-scans were ordered infrequently in the literature and in the CSMC cohort. In each set of patients, 5 PET-scans were commented upon. In both sets, 4/5 patients had radiotracer uptake, and 1/5 did not

Follow-up data were available for 114 (57 %) of the 199 patients, though the median duration of available follow-up was only 3 years (range 0–13 years) for 27 CSMC patients and was inconsistently reported for 87 patients in the literature cohort. As shown in Table 4, 67 (59 %) of the 114 patients were characterized as stable, which we defined where possible as absence of clinical and radiographic progression of disease; 30 (26 %) experienced clinical and/or radiographic deterioration; 13 (11 %) improved; and 5 (4 %) patients died from a respiratory cause (including three deaths attributed to transplant-associated complications and two attributed directly to progression of DIPNECH). Based on the available data, only one patient was diagnosed with a carcinoid tumor following an initial diagnosis of DIPNECH [16], and no patients with DIPNECH subsequently developed a high-grade neuroendocrine carcinoma.

Discussion

Systematic review of our experience combined with the systematic literature review shows that only level-3 evidence is currently available for this unusual syndrome and indicates that our current understanding of DIPNECH should be updated beyond Aguayo's initial description, wherein patients presented with diffuse NECH associated with OB and other non-neoplastic lung changes. The available data confirm that DIPNECH occurs predominantly in the elderly (median age 66 years) and in women (93 %), and that it is not associated with cigarette smoking. Some patients present with one or more carcinoid tumors and multiple small pulmonary nodules on imaging, while others present with multiple small pulmonary nodules that raise the suspicion of metastatic disease on imaging, but most present with primary respiratory symptoms. The variety of presenting symptoms suggests that DIPNECH is frequently a mimic for other conditions. Indeed, DIPNECH is rarely, if ever diagnosed preoperatively, and usually constitutes an unexpected pathologic finding. This underscores the need to confirm the histopathology of lung nodules. The lung tumors are almost always typical carcinoids, although in a few cases, atypical carcinoid tumors were reported. The smaller pulmonary nodules are usually carcinoid tumorlets associated with microscopic, multifocal NECH. To the best of our knowledge, evolution to high-grade neuroendocrine carcinoma has not been reported in patients diagnosed with DIPNECH.

Table 4 Progression and long-term outcomes of patients with dipnech

Study	Stable	Progressed[a]	Improved[b]	Death from another cause
Case reports ($n = 11$)	7	1	2	1
Aguayo et al. [10] ($n = 6$)	5	1		
Aubry et al. [16] ($n = 23$)	10	5	7	1
Carr et al. [18] ($n = 13$)		10	3	
Coletta et al. [39] ($n = 2$)	2			
Davies et al. [14] ($n = 14$)	11	2		1
Gorshtein et al. [20] ($n = 11$)	5	6		
Reyes et al. [49] ($n = 2$)	1		1	
Ruffini et al. [41] ($n = 3$)	3			
Zhou et al. [30] ($n = 2$)	2			
Total ($n = 87$)	46 (53 %)	25 (29 %)	13 (15 %)	3 (3 %)
Marchevsky et al. [12] ($n = 27$)	21 (78 %)	5 (19 %)	0	1 (4 %)

Case reports: [15, 28, 29, 31, 32, 34, 35, 38, 43, 46, 48]

Did not directly address progression of symptoms/long-term outcomes: [17, 19, 21–27, 33, 36, 37, 40, 42, 44, 45, 47, 50, 51]

[a] Progression defined as worsening clinical symptoms and/or imaging findings suggestive of worsening DIPNECH (includes those who ultimately developed metastatic disease or died of a pulmonary cause). Extrapulmonary metastases (not including lymphatic invasion) were noted in three patients. Aubry et al. metastasis to eye, rib, thyroid, skin 3 years after the initial diagnosis. Gorshtein et al. metastasis to left adrenal gland, though timing relative to DIPNECH diagnosis was unclear. Al-Ayoubi et al.: involvement of the chest wall, diagnosed synchronously with DIPNECH. Death from a pulmonary cause was noted in five patients. Aguayo et al.: one death from progressive lung disease and hypoxemia. Aubry et al.: two patients died post transplant, one within several months of the operation and the other 3 years after the operation (due to rejection). Carr et al.: one death secondary to progressive obliterative bronchiolitis. Davies et al.: one death secondary to rejection 5 years post-lung transplant

[b] Improvement defined as clinical and/or radiographic improvement

Clinical and radiological features of the CSMC patients, diagnosed using strict pathologic criteria, appeared similar to those of the DIPNECH cases in the literature who presented with lung tumors, thereby supporting the utilization of the pathologic criteria we recently proposed for the pathologic diagnosis of DIPNECH [12]. In our experience, DIPNECH has been diagnosed in previous studies in the literature in patients using less-specific criteria such as OB, pulmonary function tests, and other findings, rather than the specific pathologic criteria used in our review, as summarized in Table 1. The use of our proposed pathologic criteria is particularly helpful in patients with resected carcinoid tumors where the presence of NECH and tumorlets was an unexpected pathologic finding.

One of the surprising findings of this systematic review is the description of OB, described as a key feature in Aguayo's initial report, in only 24 % of reported cases. This may reflect underreporting of the entity, as it can be quite focal and difficult to diagnose without the aid of multiple sections and/or deeper cuts. However, we were able to demonstrate the presence of OB pathologically in

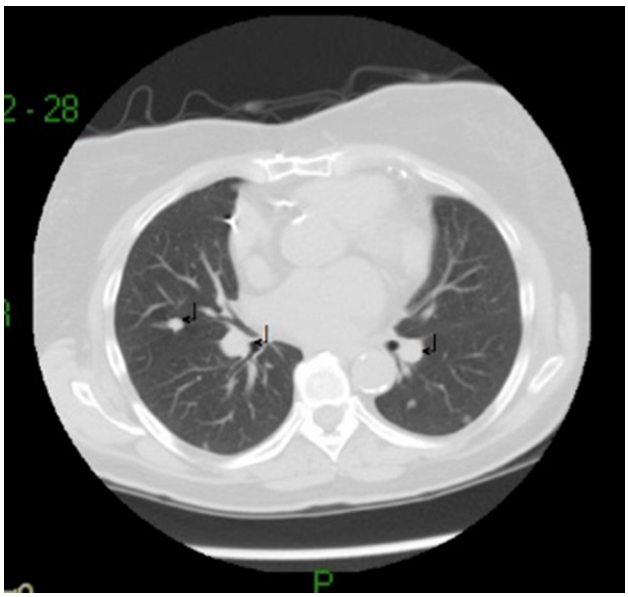

Fig. 3 Chest CT from a patient with DIPNECH who presented with multiple pulmonary nodules

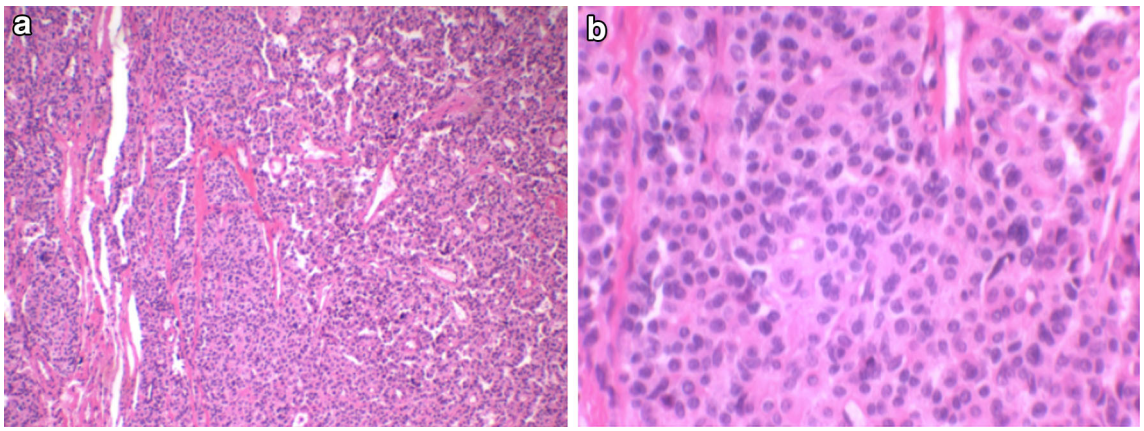

Fig. 4 **a** Typical carcinoid tumor at low power in a patient with DIPNECH. The tumor cells are arranged in nests and cords (Hematoxylin and Eosin 100×). **b** Carcinoid tumor in a patient with DIPNECH. The tumor is composed of round cells with uniform nuclei, salt-pepper chromatin, and scanty cytoplasm (Hematoxylin and Eosin 400×). Mitoses were rare and no necrosis was seen, characteristic of a typical carcinoid tumor. Atypical carcinoid tumors are unusual in DIPNECH patients, and the syndrome is not associated with the development of high-grade neuroendocrine carcinomas, such as small-cell carcinoma and large-cell neuroendocrine carcinoma

only 1 of our cases, and none of our patients developed bronchiolitis obliterans syndrome (BOS), supporting the concept that only a minority of DIPNECH patients develop this problem and that DIPNECH can be diagnosed in the absence of OB or BOS.

In patients with DIPNECH who present with carcinoid tumor(s), tumorlets, and NECH, it is logical to assume that the condition is probably preneoplastic and that the carcinoid tumor(s) evolved from intraepithelial NECH to carcinoid tumorlets, which grow until they achieve the arbitrary of 5 mm threshold required for classification as carcinoid tumor(s). However, although conceptually appealing, to date, it appears that there are insufficient well-documented data to support DIPNECH as a preneoplastic condition. We are aware of only one patient in the literature who has been described with a carcinoid tumor that developed subsequent to an initial diagnosis of DIPNECH [16], and there are no data to estimate how long it takes for NECH or tumorlets to grow into carcinoid tumors. Moreover, there is no evidence to support the concept that DIPNECH patients should be treated with octreotide or other therapies to prevent the subsequent development of carcinoid tumors. The small number of patients who were treated with octreotide showed ambiguous evidence that the therapy slowed progression and/or cured the syndrome.

Limitations to this review include its retrospective nature, incomplete follow-up data, and inconsistent description of findings associated with DIPNECH in the cases reported in the literature to date.

In summary, our study shows that the initial concept of DIPNECH needs to be updated and that current best evidence suggests that this interesting syndrome is to some extent a pathological curiosity and that it does not require specific medical therapy in most affected patients. The prognosis of these patients has been generally favorable, probably because most of the tumors were diagnosed at Stage I. Extrapulmonary metastatic disease was reported in only 3 (2 %) of 199 patients [15, 16, 20], and death was attributed directly to DIPNECH in only two patients [10, 18]. In the few patients who develop progressive obstructive pulmonary changes, there is no evidence to show that treatment with octreotide significantly alters the course of the disease. Symptomatic treatment for obstruction and lung transplantation in selected patients remain the only currently viable therapeutic options.

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Conflict of interest None.

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