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Total word count: 2497

Abstract word count: 250

"The Clinical Course of Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia"

Running Title: Course of Pulmonary Neuroendocrine Hyperplasia

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Dr. Tate is a shareholder in Amgen, Pfizer, Procter and Gamble, Kimberly Clark and Invesco Global Healthcare Fund. Dr. Carr, Dr. Chung, Dr. Duarte Achcar, Dr Lesic, Dr. Rho, Dr. Yagihashi, Dr. Swigris and Dr. Kern have no conflicts of interest to disclose.

Abstract

Background: Current understanding of the clinical course of Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) is poor and based predominantly on small case series. In our clinical experience, we have found that the diagnosis of DIPNECH is frequently delayed, as respiratory symptoms are ascribed to other lung conditions.

Objectives: To collect and analyze longitudinal clinical data: pulmonary physiology, chest high-resolution computed tomography (HRCT) imaging, and therapies to better delineate the course of disease.

Methods: We established a cohort of patients (N=30) with DIPNECH seen at our institution. We used descriptive statistics to summarize cohort characteristics and longitudinal analytic techniques to model percent predicted one-second forced expiratory volume (FEV_1%) over time.

Results: All subjects were female who presented with longstanding cough and dyspnea. The majority of subjects had a FEV_1% <50 at the time of diagnosis. Forty percent of subjects were diagnosed with asthma as the cause for physiological obstruction. The mean FEV_1% for the entire cohort showed no statistically significant decline over time, but 26% of subjects experienced a 10% decline in FEV1 within two years. Among pathology samples available for review, 28% (5 of 18) had typical carcinoids and 44% had associated constrictive bronchiolitis. We propose clinical diagnostic criteria for DIPNECH that incorporate demographic, pulmonary physiology, HRCT, transbronchial and surgical lung biopsy data.

Conclusions: DIPNECH is a female-predominant lung disease manifested by dyspnea and cough, physiological obstruction and nodules on HRCT. Additional research is needed to understand the natural history of this disease and validate the proposed diagnostic criteria.

List of Abbreviations

DIPNECH	Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia
HRCT	High-Resolution Computed Tomography
FEV_1	One-Second Forced Expiratory Volume
PNC	Pulmonary Neuroendocrine Cells
ATS	American Thoracic Society
NJH	National Jewish Health
COPD	Chronic Obstructive Pulmonary Disease
PFTs	Pulmonary Function Tests
RV	Residual Volume
TLC	Total Lung Capacity
GRP	Gastrin Releasing Peptide
AV	Alveolar Volume

INTRODUCTION

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is defined by the World Health Organization as, "…a generalized proliferation of scattered single cells, small nodules (neuroendocrine bodies), or linear proliferations of pulmonary neuroendocrine cells (PNCs) that may be confined to the bronchial and bronchiolar epithelium…" [1] Neuroendocrine hyperplasia has been known for years to occur as a secondary phenomenon in chronic lung disease, but its recognition as a primary pathologic process, independent of other lung abnormalities, has occurred only recently.[2] In patients with DIPNECH, peribronchiolar fibrosis, thought to be driven by PNC production of peptides that affect surrounding cells, may obliterate small airways, leading to a severe, progressive obstructive ventilatory defect. The amount of fibrosis varies, with greater amounts seen in tissue that also contains carcinoid tumorlets.[3] In one report of 25 patients with typical carcinoid tumors, 76% had PNC hyperplasia associated with the carcinoid and 32% had constrictive bronchiolitis associated with foci of PNC hyperplasia.[4]

DIPNECH falls within the spectrum of PNC hyperplasia that ranges from individual cells to carcinoid tumors. When the proliferation extends beyond the bronchiolar epithelium basement membrane or beyond the confines of the airway wall, the term tumorlet is appropriate. If tumorlets exceed 0.5 cm, they are designated as carcinoid tumors; thus, DIPNECH is thought to be a premalignant condition. Although most reported cases of DIPNECH-associated carcinoid tumors are typical bronchial carcinoids, there have been reports of atypical carcinoids, with metastasis to hilar lymph nodes and distant organs.[3,5,6] The molecular underpinnings of this transformation are not known.

DIPNECH affects women more often than men, although the reason for this gender bias is not clear. Symptoms include chronic cough and exertional dyspnea that may be present for many years prior to diagnosis. High-resolution computed tomography (HRCT) scans show air-trapping (demonstrated by mosaic attenuation accentuated on expiratory images), accompanied by multiple nodules and airway wall thickening.[7,8] In the largest study to date, investigators reported 19 patients with DIPNECH and described treatment in seven.[3] The five-year survival rate was 83% with varied therapeutic approaches. Although the literature contains several additional case reports and small case series, the pathogenesis, clinical course, and treatment options for DIPNECH are not well described. [9,7,10]

To advance our understanding of the clinical features and evolution of this disease over time, we conducted a retrospective study of a convenience sample of 30 patients with DIPNECH diagnosed and evaluated at our institution. We also propose diagnostic criteria for DIPNECH in the hopes of improving the accuracy and timing of the diagnosis.

MATERIALS AND METHODS

Subjects

This study was conducted in accordance with the amended Declaration of Helsinki. This protocol was approved by the National Jewish Health (NJH) Institutional Review Board (HS#2530). Ninety-three potential subjects were identified by query of the NJH Clinical Research Database

for: "Neuroendocrine Hyperplasia" and "Age ≥18" and "High-Resolution Chest CT". Of these 93 cases, 21 could be verified to have DIPNECH by a pathology report. From June 2011 to May 2013, nine additional patients were identified through the NJH pulmonary clinics, bringing the cohort to 30 subjects. Demographic and clinic data were abstracted from medical records. The majority of pulmonary function tests were performed at NJH according to American Thoracic Society (ATS) standards. Results are reported as raw values and percentage of published age-, gender- and height-specific normal values (e.g. percent predicted one-second forced expiratory volume or FEV_1%).[11,12]

Histopathology. Previously acquired lung biopsies or surgical resections (performed from 2005-2012) from 18 subjects were available for review. Immunohistochemical staining using primary neuroendocrine antibodies, (chromogranin, synatophysin and CD56) were performed to confirm the presence of neuroendocrine cells. In each of the 18 cases, airways measuring less than two mm in diameter were assessed. The total number of airways evaluated was compared with the number of airways showing neuroendocrine cell hyperplasia, as demonstrated on H & E staining and neuroendocrine immunostaining. Neuroendocrine cell hyperplasia was characterized as being confined to the bronchial mucosa, present as carcinoid tumorlets within the bronchial wall or as carcinoid tumorlets growing beyond the limits of the bronchial wall. Note was made of changes consistent with constrictive bronchiolitis.

HRCT. 26 subjects had at least one chest HRCT scan available for review. Two chest radiologists, blinded to clinical data, independently scored the scans, and discrepancies were

resolved by a third chest radiologist. HRCT scans were scored for pertinent variables,[8,13] including nodules (number, size, range, largest nodule, distribution), air-trapping, bronchial wall thickening, bronchial dilation, and parenchymal abnormalities. The predominant axial and zonal distribution of nodules was noted. Nodule size range was defined as the largest diameter of the majority of detected nodules. The size, location, shape, and margin characteristics of the largest nodule were assessed. Mosaic attenuation and air-trapping was graded on a 4-point scale, with the predominant axial and zonal distribution recorded.

Statistical Methods

Descriptive statistics were generated for baseline data. For the longitudinal analysis of FEV_1%, mixed-effects, piecewise linear regression models were used (Proc Mixed procedure in SAS) that considered time as a continuous factor. These models used least squares to fit curves to the data to generate estimates for the mean FEV_1% as a function of time in relation to DIPNECH diagnosis. An unstructured variance-covariance matrix was used to model the covariance structure among the repeated measures by subject. All statistical analyses were performed using SAS software (version 9.2; SAS Institute; Cary, NC). We considered $p < 0.05$ to represent statistical significance and did not adjust for multiple comparisons. The Mann Whitney U test was used to compare radiology features of 'rapid progressors' vs. slow-progressors. We defined rapid progression as a loss of 10% of the raw value of FEV_1 within two years.

RESULTS

All subjects were women. The average age at diagnosis was 62 years. Baseline characteristics are presented in Table 1. The majority of subjects (63%) never smoked, and the remaining subjects had quit smoking prior to their DIPECH diagnosis. The most common symptoms were chronic cough and dyspnea. In general, cough developed first, often more than ten years prior to diagnosis. Medical records for the time prior to receiving a DIPNECH diagnosis were available for 27 subjects. Of the 27 cases, 12 had been given a diagnosis of asthma, three COPD, and four bronchiolitis, none arrived at our institution with a diagnosis of DIPNECH.

Pulmonary Function Test (PFT)

All 30 subjects had at least one set of PFTs, and 27 had more than one evaluation. The median duration of pulmonary function follow-up after the diagnosis of DIPNECH was 3.94 years (range 0.34-13.89 years). Twenty-six of 30 subjects had obstructive physiology at the time of diagnosis or during the course of disease monitoring and four had mixed physiology. At diagnosis, 16 (53%) subjects had severe obstruction with a FEV_1% less than 50% predicted, and an additional 3 (10%) had very severe obstruction, FEV_1% less than 30% predicted. In general, the residual volume (RV) and total lung capacity (TLC) were increased. Upon presentation to our institution, the mean percent predicted DLCO was 72.4% (+/- 17%). Three subjects had a significant bronchodilator response according to American Thoracic Society criteria. Twelve of 21 subjects had desaturation ($SpO_2 \leq 88\%$) on walk oximetry.

Data from the longitudinal analysis of FEV_1% is shown in Figure 1. Although the data is suggestive of progressive decline, statistically, none of the slopes for any piece of the regression

line deviated from zero. Despite this, there was heterogeneity between individuals in the risk of worsening pulmonary function. Eight subjects were identified as having rapid progression, (loss of 10% of raw FEV_1 within two years of diagnosis) and another two subjects had significant long-term progression of disease. One subject died of progressive obliterative bronchiolitis due to DIPNECH.

Pathology

Eighteen samples were available for microscopic examination: 11 surgical wedge biopsies (61%), one segmentectomy (6%), and six bronchoscopic biopsies (33%). In their diagnostic evaluations, ten subjects had undergone bronchoscopy with transbronchial biopsies (Table 2): samples from six biopsies were consistent with a diagnosis of DIPNECH; one of these six went on to surgical biopsy to confirm the diagnosis. Transbronchial biopsies from the other four subjects were non-diagnostic; three went on to surgical biopsy that confirmed DIPNECH. The remaining subject was given a clinical diagnosis of DIPNECH. Several subjects were diagnosed by needle biopsy of a pulmonary nodule confirming a typical bronchial carcinoid in the setting of a high-clinical suspicion for DIPNECH (e.g., obstructive physiology and typical HRCT scan findings).

Complete results of the histologic analysis are presented in Table 3. The number of slides evaluated per case ranged from 2 to 24 (mean=7). The total number of airways evaluated per case ranged from 2 to 20 (mean=18). Among subjects who had tissue available for pathologic review, 100% (18 of 18) had carcinoid tumorlets and 28% (5 of 18) had typical carcinoid tumors.

Most of the airways evaluated demonstrated minimal to mild submucosal chronic inflammation. Constrictive bronchiolitis was present in 8 of 18 cases (44%). Of the five cases with carcinoid tumors, two also had constrictive bronchiolitis. Constrictive bronchiolitis was noted in adjacent lung parenchyma and in airways without neuroendocrine cells in 7 of 18 cases (39%). The presence of constrictive bronchiolitis on histology did not predict rapid decline in FEV_1.

Biomarkers. Seven subjects had evaluation with serum chromogranin A, serum serotonin, and 24 hour urine 5-hydroxyindolacetic acid. Four of seven subjects had elevation in serum chromogranin A levels, the remaining biomarkers were normal.

Radiologic Findings

All 26 subjects with HRCT scans available for review had pulmonary nodules. The majority (16/26, 61.5%) had greater than 20 pulmonary nodules, and over one-third had innumerable nodules (greater than 50). In 24 of 26 subjects, the majority of nodules were 6-10mm. Calcification within nodules was rare (3.8%). In 54% of subjects, the nodules were predominantly peri-bronchovascular, while in the remaining 46% the nodules were peripheral. Nodules tended to be in the lower- (54%) or mid- (27%) lung fields. The largest nodule in each subject ranged from 4-40 mm, with a median size of 9.5 mm Most nodules were round (57.7%, 15/26) or oval (23.1%, 6/26) and well-defined (73.1%, 19/26). Between radiologists there was fair agreement of imaging findings, (average Kappa 0.347) and location of abnormalities, (average Kappa 0.373). There was no correlation between decline in FEV_1% and the number or size of nodules on HRCT.

Ninety-six percent (25/26) of subjects had air-trapping, with the following percentage of segmented lung demonstrating air-trapping on expiratory scans: (0-25%: 1 [4.0%]; 26-50%: 5 [20.0%]; 51-75%: 15 [60.0%]; 76-100%: 4 [16.0%]). In the axial plane, air-trapping was most often peripheral (81%) and lobular (46.2%) in configuration. In 21 (84%) of the 25 with air-trapping, there was mosaic attenuation on inspiratory images, suggestive of more severe air-trapping. Bronchial wall thickening was common, occurring in 80.1% of subjects, but bronchial dilation was uncommon (23.1%). Foci of subsegmental scarring or atelectasis occurred in the majority of subjects (73.1%).

Treatment

Octreotide is a somatostatin analog shown to reduce the hormonal hypersecretion of neuroendocrine cells in the setting of GI and bronchial carcinoids[14]. Within our cohort, eleven subjects received treatment with octreotide during the course of disease, in the form of Sandostatin® LAR (long acting release). Of these subjects, nine had repeat pulmonary function tests available for analysis while on therapy. There was no clear trend toward improved PFTs. While on octreotide, three subjects reported improvement in cough that allowed for increased social activity. Two subjects had elevated baseline serum chromogranin A levels decreased to normal range while on octreotide.

DISCUSSION

We identified 30 patients with DIPNECH followed at our institution and detailed their clinical characteristics and disease course over time. To our knowledge, this is the largest DIPNECH cohort assembled. We observed a disease that predominately affects middle-aged women, with slowly progressive, physiological lung obstruction. The striking gender bias of this disease has been observed in previous reports and remains unexplained[5].

We observed substantial heterogeneity in longitudinal disease behavior; although the modeled slopes for FEV_1% suggested no significant declines over time for the population, there was a subset of subjects in our sample who progressed, some rapidly. There are no known predisposing factors to explain the variable clinical progression or prognosis associated with this disease. The fibrosis that accompanies foci of PNC hyperplasia—and even that which affects small airways lacking excess PNCs—has been attributed to the secretion of gastrin releasing peptide (GRP) and other substances secreted by the PNCs. These peptides require further study, but they are capable of stimulating fibroblast proliferation and promoting bronchoconstriction and chemotaxis of airway cells, which may lead to airway wall and peribronchiolar interstitial fibrosis[15]. In our cohort, we observed constrictive bronchiolitis in 44% of cases, however, the histologic presence of constrictive bronchiolitis was not a predictor of rapid progression of physiological obstruction.

At diagnosis, the mean FEV_1 was 50% predicted. Given our and other investigators' data, which suggest that disease progression is typically gradual, most patients with DIPNECH have probably lived with the disease for many years prior to diagnostic confirmation. Upon presentation to our institution, many had been misdiagnosed with more common causes of

obstructive airway disease, such as asthma (40% of subjects), despite only 10% having reversible airflow limitation. There is no know treatment for DIPNECH, although octreotide therapy subjectively improved cough and lowered serum chromogranin A levels, there was no improvement in PFTs.

To date, investigators reporting on patients with DIPNECH have relied on surgical lung biopsy to confirm the diagnosis. However, in the setting of high clinical suspicion for DIPNECH, we believe that a diagnosis can be made with transbronchial biopsy specimens. Based on the data collected in this cohort, we propose diagnostic criteria for DIPNECH (Table 4),that require prospective evaluation prior to adoption All of the subjects in our cohort who had histopathology consistent with the WHO classification of DIPNECH met at least three of the proposed minor diagnostic criteria.

The finding of carcinoid tumors in some, though not all, patients with DIPNECH has led to classification by the WHO as a pre-invasive disease. In our study, 100% (18 of 18) of patients diagnosed with DIPNECH had carcinoid tumorlets and 28% (5 of 18) of patients had typical carcinoid tumors. Studies of cell proliferation in DIPNECH versus pulmonary neuroendocrine cells proliferating as a reaction to lung injury, have shown expression of p53, p16, and Ki67 more consistently and earlier in DIPNECH than in secondary NEC proliferation[16]. This suggests there is a qualitative, possible molecular, difference between secondary NEC hyperplasia and that which occurs in DIPNECH. Molecular profiling of the lesions occurring in DIPNECH deserves future study.

CONCLUSION

DIPNECH is a neuroendocrine proliferation that is predominately seen in middle- aged women. The diagnosis is often delayed until moderate to severe obstruction is present. This disease needs to be considered in the setting of obstructive physiology, particularly when diffuse pulmonary nodules and mosaic pattern air-trapping are present on HRCT. Further studies are needed to improve understanding of the pathogenesis, particularly the gender bias of this disease, and to test the proposed diagnostic criteria. A better understanding of the molecular underpinnings may pave the way for identifying therapeutic targets.

Acknowledgements

Author Contributions:

Dr Carr had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

Dr. Chung contributed to the study design, data analysis, interpretation of results, writing and revision of the manuscript.

Dr. Duarte Achcar contributed to the study design, data analysis, interpretation of results, writing and revision of the manuscript.

Dr. Lesic contributed to the study design, data analysis, interpretation of results, writing and revision of the manuscript.

Dr. Yagihashi contributed to data collection and manuscript revision.

Dr. Rho contributed to data collection and manuscript revision.

Dr. Swigris contributed to the statistical analysis, writing and revision of the manuscript.

Dr. Tate contributed to the study design, interpretation of results and revision of the manuscript.

Dr. Kern contributed to the study design, interpretation of results and revision of the manuscript.

All authors have approved the final manuscript for publication.

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	Number (n=30) (Percentage)
Gender (male/female)	0 (0%)/ 30 (100%)
Tobacco use (former/never)	11 (37%) /19 (63%)
Median age at diagnosis	62 years Range (45-75 years)
Symptoms prior to diagnosis	
Cough	8 (27%)
< 5 years	1 (3%)
5 – 10 years	0 (0%)
> 10 years	7 (23%)
Dyspnea	6 (20%)
< 5 years	3 (10%)
5- 10 years	1 (3%)
> 10 years	2 (7%)
Combination	13 (43%)
< 5 years	3 (10%)
5 – 10 years	3 (10%)
> 10 years	7 (23%)
Diagnosis prior to DIPNECH	
Asthma	12 (40%)
COPD	3 (10%)
Bronchiolitis	4 (13%)
No diagnosis given	8 (27%)
Records unavailable	3 (10%)
Pulmonary function at diagnosis	Mean Percent Predicted (Standard deviation)
FEV_1	49.8 % (+/- 23.9)
FVC	59.1% (+/- 19.4)

FEV_1/FVC	63.4% (+/- 14.0)
RV	223.6% (+/- 97.9)
DLCO	74.7 % (+/- 17.2)
Treatment	
Oral steroids	14 (46%)
Inhaled steroids	20 (67%)
Octreotide (LAR)	11 (37%)
Resection of a carcinoid	9 (30%)

Table 1. Subjects Characteristics

Definition of Abbreviations: FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity; RV = residual volume; DLCO = diffusion capacity; LAR = long acting release;

Pathology Specimen	Number (n=30) (Percentage)
Lobectomy	2 (7%)
Wedge resection	16 (53%)
Transbronchial biopsy	6 (20%)
FNA	1 (3%)
Core needle biopsy	2 (7%)
Post-mortem	1 (3%)
Clinical diagnosis	2 (7%)
Transbronchial biopsy	
Not performed	15
Diagnostic	6
Non-Diagnostic	4 (three diagnosed by surgical resection, 1 given clinical diagnosis)
Unknown	5

Table 2. Pathology Specimens

Definition of abbreviations: FNA = fine needle aspiration

Specimen	Airways: PNCH /Total	Carcinoid tumorlet	Carcinoid tumor	Constrictive bronchiolitis	Airway inflammation
wedge Bx	5/13 (38%)	1/5 (20%)	Absent	Absent	minimal/chronic
TBBX	3/3 (100%)	3/3 (100%)	Absent	Absent	minimal/chronic
wedge Bx	5/16 (31%)	5/5 (100%)	Typical	Absent	moderate/chronic
wedge Bx	5/20 (25%)	4/5 (80%)	Typical	Absent	minimal/chronic
TBBX	2/2 (100%)	2/2 (100%)	Absent	Absent	mild/lymphocytes
EBBX	2/2 (100%)	2/2 (100%)	Absent	Absent	mild/lymphocytes
TBBX	2 /2 (100%)	2/2 (100%)	Absent	Absent	minimal/chronic
wedge Bx	15/20 (25%)	15/15 (100%)	Absent	Present	mild/lymphocytes
wedge Bx	1/13 (7.7%)	1/1 (100%)	Absent	Absent	mild/lymphocytes
wedge Bx	2 /20 (10%)	2/2 (100%)	Absent	Present	minimal/chronic
wedge Bx	7/20 (35%)	7 /7 (100%)	Typical	Present	mild/lymphocytes
wedge Bx	8/20 (40%)	8/ 8 (100%)	Typical	Present	mild/lymphocytes
wedge Bx	5/9 (56%)	3/5 (60%)	Absent	Present	mild/lymphocytes
wedge Bx	5/20 (25%)	4/5 (80%)	Absent	Present	mild/lymphocytes
wedge Bx	6/16 (37%)	6/6 (100%)	Absent	Present	mild/lymphocytes
EBBX	1/2 (50%)	1/1 (100%)	Absent	Absent	mild/lymphocytes
Sublobar	2/3 (66.7%)	1/2 (50%)	Typical	Absent	mild/lymphocytes
TBBX	1/3 (33.3%)	1/1 (100%)	Absent	Present	mild/lymphocytes

Table 3. Pathology Review of Lung Biopsies

Definition of abbreviations: EBBX = endobronchial biopsy, TBBX= transbronchial biopsy, Bx = biopsy, PNCH = pulmonary neuroendocrine cell hyperplasia.

Major Criteria	Surgical Lung Biopsy	Per World Health Organization criteria: generalized proliferation of PNE cells +/- fibrosis, excluding other pathology that may induce reactive proliferation
Minor Criteria	1) Clinical Presentation	Woman, age 45-67 years, cough +/- dyspnea 5-10 years
	2) Pulmonary Function	Increased RV, TLC, Fixed Obstruction, low DLCO that corrects with VA
	3) High-resolution CT	Diffuse pulmonary nodules 4-10mm, >20 nodules, mosaic attenuation or air trapping greater than 50% of lung
	4) Transbronchial Biopsy	Proliferation of pulmonary neuroendocrine cells
	5) Serum Markers	Elevated serum chromogranin A

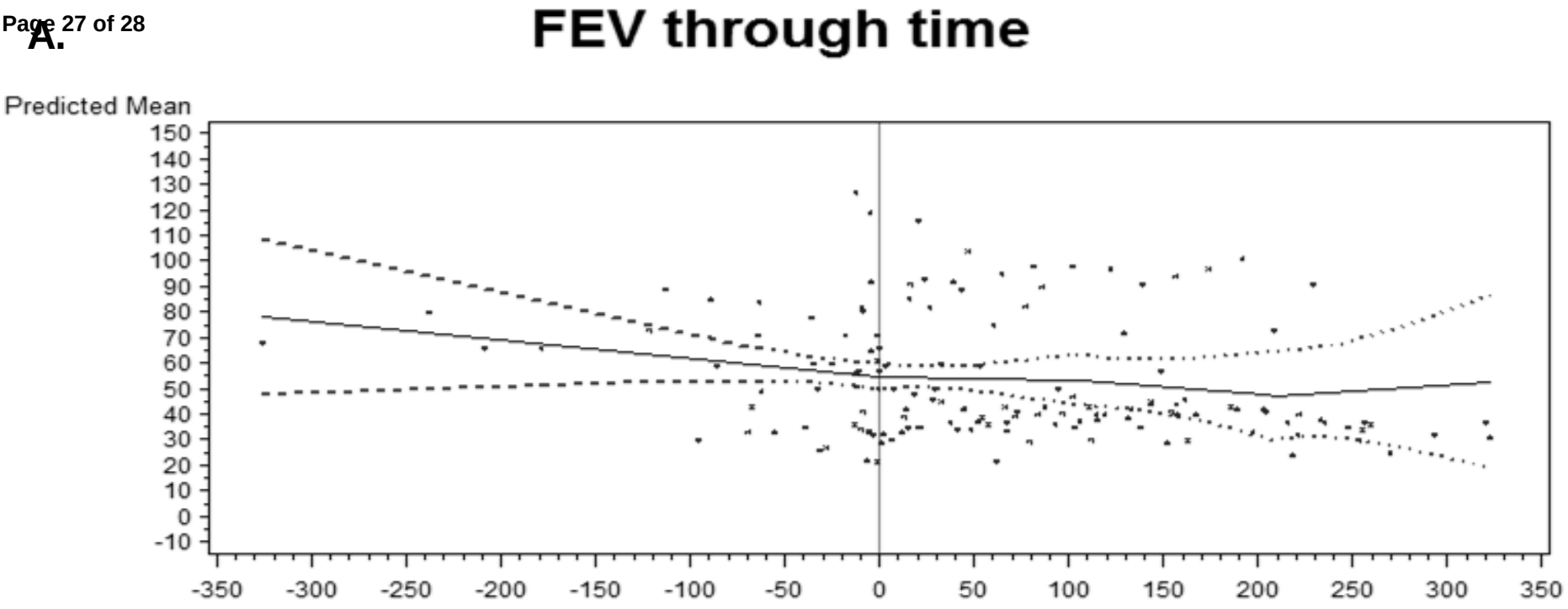
Table 4. Proposed Diagnostic Criteria for Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia.

Definition of abbreviations: RV = residual volume, TLC = total lung capacity, DLCO = diffusion capacity, VA = alveolar volume

Figure 1. Longitudinal analysis of FEV_1% within the DIPNECH cohort. (A) Modeled percentage mean FEV1 with time. Time 0 is time of diagnosis. Dashed lines indicate 95% confidence interval. (B) Percent predicted FEV1 over time for individual subjects.

Figure 2. Multiple axial images from chest CT in a patient with diffuse idiopathic neuroendocrine hyperplasia. (A) Expiratory phase CT shows extensive areas of lobular air-trapping. (B) Multiple scattered pulmonary nodules are also present on inspiratory maximum intensity projection CT.

A.



B.