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Original article

The role of transbronchial cryobiopsy in DIPNECH diagnosis

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Summary

Objective. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare condition for which the diagnostic role of transbronchial lung cryobiopsy (TBLC) remains incompletely investigated. This study compared histological samples obtained by transbronchial lung cryobiopsy (TBLC) with those obtained by surgical lung biopsy (SLB).

Methods. This is an observational retrospective study enrolling adult patients with final diagnosis of DIPNECH histologically proved by TBLC and/or SLB, from 2011 to 2025. Clinical data, pulmonary function tests, BAL findings, CT features, and histology were compared between groups.

Results. Fourteen women with a final biopsy-proven diagnosis of DIPNECH were included: 8 diagnosed by TBLC and 6 by SLB. Median age was 64 years (IQR 59-67). Pulmonary function tests showed airflow obstruction and air trapping, with median FEV1 71.4% predicted (IQR 49.8-90.0), FEV1/FVC 0.67 (IQR 0.57-0.75), and RV/TLC 47.3% (IQR 42.4-53.5). Clinical and radiological features were similar across groups. BAL showed lymphocytosis in 6/9 patients (67%). Histology showed a nonsignificant trend toward more frequent detection of constrictive bronchiolitis in SLB specimens than in TBLC specimens (66% vs 13%; p = 0.09), whereas no significant differences were observed for the other histological features. In the TBLC group, pneumothorax occurred in two cases, neither requiring drainage.

Conclusion. The study suggests that TBLC can represent a valid diagnostic alternative to SLB for DIPNECH, capturing key histological features, though apparently less sensitive for constrictive bronchiolitis. Moreover, a lymphocytic BAL pattern may be observed in DIPNECH and, if confirmed in larger cohorts, could support the diagnostic workup.

Keywords: diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, transbronchial cryobiopsy, surgical Lung Biopsy, constrictive bronchiolitis, pre-invasive lesion

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Introduction

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare and often underdiagnosed condition. The WHO classified it as a pre-invasive lesion characterized by diffuse proliferation of neuroendocrine cells, which may remain intraepithelial or extend beyond the basement membrane to form tumorlets (< 5mm) or carcinoids (≥5mm) [1]. Constrictive bronchiolitis is a common associated feature, likely driven by neuropeptide secretion and inflammatory mechanisms [1]. DIPNECH generally affects middle-aged, non-smoking women, typically presenting with dry cough, dyspnea, or wheezing. In some cases

DIPNECH can also be diagnosed in asymptomatic patients. Pulmonary function tests (PFTs) usually show obstructive or mixed defect, with a slowly progressive or stable course [2].

High resolution computed tomography (HRCT) is the gold standard for the radiological evaluation of these patients, revealing mosaic attenuation with air trapping and multiple small nodules corresponding to tumorlets or carcinoids [3].

Although a clinical-radiological diagnosis may be suggested in the appropriate context, surgical lung biopsy (SLB) remains the diagnostic gold standard (2-3). Transbronchial lung cryobiopsy (TBLC) has emerged as a valuable tool in diffuse parenchymal lung diseases, but its use in DIPNECH has been reported only in a few cases [4-6].

A recent multicenter study highlighted that the diagnostic role of transbronchial lung cryobiopsy (TBLC) remains unclear, with only a few cases reported, while surgical lung biopsy (SLB) is still considered the diagnostic gold standard [7].

The literature has demonstrated the high diagnostic accuracy of TBLC in interstitial pneumonias [8-14].

The primary objective of this study was to assess the role of TBLC through a comparison of histological samples obtained by transbronchial lung cryobiopsy (TBLC) and surgical lung biopsy (SLB). The secondary objective was to describe the clinical, radiological, and histological features of patients diagnosed using these two diagnostic approaches.

Methods

The study was approved by the Institutional Review Board (Comitato Etico Romagna-CEROM approval number:2266/2025).

We conducted a single-center retrospective observational study on adult patients with histologically confirmed DIPNECH diagnosed by TBLC or SLB. Patients were retrieved in the period between September 2011 and July 2025. The inclusion criteria were: age > 18 year, biopsy-proven DIPNECH, samples available for review.

Given the retrospective nature of the study, no predefined allocation criteria were used to assign patients to TBLC or SLB. The choice of biopsy technique was based on multidisciplinary clinical judgement, radiological features, procedural risk, technical feasibility, and patient preference.

Demographic data, comorbidities, exposure and smoking history, medications, symptoms, PFTs, and bronchoalveolar lavage (BAL) cellularity were collected from electronic medical records.

Radiological analysis

Radiological data were interpreted and scored by a thoracic radiologist (S.P. 20 years of experience). The radiological scoring method, adapted from Little et al. [3], consisted in a lobar-based assessment of nodules (categorized as ≤5 mm or ≥ 5 mm), mosaic attenuation, bronchial wall thickening, and bronchiectasis. The final score for the nodules was calculated as the sum of the scores assigned to each of the five lobes. Mosaic attenuation was scored in terms of severity (none, mild, moderate, severe) and distribution (lobular and regional).

Presence of bronchial thickening was recorded as present/absent. Other collateral findings were also recorded.

Histological assessment

Pathological data were interpreted and reviewed by two pathologists with over 20 years of experience in lung histology (V.P. and A.D.). Pathological review was conducted blinded to the patients' clinical information, but not to the biopsy technique, owing to the differences in specimen size.

Histological slides were reviewed for the presence of the following features: neuroendocrine cell hyperplasia, defined as the presence of at least five neuroendocrine cells in a minimum of three separate airways, as proposed by Marchevsky et al. [15]; tumorlets; carcinoids; constrictive bronchiolitis, defined by bronchiolar luminal narrowing or obliteration due to subepithelial fibrosis; peribronchiolar/peribronchial fibrosis; lymphocytic infiltrates, and presence of visceral pleura.

Statistical analysis

Statistical analysis was performed using R software. Descriptive statistics were used to summarize the data. Continuous variables were reported as median (IQR), while categorical variables as absolute numbers (%). Fisher's exact test and Wilcoxon rank-sum test were used to evaluate categorical and continuous variables, respectively. A p-value < 0.05 was considered statistically significant.

Results

Overall, 15 women with a final MDT diagnosis of DIPNECH were identified during the study period. One patient was excluded because histological material was not available for central pathological review; therefore, 14 women (median age 64 years, IQR 59-67) met the inclusion criteria.

Nine patients (64%) were never-smokers, 4 (27%) were former smokers, and 1 (7%) was active smoker. Three

patients (20%) were asymptomatic and were referred to our centre for the evaluation of pulmonary nodules incidentally identified on chest CT scan. Among symptomatic patients, the most common symptoms were cough (80%) and dyspnoea (53%). PFTs were available for 11 patients and showed moderate-to-severe airflow obstruction in 7 patients, together with evidence of air trapping. BAL (n = 9) showed lymphocytosis [23.9 (13.0-31.0)] in 67% of patients with increased CD4/CD8 ratios [4.7 (2.9-5.5)]. The results are summarized in the Table I.

Table I. Clinical and demographic characteristics of patients undergoing TBLC and SLB.

	TBLC	SLB	Overall	p-value
Female sex	-	-	14 (100)	-
Age at diagnosis	-	-	64 (59-67)	-
Smoking status				
Never	-	-	9 (66)	-
Former	-	-	4 (27)	-
Active	-	-	1 (7)	-
Symptoms				
Cough	-	-	11 (80)	-
Dyspnea	-	-	7 (53)	-
Chest pain	-	-	2 (13)	-
Wheezing	-	-	0 (0)	-
None	-	-	3 (20)	-
Co-existing lung diseases				
Follicular bronchiolitis in Sjögren's syndrome	-	-	1 (7)	-
Fibrotic BIP	-	-	1 (7)	-
Bioptical procedure				
TBLC	-	-	8 (53)	-
SLB	-	-	6 (47)	-
Pulmonary function test at diagnosis (n 11)				
Airway obstruction	-	-	7 (64)	-
FVC %	-	-	81.8 (64.0-103.0)	-
FEV1 %	-	-	71.4 (49.8-90.0)	-
FEV1/FVC	-	-	0.67 (0.57-0.75)	-
MEF 25 %	-	-	35.0 (22.0-42.5)	-
MEF 50 %	-	-	39.6 (22.5-51.5)	-
MEF 75 %	-	-	74.1 (51.5-100.5)	-
TLC %	-	-	86.7 (76.5-99.5)	-
RV %	-	-	114.0 (79.5-150.5)	-
RV/TLC %	-	-	47.3 (42.4-53.5)	-
DLCO %	-	-	76.4 (68.0-89.0)	-
Pre-procedure bronchoalveolar lavage (n 9)				
Macrophages %	-	-	75.1 (71.5-81.5)	-
Lymphocytes %	-	-	23.9 (13.0-31.0)	-
CD4+ %	-	-	65.5 (65.5-79.3)	-
CD8+ %	-	-	25.8 (15.0-22.8)	-
CD4+/CD8+	-	-	4.7 (2.9-5.5)	-
Neutrophils %	-	-	5.5 (2.8-7.8)	-
Eosinophils %	-	-	0.6 (0.0-1.0)	-
CT Characteristics (n 12)	7 (58)	5 (42)	-	-
Mosaic attenuation				**0.04 ***
None	0 (0)	1 (20)	1 (9)	-
Mild	0 (0)	2 (40)	2 (17)	-
Moderate	7 (100)	2 (40)	9 (75)	-
Severe	0 (0)	0 (0)	0 (0)	-

Table I. Follows from the previous page..

	TBLC	SLB	Overall	p-value
Pattern of mosaic attenuation				0.7
None	0 (0)	1 (20)	1 (9)	-
Lobular	4 (57)	2 (40)	6 (50)	-
Regional	3 (43)	2 (40)	5 (41)	-
Bronchial thickening	7 (100)	5 (100)	11 (92)	> 0.9
Total lobar score - Nodules ≥ 5 mm				0.5
0	0 (0)	1 (20)	1 (9)	-
1-5	5 (71)	4 (80)	9 (75)	-
6-10	2 (29)	0 (0)	2 (17)	-
11-15	0 (0)	0 (0)	0 (0)	-
Total lobar score - Nodules < 5 mm				> 0.9
0	0 (0)	1 (20)	1 (9)	-
1-5	5 (71)	4 (80)	9 (75)	-
6-10	1 (14)	0 (0)	1 (9)	-
11-15	1 (14)	0 (0)	1 (9)	-
Other findings				
Tree-in-bud + cavitary nodules	0 (0)	1 (20)	1 (9)	-
Tree-in-bud + consolidations	1 (14)	0 (0)	1 (9)	-
Bronchial plugs	2 (29)	0 (0)	2 (17)	-
Patchy ground glass	1 (14)	0 (0)	1 (9)	-
Fibrosis (typical f-HP pattern)	0 (0)	1 (20)	1 (9)	-
Procedural and pathological characteristics (n 14)	8 (57)	6 (43)	-	-
Number of lobes				> 0.9
1	6 (75)	4 (66)	10 (71)	-
2	2 (25)	2 (33)	4 (29)	-
Number of segments				0.6
1	3 (38)	2 (33)	5 (36)	-
2	3 (38)	4 (66)	7 (50)	-
3	1 (13)	0 (0)	1 (7)	-
4	1 (13)	0 (0)	1 (7)	-
Samples				
Larger axis diameter, mm	5.7 (5.5-6.7)	61.3 (46.3-93.0)	36.0 (5.7-46.3)	-
Smallest axis diameter, mm	4.2 (3.7-4.5)	22.0 (21.1-36.9)	16.8 (4.2-21.1)	-
Surface area, mm2	81 (59-95)	2272 (1614-6995)	2584 (80-1614)	-
Pathological characteristics				
Intramucosal linear NEC	7 (88)	6 (100)	13 (93)	> 0.9
Tumorlets	4 (50)	2 (33)	6 (43)	0.6
Constrictive bronchiolitis	1 (13)	4 (66)	5 (36)	0.09
Peribronchial fibrosis	2 (25)	0 (0)	2 (14)	0.5
Lymphocytic infiltrate	4 (50)	2 (33)	6 (43)	0.6
Visceral pleura	2 (25)	6 (100)	9 (64)	-
Accuracy and safety				
Pathological diagnosis	8 (100)	6 (100)	14 (100)	-
Pneumothorax	2 (25)	6 (100)	8 (57)	-
Drainage	0 (0)	6 (100)	6 (43)	-
Bleeding	2 (25)	0 (0)	2 (14)	0.4
Mild	1 (13)	0 (0)	1 (7)	> 0.9
Moderate	1 (13)	0 (0)	1 (7)	> 0.9
Severe	0 (0)	0 (0)	0 (0)	-
Other side effects	0 (0)	0 (0)	0 (0)	-

Data are presented as number (%) and median (interquartile range). P-value is calculated with Fisher's exact test or Wilcoxon rank sum test. Abbreviations: BIP = bronchiolocentric interstitial pneumonia, TBLC = transbronchial lung cryobiopsy, SLB = surgical lung biopsy, % = percentage of predicted, FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 second, MEF 25 = maximum expiratory flow at 25%, MEF 50 = maximum expiratory flow at 50%, MEF 75 = maximum expiratory flow at 75%, TLC = total lung capacity, RV = residual volume, and DLCO = diffusing capacity of the lung for carbon monoxide, CD4+ = CD4-positive lymphocytes, CD8+ = CD8-positive lymphocytes, IP = interstitial pneumonia, BIP = bronchiolocentric interstitial pneumonia, NECH = neuroendocrine cells hyperplasia

Radiological analysis

CT scan images were available in twelve patients. The most representative changes were: mosaic attenuation (92%; with a moderate extension in 75%) and bronchial thickening (evident in 92%), and bronchial plugs (in 17% of cases).
Most patients (75%) showed an intermediate total nodule score of 9 for both nodules < 5 mm and nodules ≥5 mm (radiological score range: 0–15) (Fig. 1).
TBLC and SLB groups showed similar radiological findings.

Procedural safety

Two TBLC patients (25%) developed pneumothorax, none requiring drainage, while all SLB patients required hospitalization for at least three days. Bleeding occurred in 2 TBLC patients (25%), both episodes were non-severe and successfully managed with Fogarty balloon bronchial occlusion.

Histological analysis

Histology showed the typical features of DIPNECH in both groups (Fig. 2, Tab. I). Intramucosal linear neuroendocrine cell hyperplasia was detected in 7/8 TBLC cases (88%) and in 6/6 SLB cases (100%; $p > 0.9$). Tumorlets were identified in 4/8 TBLC specimens (50%) and 2/6 SLB specimens (33%; $p = 0.6$). Lymphocytic infiltrates were present in 4/8 TBLC specimens (50%) and 2/6 SLB specimens (33%; $p = 0.6$). Constrictive bronchiolitis was more frequently observed in SLB specimens than in TBLC specimens (4/6, 66% vs 1/8, 13%), although this difference did not reach statistical significance ($p = 0.09$).

Discussion

This series, the largest to date describing DIPNECH diagnosed by TBLC, suggests that TBLC may be a promising alternative to SLB in identifying the hallmark histological features of DIPNECH. The diffuse distribution of neuroendocrine hyperplasia and tumorlets may facilitate their detection even in the smaller TBLC specimens, whereas bronchiolar changes, more focal,

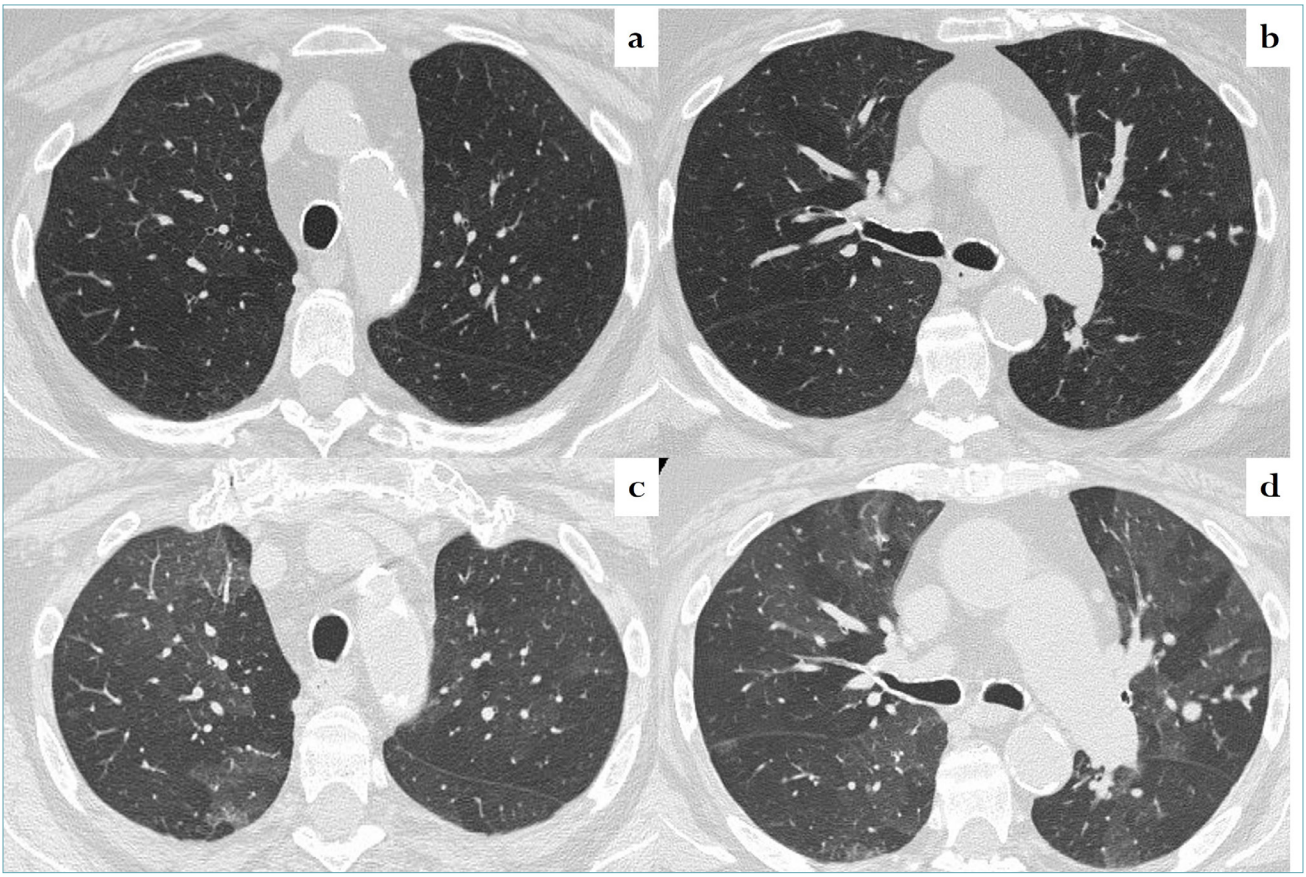


Figure 1. CT scan: a-b. Inspiratory images show bilateral hypoattenuation, a left upper lobe nodule with distal mucus plugging, and bronchial wall thickening. c-d. Expiratory images demonstrate bilateral air trapping.

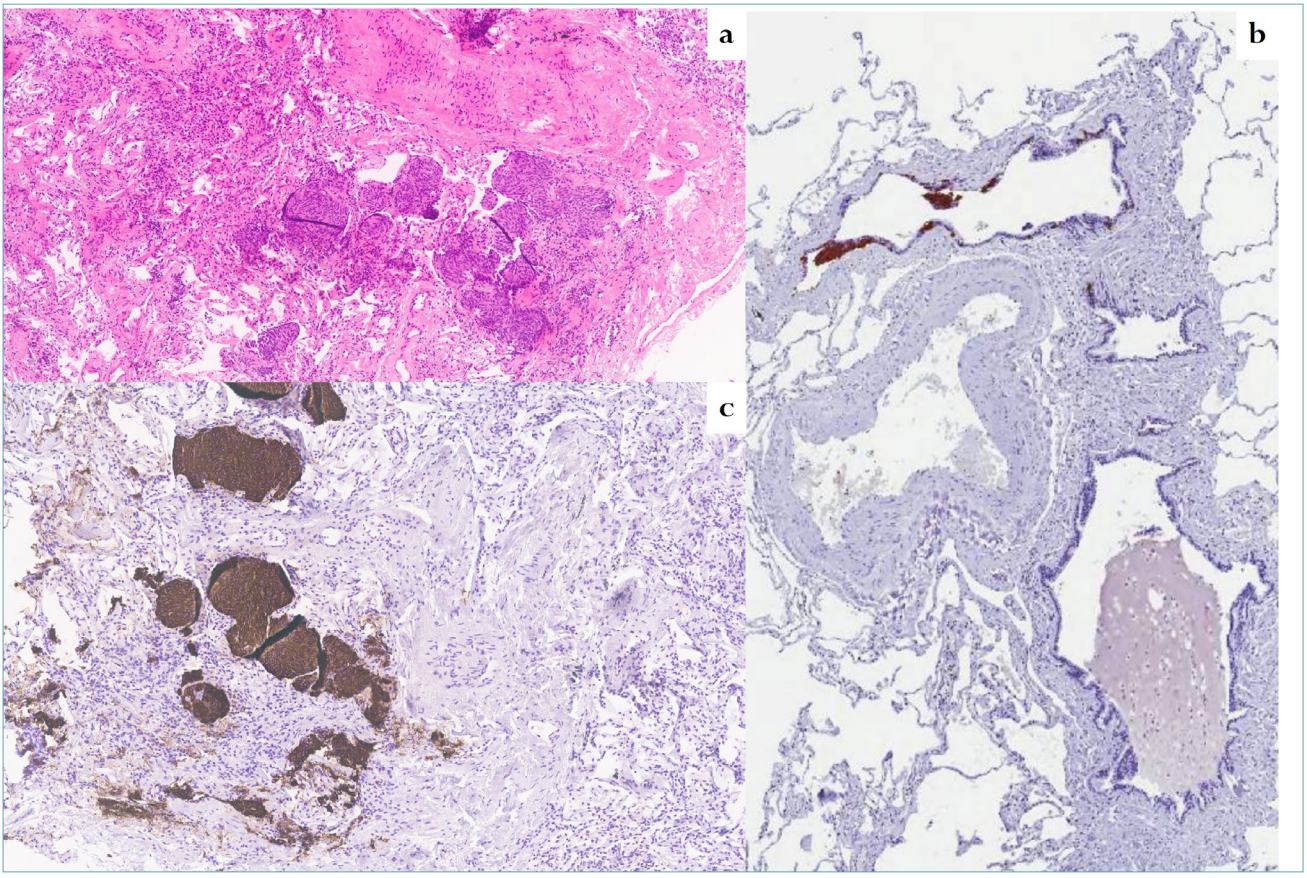


Figure 2. a. Transbronchial cryobiopsy: small cells infiltrating the wall and partially occluding the lumen of bronchioles, forming small nodules (tumorlets) x (H&E, 7.5) b. Transbronchial cryobiopsy: bronchiolar lumens with the wall thickened by fibrosis. linear neuroendocrine cells hyperplasia is present in one (chromogranin, x10) (arrow). c. Transbronchial cryobiopsy: Immunohistochemically, these cells show positive reactivity for chromogranin, a neuroendocrine marker (chromogranin, x 7.5).

could be more frequently captured by SLB.

The epidemiological, clinical, functional and radiological profile of our cohort was consistent with previous studies, being characterised by a predominance of middle-aged, mostly never-smoking women, frequent dyspnoea and dry cough, obstructive ventilatory impairment on PFTs, and classic radiological features of DIPNECH, including mosaic attenuation, bronchial wall thickening and pulmonary nodules [7].

The presence of lymphocytic infiltrates (nearly half of the specimens) and BAL lymphocytosis with an increased CD4+/CD8+ ratio (two-thirds of available BAL) in both biopsy groups appears consistent with previous literature, although only limited data are currently available [2,5,16]. The presence of a lymphocytic alveolitis in this setting may be related to the proliferation of neuroendocrine cells leading to the production of neuropeptide growth factors, such as Bombesin and Gastrin-releasing peptide [17]. Both peptides have been shown to act as proinflammatory mediators, promoting lung injury through macrophage and fibroblast activation, as well as lymphocytes and endothelial cell proliferation [17]. Further studies with larger patient cohorts are needed to better characterize BAL cell counts in DIPNECH and to assess whether it could contribute to a less invasive diagnostic approach combined with typical radiological features.

From a pathological point of view, TBLC detected the main neuroendocrine proliferative features of DIPNECH, including intramucosal linear NECH and tumorlets, with no significant differences compared with SLB. Constrictive bronchiolitis was more frequently observed in SLB specimens, although without reaching statistical significance. Constrictive bronchiolitis is characterized by subepithelial fibrosis involving membranous and respiratory bronchioles, with fibrotic remodelling surrounding rather than filling the lumen and leading to concentric narrowing or complete luminal obliteration [9,18,19]. These bronchiolar alterations are typically patchy and may be subtle, even in clin-

ically relevant disease, and can therefore be missed in smaller samples [9,18,19]. Moreover, constrictive bronchiolitis may support the diagnosis of DIPNECH, but its presence is not mandatory (7,16,20,21). In the largest recent multicentre study by O'Callaghan et al. [7], bronchiolitis was reported in only 21.0% of specimens and was classified as obliterative in a minority of these cases, supporting the concept that bronchiolar remodelling is not invariably detected in pathological specimens from patients with DIPNECH. In addition, no prognostic role of constrictive bronchiolitis has been demonstrated, as reported by Carr et al. [16]. By contrast, intramucosal linear NECH and tumorlets are relatively diffuse throughout the lung parenchyma [9,18,19] and are more frequently described in patients with DIPNECH [7]. Taken together, these findings suggest that, within a multidimensional assessment integrating clinical, radiological and pathological data, TBLC may contribute to the diagnosis of DIPNECH, although bronchiolar remodelling may be underestimated compared to SLB in selected cases. Larger prospective cohorts are needed to confirm these findings.

The pneumothorax rate was consistent with larger TBLC series [8-14], suggesting an acceptable safety profile.

This study has some limitations. First, the small sample size limits statistical power, and the findings should therefore be interpreted as exploratory. Second, the retrospective design may have introduced selection bias, as the criteria guiding the choice between TBLC and SLB were not prospectively defined. Moreover, because patients were selected on the basis of a histological diagnosis of DIPNECH, this study was not designed to assess the diagnostic yield, sensitivity, or specificity of the two procedures.

In conclusion, in this retrospective series TBLC appeared to be a safe and feasible option for the histological diagnosis of DIPNECH, and a promising alternative to SLB. Moreover, our study highlights a frequent lymphocytic BAL pattern with an increased CD4+/CD8+ ratio, which, if confirmed, could support the diagnostic workup. Prospective multicenter studies are needed to validate the role of TBLC in DIPNECH and better define its diagnostic yield.

Conflicts of interest statement

The authors declare no conflicts of interest.

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Authors' contributions

Matteo Morviducci: literature search, data collection, data analysis, statistical analysis, manuscript preparation

Sara Piciucchi: data analysis (radiology), statistical analysis, manuscript preparation, editing and review, guarantor

Stefano Oldani: data acquisition, manuscript review.

Simone Petrarulo: data acquisition, manuscript review.

Alessandra Dubini: data acquisition and analysis (histology), manuscript review.

Matteo Costantini: data acquisition and analysis (histology), manuscript review.

Paolo Palange: manuscript review.

Claudia Ravaglia: data acquisition (transbronchial biopsy procedure), manuscript review.

Venerino Poletti: conceptualization, design, definition of intellectual content, data acquisition (transbronchial biopsy procedure, histology) and analysis (histology), manuscript review, guarantor.

Ethical consideration

This study was approved by the Institutional Ethics Committee Institutional Review Board (Comitato Etico Romagna-CEROM approval number:2266/2025).

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

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