


# Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia diagnosed by transbronchoscopic cryoprobe biopsy technique

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## Keywords

Biopsy, cryoprobe, neuroendocrine, transbronchial, DIPNECH.

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## Introduction

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is an uncommon pulmonary disease, recognized by the World Health Organization (WHO) as a precursor to carcinoid tumours. Pathology is precipitated by pulmonary neuroendocrine cells (PNEC) and neuroepithelial bodies (NEB), leading to interstitial and peribronchiolar fibrosis. More common in females, patients characteristically present with chronic cough and dyspnoea, often with evidence of obstruction on pulmonary function testing (PFT). Progressive obstructive pulmonary deficits are a result of its association with obstructive bronchiolitis [1]. High-resolution chest computed tomography (CT) can be unremarkable but will frequently show mosaic attenuation with air trapping, pulmonary nodules, and fibrosis. The nodules may be so innumerable that they raise concern for metastatic malignancy. Surgical lung biopsy is the gold standard for the diagnosis of DIPNECH due to the large amount of tissue required for the proper pathological

## Abstract

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) remains a poorly understood clinical entity. It is currently classified as a premalignant condition by the World Health Organization (WHO). Symptoms are similar to those associated with obstructive lung disease, including breathlessness and cough. The presentation is often initially ascribed to other diseases such as asthma or chronic obstructive pulmonary disease. Here, we present what we believe is the first described case of DIPNECH diagnosed by transbronchoscopic cryoprobe biopsy. The patient presented with chronic cough, dyspnoea, pulmonary function tests consistent with obstruction, and a computed tomography (CT) scan of chest with multiple nodules. The patient went on to have transbronchoscopic cryoprobe biopsies of the lung, which confirmed the diagnosis of DIPNECH.

analysis [2]. Transbronchial biopsy (TBB) plays an important role in the diagnosis of various pulmonary diseases, such as sarcoidosis and malignancies; however, it has been less useful as a tool in the diagnosis of interstitial lung diseases or, in this case, DIPNECH. The primary reason for this latter observation may be the relatively small size of the biopsies obtained by routine TBB [3].

A novel approach to patients with suspected DIPNECH may be the use of transbronchoscopic cryoprobe biopsy. The specimen sizes obtained are typically larger than those obtained by TBB. This may increase the diagnostic yield of various parenchymal lung diseases and, in effect, mitigate the need for open surgical lung biopsy or video-assisted thoracic surgical biopsy [4]. The histopathological differential diagnosis includes reactive proliferation of PNEC in chronically damaged or inflamed lung; however, the absence of damaged or inflamed lung excludes this. Despite using the biopsy method, the distinct pathological findings described above would confirm DIPNECH.

## Case Report

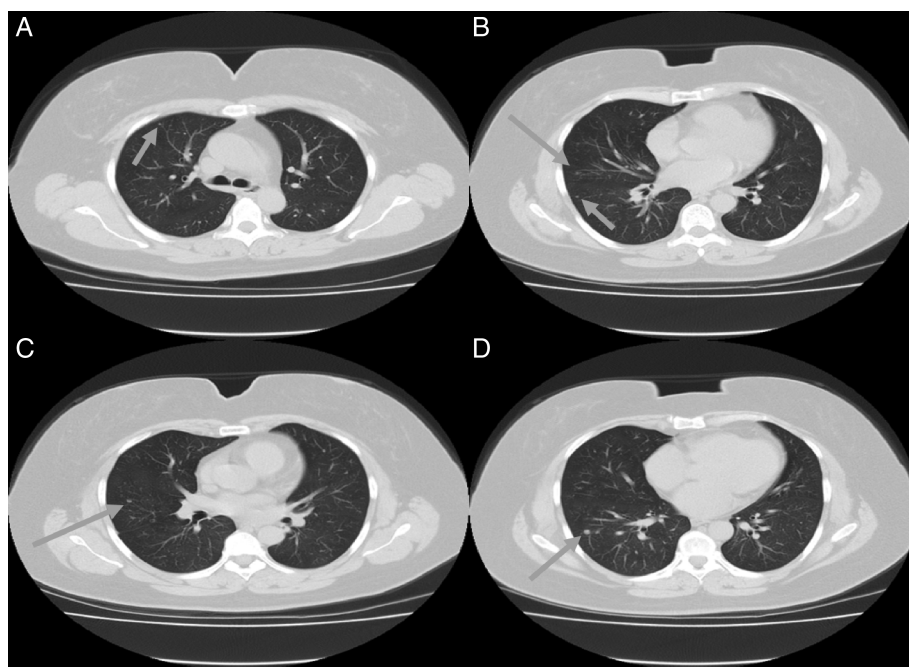
A 41-year-old Hispanic female with no smoking history presented after a 3-year history of predominantly dry cough and an abnormal CT scan of the chest. She was living in Arizona at the time of symptom onset and was diagnosed with *Chlamydia pneumoniae* on sputum cultures. She completed a 3-month course of doxycycline due to persistence of symptoms. Past medical history is significant for gastroesophageal reflux disease, well controlled with oral pantoprazole, in addition to no recent hospitalization or sick contacts. Physical examination reveals a 98°F temperature, blood pressure 122/90 mmHg, pulse 70 bpm, respirations of 15/min, peripheral capillary oxygen saturation (SpO<sub>2</sub>) 95% on room air at rest, and body mass index (BMI) of 32. Head and neck examination of any palpable adenopathy is absent. Cardiovascular examination is normal. Lungs reveal mild late-end expiratory wheezes bilaterally. Abdomen is large, without palpable organomegaly or tenderness. There is no cyanosis, clubbing, or oedema. Medications such as albuterol, montelukast, pantoprazole, tiotropium, calcium, and cyanocobalamin are inhaled. Laboratory studies are normal, including complete blood count (CBC) with differential, comprehensive metabolic panel, and serum total immunoglobulin E (IgE). Her PFT shows evidence of severe obstruction with no bronchodilator response, mild restriction, and reduced Diffusing capacity for carbon monoxide (DLCO), which is normal when corrected for alveolar volume. Her chest X-ray is unremarkable. CT chest (Fig. 1) shows air trapping with bilateral diffuse micronodularity. The lingular bronchoalveolar lavage (BAL) is effluent, with

62% lymphocytes, which is neither specific nor sensitive for DIPNECH. Biopsies from the lateral, medial, and posterior segments of the right lower lobe are obtained via transbronchoscopic cryoprobe. Histopathology (Fig. 2) in all biopsy specimens shows normal alveolar parenchyma and large amounts of bronchial wall mucosa. Within the bronchial submucosa is a focal 1.2-mm carcinoid tumourlet. Well differentiated neuroendocrine cell hyperplasia with scattered small nests and a focal linear array of PNEC are present throughout the base of the bronchial mucosa, which are consistent with DIPNECH. Few patients with DIPNECH progress to respiratory failure. She remains clinically stable, which is consistent with the majority of patients with DIPNECH.

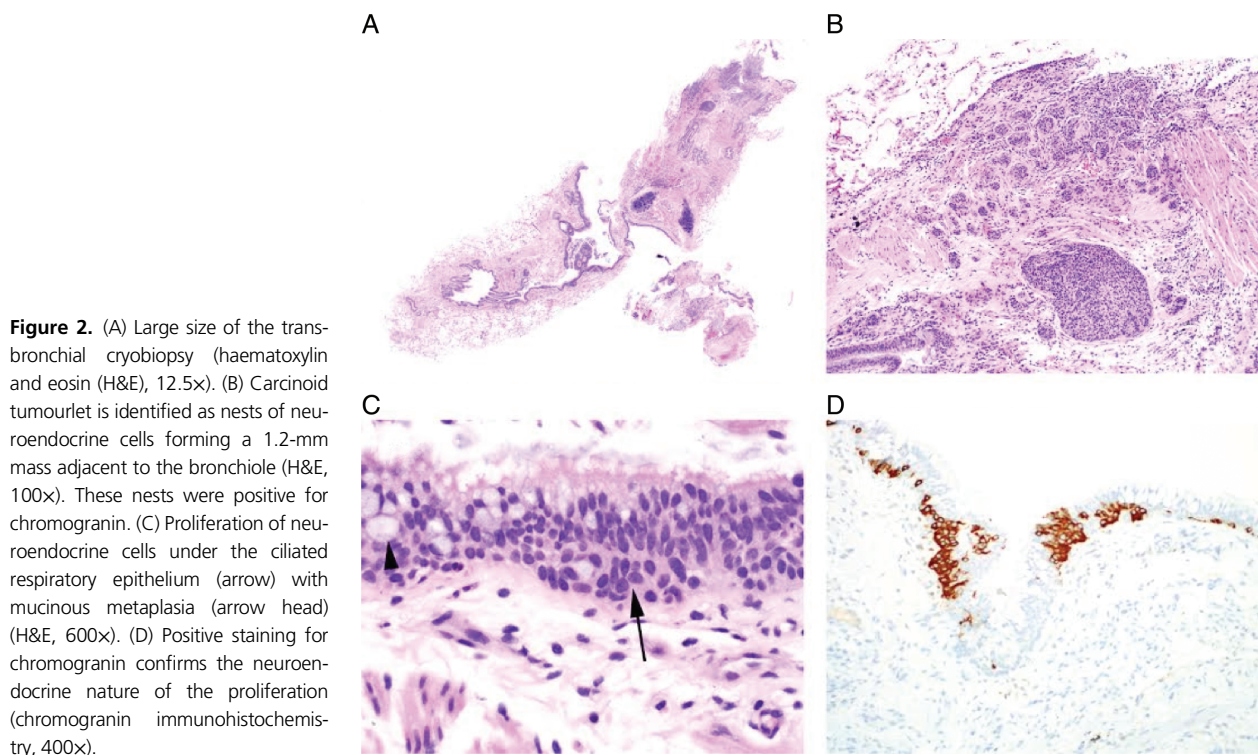
## Discussion

There has been an increased diagnostic and therapeutic role for flexible fibre-optic bronchoscopy since its introduction by Ikeda in 1968. Transbronchial biopsy is often considered in the evaluation of patients with abnormal CT scans of the chest, the limitations of which include the small size of the typical biopsy specimen and crush artefact. Diagnostic yield improves with increased quantity and size of biopsies via larger forceps. These adjustments, however, have not significantly improved the ability to diagnose a multitude of diffuse interstitial lung diseases [3].

Introduced in the late 1990s, transbronchoscopic cryoprobe has shown promise as a useful diagnostic tool for



**Figure 1.** Computed tomography of the chest without evidence of bronchiectasis but showing multiple micronodules (arrow heads) and a mosaic appearance in keeping with air trapping.



**Figure 2.** (A) Large size of the trans-bronchial cryobiopsy (haematoxylin and eosin (H&E), 12.5x). (B) Carcinoid tumourlet is identified as nests of neuroendocrine cells forming a 1.2-mm mass adjacent to the bronchiole (H&E, 100x). These nests were positive for chromogranin. (C) Proliferation of neuroendocrine cells under the ciliated respiratory epithelium (arrow) with mucinous metaplasia (arrow head) (H&E, 600x). (D) Positive staining for chromogranin confirms the neuroendocrine nature of the proliferation (chromogranin immunohistochemistry, 400x).

many diffuse parenchymal lung diseases. The cryoprobe system operates under the Joule-Thomson effect, where a compressed gas (nitric oxide or carbon dioxide) under high flow rapidly expands upon exposure to atmospheric pressure, yielding a temperature of  $-89^{\circ}\text{C}$  for  $\text{N}_2\text{O}$  and  $-69^{\circ}\text{C}$  for  $\text{CO}_2$ . The probe comes in two diameters of 1.9 mm and 2.4 mm. Prior to performing the biopsy, the probe's location is confirmed under fluoroscopy. Despite the size of probe, the tissue mass is larger and of superior quality, with fewer crush artefacts and intact structural integrity compared to the TBB specimen. A less-invasive diagnostic procedure has the potential to reduce complications following open lung biopsy, including increased 90-day mortality, cardiac arrhythmias, infections, prolonged air leakage, and persistent thoracic pain [4].

At Tampa General and James A. Haley Veterans Hospitals, this procedure is performed under general anaesthesia with endotracheal intubation. A BAL is performed prior to biopsy, after which the biopsy site is irrigated with 4 mL epinephrine. Once the site, at least 15 mm proximal from the pleura, is confirmed with fluoroscopy, the target is frozen for 3–5 s. The cryoprobe is removed with the bronchoscope from the endotracheal tube, and the sample is placed in formaldehyde solution. In the event of bleeding, 50 mL aliquots of cold saline followed by 1–2 mL topical epinephrine (1:10,000) can be used for haemostasis. Fluoroscopy is used to assess for evidence of pneumothorax.

Data collected from over 300 cryobiopsies performed at these hospitals had a 5.4% incidence of pneumothorax and no significant bleeding [5].

### Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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