


# Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia presenting as a solitary lung nodule: a rare histopathological diagnosis

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## Abstract

We present a case of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) in a 56-year-old woman, who presented to our emergency department with a 7-day history of exertional dyspnoea. Due to profound haemodynamic compromise, pulmonary embolism (PE) was suspected, and the patient underwent emergency thrombolysis on admission. A subsequent computerized tomography pulmonary angiogram revealed extensive bilateral PE. Incidentally, a 1.3 cm lesion within the right upper lobe, associated with pleural tethering, was identified. Positron emission tomography computerized tomography and, subsequently, histopathology revealed this lesion to be primary DIPNECH, a rare pre-invasive hyperplasia of neuroendocrine cells. While studies are scarce and cohort numbers are low, somatostatin analogues and protein kinase inhibitors have been proven to reduce symptoms and increase progression-free survival in DIPNECH, respectively.

## INTRODUCTION

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare pre-invasive hyperplasia of neuroendocrine cells that typically manifests in non-smoking middle-aged women. It is considered a precursor to pulmonary carcinoid tumours. Around half of patients diagnosed with DIPNECH are asymptomatic with symptomatic patients usually complaining of exertional dyspnoea, wheezing and a non-productive cough. DIPNECH is usually misdiagnosed as chronic obstructive pulmonary disorder, or asthma as pulmonary function tests may represent an obstructive picture [1]. Just under half of diagnosed DIPNECH patients have evidence of concurrent carcinoid disease [2].

## CASE REPORT

A 56-year-old Caucasian woman presented to the emergency department with a 7-day history of exertional dyspnoea. Relative past medical history included an unprovoked iliofemoral deep vein thrombosis. It is also of note that she reported a previous 20-pack-year smoking history but denied smoking for some months prior to presentation. Exposure to hazardous chemicals was not documented in patient records. Her medication history

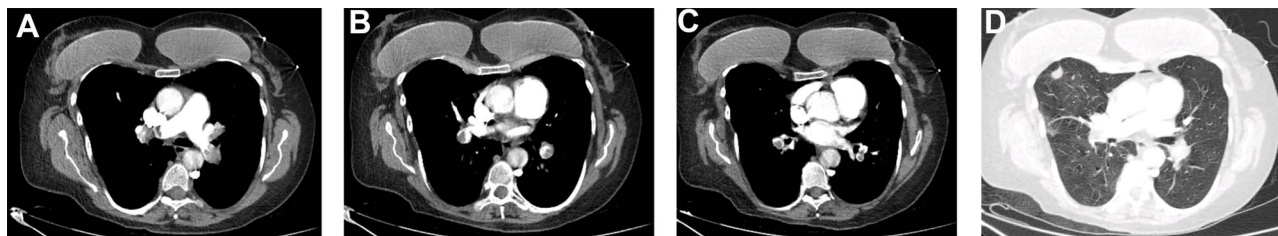
was unremarkable. She had no evidence of preceding prolonged immobility or a family history of prothrombotic conditions. Her admission observations revealed a blood pressure of 111/70 mmHg, an oxygen saturation of 97% on 5 l of oxygen and a heart rate of 124 beats per minute. She appeared pale and was tachypnoeic; however, she denied chest pain. Shortly after presentation, her systolic blood pressure dropped to 40 mmHg, and she became less responsive. A bedside ultrasound scan revealed a dilated akinetic right ventricle. She was in type 2 respiratory failure. Significant laboratory tests included an elevated white blood cell count, C-reactive protein and D-dimer. She was thrombolysed as per local pulmonary embolism (PE) protocols and a subsequent computerized tomography pulmonary angiogram revealed extensive bilateral PE with features of high-grade right heart strain (Fig. 1A–C).

An incidental finding of a 1.3 cm lesion within the right upper lobe associated with pleural tethering was seen and thought to represent benign atelectasis. She underwent a period of close observation as an inpatient and was discharged once her oxygen saturations were stable without supplementary oxygen. Echocardiography performed 7 days post-discharge was unremarkable. A follow-up computerized tomography

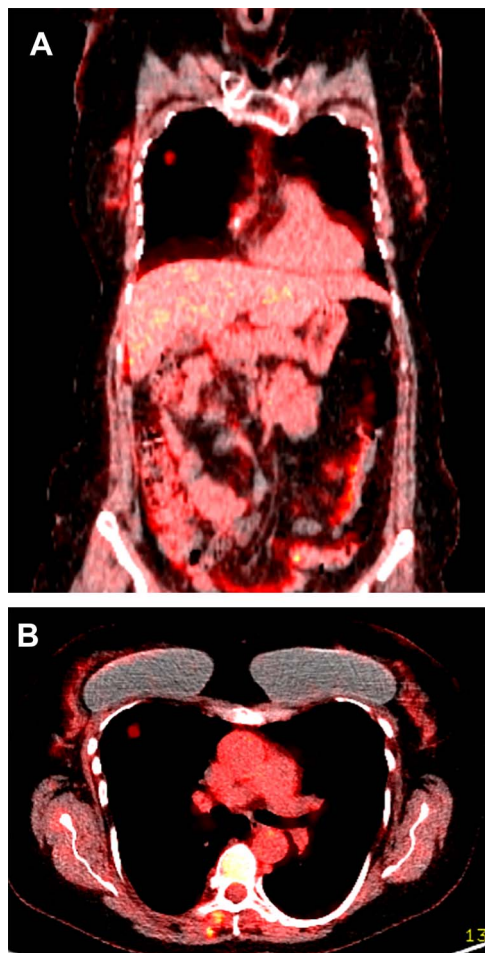
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**Figure 1.** (A–C) Axial CT scans showing diffuse bilateral pulmonary embolism. White arrows point to visible embolic disease. (D) Axial CT showing right upper lobe nodule with associated pleural tethering. White arrow points to the right upper lobe nodule.



**Figure 2.** (A, B) Positron emission tomography computerized tomography (PET-CT) scans outlining the metabolically active lesion in the right upper lobe. A white arrow points to the metabolically active lesion. (A) Coronal PET-CT scan. (B) Axial PET-CT scan.

(CT) thorax at 5 months post-discharge revealed a stable appearance of the 1.3 cm lesion. A positron emission tomography computerized tomography scan displayed a fluorodeoxyglucose-avid 10 mm right perifissural lung nodule of maximum SUV 3.4 (Fig. 2A and B).

Unprovoked PE always necessitates thorough investigation for autoimmune disorders, thrombophilia, concurrent use of thrombogenic drugs or malignancy, which was particularly relevant given synchronous evidence of a metabolically active solitary lung lesion. Distant malignancy was ruled out following further imaging

**Table 1.** Pulmonary function tests

Pulmonary function test	Value
Forced expiratory volume in 1 second (FEV1)	1.36 (55%)
Forced vital capacity (FVC)	2.34 (80%)
Ratio of FEV1 to FVC	58%

and an autoimmune and thrombophilia panel was unremarkable.

The patient underwent wide local excision of the right middle lobe of the lung 5 months after initial emergency presentation. Histopathology of surgical specimens revealed a firm well-defined lesion consisting of suppurative granulomata with fibrosis, carcinoid tumourlets and squamous metaplasia, all indicative of DIPNECH.

Follow-up CT scans have been carried out at 6-month intervals and have all been clear, with no signs of recurrence, to the present day. Short acting beta-2 agonist and steroid inhalers were administered as the patient had evidence of bronchospasm and her pulmonary function tests (Table 1) revealed a moderately obstructive picture. Bronchodilation seemed to help with symptom control. Further, lifelong anticoagulation was prescribed with regular follow-up in the outpatient respiratory clinic. If she suffered further disease progression, somatostatin analogues would be considered as a secondary therapeutic.

## DISCUSSION

DIPNECH is a pre-malignant condition characterized by diffuse proliferation of pulmonary neuroendocrine cells. It is diagnosed either incidentally or following investigation for obstructive airway disease. Common presenting symptoms are non-specific and include a non-productive cough and exertional dyspnoea. The World Health Organization proposed criteria for the histopathological diagnosis of neuroendocrine proliferative disorders in 2015. DIPNECH is defined as neuroendocrine cell proliferation confined to the airway mucosa, with nodules extending beyond bronchiolar epithelium basement membrane or the airway wall termed tumourlets (<5 mm) or carcinoid tumours (>5 mm). Radiological appearances often mimic metastatic disease [1].

Symptomatic DIPNECH has been shown to be responsive to somatostatin analogues, azithromycin and

everolimus (a protein kinase inhibitor) [3]. mTOR, an intracellular protein kinase of the phosphoinositide-3 kinase family, is a key player in the cell signalling pathway underpinning the development of neuroendocrine tumours. mTOR forms two complexes: mTORC1 and mTORC2. mTORC1 complex mediates Cap-dependent translation and elongation, mRNA and ribosomal biogenesis and mRNA translation, rRNA and tRNA transcription, transcription of lipogenic genes, autophagosome formation, lysosomal biogenesis, energy metabolism and cytoskeletal organization [4]. Protein kinase inhibitors, such as everolimus, modulate this pathway and have been proven to increase progression-free survival and possess a suitable tolerability profile [5]. Somatostatin analogues pose as another promising treatment option, improving symptoms in patients with DIPNECH, although only increasing functional expired velocity in 1 second (FEV1) in around one-quarter of tested patients [6]. While, in this reported case, our patient described symptomatic improvement from bronchodilation and inhaled corticosteroids, recent literature highlights the limitations of these management strategies. In one study less than a quarter (17%) of patients receiving bronchodilators reported symptomatic improvement and in those administered inhaled corticosteroids, only 22% experienced symptomatic improvement [7]. Notably, the same can be said for somatostatin analogue octreotide, which was successful in reducing symptoms in only 29% of patients [7].

Neuroendocrine tumours often oversecrete hormones. In one case study, DIPNECH has been associated with overproduction of adrenocorticotrophic hormone (ACTH) leading to Cushing's syndrome, a condition that increases the chance of developing thromboembolic disease [8]. In this case report, our patient was diagnosed with DIPNECH after an incidental radiological finding of a 1.3 cm lesion, found while investigating for pulmonary embolic disease. One case report has documented PE to be the initial presenting symptom in a confirmed case of bronchial carcinoid [9]. A further case report has documented unfortunate fatal paraneoplastic embolic disease in a patient with liver biopsy findings confirming metastatic disease of a poorly differentiated neuroendocrine tumour [10]. Somatostatin inhibits ACTH secretion, and this mechanism may underpin the utility of somatostatin analogues as a treatment option for DIPNECH. Obtaining a hormonal profile on all neuroendocrine tumours is paramount as it will help dictate possible treatment methods. For example, the utility of oral corticosteroids as a negative feedback mediator, to reduce ACTH production, in DIPNECH, is yet to be evidenced in studies. This is the case for numerous other proposed treatments. One may surmise that concomitant unprovoked PE in cases of DIPNECH is due to altered hormonal profiles secondary to oversecretion by neuroendocrine cells. An association analysis regarding thromboembolic disease and DIPNECH will help clarify

this relationship; however, it may be difficult to obtain, given the rarity of the condition.

For localized disease, the gold standard treatment is surgical resection, in the form of wedge resection or segmentectomy, with the latter offering greater prevention in tumour recurrence [11].

## CONFLICT OF INTEREST STATEMENT

None.

## FUNDING

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## ETHICAL APPROVAL

Not applicable.

## CONSENT

Full appropriate consent for anonymous publication gained by Dr Mostafa Negmeldin (Consultant Physician responsible for the patient's care at time of case).

## GUARANTOR

Not applicable.

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