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DIPNECH: A RARE CAUSE OF SLOW-GROWING PULMONARY NODULES IN A DYSPNOEIC PATIENT WITH A HISTORY OF BREAST CANCER

Peter Cassar[1], Dione Buhagiar[2], Jonathan Gauci[3], Kyra Bartolo[3], Adrian Mizzi[4], Andrew Mallia[5], Josef Micallef[3]

[1] Department of Nephrology, Mater Dei Hospital, Msida, Malta
[2] Department of Internal Medicine, Mater Dei Hospital, Msida, Malta
[3] Department of Respiratory Medicine, Mater Dei Hospital, Msida, Malta
[4] Department of Medical Imaging, Mater Dei Hospital, Msida, Malta
[5] Division of Nuclear Medicine, Department of Medical Imaging, Mater Dei Hospital, Msida, Malta

Corresponding author's e-mail: dione.buhagiar.1@gov.mt

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ABSTRACT

A middle-aged woman undergoing a computed tomography scan while being investigated for a retrosternal goitre, was found to have several solid intrapulmonary nodules of varying sizes with mosaic attenuation of lung parenchyma. After serial radiology follow-up, a radiologist with a special interest in thoracic imaging made the tentative diagnosis of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) during discussions at the local multidisciplinary team meeting. Radionuclide imaging was performed to assist in reaching a diagnosis. Uptake of DOTATATE by the pulmonary nodules on a background of mosaic attenuation pattern supported a diagnosis of DIPNECH. Potential secondary metastatic disease from previous breast malignancy confounded a possible earlier diagnosis of DIPNECH, with subsequent diagnostic imaging modalities leading to the rare diagnosis. The patient was treated symptomatically with oral steroids with no improvement, and subsequently with octreotide which significantly improved her condition.

KEYWORDS

DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia syndrome

LEARNING POINTS

- Clinical symptoms of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) are common to several other respiratory conditions that are found ubiquitously in the community; being aware of this rare condition will help in reaching a diagnosis in a timelier manner.
- Several potential treatments are described in the literature including steroid therapy, cytotoxic agents and somatostatin analogues, which despite their efficacy have not been demonstrated in studies; however, a small number of case reports such as this one showed an improvement in symptomatology with this treatment.

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CASE DESCRIPTION

A 60-year-old female with a history of invasive ductal carcinoma was undergoing evaluation for an intrathoracic extension of a multinodular goitre, diagnosed by ultrasound. A subsequent computed tomography (CT) scan of her neck and thorax revealed multiple intrapulmonary nodules and mosaic attenuation *(Fig. 1)*, raising concerns about potential secondary cancer deposits given the previous history of malignancy. However, follow-up FDG PET/CT scans showed no abnormal glucose metabolism, and follow-up CT a year later showed the nodules to remain stable in size. The patient continued to be monitored with serial CT scans everyone to two years over a nine-year period, during which the largest nodule slowly grew from 8 mm in 2012 to 13 mm in 2021 *(Fig. 2)*. At this point the patient was referred to a respiratory team where on review, she reported worsening shortness of breath on minimal exertion, a long-standing dry cough and occasional wheeze. Her shortness of breath limited her daily activities. Spirometry was restrictive; however, these results were confounded by a short-forced expiration time and a poor blow. Previous lung function tests in 2016 revealed an FEV1/FVC of 77% with a reliable FET of 3.78s *(Table 1)*.

At this point the patient's case was discussed by the respiratory team in a multidisciplinary meeting. After reviewing the images, a thoracic radiologist picked up on the classical mosaic attenuation and the slow-growing solid intrapulmonary nodules associated with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). A ^{68}Ga-DOTATATE PET scan was subsequently performed, which showed an increased tracer uptake in a large nodule in the left lower lobe *(Fig. 3)*, supporting the diagnosis.

The differential diagnoses included carcinoid tumour, granulomatous disease, sarcoidosis and vasculitis. Low levels of urinary 5-HIAA and chromogranin A, along with the imaging findings, made a carcinoid tumour unlikely. Infective causes of granulomatous disease were also excluded via serological tests. Sarcoidosis was ruled out based on the lack of characteristic radiological features, and the DOTATATE scan's uptake pattern typical of DIPNECH. Vasculitis was also unlikely due to the absence of autoantibodies, and the absence of radiological evidence of necrosis. A potential lung biopsy was discussed; however, this was not performed given the patient's poor physiological reserve.

During subsequent follow-up at the Respiratory Outpatients Clinic, the patient reported a significant worsening of her shortness of breath. She was started on high-dose oral steroids, with no improvement. She was admitted to hospital and the endocrinology team was consulted. She was started on a somatostatin analogue, octreotide 100 mg three times

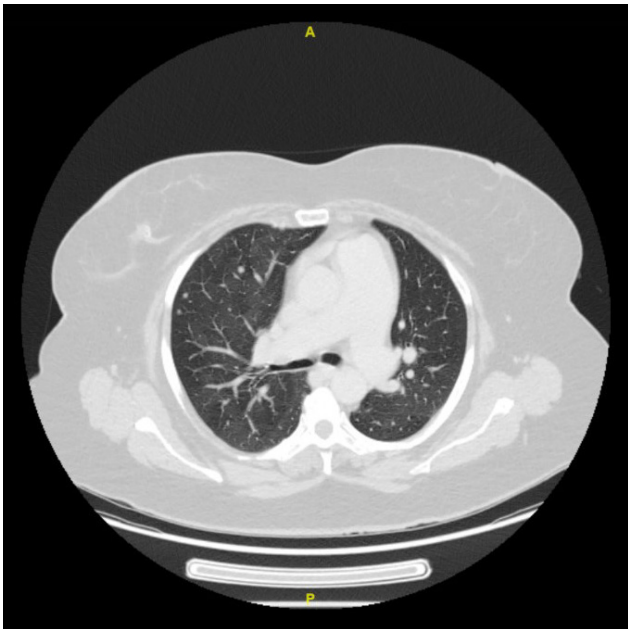

Figure 1. CT thorax showing multiple bilateral variably sized pulmonary nodules, initially thought to be secondary deposits.

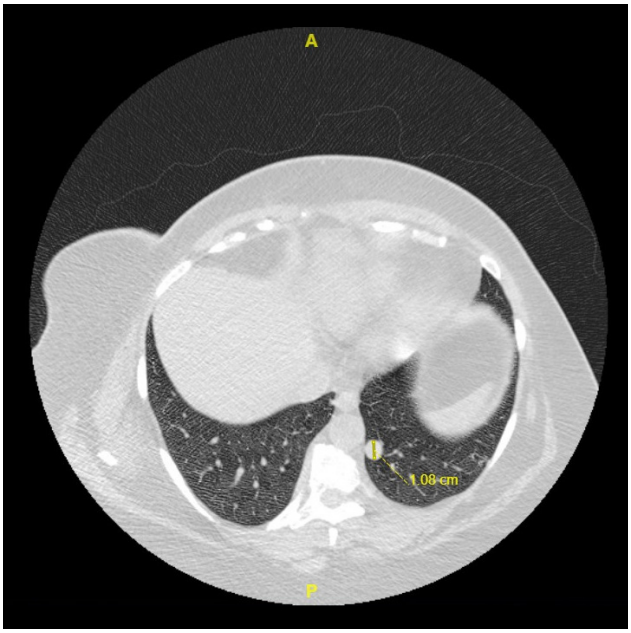

Figure 2. The largest nodule measured 1.2 x 1.3 cm in the posterior basal segment of the lower lobe.

Lung function test	Value (performed in 2016)	Value (performed in 2023)
Forced expiration volume – first second (FEV1) (litres)	1.73	1.23
Forced vital capacity (FVC) (litres)	2.24	1.25
FEV1/FVC (%)	77	99
Peak expiratory flow (litres/minute)	291	191
Forced expiration time (FET) (seconds)	3.78	1.59

Table 1. Patient's hypercoagulable test results.

daily with significant improvement in her symptoms. She was discharged, and octreotide treatment was continued as an outpatient. She has remained stable and showed objective improvement in her symptoms (MRC grade 4) and will continue to be monitored as an outpatient.

DISCUSSION

Pulmonary neuroendocrine cells, typically rare cells in the adult lung, produce physiologically active peptides that stimulate fibroblast proliferation and bronchoconstriction. DIPNECH is characterised by an abnormal proliferation of these cells within the bronchial wall, leading to obstructive and sometimes restrictive respiratory symptoms, and radiologically presenting as small airway disease and pulmonary nodules. Although DIPNECH is considered a preneoplastic condition, treatment is still symptom-driven and prognosis varies widely[1]. In this case, DIPNECH was diagnosed through radiographic evidence (contrast enhanced CT of the thorax and a ^{68}Ga-DOTATATE PET scan), clinical history, symptomatology and a multidisciplinary team (MDT) discussion. The clinical symptoms of DIPNECH overlap with common pulmonary conditions such as asthma and chronic obstructive pulmonary disease, making diagnosis ever more arduous with delays in diagnosis normally spanning multiple years. The true prevalence of DIPNECH is unclear, with estimates suggesting around 200 documented cases by 2017[2], though more case reports have been described since then.

The difficulty in diagnosing DIPNECH stems from the lack of established and validated diagnostic criteria and a consensus in the literature, while existing guidelines are based on a limited number of studies[3]. Serum biomarkers such as chromogranin A and urinary 5-HIAA have shown limited utility in DIPNECH and pulmonary carcinoid tumours, with only a few cases reporting elevated levels[4].

Radiological imaging is crucial for diagnosing DIPNECH, with features including a mosaic pattern (indicating air trapping secondary to constrictive bronchiolitis), ground-glass changes and sometimes bronchiectasis. DIPNECH is considered part of a spectrum of lung neuroendocrine

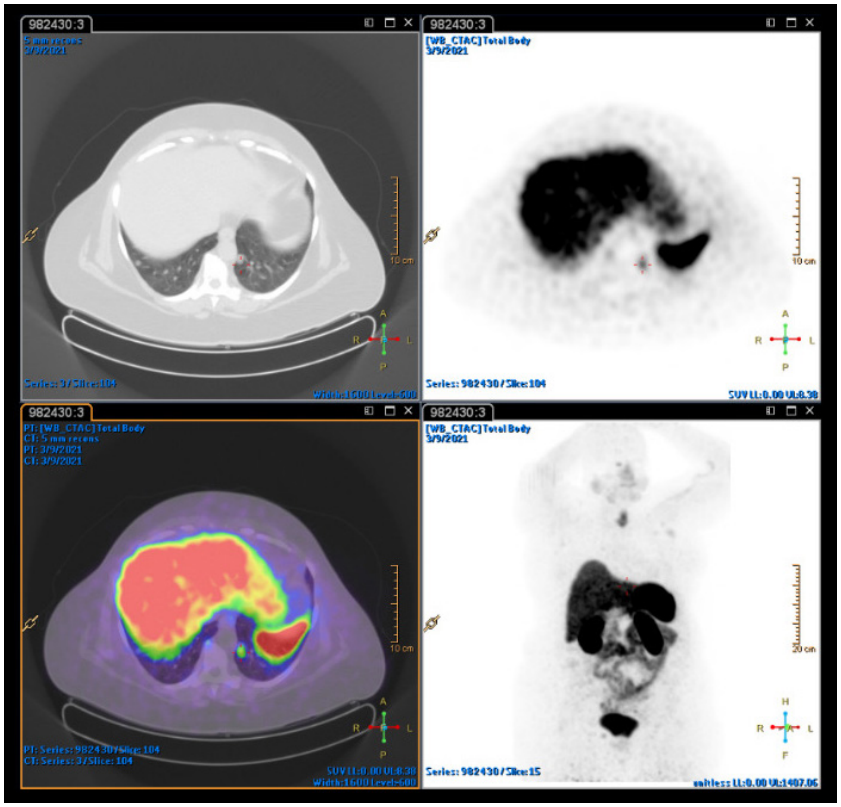

Figure 3. 204 MBq of ^{68}Ga-DOTATATE was administered intravenously and 60 minutes later, images obtained showing the focus of avid tracer uptake seemingly corresponding to the larger lung nodule in left lower lobe. Other nodules are too small to characterise further.

tumours, distinct from typical carcinoid, atypical carcinoid, and small and large cell neuroendocrine carcinomas. DIPNECH can metastasise to regional lymph nodes and, rarely, to extra-thoracic sites, and Ga-DOTATATE PET/CT imaging is potentially useful for guiding biopsies and investigating associated carcinoid tumours[5].

Bronchoscopic techniques such as bronchoalveolar lavage and endobronchial biopsies are considered limited in their diagnostic capacity given the lack of published diagnoses and experience of DIPNECH, with lung biopsy remaining the gold standard for histological diagnosis. Pulmonary function tests in DIPNECH patients often show an obstructive pattern in about half of the cases; however, it can also be restrictive or exhibit mixed obstructive and restrictive patterns[1,6].

There is lack of consensus in the literature on the clinical criteria for diagnosing DIPNECH, and it remains unclear whether histological examination alone can or should be sufficient to reach a diagnosis. Moreover, there is a lack of substantiated research that integrates histological and radiological features with clinical symptoms and pulmonary function test results, to improve diagnostic accuracy[7].

Prognosis in DIPNECH varies greatly, with patients experiencing differing severity of symptoms. Treatments discussed in the literature to address symptoms include steroids, cytotoxic agents, somatostatin analogues and surgical options such as lung resection and transplantation. However, the efficacy of these treatments remains uncertain, and therefore no universal standard of care is currently available[8].

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