Unmasking the unexpected: an unusual cause of refractory chronic cough

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Diffuse pulmonary neuroendocrine hyperplasia is a rare condition that most commonly presents with a dry cough. It can mimic late-onset asthma, but airflow obstruction is usually fixed and nodules are likely to be present on CT imaging. https://bit.ly/4eymlxW

Cite this article as: Wingfield Digby J, King J, Balata H, *et al*. Unmasking the unexpected: an unusual cause of refractory chronic cough. *Breathe* 2025; 21: 240185 [DOI: 10.1183/20734735.0185-2024].

Received: 7 Oct 2024
Accepted: 13 Nov 2024

A 76-year-old woman presented to specialist cough clinic with a 30-year history of a dry cough. This started with throat irritation, progressing to a worsening cough in the 10 years prior to presentation. The cough was exacerbated by exercise, changes in temperature and strong smells. It was partially relieved by drinking water and sucking sweets. She had a pre-existing diagnosis of asthma, post-nasal drip and had recently undergone a left total hip replacement. Her medication history included atorvastatin, inhaled beclomethasone 100 µg with formoterol 6 µg two puffs twice daily and a nasal spray (azelastine and fluticasone). Her cough had not improved following initiation of either the inhaler or nasal spray. She had also not responded to a 6-week trial of a proton-pump inhibitor for possible silent gastro-oesophageal reflux. She was retired and a never-smoker. Her verbal cough score was 9/10. Her body mass index was 30 $kg \cdot m^{-2}$ and her cardiorespiratory examination was unremarkable, aside from a mild expiratory wheeze. Further investigations were organised to evaluate her symptoms (figure 1).

Task 1

What do these investigations show (figure 1)?

a) Normal findings
b) Restrictive lung function and interstitial infiltrates
c) COPD
d) Right lower zone nodule and reversible airflow obstruction
e) Right-sided pleural effusion

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The patient was started on a long-acting muscarinic inhaler, and further investigations were organised to evaluate the pulmonary nodule. Initially a computed tomography (CT) of the thorax was performed, which confirmed a 13 mm right middle lobe nodule. A lung cancer predictor score, the Brock score, showed a 14% nodule risk, so following lung cancer multidisciplinary team (MDT) discussion, a full body positron emission tomography (PET) was organised (figure 2).

Task 2

What do these single slice images demonstrate (figure 2)?

a) Multilobar inflammatory changes and PET-avid nodule right lower lobe
b) Bronchiectasis and a PET-avid nodule right middle lobe
c) Usual interstitial pneumonia and non-PET-avid nodule right lower lobe
d) Mosaicism and non-PET-avid nodule right middle lobe
e) Usual interstitial pneumonia and PET-avid nodule right middle lobe

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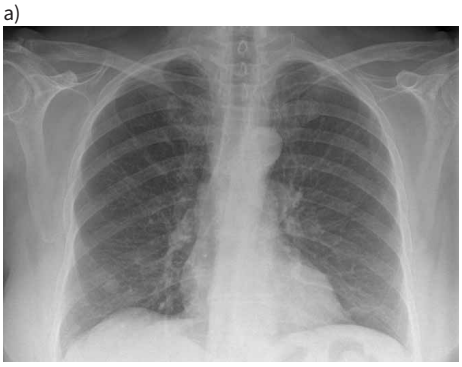
a)



b)

F_{ENO}	10 ppb
Blood eosinophils	0.07×10^9 L^{-1} (expected range: 0.00–0.40 L^{-1})
Total IgE	8.5 kU·L^{-1} (expected range: 0–114 kU·L^{-1})
***Aspergillus fumigatus* IgE**	<0.10 kUA·L^{-1} (expected range: 0.00–0.35 kUA·L^{-1})

c)

FEV_1	1.08 L (58 % pred)
FVC	2.43 L (100% pred)
FEV_1/FVC	0.45
FEV_1 after bronchodilator (2.5 mg/2.5 mL salbutamol)	1.32 L (+22%)

d)

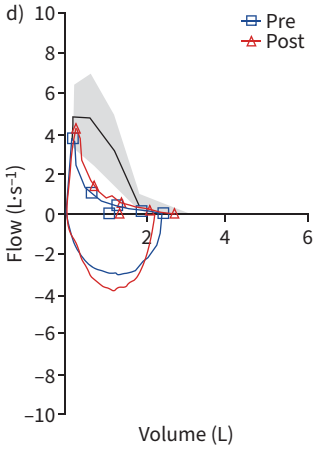


FIGURE 1 a) Posteroanterior chest radiograph, b) blood tests and exhaled nitric oxide fraction (F_{ENO}), c, d) spirometry with reversibility. FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity.

The patient subsequently underwent a CT-guided biopsy of the lesion, which this was technically difficult due to her severe chronic cough. Samples obtained showed normal lung parenchyma. Following a further MDT discussion, a unifying diagnosis was considered, so a ^{68}Ga-DOTATOC (radiolabelled somatostatin analogue) PET-CT was suggested, alongside 24-h urine collection for serotonin metabolites. The results of these investigations are shown in figure 3.

Task 3

Which of the following symptoms and signs are associated with carcinoid syndrome?

a) Flushing, diarrhoea and valvular heart disease
b) Hypotension
c) Ataxia
d) Tachypnoea
e) Pancreatic insufficiency

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The patient did not have signs or symptoms of a carcinoid syndrome, despite slightly elevated 5-hydroxyindoleacetic acid levels. The patient underwent robotic-assisted thoracoscopic surgery, right middle lobectomy and anterior thoracotomy and nodal harvest. A section of the nodule and lung tissue is shown in figure 4.

The final diagnosis was diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) with an associated carcinoid tumour (T1a N0 M0).

Task 4

Which of the following are true in relation to DIPNECH?

a) The female to male ratio is approximately 10:1
b) Chemotherapy is the first-line treatment
c) Chronic dry cough is the most frequently reported symptom
d) It can be hard to distinguish clinically from asthma
e) It is usually seen in male smokers

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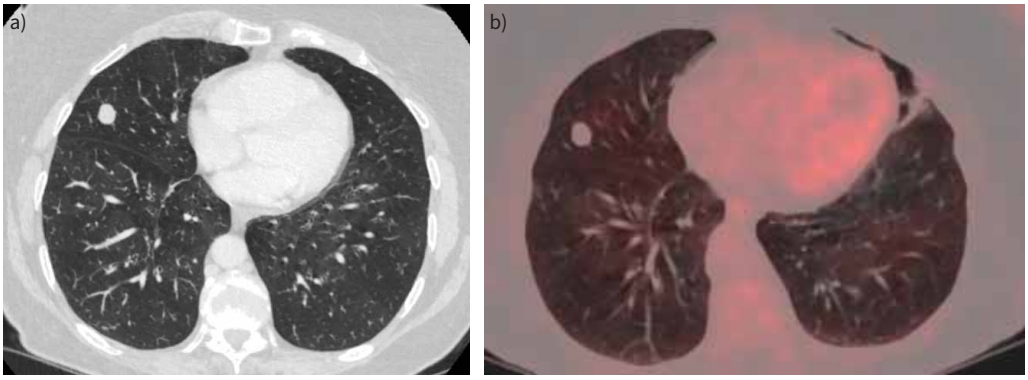


FIGURE 2 Slices from a) high-resolution computed tomography of the thorax and b) positron emission tomography scan.

Patient outcome

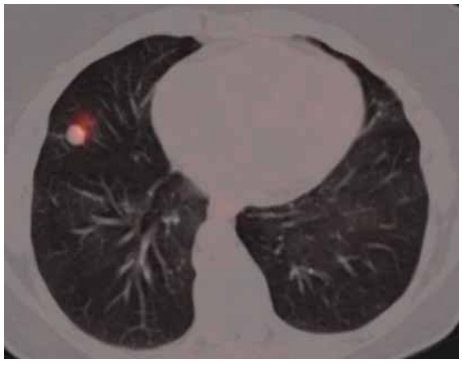
The patient recovered well from surgery and was started on a combined corticosteroid/bronchodilator inhaler (medium dose) long term. Her cough continued, but the severity was greatly reduced following a block of speech and language therapy, which was given alongside regular, low-dose, modified-release morphine sulphate. Her symptoms had largely resolved 18 months after initial presentation to our cough clinic.

Discussion

DIPNECH is rare lung-condition, first described in 1992 [1], that presents with non-productive cough and dyspnoea, typically in nonsmoking females in their fifth to seventh decade of life [2, 3]. Diagnosis is based on histology, which shows neuroendocrine cell proliferation within the bronchial epithelium of the small airways. Radiologically, this results in air trapping, bronchial wall thickening and mosaic changes [3–5]. This usually gives rise to airflow obstruction (FEV_1/forced vital capacity ratio <0.7) on spirometry [6]. Neuroendocrine cells that cluster and invade through the basement membrane are described as carcinoid tumourlets (⩽5 mm) or tumours (>5 mm) [7].

Focal neuroendocrine hyperplasia (NECH) can be associated with altitude, smoking and several respiratory conditions (*e.g.* asthma, cystic fibrosis, bronchiectasis) [8]. DIPNECH describes diffuse idiopathic neuroendocrine cell hyperplasia [9], leading to constrictive bronchiolitis [10].

The commonest symptom in DIPNECH is chronic cough (71%), followed by dyspnoea (63%) and wheeze (25%) [11]. Therefore, it can easily be mistaken for late-onset asthma. Treatment of DIPNECH is based on the results of small observational studies. Inhaled and/or oral steroids are often trialled, but evidence for



Test	Value	Reference range
24-h urinary 5-HIAA excretion	58 µmol per 24 h	4–46 µmol per 24 h

FIGURE 3 Nuclear medicine (NM) ^{68}Ga-DOTATOC positron emission tomography (PET)-computed tomography (CT) scan and 24-h urine collection results. There is clear uptake of the somatostatin analogue on the NM ^{68}Ga-DOTATOC PET-CT scan. 24-h 5-hydroxyindoleacetic acid (5-HIAA) levels are increased in the urine. This is in keeping with a carcinoid tumour.

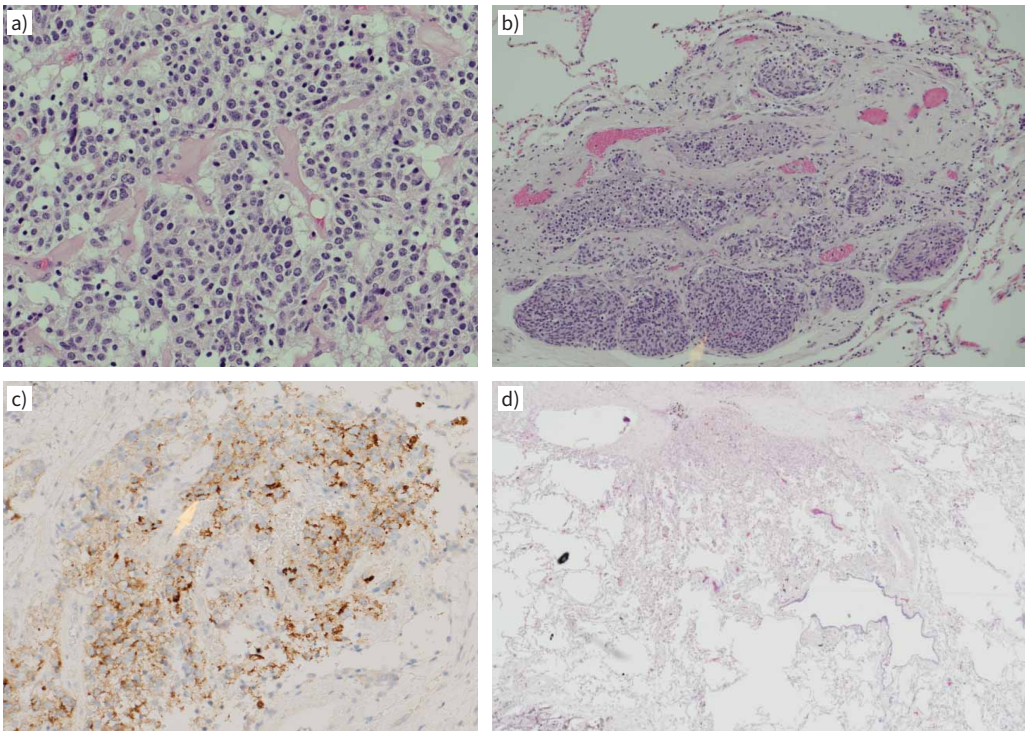


FIGURE 4 Histopathology. a) Haematoxylin and eosin stain (×200); b) background neuroendocrine tumourlet (×10); c) nodule stained with chromogranin (×200); d) background lung tissue (×20). Histopathology description: the nodule was typical for a carcinoid tumour (positive for CD56, chromogranin and synaptophysin, but negative for thyroid transcription factor (TTF)-1). Additionally, there are multiple foci of pulmonary neuroendocrine proliferation (positive for CD56, chromogranin and synaptophysin) within the background lung including focal neuroendocrine hyperplasia and multiple neuroendocrine tumourlets. The lung tissue shows obstructive bronchiectasis and peribronchial pneumonitis, as well as mild background emphysema.

these is limited [11]. Cytotoxic agents are not recommended, but somatostatin analogues can be used; interestingly, small studies have shown improvement in cough symptoms with this treatment [12]. Typical clinical features, spirometry, imaging findings and treatment of DIPNECH are summarised in table 1.

Prognosis is variable, with most cases following an indolent course. Rarely constrictive bronchiolitis can progress rapidly causing severe airflow obstruction and respiratory failure, which can occasionally necessitate lung transplantation [1]. CT surveillance of tumours and tumourlets is advised.

Carcinoid tumours are typically round-to-ovoid, solid, non-necrotic and are treated according to TNM (tumour, node, metastasis) staging, histology and patient performance status [13]. These tumours are derived from APUD cells (amine precursor uptake and decarboxylation), which convert amine precursors into serotonin or catecholamines. This can result in elevated levels of 5-hydroxyindoleacetic acid in the urine or chromogranin A/B in serum [14], and is seen in 20–30% of gastrointestinal neuroendocrine tumours, but is less common in bronchial carcinoids (5%) [15]. Symptoms required for diagnosis are

TABLE 1 Typical clinical features, spirometry, imaging findings and treatment of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Clinical features	Spirometry	Cross-sectional imaging	Treatment
Incidental finding	Usually obstructive, but can be normal and occasionally mixed/restrictive	Cardinal features:	Not well studied
Chronic cough		Nodules	Inhaled and oral corticosteroids
Dyspnoea and wheeze		Air trapping	Surgery or surveillance for tumours/tumourlets
		Mosaic attenuation	Consider somatostatin analogues

diarrhoea and flushing, but palpitations, wheeze and abdominal pain can also occur. Rarely valvular heart disease and pellagra (dermatitis, dementia, and diarrhoea in association with low tryptophan) can develop [14]. It is important to screen for symptoms and signs of carcinoid syndrome in DIPNECH.

Conclusion

DIPNECH is a rare disorder that typically presents with a dry cough and wheeze, it can easily be mistaken for asthma or cough hypersensitivity syndrome. Like refractory chronic cough, it usually presents in nonsmoking females above the age of 50 years old. The diagnosis should therefore be considered in patients with cardinal imaging features, particularly a combination of mosaicism and diffuse smooth nodules. The diagnosis is based on typical histopathological features, including diffuse neuroendocrine hyperplasia in the small airways, which is often seen in conjunction with a carcinoid tumour or tumourlets. Small case series suggest somatostatin analogues may improve cough severity in this cohort.

Answer 1

d. The chest radiograph shows a round, well demarcated nodule in the right lower zone. Otherwise, pulmonary appearances are normal. The spirometry shows moderate airflow obstruction with reversibility (forced expiratory volume in the first second (FEV_1) $\geqslant$12% and >200 mL after salbutamol), suggestive of asthma. There is no evidence of Type 2 (TH2) high inflammation.

<< Go to Task 1

Answer 2

d. The CT thorax shows areas of different attenuation, with darker and lighter areas in a patchwork pattern (mosaicism). There is a smooth oval nodule in the right middle lobe. There were also scattered sub-centimetre nodules elsewhere (not appreciated on this single slice image). The nodule shows a low standardised uptake value (SUV), suggesting low metabolic activity.

<< Go to Task 2

Answer 3

a. Carcinoid syndrome is discussed in the case discussion. Cardinal features include flushing, diarrhoea and wheeze. Rarely, right-sided valvular heart disease can develop. Carcinoid can be associated with hypertension, but not hypotension. It is not associated with the other options.

<< Go to Task 3

Answer 4

a, c and d are true (see the discussion section).

<< Go to Task 4

Conflict of interest: J. Wingfield Digby and J. King have nothing to disclose. H. Balata reports payment or honoraria for lectures, presentations, manuscript writing or educational events from ESMO Lung Preceptorship Course and UCLH Advanced Bronchoscopy Course; and support for attending meetings from IASLC and BTS. J. Smith reports grants from Merck, NIHR Biomedical Research Centre Funding and Wellcome; consultancy fees from Merck, Bellus Health, Bayer, Shionogi, Algernon, AstraZeneca, Boehringer Ingelheim, Chiesi, Nocion, Seyltx, GlaxoSmithKline and Axalbion; payment or honoraria for lectures, presentations, manuscript writing or educational events from Merck and GlaxoSmithKline; support for attending meetings from GSK; receipt of equipment, materials, drugs, medical writing, gifts or other services from Vitalograph; and the following financial (or non-financial) interests: the VitaloJAK algorithm has been licensed by Manchester University Foundation Trust (MFT) and the University of Manchester to Vitalograph Ltd and Vitalograph Ireland (Ltd). MFT receives royalties which may be shared with the clinical division in which J. Smith works. P. Marsden reports grants from MSD; consultancy fees from Trevi; and payment or honoraria for lectures, presentations, manuscript writing or educational events from Olympus.

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