Rare disease

Diffuse idiopathic neuroendocrine cell hyperplasia: an unusual cause of breathlessness and pulmonary nodules

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Summary

A 66-year-old woman presented with dry cough and subsequent intermittent breathlessness and wheeze. During this time she was treated by her general practitioner for chronic obstructive pulmonary disease. When her symptoms worsened and her lung function had deteriorated, a high resolution CT scan was undertaken. This showed bilateral fine nodules. Investigations did not support a diagnosis of vasculitis and sarcoidosis was suspected. A lung biopsy was performed that showed diffuse idiopathic neuroendocrine cell hyperplasia. At follow-up, to date, the patient remains symptomatic but has not progressed or developed a carcinoid tumour.

BACKGROUND

Diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) is a rare condition with only 46 cases having been reported in the literature to date.¹⁻³ It often presents with symptoms of obstructive airways disease and may take many years to diagnose. A small number of patients will have evidence of carcinoid tumours at diagnosis, which may be amenable to treatment with curative intent. This case report aims to increase awareness of this rare but important condition so that it can be considered in the differential diagnosis when patients with common symptoms fail to respond to conventional treatment and when imaging shows bilateral pulmonary nodules.

CASE PRESENTATION

A 66-year-old woman was referred to the respiratory clinic in 2006 with a 10-year history of cough productive of sputum and progressive breathlessness. Her general practitioner had diagnosed chronic obstructive pulmonary disease (COPD) and prescribed a combination long-acting β -agonist and steroid inhaler, short-acting anticholinergic inhaler and oral aminophylline. These treatments had settled her cough but she was now breathless climbing stairs. Her chest was clear to auscultation.

INVESTIGATIONS

Chest x-ray was normal. Pulmonary function tests are shown in table 1.

DIFFERENTIAL DIAGNOSIS

Chronic asthma/COPD were the working diagnoses.

TREATMENT

No change to current treatment, pending further investigations.

OUTCOME AND FOLLOW-UP

At review in August 2006 she remained breathless on exertion and her exercise tolerance had fallen to 100 yards. She was still coughing, producing white sputum, and had symptoms of gastro-oesophageal reflux. Her chest was clear to auscultation. Spirometry is shown in Table 1. Her eosinophil count was normal. At that point, a proton pump inhibitor was started as treatment for reflux and a high resolution CT scan was arranged to look for bronchiectasis or interstitial lung disease (figure 1). This was performed on 11 July 2006 and showed bilateral fine nodules. There was no evidence of bronchiectasis. When the images were reviewed by the radiologist they were thought to be most

Table 1 Pulmonary function tests

Date	June 2006		August 2006		July 2007	
	Value	% predicted	Value	% predicted	Value	% predicted
FEV ₁ (l)	0.92	41	0.75	33	0.89	43
FVC (l)	1.42	50	1.1	39	1.44	59
FEV ₁ /FVC (%)	65		68		62	62
TLC (l)	4.03	84	*		3.13	66
RV (l)	2.45	126	*		1.63	83
TLCO (ml/min/mm Hg)	5.62	79	*		3.97	56
KCO (ml/min/mm Hg/l)	1.97	132	*		1.84	124

* indicates that the measurement was not undertaken

FEV₁, forced expiratory volume; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; TLCO, carbon monoxide transfer factor; KCO, Carbon monoxide transfer coefficient.

Figure 1 High resolution CT scan July 2006.

Figure 2 High resolution CT scan July 2007.

Figure 3 Histology of lung biopsy.

likely to be incidental, but recommended a repeat CT scan. In view of her minimal smoking history (<1 pack year in her teens), a 1-year follow-up scan was arranged. This was performed on 16 July 2007 and showed persistence of the nodules but with no interval change (figure 2). The differential diagnosis was thought to be wide but benign, given the stable size of the nodules over a 1-year period. At review in January 2008, her breathlessness was stable and on auscultation she had crackles and wheeze bilaterally. Full pulmonary function tests undertaken are shown in table 1. Anti-neutrophil cytoplasmic antibodies and antinuclear antibodies were negative and serum angiotensin-converting enzyme and calcium were normal. A provisional diagnosis of pulmonary sarcoidosis was made and the patient was referred for biopsy by video-assisted thoracoscopic surgery. This was undertaken on 28 February 2008.

Histopathological analysis of the biopsy revealed DIPNECH (figure 3). At follow-up, to date, the patient remains symptomatic but has not progressed or developed a carcinoid tumour.

DISCUSSION

DIPNECH is a rare condition. Forty-six cases have so far been reported in the literature.^{1 2 3} The majority have airways disease symptoms. It is known that reactive hyperplasia of neuroendocrine cells can occur in the setting of airways fibrosis and inflammation or as an adaptive response to hypoxia.^{4 5} In DIPNECH there is the presence of neuroendocrine cell hyperplasia with physiological evidence of airflow obstruction that is otherwise unexplained.

In the 1999 WHO classification of lung tumours, DIPNECH was included as a pre-neoplastic lung lesion. In DIPNECH there is hyperplasia of neuroendocrine cells in the airways without invasion beyond the basement membrane. If the cells extend into the interstitium and are <5 mm, the lesion is classified as a carcinoid tumourlet. If >5 mm it is a carcinoid tumour.⁶ A retrospective study of surgical specimens undertaken in 2007 found that 28 of 294 patients with a carcinoid tumour or tumourlet had two or more lesions. In total, 93% of cases were women with a mean age of 65 years. Half of those with multiple nodules had respiratory symptoms. Only one patient had a clinical syndrome resembling DIPNECH.

Several theories exist as to the pathophysiology of DIPNECH. It has been suggested that the neuroendocrine cells release gastrin-releasing peptide and fibroblast growth factors causing pulmonary fibrosis.⁴ Alternatively, epidermal growth factor receptor over expression may play a significant role in producing fibrosis providing a potential target for treatment strategies in the future.⁷ Others propose that hyperplastic neuroendocrine cells secrete bombesin, which leads to fibroblast and smooth muscle proliferation.⁸

Most patients have persistent but stable disease. There is no specific treatment. Most patients receive conventional treatment for airways disease including inhaled and oral steroids.⁹ A minority present with interstitial lung disease and are treated with oral corticosteroids.⁸ There is no agreed method or timescale for surveillance regarding the possible development of carcinoid tumours.

Learning points

- ▶ DIPNECH can present with evidence of obstructive or restrictive lung disease.
- ▶ Consider DIPNECH in the differential diagnosis of bilateral pulmonary nodules.
- ▶ DIPNECH can only be diagnosed by lung biopsy.

Competing interests None.

Patient consent Obtained.

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