CASE REPORT

DIPNECH presenting on a background of malignant melanoma: new lung nodules are not always what they seem

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SUMMARY

The coexistence of lung nodules on a CT scan with worsening respiratory symptoms in the context of previous malignant melanoma would usually signify metastatic disease. The cause of the lung nodules in this 69-year-old woman turned out to be diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) with tumourlets. DIPNECH is extremely rare, with fewer than 100 cases reported in the literature worldwide. The key to making this diagnosis was that the nodules were not avid on a positron emission tomography-CT scan, as would have been expected in metastatic melanoma. This led to a biopsy diagnosis. At the time of writing, the patient remains symptomatic with stable disease.

BACKGROUND

Diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) is an extremely rare pulmonary condition. It was first formally described in 1992 and was recognised in 2004 by the WHO as a precursor to pulmonary carcinoid tumours.¹ It can take a long time to diagnose and may present with symptoms of obstructive airways disease,² or restrictive problems. DIPNECH is being recognised with increasing frequency, but only limited information on diagnosis and treatment is available in the literature.^{3 4}

CASE PRESENTATION

A 69-year-old woman was referred to the respiratory clinic with worsening shortness of breath on exertion, to the point that she was breathless walking up a flight of stairs. She was referred by the plastic surgeons, with whom she was having routine follow-up for a superficial malignant melanoma.

Her gradually progressive exertional dyspnoea had begun 8 years earlier. She presented to her general practitioner (GP) with shortness of breath and a cough, and was diagnosed with chronic obstructive pulmonary disease (COPD). CT imaging at the time demonstrated focal scarring of the right middle lobe and, to a lesser extent, the lingula.

There was a very minimal smoking history of less than 1 pack-year with no prior exposure to toxic inhalants or animals. Other than the melanoma, there was no other significant medical or family history.

INVESTIGATIONS

An initial chest X-ray 6 weeks prior to her respiratory clinic appointment suggested pneumonia. She was treated with two courses of antibiotics and her symptoms improved somewhat. A repeat chest X-ray 6 weeks later demonstrated persistent right lower zone opacification, and she therefore proceeded to CT imaging. This revealed multiple lung nodules scattered throughout both lungs and some focal fibrosis (figure 1). The nodules were not seen on the first CT scan several years previously. Given the history of melanoma, it was felt that these appearances were strongly suggestive of multiple lung metastases.

A positron emission tomography (PET)-CT scan was carried out further to characterise the lung nodules. The presence of multiple lung nodules was confirmed in the CT phase, but these were not shown to be avid on the PET phase (figure 2). This suggested a cause other than one of metastatic melanoma.

Following this unexpected result, a video-assisted thoracoscopic surgery (VATS)-assisted biopsy was carried out. This confirmed a histopathological profile of typical carcinoid tissue. The lesions were tumourlets (pT1a, N0, M0) of <5 mm in diameter, with background hyperplasia of the neuroendocrine cells. This conferred a diagnosis of carcinoid tumourlets arising against a background of DIPNECH.³

DIFFERENTIAL DIAGNOSIS

A provisional diagnosis of metastatic malignant melanoma with a background of COPD was made. At biopsy, the diagnosis was changed to DIPNECH.

Figure 1 CT scan showing fibrosis with bilateral lung nodules.

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Figure 2 A positron emission tomography (PET)–CT scan in (A) the CT phase confirming the presence of lung nodules and (B) the PET phase demonstrating no avidity of the nodules.

TREATMENT

There were no changes to the current treatment, which consisted of a corticosteroid inhaler and a long-acting β -agonist inhaler.

OUTCOME AND FOLLOW-UP

The patient was referred to a tertiary centre for the management of neuroendocrine tumours for ongoing monitoring. Until now, her symptoms are persistent but stable and she has not developed a carcinoid tumour.

DISCUSSION

DIPNECH is a very rare condition. It was first formally described in 1992 in a case series of six patients with no other lung disease.⁵ There was no clinical association with smoking. Five of the patients were female. Five of the six had stable disease at follow-up, and one died of progressive disease. There have since been fewer than 100 cases reported in the literature worldwide.

DIPNECH is a histological diagnosis, characterised by the proliferation of neuroendocrine cells in the lungs. The WHO formally recognised DIPNECH in 2009 as a precursor to pulmonary carcinoid tumours. It is thought to be a spectrum of disease,⁶ as the cells are histologically identical to carcinoid cells. According to this classification, cells are designated as DIPNECH where the hyperplasia does not extend beyond the basement membrane. If there are lesions of <5 mm in diameter, these are tumourlets, whereas lesions of >5 mm are carcinoid tumours.⁷

Neuroendocrine cell proliferation may lead both to obliterative bronchiolitis and occlusion of the bronchial lumina. Therefore, an obstructive, mixed or occasionally restrictive picture may be found on pulmonary function tests. Clinically, presenting symptoms are cough and breathlessness, especially on exertion. Histological findings in DIPNECH are the same as those found in pulmonary carcinoid. A degree of neuroendocrine proliferation can sometimes be seen in reactive or inflammatory processes in the lungs, but it should be noted that DIPNECH is a primary proliferation.⁵

This case reports a diagnosis of DIPNECH with tumourlets on a background of previous malignant melanoma. In a significant number of cases, there is a history of malignancy at other sites. At present, there is not enough information in the literature to determine whether there may be an association between DIPNECH and malignancies other than carcinoid. A plausible explanation is that the increased use of imaging leads to an increased frequency of lung nodule biopsy in patients with known malignancies. Consequently, DIPNECH is more likely to be diagnosed.⁸

The management of DIPNECH remains controversial because there are not yet any consensus guidelines for its management. This is largely due to the small number of cases reported. The management options include oral or inhaled corticosteroids, especially in patients who demonstrate a degree of reversibility on lung function tests. Somatostatin analogues and even lung

transplant have been successful in isolated cases. Despite the increased risk of pulmonary carcinoid tumours, most patients have stable disease over time. In these patients, an active surveillance policy can be taken, with regular follow-up. Owing to the rarity of this condition and lack of consensus on management and prognosis, there would be a significant potential benefit in the creation of a centralised database.

Learning points

- ▶ Diffuse neuroendocrine cell hyperplasia (DIPNECH) is a rare disease. It is considered to be a precursor to carcinoid tumours.
- ▶ Although rare, DIPNECH should be included in the differential diagnosis of multiple lung nodules.
- ▶ It may present with non-specific respiratory symptoms which are often attributed to other causes.
- ▶ A diagnosis of DIPNECH can only be made on biopsy.
- ▶ DIPNECH is increasingly diagnosed where there is a history of other malignancy, perhaps due to increased use of imaging. There is scope for further investigation of this in the future.

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REFERENCES

- 1 Travis WD, Brambilla E, Muller-Hermlink HK, *et al*. *Pathology and genetics of tumours of the lung, pleura, thymus and heart*. World Health Organization classification of tumours. Lyon: IARC Press, 2004.
- 2 Tippet VM, Wathen CG. Diffuse idiopathic neuroendocrine cell hyperplasia: an unusual cause of breathlessness and pulmonary nodules. *BMJ Case Rep*. Published Online First: 1 Dec 2010. doi:10.1136/bcr.05.2010.3006
- 3 Brambilla E, Travis WD, Colby TV, *et al*. The new World Health Organization classification of lung tumours. *Eur Respir J* 2001;18:1059–68.
- 4 Nassar AA, Jaroszewski DE, Helmers RA, *et al*. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, a systematic overview. *Am J Respir Crit Care Med* 2011;184:8–16.
- 5 Aguayo SM, Miller YE, Waldron JA Jr, *et al*. Brief report: idiopathic diffuse hyperplasia of pulmonary neuroendocrine cells and airways disease. *N Engl J Med* 1992;327:1285–8.
- 6 Davies SJ, Gosney JR, Hansell DM, *et al*. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: an under-recognised spectrum of disease. *Thorax* 2007;62:248–52.
- 7 Greenberg AK, Yee H, Rom WN. Preneoplastic lesions of the lung. *Respir Res* 2002;3:20–30.
- 8 Warth A, Herpel E, Schmähl A, *et al*. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) in association with an adenocarcinoma: a case report. *J Med Case Rep* 2008;2:21.

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