Diffuse intrapulmonary neuroendocrine cell hyperplasia

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Diffuse intrapulmonary neuroendocrine cell hyperplasia is a rare, potential precursor lesion to typical pulmonary carcinoid tumours. Fewer than 50 cases have been reported in the literature. Their pathogenesis, clinical significance and management is controversial. A patient who presented with diffuse intrapulmonary neuroendocrine cell hyperplasia associated with a primary typical carcinoid tumour of the lung is reported.

Key Words: Carcinoid tumour; Lung cancer; Neuroendocrine tumours

Learning Objectives
- Ability to recognize the presentation and clinical associations of diffuse intrapulmonary neuroendocrine cell hyperplasia (DIPNECH).
- Understand the limited available evidence for optimal management of DIPNECH.

CanMEDS competency: Medical Expert

Pretest
- What is DIPNECH?
- What is the optimal management of DIPNECH?

Figure 1) Bilateral lower lobe nodules with air trapping

Figure 2) Right middle lobe typical carcinoid tumour

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cells arranged in nests and trabeculae had very low cellular proliferation (<1 mitosis/10 high-power fields) and no necrosis (Figure 3). There were multiple peribronchiolar and subpleural foci of neuroendocrine cell proliferation exhibiting linear subepithelial proliferation limited by the basement membrane (DIPNECH), as well as tumourlets (0.1 cm to 0.4 cm in greatest dimension) penetrating the basement membrane (Figure 4). The right lower wedge resections also revealed DIPNECH separate from carcinoid tumourlet foci (0.2 cm to 0.4 cm).

Her case was reviewed in thoracic oncology multidisciplinary rounds. The consensus was no adjuvant therapy but continued surveillance with clinical assessment and thoracic CT every four months. The role of surgery in the management of DIPNECH is controversial (1). DIPNECH is believed by some to be an under-recognized entity, poorly defined. Long-term surveillance is generally accepted to monitor for progression to typical carcinoid tumour (8). However, optimal time intervals for surveillance and the preferred imaging modality is yet unclear. With regard to demographics, DIPNECH is reported four times more frequently in women than in men, usually nonsmokers in the fifth or sixth decade of life (1,7). The most frequent radiographic features include mosaic air trapping and multiple small nodules (1).

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In case series, DIPNECH is found in association with typical carcinoid tumours, especially peripherally located spindle cell typical carcinoids (7,9-11). It is not reported in association with high-grade pulmonary neuroendocrine tumours such as small-cell lung carcinoma or large cell neuroendocrine carcinoma (1). One series reported DIPNECH with multiple endocrine neoplasia type 1 (7), and another with adenosarcoma of mixed subtype and partial neuroendocrine differentiation (12). Very rarely, it is reported with ectopic adrenocorticotrophic hormone production (13) and elevated serum carinoembryonic antigen levels in the absence of pulmonary or primary gastrointestinal adenosarcoma (14). DIPNECH has also been found on surgical lung biopsy of patients with respiratory failure of unclear etiology requiring intubation and mechanical ventilation (15).

The gold standard for definitive diagnosis of DIPNECH is surgical lung biopsy (15). A diagnosis cannot be reliably achieved with a transbronchial or transthoracic biopsy. Surgical biopsy with sizable tissue is desired because, by definition, DIPNECH is a multifocal process (neuroendocrine hyperplasia in the peribronchial areas as well as often in the distal parenchyma confined to the epithelium).

Although fibrosis may be evident between the smooth muscle layer and epithelium of the small airways (1), some hypothesize fibrosis is due to neuroendocrine proliferation with peptides (bombesin) produced by neuroendocrine cells and not vice versa (9,11). To date, no characteristic molecular alterations associated with DIPNECH have been identified. In addition to fibrosis, DIPNECH has been recognized as a reactive process in the setting of chronic inflammatory disease processes including bronchiectasis and oblitative bronchiolitis (1,6).

The natural history of DIPNECH appears to be favourable; most patients experience stable or very slowly progressive disease (3). A small number of cases report progressive DIPNECH leading to severe diffuse small airway obstruction and respiratory failure from endobronchial lesions and fibrosis requiring intubation (9,10,15).

Owing to its rarity, the optimal management of DIPNECH remains poorly defined. Long-term surveillance is generally accepted to monitor for progression to typical carcinoid tumour (8). However, optimal time intervals for surveillance and the preferred imaging modality is yet unclear. With respect to the symptoms of obstructive airway disease, inhaled bronchodilators or steroids may prove to be beneficial. The role of surgery in the management of DIPNECH is controversial and, in existing case series, has been limited to patients who develop an associated carcinoid tumour (3,16).
Post-test

• What is DIPNECH?
DIPNECH is a rare disease of diffuse airway neuroendocrine cell hyperplasia. The WHO defines DIPNECH as a proliferation of scattered single pulmonary neuroendocrine cells, nodules or linear proliferations of these cells confined to bronchial and bronchiolar epithelium. DIPNECH may be associated with a clinical-pathological syndrome of airway obstruction or interstitial lung disease (wheeze, dyspnea, cough) due to the histological findings of neuroendocrine cell proliferation and bronchiolar fibrosis.

• What is the optimal management of DIPNECH?
The optimal management of DIPNECH is poorly defined owing to its rarity. Long-term surveillance is advocated to monitor for progression to typical carcinoid tumour. The role of pulmonary resection is currently limited to patients with an associated carcinoid tumour. Inhaled bronchodilators or steroids may aid in symptom management of obstructive airway disease.

REFERENCES
