AMJ Australasian Medical Journal [AMJ 2021;14(2):43-47

A case series of 7 patients with Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) in New South Wales Australia

Lisa Basler[1] Marsa Hosseinzadeh[2], Dariush Daneshvar[2], and Peter Wu[1]

1. Respiratory and Sleep Medicine Westmead Hospital, New South Wales, Australia
2. Pathology West/ICPMR Westmead Hospital, New South Wales, Australia

CASE SERIES

Please cite this paper as Basler L, Hosseinzadeh M, Daneshvar D, Wu P. A case series of 7 patients with Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) in New South Wales Australia. AMJ 2021;14(2):43–47.
https://doi.org/10.35841/1836-1935.14.2.43-47

Corresponding Author:
Dr Marsa Hosseinzadeh
Pathology West/ICMPMR Westmead Hospital, Hawkesburry Rd, 2145 Westmead NSW, Australia
Email: marsa.hosseinzadeh@health.nsw.gov.au

ABSTRACT

Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) is a rare and poorly understood entity, defined as a generalised proliferation of pulmonary neuroendocrine cells arranged in scattered single cells, small nodules or linear patterns that do not invade beyond the bronchial epithelial basement membrane.

The diagnosis of DIPNECH requires clinical, radiological and histopathology correlation. However, it is often diagnosed incidentally on histopathological examination of lung biopsy specimen performed for other reasons or discovered due to investigations for unexplained respiratory symptoms.

In the first publication of a case series of DINPNECH and NECH in Australia, we describe seven histopathologically confirmed cases of DIPNECH or NECH. All patients were females, aged 57–70, mostly non-smoker. The most common presenting symptoms were dry cough and progressive dyspnoea. 71 per cent of patients had typical radiological findings with nodular changes.

Key Words
NECH, DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, pulmonary nodule

Implications for Practice:

1. What is known about this subject?
DIPNECH is a rare pulmonary disorder that is typically characterised by non-specific respiratory symptoms, evidence of small airway disease and nodular changes on computed tomography, confirmed on histopathology.

2. What new information is offered in this case study?
In this study, we observed that the patients' demographics in our local population were similar to other parts of the world. Also, despite typical clinical and radiological findings, the histopathology diagnosis was often only made incidentally following lung biopsies or resections performed for other alternative reasons. This underlies the issue of delayed or missed diagnosis of DIPNECH.

3. What are the implications for research, policy, or practice?
In patients with an unresolved cough and/or dyspnoea despite optimal management, who have radiological changes of small airway disease or lung nodules, DIPNECH should be considered as a differential diagnosis and confirmed histologically if required.

Background

Neuroendocrine cell hyperplasia (NECH) is a histological description, characterized by foci of neuroendocrine cell hyperplasia that do not invade beyond the bronchial epithelial basement membrane.

NECH is generally found in asymptomatic patients with normal pulmonary function tests. It is considered to be a reactive response to chronic airway injury and environmental exposure. As such, it has been seen in conditions such as smoking, cystic fibrosis,

bronchopulmonary dysplasia, asthma, diffuse panbronchiolitis, chronic exposure to high altitude, bronchiectasis and pulmonary fibrosis.[1]

In contrast, DIPNECH is a primary pulmonary disorder characterised histologically by a diffuse bronchiolocentric proliferation of neuroendocrine cells. This proliferation can range from hyperplasia to tumourlets and carcinoid tumours. In order to establish diagnosis of DIPNECH, Marchevsky et al.[2] suggested presence of multifocal NECH combined with more than three tumourlets as the minimum pathological criteria.

To date, there are under 200 cases reported in the literature. To our knowledge, there are no publications on DIPNECH in Australia, and we, therefore, believe that analysing a case series of seven cases with DIPNEH in the Sydney, Australia, and compare it to the existing literature from other parts of the world is essential.

Case details

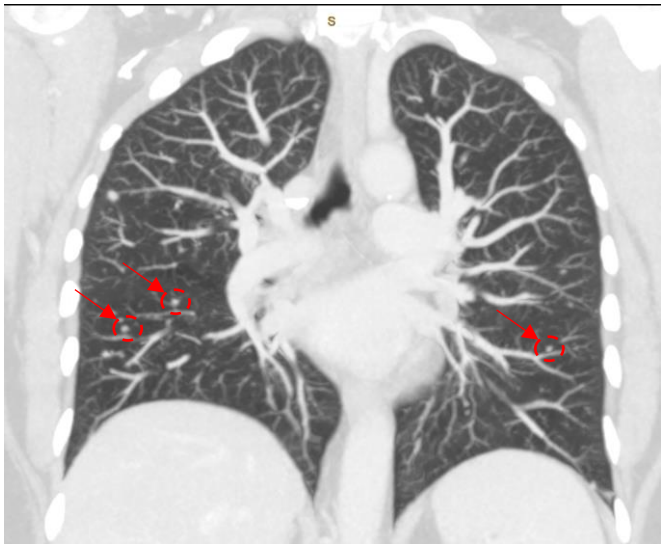
A retrospective study of our department archive (Tissue Pathology & Diagnostic Oncology, ICPMR, Pathology West, New South Wales, Australia) identified seven histopathologically confirmed cases of DIPNECH or NECH.

The summary of the key findings has been listed in Table 1.

All seven cases were female with a mean age of 64 at diagnosis (range 54–70). Cough was the presenting complaint in four out of seven patients, mostly a non-productive cough. Mild dyspnoea on exertion was reported by one of our patients. Four out of seven patients had no smoking history, two were active smokers at the time of presentation, and one of the patients was an ex-smoker (ceased smoking nine years prior). Other co-morbidities encountered in our patients include two cases of gastro-oesophageal reflux disease, one case of obstructive sleep apnea, one case of hypothyroidism and one patient with endometrial adenocarcinoma. Radiologically, six patients had pulmonary nodules on CT examination (Figure 1).

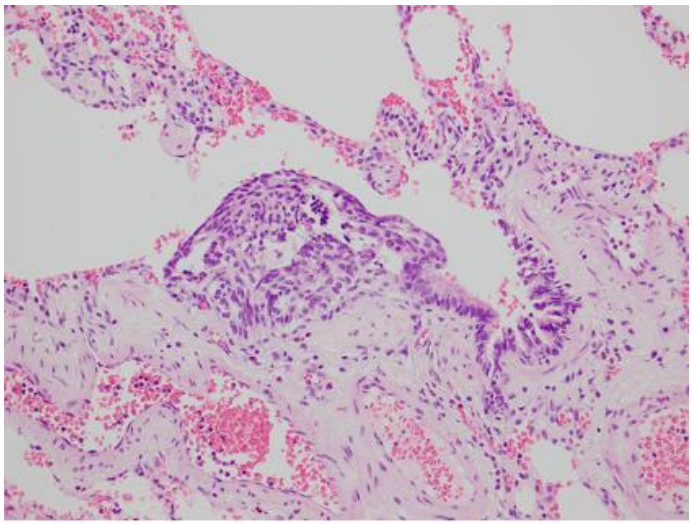
Histopathological diagnosis was rendered incidentally in five out of seven patients who underwent lung lobectomy, one wedge resection and one percutaneous CT guided core biopsy. The reasons for lobectomies were carcinoid tumour in three, and adenocarcinoma in two patients. One case underwent a lobectomy for adenocarcinoma and wedge resection for pulmonary nodules diagnosed on CT scan. In the patient whose diagnosis was made on percutaneous CT-guided core biopsy, initial clinical and imaging impression was metastatic endometrial adenocarcinoma to the lung.

Figure 1: CT scan of a 64-year-old female with multiple bilateral pulmonary nodules



In all seven cases, microscopic examination showed neuroendocrine cells with round to oval nuclei, finely granular chromatin, and eosinophilic cytoplasm. These were arranged in linear or nodular aggregates at the base of bronchial epithelium without basement membrane breach (NECH) or set in a fibrous stroma with breach of basement membrane in tumourlets (≤5mm) and carcinoid (>5mm) (Figure 2).

Figure 2: Neuroendocrine cell hyperplasia with thickening of bronchiolar mucosa



Discussion

DIPNECH is recognised by WHO as a preneoplastic condition that may give rise to pulmonary neuroendocrine tumourlets or carcinoid tumours.[3]

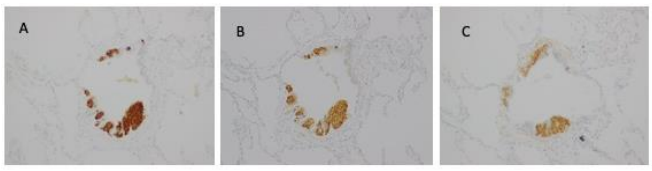
Epidemiologically, DIPNECH is ten times more common in middle-aged females and is usually not associated with smoking, unlike other forms of NECH.[4]

The symptomology is variable, and patients may present with symptoms of airflow limitation secondary to the bronchiolocentric proliferation of DIPNECH, resulting in constrictive bronchiolitis. These symptoms may include chronic non-productive cough, dyspnoea and wheezing and are often mistaken for the diagnosis of asthma, particularly in the context of an obstructive ventilatory defect.[4,5] The lung function can demonstrate an obstructive or a concomitant obstructive and restrictive pattern, with a purely restrictive pattern being rare.[4,5]

DIPNECH cannot be seen on conventional chest X-ray. However, a CT scan of the thorax may show typical findings of small airway disease, with mosaic attenuation on the inspiratory series of a high resolution CT scan associated with gas trapping on the expiratory series, due to the constrictive bronchiolitis. Other radiological features that have been described include pulmonary nodules, bronchial wall thickening and bronchiectasis.[6,7]

On histopathology examination, all neuroendocrine proliferations (NECH and DIPNECH) are highlighted by immunohistochemical studies for keratin and neuroendocrine markers such as chromogranin, synaptophysin and CD56 (Figure 3).

Figure 3: Neuroendocrine cells express A: chromogranin, B: synaptophysin and C: CD56



Chronic inflammatory cell infiltrates, wall thickening and fibrosis of the involved airways leading to narrowing obliteration of the bronchiole is a hallmark of constrictive obliterative bronchiolitis and a typical finding of DIPNECH.[4]

To date, DIPNECH has been reported in only small case series, and some case reports only. In our local case series of DIPNECH, we could observe a few interesting points. Firstly, all seven patients were female and aged between 57 and 70 years (average age 64 years). This is similar to the observation Marchevsky et al.[2] made in their analysis of surgical lung biopsies in Los Angeles (United States of America) where the average age was 72 years, and 87 per cent were female. According to the medical records, four patients were non-smokers, two active smokers and one ceased nine years before the diagnosis of NECH.

Cough was the predominant symptom in four cases, with one patient, in addition, complaining of mild exertional dyspnoea. Progressive dry cough, dyspnoea and/or wheezing are the typical symptoms of DIPNECH and often mistakenly lead to the diagnosis of gastro-oesophageal reflux disease, asthma and chronic obstructive pulmonary disease (COPD).[3-5,8-9] The latter two diagnosis is often supported by the obstructive ventilatory defect that often can be observed on pulmonary function tests. However, according to the literature, a combined obstructive and restrictive and a normal pulmonary function test has been described as well.[3-5,8-9] Unfortunately, in our case series, lung function was documented in medical records in only three cases, with the results being normal in two cases and an obstructive ventilatory defect in one other case.

The radiologically described nodular changes were seen in five out of seven cases. In one patient, no radiology finding was documented on medical records and imaging was not retrievable.

In terms of therapy, there is no general consensus on optimal management of DIPNECH. Oral and/or inhaled glucocorticoids, chemotherapy, surgical resection and even lung transplantation have all been proposed and are described in the literature as treatment options.[3-5,8] Since a chronic inflammatory process is believed to contribute to the development of DIPNECH via secretion of neuropeptides[10] by the neuroendocrine cells as a response to the inflammation, glucocorticoids are generally used in symptomatic patients.

A Somatostatin analogue, octreotide, with its documented effect on reducing Neuropeptide secretion in pulmonary carcinoids has been trialled and shown some effect on the disease by offering symptomatic relief especially with regard to ameliorating cough.[11]

There is limited data regarding the long-term outcome of DIPNECH and NECH. The prognosis varies largely, ranging between 0-25 (average 7.8) years survival in the literature

as summarised by a review paper by Giulio Rossi et al. [12]. Most cases present as a slowly progressive or stable disease. However, especially in the subgroup presenting with constrictive bronchiolitis, the disease can often demonstrate a progressive course which eventually lead to end stage lung disease. This may warrant lung transplantation.[5,8,12]

Conclusion

In summary, DIPNECH is a rare disease. Our findings indicate that, it is often found incidentally in a surgical specimen resulting in a delayed or missed diagnosis. High index of suspicion and close follow up remain the key for early diagnosis and management of patients with indolent pulmonary symptoms.

References

1. Benson RE, Rosado-de-Christenson ML, Martínez-Jiménez S, et al. Spectrum of pulmonary neuroendocrine proliferations and neoplasms. Radiographics. 2013;33:1631–1649.
2. Marchevsky AM, Wirtschafter E, Walts AE, et al. The spectrum of changes in adults with multifocal pulmonary neuroendocrine proliferations: what is the minimum set of pathologic criteria to diagnose DIPNECH? Hum Pathol. 2015;46:176–181.
3. Gosney JR, Austin JHM, Jett J, et al. Diffuse pulmonary neuroendocrine cell hyperplasia. In: Travis WD, Brambilla E, Burke AP, et al., eds. WHO classification of tumours of the lung, pleura, thymus and heart. Lyon, IARC Press. 2015;78–79.
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. Carr LL, Chung JH, Achcar RD, et al. The clinical course of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. Chest. 2015;147:415–422.
6. Lee JS, Brown KK, Cool C, et al. Diffuse pulmonary neuroendocrine cell hyperplasia: radiologic and clinical features. J Comput Assist Tomogr. 2002;26:180–184.
7. Chassagnon G, Favelle O, Marchand-Adam S, et al. DIPNECH: when to suggest this diagnosis on CT. Clin Radiol. 2015;70:317–325.
8. Davies SJ, Gosney JR, Hansell DM, et al. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: an under-recognised spectrum of disease. Thorax. 2007;62:248–522.
9. Koliakos E, Thomopoulos T, Abbassi Z, et al. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: a case report and review of the literature. Am J Case Resp. 2017;18:975–979.
10. Degan S, Lopez GY, Kevill K, et al. Gastrin-releasing peptide, immune responses, and lung disease. Ann N Y Aca Sci. 2008;1144:136–147.
11. Chauhan A, Ramirez RA. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) and the role of somatostatin analogs: a case series. Lung. 2015;193:6.
12. Rossi G, Cavazza A, Spagnolo P, et al. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia syndrome. Eur Respir J. 2016;47:1829–1841.

PEER REVIEW

Not commissioned. Externally peer-reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

No funding for this case series.

PATIENT CONSENT

The authors, Lisa Basler, Marsa Hosseinzadeh, Dariush Daneshvar and Peter Wu declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).

This submission is compliant with the requirements of local research ethics committees

Table 1: Key findings

Sex	Age (years)	Respiratory Symptoms	Smoking	PFT	Radiological Diagnosis	Histological Diagnosis	Reason for Resection/CT-guided biopsy
F	70	Left-sided chest pain	Non-smoker		nodule (17mm) in LLL, nodule (9mm) in RML	Multiple foci of neuroendocrine cell hyperplasia (0.2–1mm)	Wedge resection for Carcinoid in LLL
F	69	Nil documented	Active, 40PY		RML nodule (15x13mm) and smaller nodules in RML (max 3mm) and nodule (7x6mm) in LLL	A carcinoid tumourlet (4mm) and a focus of neuroendocrine cell hyperplasia (1.5mm)	Resection for Carcinoid RML
F	57	Chronic dry cough	Active	FEV_1/FVC=57%		Two carcinoid tumourlets (2 and 4mm) and a focus of neuroendocrine cell hyperplasia (1mm)	Resection for Carcinoid RML
F	63	Dry cough	Ceased		RML nodule 6×9×10mm. Nil other lung parenchymal changes.	Multiple foci of neuroendocrine cell hyperplasia (0.3–1mm)	Resection for Adenocarcinoma RML
F	60	Dry cough	Non-Smoker		Bilateral pulmonary nodules	A focus of peribronchiolar neuroendocrine cell hyperplasia (1mm)	Resection for Adenocarcinoma RUL.
F	68	Nil documented	Non-Smoker	FEV_1/FVC=69%	Ill-defined ground glass Opacity RUL (14mm), nodule (7mm) RLL, two nodules (max 7mm) in LLL	A carcinoid tumourlet (2mm) and a focus of neuroendocrine cell hyperplasia (0.2mm)	Resection for Adenocarcinoma RUL, Wedge resection RLL for pulmonary nodules
F	64	Dry cough, mild SOB on exertion	Non-Smoker	FEV_1/FVC=75%	Numerous bilateral pulmonary nodules measuring up to 7mm	Carcinoid tumour in the largest biopsied nodule	CT-guided core biopsy of the largest nodule in LLL