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Original article

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)—An uncommon precursor of a common cancer?

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ABSTRACT

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare, likely under recognized entity. We report on six cases of DIPNECH that were seen in Saskatoon, SK. The cases largely have the characteristics of the typical patient profile thus far described in the literature, consistent with the limited information reported to date. Furthermore, one case had co-existing squamous cell carcinoma, which has not been previously described, and one case had concomitant adenocarcinoma. In this context, we explore the hypothesis of whether DIPNECH could play a role as an uncommon precursor in pulmonary tumorigenesis. We also propose improved diagnostic criteria for DIPNECH, which are currently ill-defined.

Introduction

DIPNECH is infrequently reported, with less than 100 cases in the English literature [1].

Pulmonary neuroendocrine cells (PNEC) are specialized epithelial cells distributed throughout the entire respiratory tract. DIPNECH's current WHO classification includes any of the following: (a) generalized proliferation of PNEC hyperplasia of scattered single cells, (b) small nodules (NE bodies) or (c) linear proliferations confined to the respiratory epithelium without invasion beyond the basement membrane [2,3]. This entity is considered as one possible precursor of pulmonary neuroendocrine neoplasia [4–7].

DIPNECH that breaks through the basement membrane and invades locally is called a tumorlet (≤5 mm) and nodules >5 mm in diameter are classified as carcinoid tumors [3,4]. A tumorlet is characterized by peribronchial or peribronchiolar invasion by neuroendocrine cells (NECs) with the development of a fibrotic stroma, forming discrete lesions distinct from intramucosal aggregates of PNECs [7].

We present six cases of DIPNECH in association with tumorlets and carcinoid tumors. One case occurred concomitantly with adenocarcinoma, and one with squamous cell carcinoma; the latter is a novel finding. We hypothesize that DIPNECH may be a potential precursor in the oncogenesis not only of carcinoid tumors, but also of squamous cell carcinomas and adenocarcinomas. In addition, we believe the diagnostic criteria for DIPNECH needs to be more specific and postulate improved definitions for this entity.

Materials and methods

We present six patients with an average age of 71, of which five were female and three were smokers. They had undiagnosed symptoms for many months and years as well as characteristic findings on imaging (Table 1).

A literature review was conducted on Medline, with four search items, 'DIPNECH', 'diffuse idiopathic pulmonary neuroendocrine hyperplasia', 'precancerous conditions', and 'lung neoplasms' exploded. The independent searches were combined and the resultant articles reviewed. The primary papers were analyzed with inclusion of all relevant secondary references. The original searches brought up 180,000 papers total. After combining the four searches, there were 43 papers of relevance. This search

Abbreviations: DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; PNEC, pulmonary neuroendocrine cells; CT, computed tomography; NE, neuroendocrine; ACTH, adrenocorticotropic hormone; BASC, bronchioalveolar stem cell.

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Table 1
Clinical characteristics of the six index patients with DIPNECH.

Patient	Age	Sex	Smoking history	Obstructive symptoms	Duration of symptoms	Imaging	Lesion identified in the lung
1	62	F	+	COPD	Incidental	Multiple nodules	Tumorlets + Carcinoid
2	64	F	–	SOB	6m	Multiple nodules	Tumorlets
3	69	F	–	Bronchiectasis, chronic cough	25y	Multiple nodules	Tumorlets + Carcinoid
4	68	M	+	COPD	Multiple years	Bronchiectasis and opacities	Tumorlets + Squamous cell carcinoma
5	76	F	+	COPD	Multiple years	Stable spiculated nodule	Tumorlets + Adenocarcinoma
6	92	F	NA	NA	NA	NA	Tumorlets Lung + Gastric Adenocarcinoma

Abbreviations: COPD, chronic obstructive pulmonary disease; SOB, shortness of breath; NA, not available; DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia.

was limited to manuscripts presently published in the English literature.

Results

Histopathological examination

Regarding the DIPNECH component, all six patients had no evidence of lymphovascular or pleural invasion, mitotic activity, or necrosis. The lesions formed multiple foci of nests of monomorphic cells, ranging in size from 1–12 mm (Fig. 1a). The cells had a round to slightly ovoid, sometimes spindled, nuclei with scant eosinophilic cytoplasm. Tumorlets were predominantly present in a peribronchiolar distribution (Fig. 1b).

In all cases but one, only one lobe was available for examination. The foci of tumorlets were separated by 2–11 mm in our cases (Fig. 1c).

Two cases had the presence of co-existing invasive carcinoma, one squamous cell and one adenocarcinoma. DIPNECH was present in both the upper and lower lobes, while the squamous cell carcinoma was in the upper lobe. The adenocarcinoma and DIPNECH were both present in the only lobe examined. The minimum distance between invasive carcinoma and DIPNECH was 2.5 mm.

Discussion

Bronchial neuroendocrine cells, or Kulchitsky cells, are the first cells to originate from the endoderm to form and differentiate into pulmonary epithelium during the early development of the lung [6]. NECs are situated at the base of the bronchial and bronchiolar mucosa [8]. However, the cells are rare in adults. PNECs may be solitary or occur as clusters and form part of the dispersed or diffuse endocrine system [9]. DIPNECH is the earliest manifestation of neuroendocrine disease in the bronchopulmonary system and is considered a pre-invasive lesion, a precursor of carcinoid tumors and tumorlets [4,5,10]. A large series of 1090 lung resection specimens detected DIPNECH in 3 cases associated with typical carcinoid tumors [11]. Another study showed that of 25 patients who underwent resection for lung peripheral carcinoid tumors, 19 had NE cell hyperplasia in addition to the main tumor [12]. Although both DIPNECH and tumorlets are associated with a peripheral localization of carcinoids [13], the majority of central carcinoid [6] tumours and bronchopulmonary carcinoid tumours do not appear to arise in a background of antecedent DIPNECH [14]. Although 2/3 of patients with peripheral carcinoid tumors have DIPNECH in the adjacent bronchiolar epithelium, the relationship between the two is not currently understood. Further investigation will be needed to determine whether PNEC hyperplasia precedes the development of tumorlets or carcinoid tumors, especially central carcinoids [13].

Cytokines and growth factors are secreted by PNECs (such as gastrin releasing peptide, bombesin, and fibroblast growth factor), which stimulate fibroblasts and airway cell chemotaxis, which in turn results in bronchiolar fibrosis and an obstructive pattern on pulmonary function tests [1,13,15,16]. Indeed, reports confirm that patients present with obstructive lung disease, which is often correlated with the typical mosaic perfusion pattern seen on imaging [4]. However, it is possible for patients to be asymptomatic or have only mild functional alterations [5]. In our cases, the lesions are peri-bronchial, likely contributing to the obstructive presenting symptoms, similar to previously reported cases.

Most patients are females between 5th and 6th decades, non-smokers, have obstructive lung symptoms, and have peripheral lesions [1,5,13]. The demographic and presentation of disease in our cases supports the current literature with the exception of three of six patients being smokers (Table 1).

Atypical presentations of DIPNECH are possible with aberrant hormone production, such as ACTH [17]. Six cases have been reported of DIPNECH co-existing with adenocarcinoma [18–20]. One of the cases in our series presented with an invasive adenocarcinoma, while a second case had concurrent invasive squamous cell carcinoma. In this context, we hypothesize that DIPNECH may be an uncommon precursor for multiple types of lung neoplasms as illustrated in Fig. 2 and discussed below.

Controversy exists regarding the true nature of DIPNECH. Many have proposed that DIPNECH is a pre-invasive lesion for carcinoid tumors of the lung. Others have postulated that a subset of adenocarcinomas may have a distinct tumorigenesis related to PNEC hyperplasia [18]. Additionally, we postulate that DIPNECH may, in select cases, also be a precursor for squamous cell carcinomas and adenocarcinomas through field cancerization leading to progenitor (DIPNECH) induced tumorigenesis (Fig. 2). It has been reported that multiple pre-invasive lung cancer lesions arise in different areas of the lungs, giving rise to spatially distinct lesions. Furthermore, it is suggested that multifocal pre-invasive lesions are most commonly derived from a common clonal ancestor. The data also showed that while clonal, the lesions were not continuous, suggesting that cellular migration occurred with subsequent clonal expansion in new environments with normal epithelium between lesions [21]. Similarly, DIPNECH is a patchy process, with histologically normal areas between foci of tumorlets. Perhaps in certain cases, epithelial precursor cells produce a clonal ancestor that gives rise to DIPNECH with a predilection to differentiate to carcinoid, squamous cell or adenocarcinoma. Another possibility is that the multifocal nature of DIPNECH may be related to stromal modulation of the tumor microenvironment resulting in tumorigenesis with field cancerization that may be a result of (a) multiple different mutations occurring in parallel, (b) expansion of a single mutant/multiple clones occurring in parallel or (c) same mutation occurring multiple times at different times. Perhaps outside of the traditional