DIPNECH – a preneoplastic lesion or a separate biological entity?

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ABSTRACT

Introduction: DIPNECH is a very rare condition with under 100 cases reported in the scientific literature worldwide. The new WHO classification of lung tumors considers it as a preneoplastic condition, leading to further growth of pulmonary carcinoid tumors. Prior to that, proliferating neuroendocrine, or NE cells in the respiratory epithelium develop into tumorlets – lesions less than 5mm in the largest size, visible in diagnostic imaging as round shadows and sometimes mistake for metastases of a tumor of unknown origin.
Purpose: The goal here is to strongly recommend the foundation of a world wide web (www) based portal with clinical information about DIPNECH, also, if possible, containing reports of all the cases ever diagnosed. This will create an easily accessible source of information, which could increase the rate of diagnosis for this condition. Thanks to further possibilities of scientific exchange and development such as a database could become a vast archive of pulmonary preneoplastic lesions with possible clues to understanding mechanisms of carcinogenesis.
Discussion: It is yet unclear, if DIPNECH could be a predecessor of other neuroendocrine tumors, at least being one of their possible origins, or is the growth of NE cells around the primary neuroendocrine tumor a reaction for airway obstruction and hypoxia.
Conclusion: According to information gathered through electronic search, further scientific investigation of DIPNECH might be very helpful in understanding carcinogenesis in lung.
Key words: DIPNECH, PNECH, neuroendocrine cell hyperplasia, pulmonary preneoplastic lesions, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

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INTRODUCTION

Among all pulmonary neoplastic lesions in adults, DIPNECH, or diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, remains extremely rare with less than 100 cases reported worldwide [1]. Although it has been postulated to create an international data center to gather information about newly diagnosed cases, as for December 2013, the initiative was not accomplished and the need for establishing such a database remains at high importance. There is strong evidence that DIPNECH leads to carcinogenesis in case of pulmonary carcinoid tumors, so suggestions were made to alter the classification of pulmonary neuroendocrine tumors by dividing them in two groups, one consisting of typical and atypical carcinoids as low-grade malignancies of the lung originating from DIPNECH and the other, containing the high-grade malignant neoplasms, like the small-cell carcinoma and the large-cell neuroendocrine carcinoma of the lung [2 – 5]. However, some case reports show a picture of DIPNECH as a separate disease and in those particular cases, even in follow-up, there is no sign for further cancer development on its basis. The disease itself may cause death by pulmonary failure [6]. In this article the reader will find an overview of case reports and general reference papers considering DIPNECH based on electronic search. The search was conducted using standard on-line browsing engines through the libraries of National Center for Biotechnology Information, National Library of Medicine and National Institutes of Health, Bethesda, MD, USA. The keywords used to perform the search were DIPNECH and *diffuse idiopathic neuroendocrine cell hyperplasia*. All the records regarding NEHI or *neuroendocrine hyperplasia of infants* were intentionally omitted as NEHI is an interstitial lung disease and has not been classified as a preneoplastic lesion.

1. The WHO classification

According to WHO classification of lung tumors, DIPNECH is a separate lesion regarded to as a preneoplastic condition for tumorlets, and typical/atypical carcinoids, but only those located peripherally [1]. In the revised edition of this classification dating 2001, the atypical adenomatous hyperplasia or AAH was also mentioned as a separate entity, developing into adenocarcinoma of the lung [1]. These two conditions are since described as the only proven-to-be preneoplastic changes in the lung. In some cases, proliferating pulmonary neuroendocrine cells develop into tumorlets- small changes in the respiratory epithelium less than 5mm in diameter, sharing histological features with carcinoids. However, carcinogenesis of pulmonary neoplasms, including neuroendocrine tumors, remains a subject to discuss due to unknown origins of cancer cell lines [3, 5, 7].

2. The pulmonary neuroendocrine cells

DIPNECH originates in an uncontrolled linear growth of pulmonary neuroendocrine (NE) cells. These cells are very similar to those existing in gastrointestinal tract when observed in light microscopy, first described by Kultschitzky [5], so they are also known as pulmonary Kultschitzky-like cells, Feyrter cells, or enterochromoffin cells. Pulmonary NE cells create part of the APUD system and pulmonary neuroendocrine system, playing a major role in the development of lung tissue in embryos and behaving as chemoreceptors in post-embryonic life [3, 4, 6]. Although their morphology resembles neuronic cells, the pulmonary NE cells develop undoubtedly from endodermic precursors [5]. These cells are the first to differentiate in the epithelium at the earliest stages of lung development, controlling further growth and organization of pulmonary tissue. In fully formed human lung, most NE cells exist solitarily in the ciliated epithelium or can be found in groups, known as pulmonary neuroendocrine bodies (NEBs). When fully formed, these cells secrete serotonin in response to low oxygen concentrations based on particle pressure detected by chemoreceptors on the luminal part of their cell membrane. Serotonin or 5-HT (5-hydroxytriptamin) acts on vascular endothelium causing vasoconstriction [5, 8]. Thanks to this mechanism, bloodstream is being redirected from less airy areas of the lung to those with higher oxygen concentration, providing more effective gas exchange. There are suggestions, that pulmonary NE cells may also control processes of regeneration after lung injury [4].

3. Clinical symptoms and radiologic findings

Although typical clinical features of a patient diagnosed with DIPNECH are the age between 60 and 70 years, female, it may also occur in much younger individuals of both genders [9]. The patients are mostly asymptomatic and in such a case, the finding is incidental. Some of them develop symptoms, such as unproductive cough and episodes of dyspnea, so DIPNECH is often mistaken for asthma bronchiale [10]. The majority of those patients have never smoked a cigarette in their entire life. When it comes to radiologic diagnostics, the findings are sometimes very similar to metastases with an unknown primary tumor [11]. In high resolution computed tomography (HR CT) scans, the image shows multiple micronodules, often with associated mosaic attenuation and ground-glass pattern with evidence for centrilobular distribution, air tapping and constrictive bronchiolitis [4]. Some sources describe linear proliferations of pulmonary NE cells with tumorlets, visible in the peripheral parts of the lung on high resolution CT scans [9, 12, 13].

4. Morphology and immunohistochemistry

Although clearly visible in radiographic examinations, DIPNECH is diagnosed by the 'golden standard' of tissue biopsy, examined in light microscopy with immunohistochemical staining [8]. The markers of neuroendocrinity in pulmonary NE cells, used specifically in our laboratory practice, are CD56 or NCAM, synaptophysin and chromogranin A.

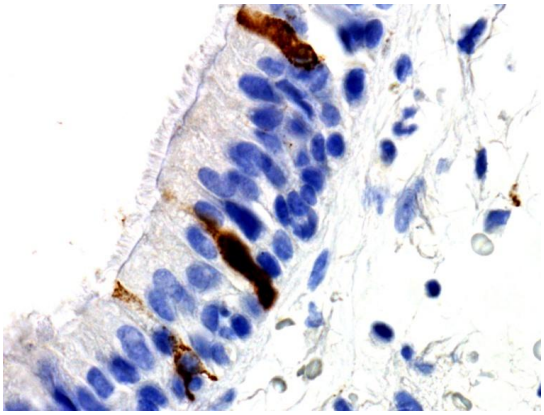

Figure 1. Typical neuroendocrine cells in the ciliary pulmonary epithelium, staining for chromogranin. Note the two poles of a single NE cell, one of them directing into the lumen of an airway, possibly with the expression of chemoreceptors and the other, lying very closely to the vesicular wall. The pulmonary neuroendocrine cells in the normal airway epithelium constitute about 0.4% of all cell types. Magn. 400x. *Image courtesy of Białystok Medical University, Department of Medical Pathomorphology*.

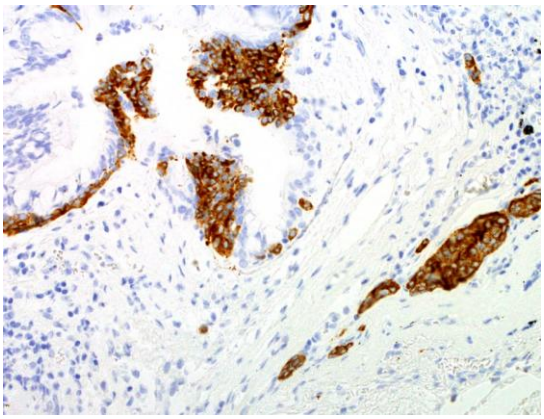

Figure 2. A picture of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, staining for synaptophysin. One of two cases diagnosed in our research center. Magn. 200x. *Image courtesy of Białystok Medical University, Department of Medical Pathomorphology*.

5. Antigen profiling

Above other functions of pulmonary NE cells, some investigators distinguish their role in the process of lung tissue regeneration after injury. It has not yet been specified, what kind of injury may cause a diffuse and uncontrolled growth of NE cells. A mechanism has been described, in which primary linear proliferation is followed by aggregation of NE cells and the creation of tumorlet lesions, which seems to be the closest to further carcinogenesis [5, 8, 14]. Despite that, there is no evidence for malignant transformation in a pulmonary NE hyperplasia as a response to tissue damage [5,8].

In the matter of antigen profiling, a huge research was carried out and reported by Gosney et al. [8]. The workgroup divided antigen staining into four groups. First group included epithelial differentiation factors, such as cytokeratins of classes 7 (CK7), 20 (CK20) and 34bE12, and thyroid transcription factor (TTF)-1. The second group contained markers of neuroendocrine differentiation, that is (NCAM; CD56), chromogranin A (ChrA), protein gene product (PGP) 9.5, neurone-specific enolase (NSE) and synaptophysin (syn). The following two groups of antigens included markers for major peptide products of pulmonary NE cells, such as gastrin-releasing peptide (GRP), calcitonin, calcitonin gene related peptide (CGRP) and number of proteins involved in cell proliferation and the process of apoptosis [8, 15].

The results of this research showed, that there is virtually no difference in antigen profiles for proliferating pulmonary NE cells, either the growth is ongoing as a reaction to postulated injury or is it described as idiopathic [7, 16-18]. A point of malignant transformation was not yet discovered.

CONCLUSIONS

There is much controversy in attempts to finding a universal precursor cell, or a mechanism that leads to the development of lung cancer [4, 6, 8, 19-22]. Pulmonary neuroendocrine tumors seem to be a topic to discuss in the first place as possibly presenting the strongest evidence for earliest stages of carcinogenesis [5, 8]. Despite this fact, subtle molecular and genetic changes in the development of pulmonary neoplasms remain beyond reach, so as are triggers causing them to occur. When DIPNECH is taken into consideration as a separate lesion, it seems that a specific group of pulmonary malignancies is not combined with cigarette smoke or environmental pollution [23-25]. There is a strong need for the creation of a database, working similar to an internet portal, in first place gathering data about DIPNECH, such as case reports and analysis. It will also give the ability to contact other researchers and exchange scientific information by

traditional resources. Major points of interest here are to improve the diagnostic ratio for this condition and to allow scholars and scientists to work on this problem and additionally find clues for other carcinogenic mechanisms in the lung.

Conflict of interests

The authors of this paper declare no competing interests in the publication of this manuscript.

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