

CASE STUDY

COEXISTENCE OF PULMONARY FIBROSIS AND PROLIFERATION OF PULMONARY NEUROENDOCRINE CELLS FORMING TUMORLET

DOI: 10.36740/WLek202107136

Iga Panek¹, Maciej Liczek¹, Igor Rakoczy¹, Patrycja Węglarz¹, Marcin Braun², Michał Panek¹, Piotr Kuna¹¹DEPARTMENT OF INTERNAL MEDICINE, ASTHMA AND ALLERGY MEDICAL UNIVERSITY OF LODZ, POLAND²DEPARTMENT OF PATHOLOGY, CHAIR OF ONCOLOGY, MEDICAL UNIVERSITY OF LODZ, POLAND

ABSTRACT

Tumorlet is a disease rarely diagnosed in clinical practice. It is characterized by pulmonary neuroendocrine cell (PNEC) proliferation which invades the bronchiolar basement membrane and forms nodules with a diameter smaller than 5 mm.

Case report: 72-year-old female patient was suffered for many years from progressive dyspnea and coughing with evidence of pulmonary fibrosis on high resolution computed tomography (HRCT). As a result of a lung biopsy, based on immunohistochemical tests, a 2 mm cluster of neuroendocrine cells (NEC) was found and it was diagnosed as tumorlet. Due to a long-term, insidious progress of the disease, as well as sex and age of the patient, the case emphasizes that differential diagnosis should include tumorlet as well as diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) as a more extensive manifestation of neuroendocrine cell proliferation in the respiratory tract.

KEY WORDS: dyspnea, IPF, tumorlet, DIPNECH

Wiad Lek. 2021;74(7):1767-1769

INTRODUCTION

The presence of neuroendocrine cells in the respiratory tract is a physiological state – they constitute a part of the diffuse endocrine system. They fulfil a secretory function regulating local growth of the epithelium, and, as chemoreceptors they take part in detection of oxygen deficiency. Mutations as well as excessive proliferation within these cells may lead to neoplastic diseases ranging from mild carcinoids to highly malignant small lung cell carcinoma (SCLC) and large cell neuroendocrine lung carcinoma (LCNEC) [1]. One of manifestations of proliferation of neuroendocrine cells (PNC) is DIPNECH and, if the basal membrane is invaded by these cells, we may distinguish between the tumorlet (a lesion smaller than 5 mm) or carcinoid (a lesion greater than 5 mm). The size is the only criterion differentiating tumorlet from carcinoid [2]. Most researchers emphasize that tumorlet is one of the DIPNECH spectrum conditions, however, according to some data, three tumorlets in surgical pathology specimens are sufficient for diagnosing DIPNECH. The disease was first reported in 1953. At present, the World Health Organization (WHO) defines DIPNECH as “a generalized proliferation of scattered single cells, small nodules (neuroendocrine bodies), or linear proliferations of pulmonary neuroendocrine cells (PNCs) that may be confined to the bronchial and bronchiolar epithelium”, specifying that it is a pre-neoplastic stage of lung cancer [2, 3]. When progressing, the disease may remain latent for many years being concealed by bronchial asthma or non-specific pulmonary fibrosis [2]. The 5-year survival rate in DIPNECH refers to about 83% of the patients [4].

THE AIM

The aim of this case report is to provide a topic of neuroendocrine tumors and significance this theme in the differential diagnosis of dyspnea.

CASE REPORT

A 72-year-old female patient, non-smoker with history of gastro-esophageal reflux disease (GERD) and arterial hypertension, was referred to a pulmonary outpatient clinic in November 2017 due to dyspnea aggravating for the last few years and deterioration of exercise capacity. The patient had no occupational exposure. On examination, bilateral basal crackles were heard. A spirometry test showed no obstruction; diffusion of carbon monoxide was considerably reduced (DLco-SB K indicator below 1 percentile). Due to the suspicion of pulmonary fibrosis, high resolution computed tomography (HRCT) of the chest was performed. The examination revealed ground glass opacities, fibrotic lesions in the peripheral regions of the lungs, more prominent in the lower lobes, and exacerbation of fibrotic lesions with signs of bronchiectasis and honeycomb appearance (Fig. 1), which may indicate idiopathic pulmonary fibrosis (IPF). HRCT also demonstrated extensive hernia with displacement of the stomach into the chest which was a possible cause of GERD occurrence in the patient.

In bronchoscopy mucous membrane was swollen and easily bleeding. Furthermore, sample of bronchoalveolar lavage fluid (BALF) had no typical signs of hypersensitivity pneumonitis (HP). Serum anti-neutrophil cyto-



Fig. 1. A-C. HRCT scans: ground glass opacities (GGO), fibrotic lesions in the peripheral regions (prominent in the lower lobes), bronchiectasis and honeycomb appearance.

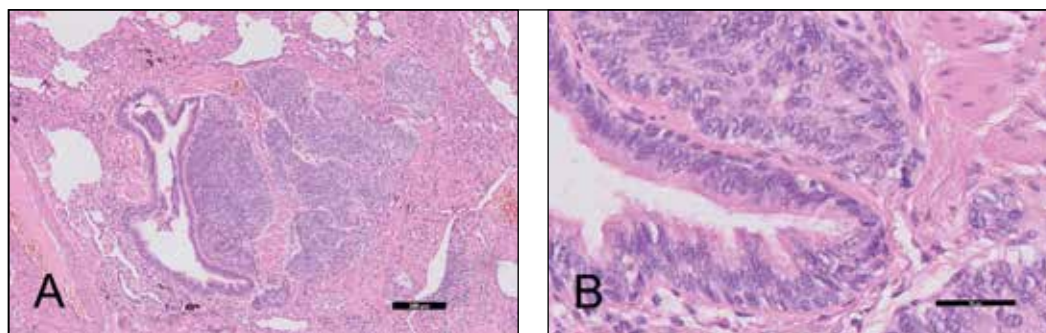


Fig. 2. Photomicrograph of the histology of lung section from biopsy. It shows 2 mm aggregation of neuroendocrine cells forming a tumorlet (H-E stain). A. Magnification x5 B. Magnification x40

plasmic antibodies (c-ANCA and p-ANCA) was within the normal limits.

An X-ray of the chest disclosed distension of the left lung and shadow (67x11 mm) occurring over its field. Therefore, the next diagnostic step was a video-assisted thoracoscopic surgery (VATS) biopsy.

Histopathology examination revealed a fragments of the lung parenchyma with emphysematous, atelectatic changes and accompanying fibrosis. Honeycomb appearance was not observed. The changes were regularly located, mainly around bronchiolar ectasia, partly also in the subpleural region. In the fibrotic stroma, moderate lymphocytic reaction occurred with numerous histiocytes and few multinucleate cells; granuloma-like structures were found focally. Additionally, a 2-mm cluster of neuroendocrine morphology cells was observed (Fig. 2) (immunophenotype AE1/AE2 (+), CD56 (+), chromogranin (+), Ki-67 <1%) (Fig.3). Based on the size and characteristic staining, the lesion could be

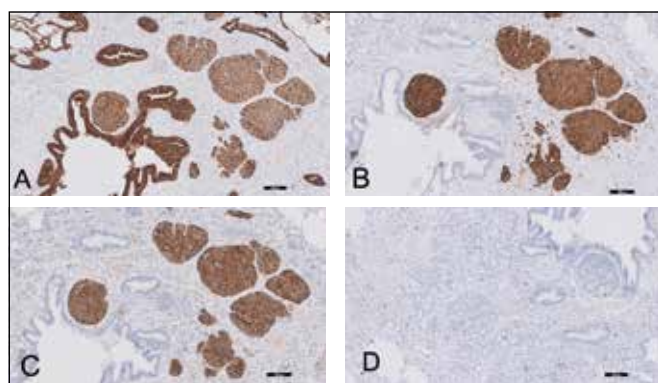


Fig. 3. Positive immunohistochemical staining for: A. AE1/AE3, B. chromogranin, C. CD56 and D. Ki-67 < 1%. Magnification x10.

diagnosed as a tumorlet. The decision was taken to include prednisone administered orally, in a dose of 30 mg/d. After a week, a slight improvement in the patient's condition was observed (alleviation of the symptoms and reduction of crackles), therefore the dose of glucocorticoid was decreased to 20 mg/d. A follow-up HRCT performed six months after the commencement of the treatment showed no evidence of evolution, however, the ground glass opacity and bronchiectasis remained. Following oncological consultation, it was decided to refer the patient to another oncology unit for targeted therapy. After hospitalization in the oncology department, the current treatment with oral corticosteroids (prednisone 20 mg/d) was maintained. The patient, without showing disease progression, remains under the care of the pulmonologist.

DISCUSSION

Studies concerning DIPNECH are scarce, which results from a small number of diagnosed cases and analyzed patients. So far, a report which includes the greatest number of patients with DIPNECH was presented by Davies et al. who reviewed 19 individuals suffering from the disease and diagnosed within 14 years, and Carr et al. who analyzed a group of 30 patients [3, 4]. In their studies, they suggested diagnostic criteria including demographical data, pulmonary physiology, HRCT imaging and transbronchial and surgical lung biopsy. Other studies and case reviews carried out over the last few dozens of years involved much smaller groups of patients. It is believed, however, that although so few cases have been studied so far, the population of these patients may be much larger [4], which is proved by the presence of neuroendocrine cell hyperplasia (NECH) and/or tumorlets in the lungs of patients who underwent surgery

due to, among others, carcinoid, adenocarcinoma or granulomatous pneumonia [5]. The population most commonly afflicted with the disease are females aged between 50 and 70 years, however, the condition often manifests itself by minor symptoms only or symptoms do not occur at all [5]. Additionally, in this group of patients the disease is often misdiagnosed as bronchial asthma due to the occurrence of coughing and dyspnea as well as signs of pulmonary obstruction in a spirometry test caused by blockage of the airways. Aguayo et al. who in the 1990's considerably extended the current knowledge on DIPNECH concluded that the airway obstruction is a condition secondary to chronic inflammation caused by peptides secreted by neuroendocrine cells such as bombesin [6]. Due to lack of substantial scientific evidence that could prove the above-mentioned hypotheses, based on the current knowledge, it is not possible to establish which of the presented lesions are primary and which of them are secondary. Typical HRCT manifestations of DIPNECH are mosaic perfusion caused by air trapping, bronchial wall thickening and bronchiectasis. In the case of co-occurrence of tumorlet and carcinoid, there are also nodules, accompanied by scarring and emphysema, which are the nest of hyperplastic cells [7]. Other changes that may be observed on CT scans also include fibrosis which occurs secondarily to proliferation of neuroendocrine cells [8]. Since the disease is rare, no treatment standards have been developed yet, however, there are certain premises confirming a beneficial effect of glucocorticoids, interferon alfa and chemotherapeutic agents [1].

In the presented case, the patient mostly showed signs of pulmonary fibrosis such as dyspnea and basal crackles. Additionally, HRCT imaging most probably indicated idiopathic pulmonary fibrosis (IPF). A VATS biopsy from middle lobe of right lung revealed a single 2 mm cluster of neuroendocrine cells which, based on identification of the specific receptor profile (AE1/AE3 "+", CD56 "+", chromogranin "+"), could be diagnosed as a tumorlet. As only one cluster of neuroendocrine cells was found and the criteria suggested by Carr et al. were not fulfilled, it was not possible to definitely confirm the co-occurrence of DIPNECH in the patient [3]. The present signs of pulmonary fibrosis indicate a long-term progress of the disease that produced its symptoms probably only with the secondary development of fibrosis. DIPNECH and changes representing the spectrum, such as tumorlet, are diagnosed extremely seldom in the population. Oligo-symptomatic long-term activity of the disease, which may be developing concealed by obstructive diseases or those accompanied by pulmonary fibrosis, makes diagnosing much more difficult as it is mainly based on invasive methods such as lung biopsy.

CONCLUSIONS

These facts and the presented clinical case point to difficulties in diagnosing DIPNECH diseases. However, DIPNECH should be considered in non-smokers female patients aged over 50 years with dyspnea.

REFERENCES

1. Benson REC, Rosado-de-Christenson ML, Martínez-Jiménez S, Kunin JR, Pettavel PP. Spectrum of Pulmonary Neuroendocrine Proliferations. *RadioGraphics*. 2013;(33):1631–49.
2. Stenzinger A, Weichert W, Hensel M, Bruns H, Dietel M, Erbersdobler A. Incidental postmortem diagnosis of DIPNECH in a patient with previously unexplained 'asthma bronchiale'. *Pathol – Res Pract [Internet]*. 2010;206(11):785–7. Available from: <http://dx.doi.org/10.1016/j.prp.2010.04.003>
3. Carr LL, Chung JH, Achcar RD, et al. The Clinical Course of Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia. *Chest*. 2015;147(2):415–22.
4. 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.
5. Marchevsky AM, Wirtschafter E, Walts AE. The spectrum of changes in adults with multifocal pulmonary neuroendocrine proliferations: what is the minimum set of pathologic criteria to. *Hum Pathol [Internet]*. 2015;46(2):176–81. Available from: <http://dx.doi.org/10.1016/j.humpath.2014.10.019>
6. Aguayo S, Miller Y, Waldron JJ, et al. Brief report: idiopathic diffuse hyperplasia of pulmonary neuroendocrine cells and airways disease. *N Engl J Med*. 1992;327(18):1285–8.
7. Koo CW, Baliff JP, Torigian DA, Litzky LA, Gefter WB, Akers SR. Spectrum of Pulmonary Neuroendocrine Cell Proliferation: Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia, Tumorlet, and Carcinoids. *AJR Am J Roentgenol*. 2010;195(3):661–8.
8. He P, Gu X, Wu Q, Lin Y, Gu Y, He J. Case Report Pulmonary carcinoid tumorlet without underlying lung disease: analysis of its relationship to fibrosis. *J Thorac Dis*. 2012;4(6):655–8.

ORCID and contributionship:

Iga Panek – 0000-0003-1348-887X ^D
 Maciej Liczek – 0000-0003-0583-0815 ^D
 Igor Rakoczy – 0000-0001-7748-8890 ^D
 Patrycja Węglarz – 0000-0001-8389-2523 ^D
 Marcin Braun – 0000-0003-3804-7042 ^B
 Michał Panek – 0000-0002-3718-4793 ^{A,E,F}
 Piotr Kuna – 0000-0003-2401-0070 ^F

Conflict of interest:

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Iga Panek

Department of Internal Medicine, Asthma and Allergy
 Medical University of Lodz, Poland
 e-mail: iga.panek@gmail.com

Received: 16.03.2021

Accepted: 06.05.2021

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article