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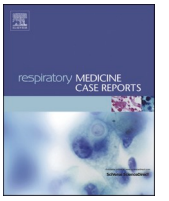

Case report

A case of multiple lung carcinoid tumors localized in the right lower lobe

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ABSTRACT

Typical pulmonary carcinoid (TC) tumors are low-grade neuroendocrine tumors and usually detected as indolent solitary tumors. We herein report a case of multiple pulmonary carcinoid tumors and tumorlets localized in the right lower lobe with no underlying lung disorders suggesting diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). A 28-year-old man with multiple 1-to-8-mm pulmonary nodules in the peripheral pulmonary parenchyma of the right lower lobe was referred to our hospital. The patient underwent a surgical biopsy. Pathological examination revealed multiple nodules composed of spindle cells, and immunohistochemistry revealed staining for chromogranin A, synaptophysin, and CD56, suggesting neuroendocrine tumors. He was diagnosed as having multiple TC tumors and tumorlets. Neuroendocrine cell hyperplasia (NECH) was also observed on some bronchioles. A follow-up CT scan after 6 months showed no changes in the sizes of the nodules and no new lesions. The present case was histopathologically compatible with DIPNECH but it occurs mainly in elderly women. The patient might be in an early stage of DIPNECH before progression to symptomatic DIPNECH. In conclusion, clinicians should consider the possibility of carcinoid tumors and tumorlets in cases with multiple pulmonary nodules even if they are localized in one lobe.

1. Introduction

Typical pulmonary carcinoid (TC) tumors are low-grade neuroendocrine tumors that account for approximately 1% of lung neoplasms [1]. TC tumors are usually detected as indolent solitary tumors and have a good prognosis after surgical resection [2]. TC tumors develop mainly in bronchi but can sometimes develop in peripheral bronchioles, and associated neuroendocrine cell hyperplasia (NECH) has been reported [3]. Pulmonary neuroendocrine cells are sparsely present in bronchi and bronchioles, and NECH is also observed with chronic lung disease, such as interstitial pneumonia and obstructive lung disease; this is considered to be a reactive change to hypoxia [4,5]. In 1992, Aguayo et al. reported 6 non-smoking patients with diffuse NECH and tumorlet or carcinoid tumors causing peribronchiolar fibrosis and an obstruction pattern on pulmonary function tests [6]. This syndrome has been recognized as

Abbreviations: 18F-FDG PET, 18-fluorodeoxyglucose positron-emission tomography; COVID-19, coronavirus disease 2019; DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; HR-CT, high-resolution CT; NECH, neuroendocrine cell hyperplasia; SUVmax, maximum standardized uptake value; TC, Typical pulmonary carcinoid; MinIP, minimum intensity projection; MIP, maximum intensity projection.

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diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) and is described as a preneoplastic condition in the 2004 World Health Organization (WHO) classification. DIPNECH is a rare disease and is considered a primary disease, rather than a reactive change. Because the clinicopathological characteristics of DIPNECH remain unclear and its pathological definition is ambiguous, the diagnosis is often confused with reactive NECH [3,7–9].

Herein, we report a case of multiple pulmonary carcinoid tumors and tumorlets in the right lower lobe with no underlying lung disorders suggesting DIPNECH.

2. Case report

A 28-year-old man with a 6-pack-year history of smoking and no medical history presented with fever after a business trip. A chest CT scan was performed to rule out coronavirus disease 2019 (COVID-19); multiple 1-to-8-mm pulmonary nodules were detected in the peripheral pulmonary parenchyma of the right lower lobe, but the nodules were not aggregated. Small lung cysts were also observed in the peripheral pulmonary parenchyma of the right lower lobe, suggesting obstructive changes (Fig. 1A–C). The fever disappeared within several days, but the pulmonary nodules were still observed after two months. At first, some type of pulmonary infection was suspected, but laboratory tests were normal including those for cryptococcus antigen, beta-D-glucan, and an enzyme-linked immunospot assay for the diagnosis of tuberculosis. An 18-fluorodeoxyglucose positron-emission tomography (18F-FDG PET)/CT study to rule out metastatic pulmonary nodules showed a slight uptake at the nodular site with a maximum standardized uptake value (SUVmax) of 1.8 without any evidence of primary tumors. The patient underwent a video-assisted thoracoscopic wedge resection as a surgical biopsy. Pathological examination of the resected specimen revealed multiple nodules composed of spindle cells, and immunohistochemistry revealed staining for chromogranin A, synaptophysin, and CD56, suggesting neuroendocrine tumors (Fig. 2). The MIB-1 index was less than 1%, and he was diagnosed as having multiple typical carcinoid tumors and tumorlets. NECH was also observed on some bronchioles (Fig. 3). Underlying disorders such as fibrosis, emphysema or inflammation were not observed. DIPNECH was suspected based on the pathological and CT imaging findings. After the biopsy, a high-resolution CT (HR-CT) scan was performed in the inspiratory and expiratory positions. The maximum intensity projection (MIP) reformation and the minimum

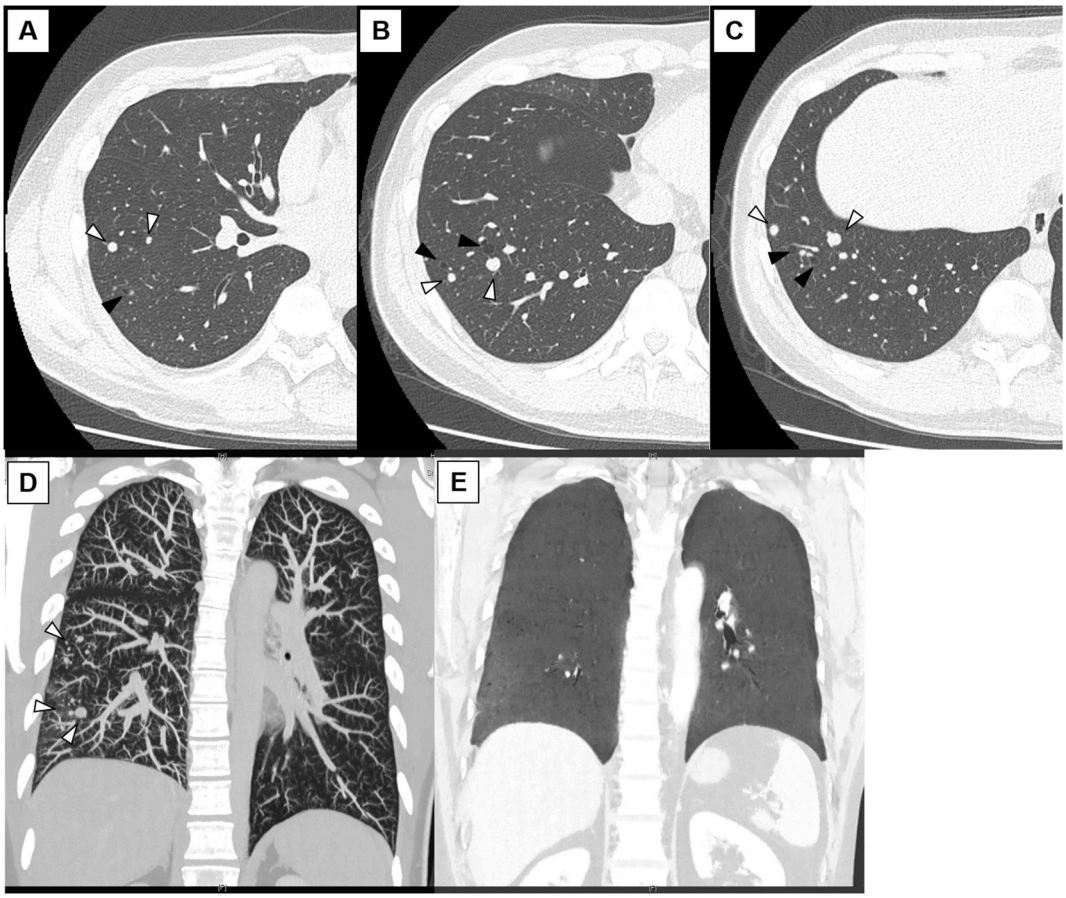

Fig. 1. A-C) Preoperative chest HR-CT image shows multiple 1-to-8-mm round nodes (white arrowheads). The black arrowheads indicate sporadic pulmonary cysts. These findings were limited to the right lower lobe, but they were not aggregated. D) The maximum intensity projection (MIP) reformation and E) the minimum intensity projection (MinIP) reformation of post operative HR-CT. The white arrowheads indicate residual nodules in the right lower lobe. Mosaic perfusion was not demonstrated.

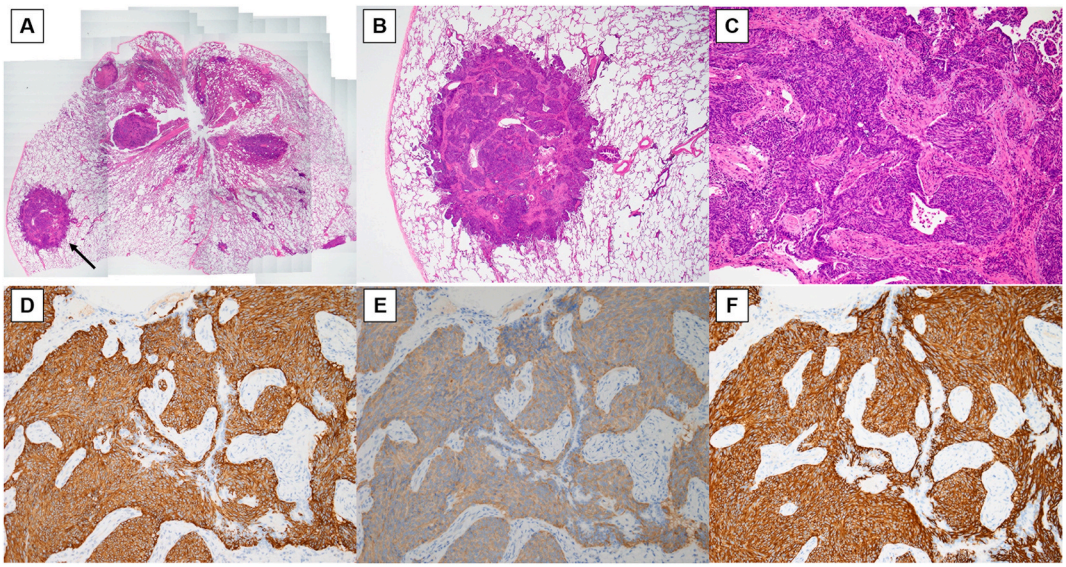

Fig. 2. A) Histopathological examination of the resected specimen shows tumors with diameters of 1–5.1 mm and cell proliferation in the bronchioles. B, C) High-magnification image of the tumor shown by the black arrow in A). Prominent spindle cells and fibrovascular stroma can be seen. Immunohistochemistry showed cytoplasmic staining for D) chromogranin A, E) synaptophysin, and F) CD56.

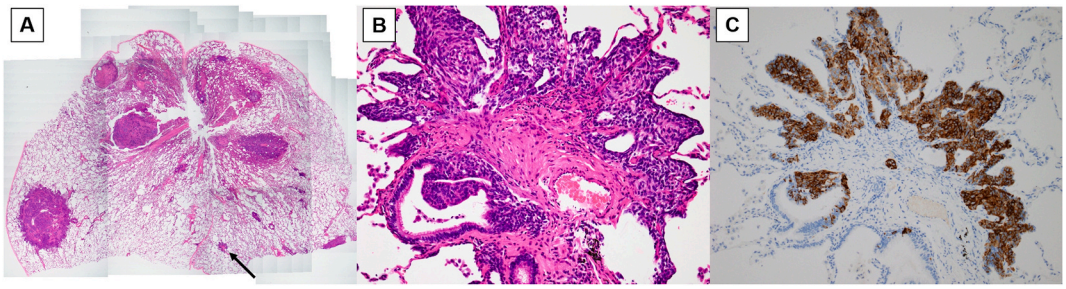

Fig. 3. Pathological findings of neuroendocrine cell hyperplasia. A) Low-magnification image (black arrow) and B) high-magnification image of an area of neuroendocrine cell hyperplasia. C) CD56 staining showed a linear proliferation of clusters of neuroendocrine cells on the epithelial membrane of bronchioles.

intensity projection (MinIP) reformation were also confirmed to screen for undetected nodules and airway obstructions in other lobes. The residual peripheral nodules and airway trapping with small lung cysts in the right lower lobe were observed, but no signs of mosaic perfusion were seen (Fig. 1 D, E). All the nodules could have been resected by performing a right lower lobectomy, but the preservation of lung function was thought to be appropriate. A follow-up CT scan after 6 months showed no changes in the sizes of the nodules and no new lesions.

3. Discussion

Several uncertainties regarding the diagnosis of DIPNECH persist because of the lack of diagnostic criteria and the limited number of case reports. Wirtschafter et al. reported 30 DIPNECH cases that they treated and an additional 169 cases that were identified in a systematic review [8]. According to their report, the present case is atypical in epidemiology, since the reported median age at diagnosis was 66 years and 93% of the cases were female. In the 2021 WHO classification, the definition of DIPNECH is "*multifocal hyperplasia of pulmonary neuroendocrine cells associated with tumorlets. It is a preinvasive condition that may develop into carcinoid tumors*," and Marchevsky et al. reported the pathological findings of 70 lung specimens with multifocal neuroendocrine cell proliferations and proposed diagnostic criteria for DIPNECH as "*multifocal NECH combined with 3 or more carcinoid tumorlets*" [9,10]. The present case was histopathologically compatible with DIPNECH and without underlying chronic pulmonary diseases causing secondary neuroendocrine cell proliferations. An HR-CT scan can provide additional information for the diagnosis of DIPNECH. HR-CT features include more peripheral multiple small nodules than in segmental bronchi, mosaic perfusion, and air trapping sings. MIP reformation is useful for the detection of peripheral nodules, while MinIP reformation is useful for the detection of mosaic perfusion [11]. Mosaic perfusion reflects the attenuation of vessels and the pulmonary parenchyma following constrictive bronchiolitis, which bronchial obstruction arising from NECH causes. An HR-CT scan with MIP and MinIP reformation was performed in the present case after a video-assisted thoracoscopic wedge resection to obtain a surgical biopsy specimen, but neither nodules in the other lobes nor mosaic perfusion were

detected. Mosaic perfusion could be a chronic change with airway trapping. Considering the age of the patient, the lung condition might be at a stage prior to progression to vasoconstriction. Although it is expensive and special, Ga- edotreotide PET-CT may be a useful to detect additional nodules.

The clinical course and treatment of DIPNECH are variable. Most of the reported symptomatic cases showed the slow progression of obstructive respiratory dysfunction after long-term stability. The progression of respiratory failure leading to death or requiring lung transplantation was also reported in a small minority of cases [8,12]. Medical treatments mainly consist of inhaled corticosteroid therapy for obliterative bronchiolitis. Cytotoxic agents are ineffective against neuroendocrine tumors. On the other hand, the treatments for asymptomatic DIPNECH are unknown because of a lack of long-term follow-up studies. Rossi and others have propounded the concept of "DIPNECH syndrome" [7]. They defined that "DIPNECH syndrome" is respiratory symptomatic DIPNECH with the radiological and the histopathological features. According to their proposal, the present case might be tumorlets and carcinoid-related NECH. However, the patient also might be in an early stage of DIPNECH before progression to symptomatic DIPNECH, since signs of bronchiole obstruction were observed using HR-CT. The most unusual finding in the present patient was the localization of the tumors and NECH in the right lower lobe. Almost all DIPNECH cases are bilateral, except for one reported right-side unilateral case [13]. This finding would be understandable if there had been a background disease, such as interstitial pneumonia, emphysema or bronchiectasis, localized in the right lower lobe. However, we could not find any abnormal findings other than the tumorlets, carcinoid tumors and airway obstructions. Considering the possible development of bilateral lung and chronic respiratory failure, a right lower lobectomy might have been excessive. The development of high-grade neuroendocrine tumors, such as small cell lung cancer or large cell neuroendocrine carcinoma, from DIPNECH has not been reported to date, but increase in size of nodules and lymph-nodes or distant metastases after long term follow-up were reported [14–16]. We decided to follow the patient carefully with annual CT surveillance instead of performing additional surgery.

In conclusion, clinicians should consider the possibility of carcinoid tumors and tumorlets with NECH in cases with multiple pulmonary nodules and signs of airway obstruction even if they are localized in one lobe. A surgical biopsy should be considered for pathological diagnosis. Further studies, especially of long-term outcomes, are needed to determine the best treatment and follow-up schedule.

Statement of ethics

Written informed consent was obtained from the patient to publish the information, including the radiological and pathological images.

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Author contributions

Yuho Maki: Conceptualization, Data Curation. Kazuhiro Okada: Writing - Original Draft. Ryuji Nakamura: Writing - Original Draft. Yutaka Hirano: Writing - Original Draft. Toshiya Fujiwara: Conceptualization, Writing - Original Draft. Rie Yamasaki: Resources, Data Curation, Visualization. Kouichi Ichimura: Resources, Data Curation. Motoki Matsuura: Conceptualization, Writing - Review & Editing, Supervision.

Declaration of competing interest

Yuho Maki and the co-authors have no conflicts of interest to report.

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