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Incidental Pulmonary Tumorlets in a Patient With Bronchiectasis and Aspergillus Infection: A Case Report

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 65-year-old
Final Diagnosis: Bronchiectasis • pulmonary microcarcinoid
Symptoms: Coughing
Clinical Procedure: —
Specialty: Pathology
Objective: Rare coexistence of disease or pathology

Background: Pulmonary carcinoids are rare pulmonary neuroendocrine neoplasms with incompletely understood pathogenesis. Although chronic inflammation is a suspected contributing factor, the specific association between bronchiectasis and pulmonary tumorlet development remains unclear.

Case Report: A 65-year-old nonsmoking woman exhibited recurrent respiratory symptoms and infections associated with bronchiectasis. She also had a history of *Aspergillus fumigatus* infection for which she had not received regular treatment. She was admitted for surgical management due to recurrent pulmonary infections and poorly tolerated symptoms, including persistent cough and sputum production. Chest computed tomography revealed cystic bronchiectasis without evidence of tumor-related lesions. After surgical resection of the affected pulmonary segment, histopathological examination revealed subepithelial tumor infiltration beneath the endobronchial lining, comprising nests of uniform, cytologically bland cells with centrally located nuclei, moderately granular cytoplasm, and a characteristic "salt-and-pepper" chromatin pattern. The largest lesion measured less than 5 mm, and mitotic figures were rare (< 2 per 2 mm^2). The patient was diagnosed with bronchiectasis with cystic dilatation, fungal infection, and associated pulmonary tumorlets. Immunohistochemical staining showed broad positivity for chromogranin A and synaptophysin, with a Ki-67 proliferation index of approximately 2%, determined by counting all tumor cells. At the 3-month postoperative follow-up, no new bronchiectatic changes or pulmonary nodules were observed.

Conclusions: This report describes the incidental discovery of peripheral pulmonary tumorlets in an older nonsmoking woman with bronchiectasis and *Aspergillus* infection. These tumorlets were only detected during postoperative histopathological examination. Such findings underscore the importance of systematic pathological sampling to avoid overlooking occult neuroendocrine proliferative lesions, particularly in bronchiectasis cases.

Keywords: Carcinoid Tumor • Lung • Bronchiectasis • Aspergillus
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Introduction

Pulmonary neuroendocrine tumors include typical carcinoids (TCs), atypical carcinoids (ACs), small cell lung carcinomas, and large cell neuroendocrine carcinomas [1]. The precise pathogenic mechanisms underlying pulmonary carcinoids (PCs) remain unclear. PCs show no clear association with sex or smoking, although environmental exposures and inflammation may contribute to their development [2].

Bronchiectasis is characterized by airway dilation, impaired mucociliary clearance, chronic infection, and dysregulated inflammation, which collectively contribute to progressive pulmonary dysfunction [3]. A previous study detected an increased risk of lung cancer in patients with bronchiectasis [4]. However, the relationship between PCs and bronchiectasis remains unclear. Although bronchiectasis is a common manifestation of various chronic respiratory conditions, few studies have examined this association. Furthermore, the role of immune mechanisms in PC pathogenesis has not been fully elucidated. Previous studies have suggested that gliotoxin, produced by *Aspergillus*, may suppress T-cell function, creating an environment favorable to tumor development [5]. However, evidence supporting this hypothesis remains insufficient, and the association between carcinoids and chronic lung disease is not well established.

This report describes a rare case of chronic *Aspergillus* infection, bronchiectasis, and pulmonary tumorlets. Notably, the tumorlets were not identified via computed tomography (CT) and were not apparent on gross examination. These findings underscore the importance of systematic and comprehensive tissue sampling in patients with chronic pulmonary disease, given that microscopic neuroendocrine proliferative lesions may otherwise remain undetected.

Case Report

A 65-year-old nonsmoking woman was admitted with a clinical diagnosis of bronchiectasis. Two years earlier, she had presented to another hospital with cough and sputum production, leading to a diagnosis of pulmonary *Aspergillus fumigatus* infection. According to the patient, she had not received regular treatment during the intervening 2 years, and her symptoms had persisted. Regarding her history of antifungal therapy, the patient reported completing only 2 boxes of antifungal medication prescribed at the initial hospital visit. Due to a lack of noticeable clinical improvement, she discontinued the medication and received no further antifungal treatment. The patient was admitted to our hospital for surgical management because of recurrent pulmonary infections and poorly tolerated symptoms, including persistent cough and sputum production.

Physical examination revealed crackles on auscultation over the left upper lung field. CT demonstrated cystic bronchiectasis in the left upper lobe, accompanied by patchy dense opacities. The diagnosis was bronchiectasis with superimposed infection in the left upper lobe (**Figure 1**). During hospitalization, polymerase chain reaction testing of sputum detected *A. fumigatus*; no bacterial pathogens were identified. Based on the patient's reported findings from the previous hospital, the results of the current evaluation, her incomplete antifungal treatment history, and persistent clinical symptoms, we suspected that the fungal infection had persisted.

Although formal pulmonary function testing was not performed, the patient's clinical status and normal arterial blood gas results suggested preservation of respiratory function. After a complete preoperative workup, surgical resection of the affected pulmonary segment was performed. Gross examination of the resected specimen revealed bronchiectatic airways containing purulent secretions; no additional macroscopic lesions were identified. A cross-section of the resected lung segment showing the most severe bronchiectasis, along with adjacent lung tissue, was selected and divided into 2 blocks for embedding. Additionally, 2 samples of macroscopically dilated bronchi and surrounding lung tissue were randomly selected and embedded together.

Histological examination revealed substantially dilated bronchial lumina accompanied by extensive fibrosis, hyalinization, and mild acute and chronic inflammatory cell infiltration. Aggregates of fungal hyphae were identified within the dilated bronchi (**Figure 2**). Adjacent to the ectatic bronchi, multifocal nests of neuroendocrine cells were observed (**Figure 3**). These lesions demonstrated submucosal infiltration and consisted of uniform, small, round cells arranged in nests, cords, and trabeculae. The cells exhibited centrally located nuclei with characteristic "salt-and-pepper" chromatin and moderately granular cytoplasm (**Figure 3**). Numerous pulmonary tumorlets were identified in a single tissue section. Given their large number, an exact count was not feasible. No definite neuroendocrine cell hyperplasia (NECH) independent of the tumorlets was identified in the examined sections. The largest tumor nest measured less than 5 mm in greatest dimension. Multiple nests of neuroendocrine cells extended beyond the bronchiolar basement membrane into the surrounding lung interstitium, consistent with pulmonary tumorlets. The bronchiolar wall itself was not involved in these lesions.

Furthermore, imaging findings lacked the characteristic radiological features of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). The patient also did not exhibit the typical clinical syndrome associated with small-airway obstruction. Instead, the neuroendocrine cell proliferations were closely associated with prominent bronchiectatic changes. Collectively, these findings were considered more

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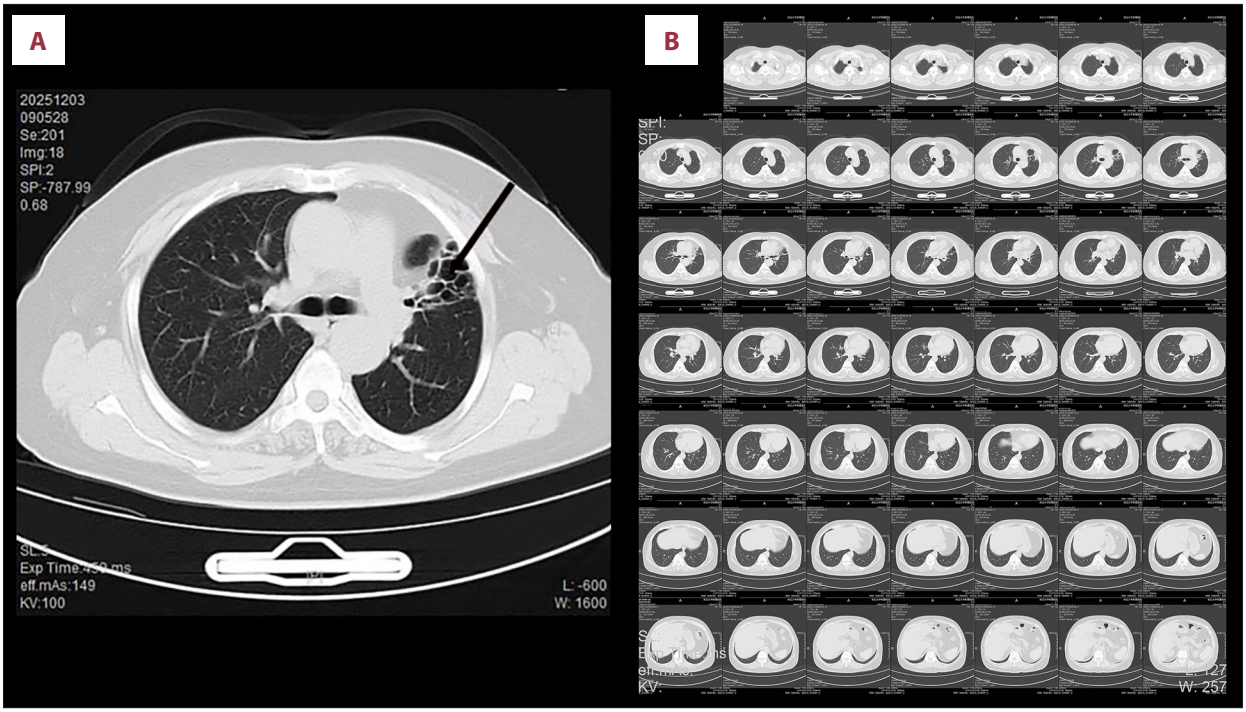


Figure 1. (**A, B**) Computed tomography images showing areas of bronchiectasis (arrow). No tumors were identified via computed tomography.

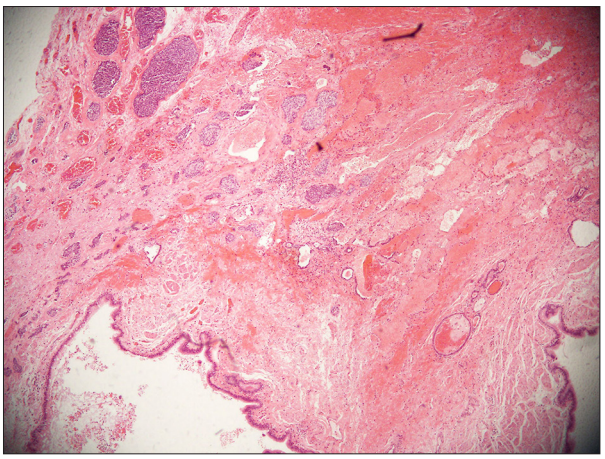


Figure 2. High-power histological image showing dilated bronchi, denuded bronchial epithelium, and fungal aggregates within the bronchial lumen (× 100).

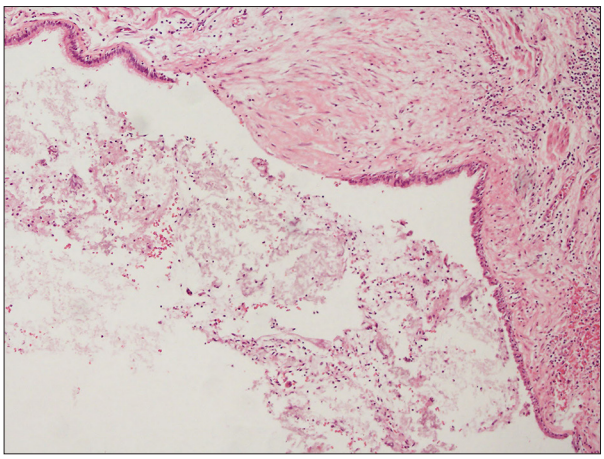


Figure 3. Low-power histological image showing prominent bronchiectatic changes with fibrosis and chronic inflammation. Multiple pulmonary tumorlets are present adjacent to the ectatic bronchi (arrows) (× 40).

consistent with multiple pulmonary tumorlets arising in the setting of bronchiectatic disease; they were deemed less consistent with DIPNECH.

The largest lesion measured less than 5 mm. Mitotic figures were rare (< 2 per 2 mm^2). Immunohistochemical staining showed broad positivity for thyroid transcription factor 1, chromogranin A, and synaptophysin. Evaluation of Ki-67 immunoreactivity demonstrated a proliferation index of approximately 2% in all tumor cells. The Ki-67 labeling index was calculated as the proportion of positively stained tumor nuclei among all tumor cells (positive and negative) in the evaluated regions (**Figure 4**).

According to the 2021 World Health Organization (WHO) classification of thoracic tumors, PCs are classified as pulmonary neuroendocrine neoplasms [1]. In a large cohort from the National Cancer Database, TCs represented approximately 87% of PCs, whereas ACs represented approximately 13%, indicating that

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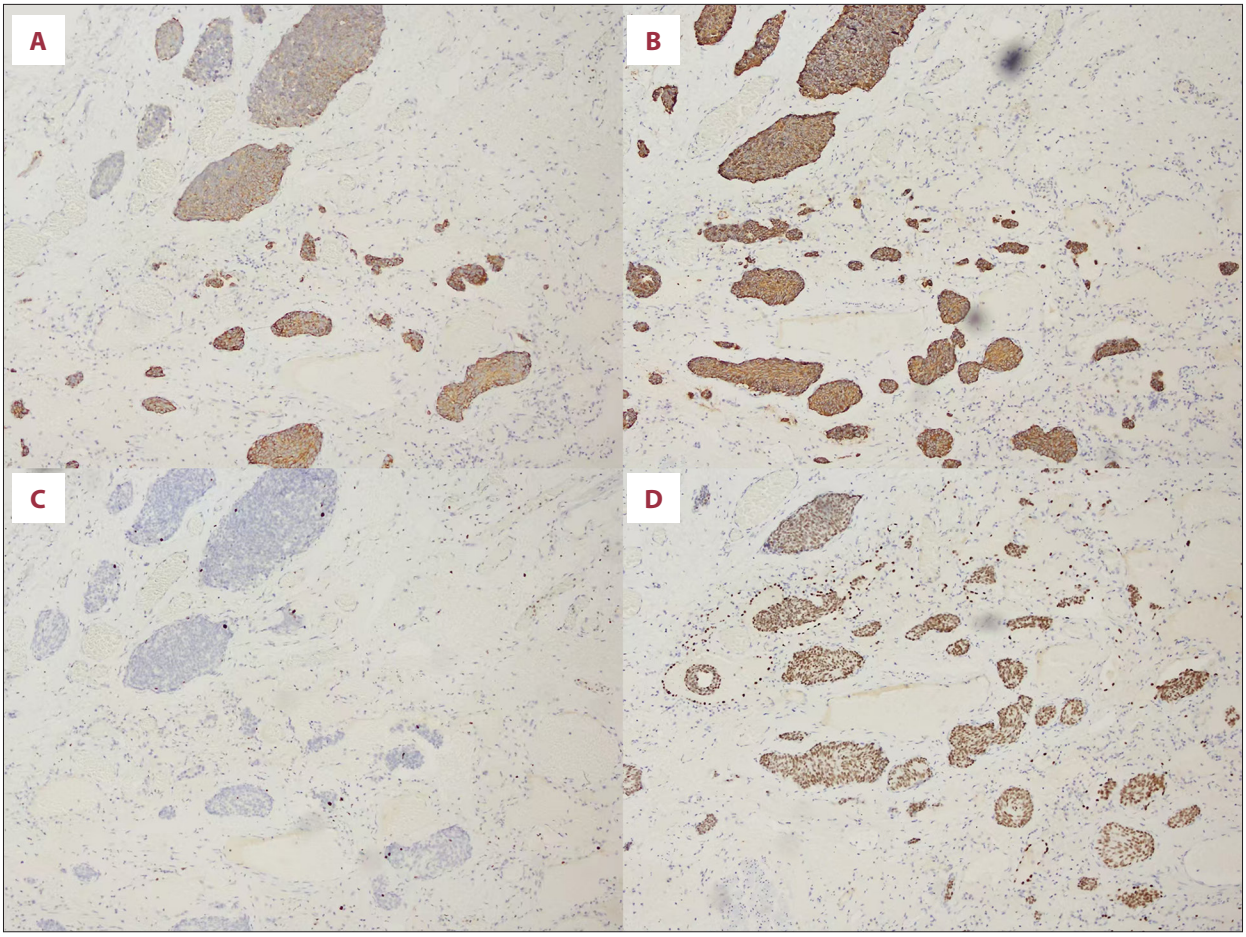


Figure 4. Immunohistochemical staining. (**A**) Positive staining for synaptophysin. (**B**) Positive staining for chromogranin A. (**C**) Ki-67 staining showing a low proliferation index (approximately 2%). (**D**) Positive staining for thyroid transcription factor 1.

TCs are the predominant subtype [6]. Diagnostic criteria for these subtypes are primarily based on morphology; mitotic count and the presence of necrosis serve as the main criteria for classification. Although not an essential criterion, the Ki-67 proliferation index is a useful adjunct. TCs often have a Ki-67 index of less than 5%; ACs generally have an index ranging from 9% to 18%. TCs are well-differentiated, low-grade tumors, whereas ACs are more aggressive and have a higher proliferative index [1]. Most bronchial carcinoid tumors arise in the central airways, constituting approximately 70% to 90% of cases, whereas approximately 10% to 25% occur in the peripheral airways [7]. Pulmonary tumorlets are neuroendocrine cell proliferations measuring less than 5 mm [1,8]. The pathological findings in our case were more consistent with pulmonary tumorlets, which are characterized by small nodular proliferations of neuroendocrine cells extending beyond the bronchiolar basement membrane into the adjacent pulmonary parenchyma and measuring less than 5 mm in diameter.

The final pathological diagnosis was bronchiectasis with cystic dilatation, fungal infection, and associated pulmonary tumorlets. The resection margins, pulmonary capsule, and bronchus did not exhibit tumor cells.

Because pathological examination was performed postoperatively rather than intraoperatively, lymph node dissection was not carried out. The patient received no additional treatment, such as radiotherapy or chemotherapy. At the time of manuscript preparation, she had a 2-year and 3-month history of bronchiectasis. Given that the tumorlets were diagnosed incidentally, their actual duration could not be determined. Thus, their long-term clinical behavior and prognosis remain uncertain. At the 3-month postoperative follow-up, chest CT revealed no new bronchiectatic changes or pulmonary nodules. Long-term follow-up is planned to monitor the clinical course and assess the patient's long-term outcomes.

Discussion

PCs are relatively rare pulmonary neuroendocrine neoplasms, which represent approximately 2% of malignant pulmonary

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Table 1. Recently reported cases of pulmonary neuroendocrine cell proliferative lesions associated with bronchiectasis.

Case summary (age/sex/lesion size/associated conditions)	Histological features	Reference
67 years, male; aspergilloma, multiple tumorlets, bronchiectasis, and DIPNECH	Samples obtained from cavitated bronchial wall revealed groups of uniform cells and scattered cells within a microscopic focus measuring less than 5 mm in diameter	Yazgan et al [16]
54 years, male; lesion diameter < 5 mm; bronchiectasis, multifocal NECH, and pulmonary sclerosing pneumocytoma	Multifocal hyperplasia of neuroendocrine-like cell nests was observed around dilated bronchus; individual foci measured less than 5 mm in diameter	Han et al [17]
57 years, female; nodules < 5 mm in diameter; DIPNECH with multiple tumorlets, chronic inflammation, and bronchiectasis	Hyperplasia of oval and short spindle-shaped cells was observed in linear or nodular arrangements, with focal extension through bronchial wall and nodular infiltrative growth	Jin et al [18]
54 years, male; nodules < 5 mm in diameter; DIPNECH with multiple tumorlets, chronic inflammation, and bronchiectasis	Hyperplasia of oval and short spindle-shaped cells was observed in linear or nodular arrangements, with focal extension through bronchial wall and nodular infiltrative growth	Jin et al [18]
61 years, male; nodules < 5 mm in diameter; adenocarcinoma, DIPNECH with multiple tumorlets, chronic inflammation, and bronchiectasis	Adenocarcinoma was identified alongside hyperplasia of oval and short spindle-shaped cells arranged in linear or nodular patterns, with focal extension through bronchial wall and nodular infiltrative growth	Jin et al [18]

Abbreviations: DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; NECH, neuroendocrine cell hyperplasia.

tumors [2]. This type of pulmonary neuroendocrine neoplasm is thought to arise from the proliferation of pulmonary neuroendocrine cells, rare airway epithelial cells that exhibit both neuronal and endocrine features [9,10]. Over the past few decades, the incidence of PCs has increased [11]; however, this trend may be partially attributable to advances in diagnostic techniques, rather than a true increase in disease occurrence. The precise pathogenesis of PCs remains unclear. In clinical practice, contrast-enhanced CT is considered the gold standard for localizing PCs, whereas pathological examination remains essential for accurate classification and grading [12].

In the present case, multiple pulmonary tumorlets were identified in a patient with a 2-year history of bronchiectasis and *Aspergillus* infection. We also reviewed 5 similar cases reported in recent years (**Table 1**). Although the diagnoses of pulmonary neuroendocrine lesions varied, including pulmonary tumorlets and DIPNECH, all patients displayed concurrent bronchiectasis. Although chronic hypoxia has been proposed as a potential stimulus for pulmonary neuroendocrine cell proliferation [13], the relationship between bronchiectasis and tumorlet development remains uncertain in our case. It is unclear whether bronchiectasis contributed to tumorlet formation or whether the 2 conditions merely coexisted. *A. fumigatus* infection can exacerbate local symptoms and increase the risk of complications [14]. Furthermore, *A. fumigatus* produces gliotoxin, a metabolite that has been shown to suppress T-cell function [5]. However, it remains unclear whether *A. fumigatus* influences the development of pulmonary neuroendocrine tumors; further investigation is warranted.

DIPNECH is a preinvasive neuroendocrine proliferation that can progress to tumorlets or carcinoids in some cases [2]. Furthermore, PCs frequently coexist with other respiratory diseases. In the present case, tumorlets were incidentally identified during pathological examination of surgically resected bronchiectatic lung tissue. Pathological and clinical DIPNECH were defined according to the 2021 WHO classification of thoracic tumors. However, the WHO classification provides only a brief description of DIPNECH; its diagnostic criteria and clinicopathological characteristics have been described more comprehensively in subsequent authoritative publications. Clinical DIPNECH was defined by symptoms associated with airway obstruction, mosaic attenuation on CT, and/or bilateral pulmonary nodules; pathological confirmation of pulmonary NECH or tumorlets is optional [15]. Although multiple pulmonary tumorlets were identified, no definite NECH independent of the tumorlets was observed. Given the patient's bronchiectasis and the absence of characteristic clinical and radiological features of DIPNECH, the present findings were considered more consistent with pulmonary tumorlets occurring in the setting of chronic bronchiectatic disease; they were deemed less consistent with DIPNECH.

Conclusions

This report describes the incidental discovery of peripheral pulmonary tumorlets in an older nonsmoking woman with bronchiectasis and *Aspergillus* infection. No tumors were identified on CT images, and pulmonary tumorlets were only detected

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during postoperative histopathological examination. These findings underscore the importance of systematic pathological sampling to avoid overlooking occult neuroendocrine proliferative lesions, particularly in patients with bronchiectasis.

Institution Where Work Was Done

Yanbian University Hospital, Yanji, Jilin, PR China.

Patient Consent

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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