

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Case series and a review of the literature

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Abstract

Rationale: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare idiopathic disease with only about 100 cases reported in the literature.

Patient concerns: Here, we presented 4 cases of DIPNECH. Four patients included 2 females and 2 males, aged 54 to 64 years old; 3 had no smoking history and 1 had history of smoking for 30 years. Surgical resection was performed for every patient. Cases 1 and 3 did not receive postoperative chemotherapy or radiotherapy, and case 2 received 4 times of postoperative chemotherapy. Case 4 just finished the operation and after a period of time, he will receive postoperative chemotherapy.

Diagnoses: Case 1: A 57-year-old female had chest pain, and computer tomography (CT) examination prompted a mass shadow of left lung lower lobe. Case 2: A 64-year-old female had cough and expectoration for more than 1 month. CT examination showed: a lump with diameter of about 2.5 cm and irregular edge was in right lung upper lobe, being largely possibly lung cancer. Case 3: A 54-year-old male, CT examination accidentally found a long strip-shaped nodule in left lung oblique fissure when checkup's, and he had no fever, cough, expectoration, chest tightness, or chest pain. Case 4: A 61-year-old male, checkup's CT examination accidentally found a nodule, fibrosis, bronchiectasis, and secondary infection in the left lower lobe. Combined with pathological morphology and immunohistochemistry, cases 1 and 3 were diagnosed as DIPNECH with multiple carcinoid tumorlet formation and chronic inflammation and bronchiectasis, case 2 was diagnosed as an adenocarcinoma with DIPNECH and multiple carcinoid tumorlet formation, case 4 was diagnosed as an adenocarcinoma with DIPNECH and multiple carcinoid tumorlet formation and chronic inflammation and bronchiectasis.

Interventions: Surgical resection was performed for every patient. Cases 1 and 3 did not receive postoperative chemotherapy or radiotherapy, and case 2 received 4 times of postoperative chemotherapy. Case 4 just finished the operation and after a period of time, he will receive postoperative chemotherapy.

Outcomes: Four patients have been followed up and have had good condition.

Lessons: DIPNECH is often found accidentally in a surgical specimen, is easily missed, and needs careful observation. Immunohistochemistry is necessary to make this diagnosis.

Abbreviations: APUD = amine precursor uptake and decarboxylation, CgA = chromogranin A, CT = computer tomography, DIPNECH = diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, PNECs = pulmonary neuroendocrine cells, Syn = synaptophysin.

Keywords: clinicopathological characteristics, differential diagnosis, DIPNECH

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1. Introduction

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is rare.^[1] It is common in chronic lung injury, such as bronchiectasis, pulmonary interstitial fibrosis, pulmonary abscess and pulmonary tuberculosis, and also can be found in lung tissue without underlying disease.^[2] WHO Classification 2015 has considered it as a precancerous lesion of a lung neuroendocrine tumor; it is defined as: within bronchial mucosal epithelium, there is diffuse clustered, linear or nodular neuroendocrine cell hyperplasia without basement membrane breakthrough.^[3] If localized infiltrative growth and nodule formation are shown with basement membrane breakthrough, nodule diameter ≤ 5 mm is called a carcinoid tumorlet and nodule diameter > 5 mm is called a carcinoid.^[3,4]

2. Methods

We retrospectively collected 4 cases of DIPNECH after pulmonary lobectomy or wedge resection. From October 2013

to April 2018, 4 patients of DIPNECH were evaluated and managed in our hospital, and followed up in the outpatient department after surgery until July 2018. Surgeries were performed in the Department of Thoracic and Cardiovascular Surgery of our hospital by Dr Wang (chief attending) and his regular medical team under general anesthesia. Clinical data were collected and analyzed in July 2018.

Informed consent was obtained from all the patients and the study was carried out with the approval of Hospital Ethical Review Committee of the Affiliated Hospital of Jiangnan University (Wuxi Fourth People's Hospital) (reference number LS2016022).

3. Results

3.1. Case 1

A 57-year-old female had no smoking history and manifested as left chest pain without obvious incentive, occasionally with cough

and expectoration but without chest tightness, shortness of breath, fever, or chills; after admission, lung function test showed mild restriction, mild obstructive ventilatory dysfunction, and moderate obstruction of small airway. Bronchoscopy found chronic inflammation of left lung bronchial mucosa and a granular uplift at the opening of left lower lung basal segment; bronchoscopic pathology was chronic inflammation of lung tissue. Computer tomography (CT) examination showed a mass shadow of left lung lower lobe with unknown nature. Surgical resection was performed. Intraoperative findings: a lump was in left lung lower lobe and was near hilus, had size of about $6 \times 5 \times 4$ cm, was hard and had no external invasion. Macroscopic observation showed that some area of lung tissue was grayish white. Microscopic observation showed that on basis of fibrosis, chronic inflammation, and bronchiectasis, there was oval and short fusiform cell hyperplasia displayed linear or nodular arrangement, and partially broke through bronchial wall and

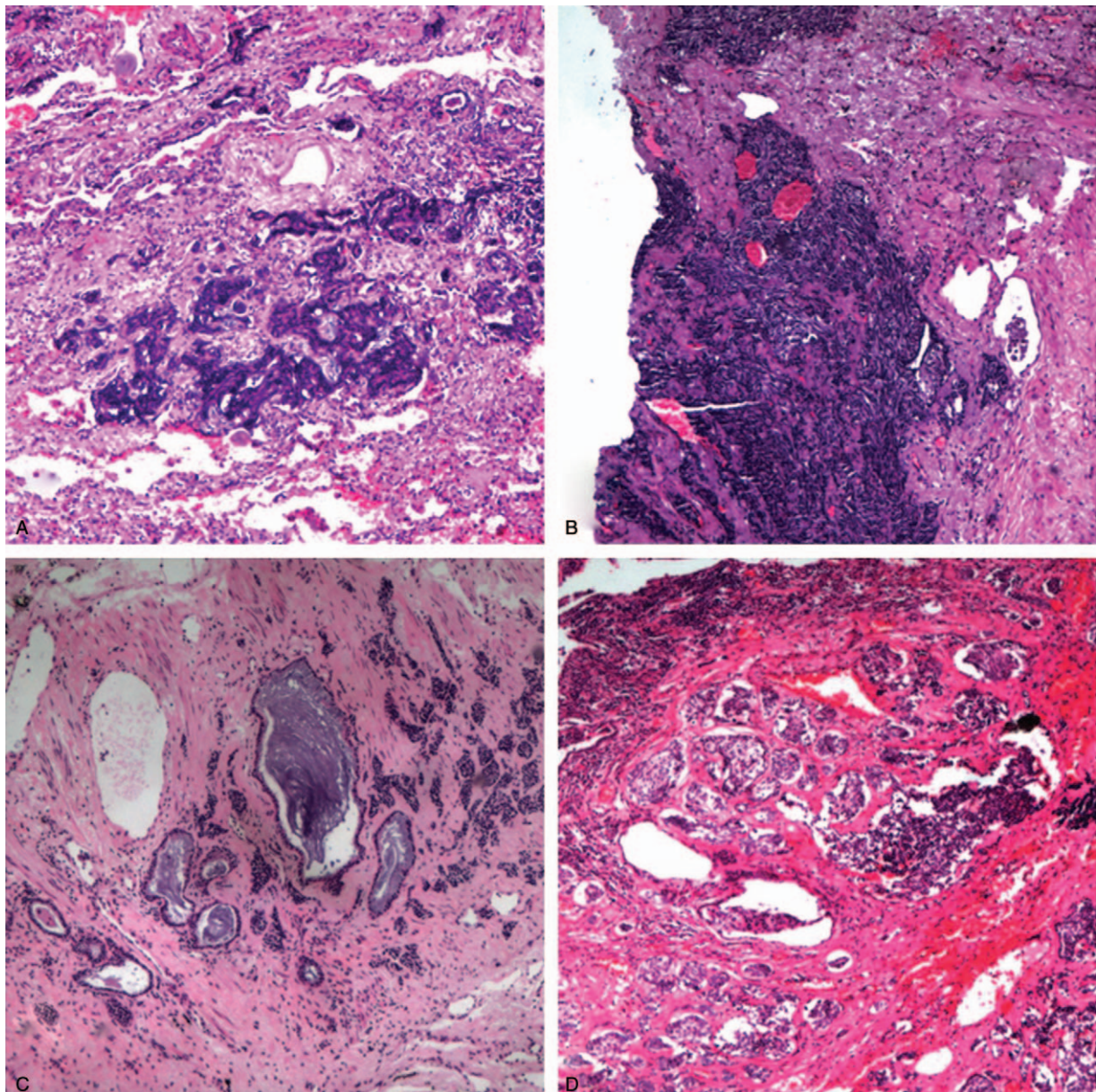


Figure 1. (A–D) Histological appearance of cases 1 to 4, magnification $\times 10$.

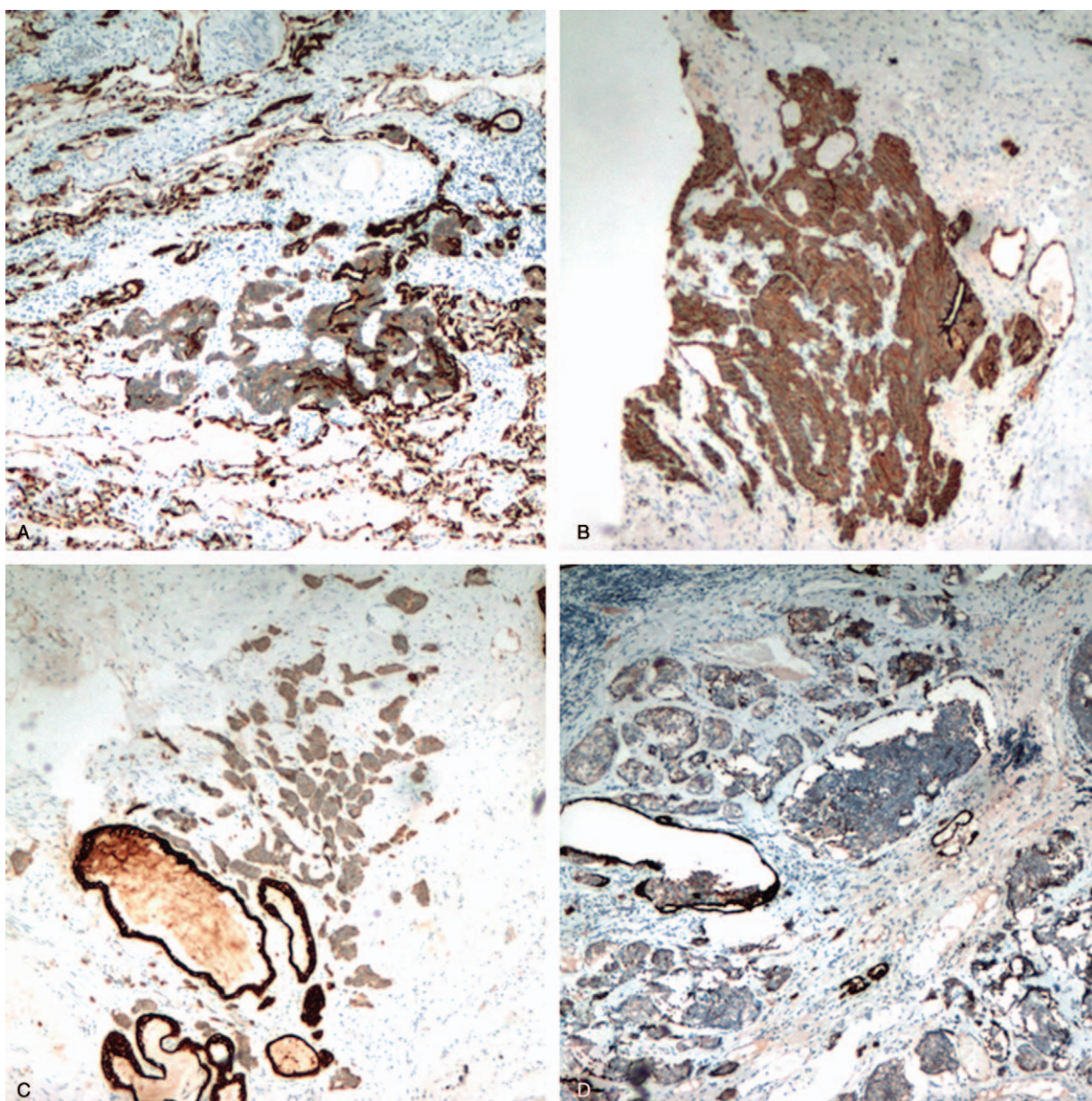


Figure 2. (A–D) Tumor cells of cases 1 to 4 were positive for AE1/AE3 with immunohistochemical staining, magnification $\times 10$.

displayed nodular infiltrative growth; nodules were all < 5 mm in diameter; cell size and morphology were relatively consistent; chromatin was fine granule-like (Fig. 1A). Immunohistochemical staining of the cells all showed AE1/AE3 (+), synaptophysin (Syn) (+), chromogranin A (CgA) (+), and Ki-67 hyperplasia index $< 2\%$ (see Figs. 2A, 3A, 4A, and 5A for detail). The patient did not receive any postoperative therapy. After 3 years follow-up, the patient was in good condition.

3.2. Case 2

A 64-year-old female had no smoking history. The patient had cough and expectoration for more than 1 month. After admission, CT examination showed: a lump with diameter of about 2.5 cm and irregular edge was in right lung upper lobe, being largely possibly lung cancer. Surgical resection was

performed. Intraoperative finding: a tumor with diameter of 2.5 cm in right lung upper lobe; the intraoperative frozen rapid diagnosis: an adenocarcinoma (in right lung upper lobe). Macroscopic observation showed a lump with diameter of about 2.5 cm; microscopic observation showed that beside an adenocarcinoma, case 2 showed the same characteristics with case 1 (see Figs. 1B, 2B, 3B, 4B, and 5B for detail). Case 2 received 4 times of postoperative chemotherapy. After 3 years follow-up, the patient was in good condition.

3.3. Case 3

A 54-year-old male, had no smoking history and had no fever, cough, expectoration, chest tightness, or chest pain, and he was admitted because checkup's CT examination accidentally found a long strip-shaped nodule in left lung oblique fissure. After

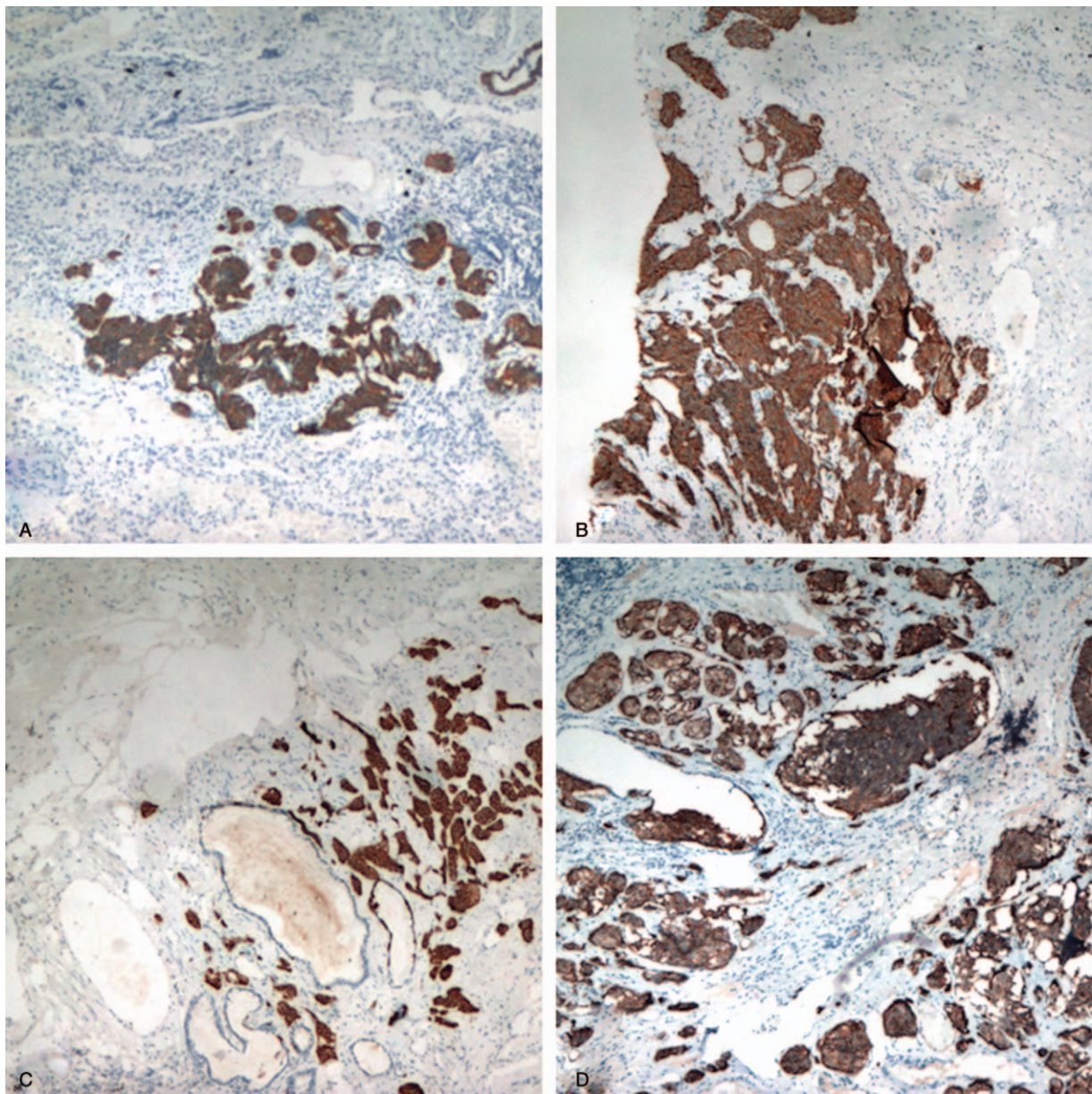


Figure 3. (A–D) Tumor cells of cases 1 to 4 were positive for Syn with immunohistochemical staining, magnification $\times 10$.

admission, pulmonary function test showed mild restriction, mild obstructive ventilatory dysfunction, and mild obstruction of small airway. Due to unknown nature of the nodule, surgical resection was performed. Macroscopic observation showed that some area of lung tissue was grayish white. Microscopic observation showed the same characteristics with cases 1 and 2 (see Figs. 1C, 2C, 3C, 4C, and 5C for detail). The patient did not receive any postoperative therapy. After 3 years follow-up, the patient was in good condition.

3.4. Case 4

A 61-year-old male had smoking history for 30 years. Checkup's CT examination accidentally found a nodule, fibrosis, bronchiectasis, and secondary infection in the left lower lobe. Left inferior lung resection was performed in the hospital. Two gray lesions

were seen in the left lower lung during operation. The diameters were 1 and 1.5 cm, respectively. Macroscopic observation showed 2 area of grayish white. With microscopic observation, 1 lesion was adenocarcinoma, the other was on the basis of chronic inflammation, fibrosis, and bronchiectasis, showed the same characteristics as cases 1 to 3 (see Figs. 1D, 2D, 3D, 4D, and 5D for detail). The patient had just finished the operation and after a period of time, he will receive postoperative chemotherapy. He is in good condition now.

4. Discussion

Modern medicine believes that lungs are not only a respiratory organ but also a very important endocrine organ. In 1938, Stella^[5] first reported that in lungs, there were clear cells that could release local active body fluid products, namely pulmonary

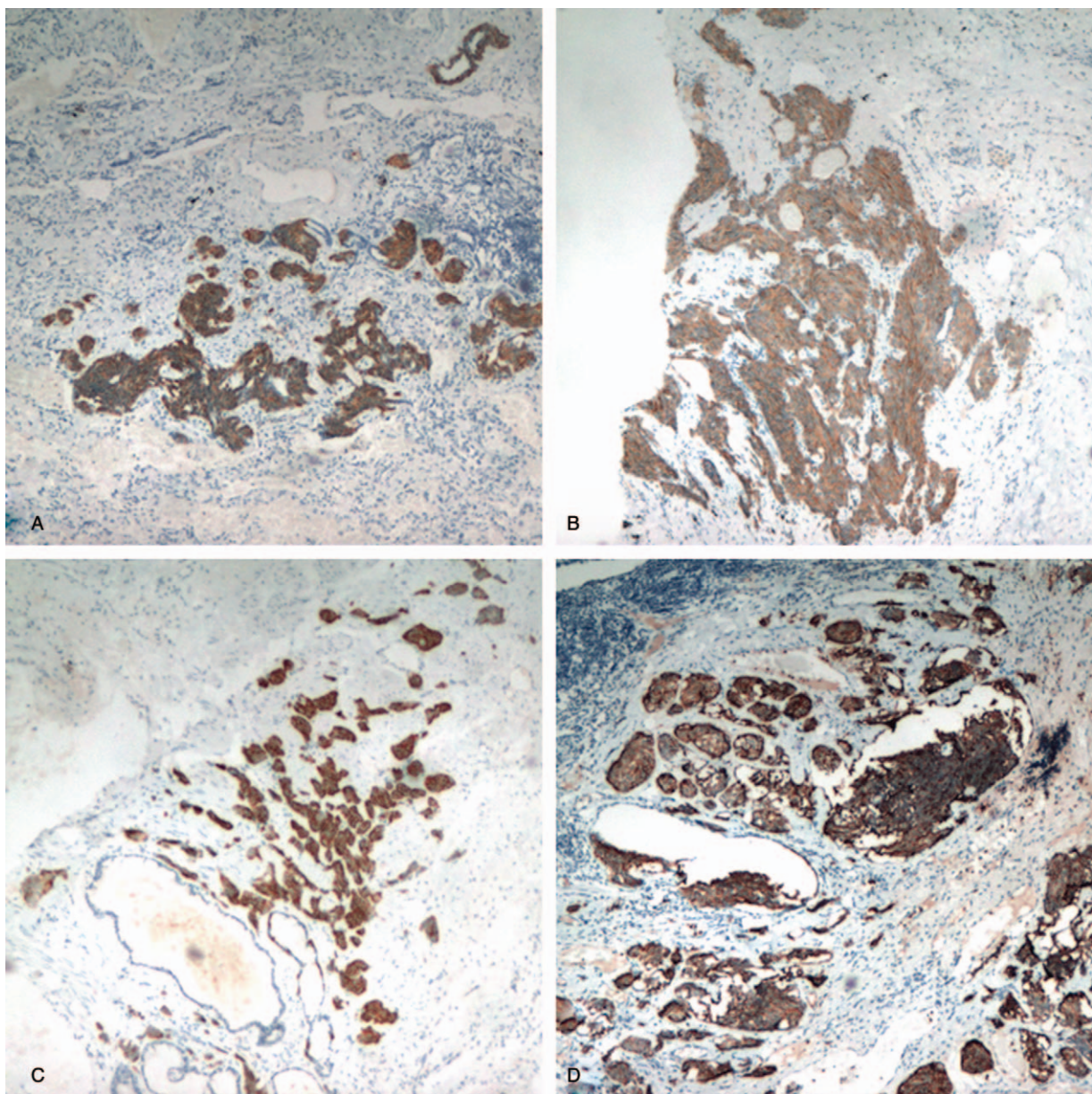


Figure 4. (A–D) Tumor cells of cases 1 to 4 were positive for CgA with immunohistochemical staining, magnification $\times 10$.

neuroendocrine cells (PNECs). Depending on number and morphology of the cells, PNECs can be divided into isolated PNECs and clustered PNECs.^[6,7] Isolated PNECs are usually distributed as individual cells at the entire tracheal mucosa and at junction of large bronchi, accounting for 0.41% of epithelial cells, and has a variety of morphologies, being most commonly conical or oval. Clustered PNECs are distributed in clusters, each composing of 4 to 10 cells, and locate in bronchial and bronchiolar epithelium, forming pulmonary neuroepithelial bodies. Under normal circumstance, PNECs are scattered in a single one or a small cluster within bronchiolar and bronchial mucosal epithelium.^[8] PNECs are argyrophil cells and belong to amine precursor uptake and decarboxylation (APUD) system. The APUD system refers to a type of endocrine cells distributed in the body that can take up the amine precursor and decarboxylate it into amine hormone. Substances secreted by PNECs play an important role in lung growth and development, normal

physiological function, and protection and regulation under abnormal state. Reactive hyperplasia of PNECs is often seen in cases of lung tissue inflammation, injury, and long-term exposure to toxic product, and is believed to be associated with regenerative repair after long-term chronic injury to airway or alveoli.^[9] However, sometimes PNEC hyperplasia can occur in lung tissue without underlying disease, thus some scholars have proposed concept of DIPNECH. DIPNECH is a rare idiopathic disease associated with neuroendocrine cell hyperplasia and occlusive bronchitis. It was first reported by Aguayo in 1992.^[10] In recent years, with increase in number of reports in the world, DIPNECH has gradually become an accepted disease term.^[2,11,12]

DIPNECH, a carcinoid tumorlet, and a carcinoid are different stages of the same lesion and have different histological manifestations, but have continuity and correlation. WHO defines DIPNECH as precancerosis of a carcinoid tumorlet and a

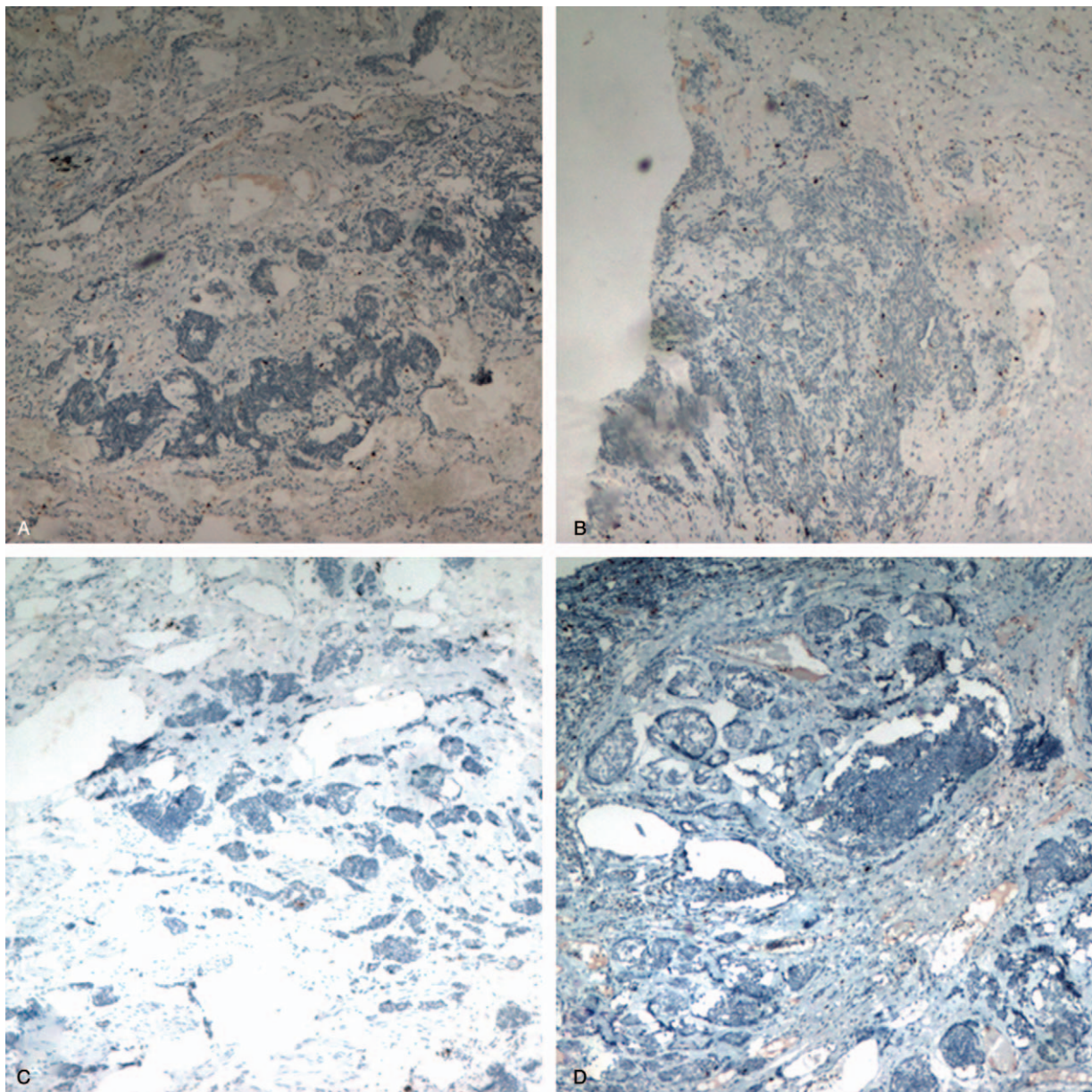


Figure 5. (A–D) With immunohistochemical staining, Ki-67 hyperplasia index of cases 1 to 4 were very low, <2%, magnification $\times 10$.

carcinoid.^[13] A study found that pathological specimens of DIPNECH patient were often accompanied with a carcinoid tumorlet or a typical carcinoid: 40% were accompanied with a carcinoid, and 70% were accompanied with a carcinoid tumorlet.^[12]

4.1. Clinical characteristics

DIPNECH has low incidence and can occur at any age, but typical cases are common in elderly, female and nonsmoking population. Onset is occult, there may be no clinical symptoms, or there is long duration of dry cough, dyspnea, and the like and sometimes its shown symptoms are often associated with a concomitant disease, and pulmonary function test shows obstructive or mixed obstructive restrictive ventilatory dysfunction.^[13] DIPNECH is often accompanied with chronic airway inflammation and diseases that can cause severe fibrosis in lungs,

such as bronchiectasis; it can also be found in isolated intralobar tissue of pulmonary sequestration and in pulmonary benign and malignant tumors, etc.;^[14–16] however, it is also sometimes seen in patients accompanied with a carcinoid tumorlet or a carcinoid and without airway inflammation or diffuse pulmonary interstitial fibrosis. DIPNECH and a carcinoid tumorlet have small lesions, and images often manifest as concomitant diseases such as bronchiectasis or pulmonary interstitial inflammation and show no nodular lesion, thus DIPNECH and a carcinoid tumorlet are rarely diagnosed before surgery. Literature suggests that patients with bronchiectasis or a cyst-like lesion in clinical setting receive thin-layer high-resolution enhanced CT examination to carefully exclude any pulmonary nodular lesion and to pay attention to differentiating infection, inflammation, a malignant lung metastasis, and the like, thereby improving detection rate of the disease.^[17] Among 4 cases in this group, 2 females and 2 males, aged 54, 57, 61, and 64 years old, 3 without smoking

history, 1 with smoking history. Two cases had no symptom, and 2 cases manifested as cough and expectoration; the preoperative CT diagnosis of case 1 was a left lung lower lobe mass shadow with unknown nature; the preoperative CT diagnosis of case 3 was a long strip-shaped nodule in left lung oblique fissure with unknown nature; the preoperative CT diagnoses of cases 2 and 4 were lung cancer. No preoperative CT examination found a micronodular lesion, so that DIPNECH and a carcinoid tumorlet were not diagnosed; all of them were accidentally found in postoperative specimens.

4.2. Pathological morphology

Under a light microscope,^[2,3,11–16] a DIPNECH lesion is confined within bronchial mucosal epithelium and manifests as: round, oval, short fusiform cells with relatively consistent size and shape showing: hyperplasia; number increase; large nuclei; less cytoplasm; nuclei are deeply stained or are fine granule-like; nucleoli are unobvious. Cells are not heteromorphous, mitotic phase is not common, and there is no necrosis. Cells may be scattered in individual ones or be line-like, or form small nests at base of bronchiolar epithelium, and even completely replace bronchiolar epithelium, resulting in narrow lumen but not penetrating basement membrane. If cells penetrate basement membrane to infiltrate fibrotic interstitium and show nodular growth and the nodule diameter is 2 to 5 mm, it is a carcinoid tumorlet. Firm diagnoses of DIPNECH and a carcinoid tumorlet are mainly based on immunohistochemical staining. Immunohistochemically stained neuroendocrine markers CgA, Syn, and CD56 are all positive, CK and TTF1 are also positive, and CK5/6 and P40 are negative. Four patients in this group all had the above characteristics in histopathological morphology and immunohistochemical staining. Two cases were DIPNECH and multiple carcinoid tumorlet formation with pulmonary interstitial fibrosis, bronchiectasis, and chronic inflammation; 1 case was an adenocarcinoma with DIPNECH and multiple carcinoid tumorlet formation, 1 case was an adenocarcinoma with DIPNECH and multiple carcinoid tumorlet formation and pulmonary interstitial fibrosis, bronchiectasis, and chronic inflammation; among the adenocarcinoma and DIPNECH and a multiple carcinoid tumorlet, there was no transition. DIPNECH and multiple carcinoid tumorlets are small and diagnoses are difficult to be made before surgery, thus when we observe postoperative lung specimens, especially sections of specimens obtained by surgical resection due to bronchiectasis or a chronic inflammatory lesion, we need to be careful and take more specimens to prevent a missed diagnosis.

4.3. Differential diagnoses

4.3.1. A malignant tumor with multiple intrapulmonary metastases. Early DIPNECH imaging examination can show no change, however, when it forms multiple carcinoid tumorlets or even carcinoids, imaging examination often shows multiple nodular lesions in lungs; thus, it is easy to wrongly believe that they are a malignant tumor with multiple intrapulmonary metastases.^[4] For some malignant tumor patients with multiple metastases in lungs, by asking their history, symptoms caused by the primary lesion are often found; in some patients with indistinct symptoms, a primary lesion often can be found through careful search. For postoperative lung tissue specimens, a diagnosis can also be clearly made by observing histological morphology and performing immunohistochemical examination. Therefore, for patients with multiple nodular lesions in

lungs, a diagnosis of malignant tumor with multiple intrapulmonary metastases should not be indiscreetly made.

4.3.2. Small cell lung cancer. Small cell cancer has obvious cell atypia. The nuclei are irregular in shape, fine in chromatin, and numerous in karyomitosis. Necrosis is often seen in small cell lung cancer. The proliferation index Ki-67 is often very high. It is easier to identify with DIPNECH by careful observation.

4.3.3. Minute pulmonary meningothelial-like nodule. Removed or biopsied lung tissue is generally asymptomatic and is of unknown etiology. Microscopically, epithelioid cells are arranged in nests or bundles, and often show nodular hyperplasia around small veins; the nodules generally have diameter of <3 mm and are more common in women.^[18] Originally, they were considered as benign hyperplasia of the chemoreceptor precursor,^[19] and later, studies found that minute pulmonary meningothelial-like nodule cells did not have endocrine granules but were similar to meningioma cells.^[20] They can be distinguished from DIPNECH and a carcinoid tumorlet by immunohistochemical staining of neuroendocrine markers and the like.

There are some limitations of our study. The sample size of DIPNECH was not large enough, which will result in sampling error. And it is retrospective analysis and lacks systematic prospective data. In the future, we will continue to collect these diseases and we will continue to follow up these 4 cases to learn more about the clinical, pathological, and prognostic characteristics of DIPNECH.

5. Conclusion

DIPNECH is a rare idiopathic disease. Our findings indicate that it is often found accidentally in a surgical specimen and the diagnosis of DIPNECH is often delayed. Immunohistochemistry is necessary to make this diagnosis.

Author contributions

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Writing – review & editing: Linfang Jin, Xiaowei Qi.

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