Respir Case Rep 2023;12(1):30-35 DOI: 10.5505/respircase.2023.63383

Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia as a Rare Cause of Persistent Cough and Hemoptysis: A Case Report

Diffüz İdiyopatik Pulmoner Nöroendokrin Hücre Hiperplazisi; Kronik Öksürük ve Hemoptizinin Nadir Bir Nedeni: Olgu Sunumu

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Abstract

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is an extremely rare but underdiagnosed pulmonary disorder at the benign end of the neuroendocrine cell proliferation spectrum of preinvasive lung lesions. The cause of DIPNECH is currently unknown. The diagnosis can be suggested when chest CT demonstrates characteristic findings, including multiple non-calcific bronchocentric random nodules and mosaic attenuation. DIPNECH should be considered in differential diagnoses of patients with pulmonary symptoms and chest CT findings of nodules with mosaic attenuation. It is vital to recognize it since it is thought to be a precursor of peripheral carcinoid tumors. Contrary to the literature, many peripheral carcinoid tumors developed relatively quickly and caused severe hemoptysis due to hypervascularity. The patient differs considerably from other cases in the literature regarding the clinical course, with bone involvement at the initial diagnosis and liver metastases that quickly spread and developed calcification.

Keywords: *Pulmonary, neuroendocrine cell hyperplasia, computed tomography.*

Öz

Diffüz İdiyopatik Pulmoner Nöroendokrin Hücre Hiperplazisi (DIPNECH), akciğerin pre-invazif lezyonlarının nöroendokrin hücre proliferasyon spektrumunun iyi huylu ucunda yer alan, oldukça nadir fakat tanısı zor bir hastalıktır. DIPNECH'in nedeni tam olarak bilinmemektedir. Tanı, Toraks BT'de çok sayıda kalsifik olmayan bronkosentrik nodüller ve mozaik atenüasyon gibi karakteristik bulgular görüldüğünde düşünülmelidir. DIPNECH, solunumsal semptomlarla başvuran, Toraks BT'de nodül ve mozaik atenüasyon bulguları olan hastaların ayırıcı tanısında mutlaka yer almalıdır. Periferik karsinoid tümörlerin öncüsü olarak kabul edildiğinden tanınması hayati önem taşır. Olgumuzda literatürün aksine birçok periferik karsinoid tümör nispeten hızlı gelişmiş ve hipervaskülariteye bağlı olarak ciddi hemoptiziye neden olmuştur. Hasta, ilk tanı anında mevcut olan kemik tutulumu ve kısa sürede yayılarak kalsifikasyon geliştiren karaciğer metastazları ile klinik seyir açısından literatürdeki diğer olgulardan oldukça farklıdır.

Anahtar Kelimeler: *Pulmoner, nöroendokrin hücre hiperplazisi, bilgisayarlı tomografi.*

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Submitted (Başvuru tarihi): 16.08.2022 ***Accepted (Kabul tarihi):*** 03.01.2023

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Pulmonary neuroendocrine cells (PNECs) are a rare epithelial cell type scattered in the respiratory epithelium. The main functions of PNECs are airway oxygen sensing, pulmonary blood flow regulation, bronchial tonus control, and immune response modulation (1,2). Neuroendocrine cell hyperplasia (NECH) may be reactive or idiopathic. Reactive NECH might be detected in various conditions characterized by hypoxia.

Here, we present a case diagnosed with DIPNECH with distant organ metastasis and pulmonary hemorrhage after months of unexplained pulmonary symptoms.

CASE

A 40-year-old male smoker presented to our pulmonology clinic with long-term complaints of progressive nonproductive cough and dyspnea on exertion. Past medical histories included private treatment. He had no comorbidities, significant environmental exposures, or family history of lung diseases. He had several hospital admissions due to coughing and was clinically misdiagnosed and treated for asthma for several months. On admission, his blood pressure was 135/70 mmHg, his heart rate was 78 bpm, his temperature was 37.2°C, his respiratory rate was 20 cpm, and his SpO_2 was 96%. On physical examination, the only distinguishing feature was coarseness in the lung sounds. All laboratory parameters, including rheumatological markers, were within normal limits. Imaging was performed due to ongoing coughing and shortness of breath. He had his first chest computerized tomography (CT) scan in 2014. A noncontrast chest CT revealed numerous subcentimeter pulmonary nodules in the upper and intermediate zones, primarily along the bronchovascular bundles in a centrilobular distribution. The largest nodule was located in the right upper lobe, measuring 0.8 x 0.7 mm. Mosaic attenuation was also observed, but it was not severe. Mediastinal lymphadenopathy was not observed (Figures 1 and 2). Patchy, widespread, sclerotic, and nondestructive lesions were observed in bone structures, especially in the thoracic vertebrae, sternum, and ribs (Figure 3). In addition, there were a few subcentimeter-sized hypodense foci in the liver in a random and scattered pattern (Figure 4). Lesions in the liver were not suitable for an ultrasound-guided biopsy. Abdominal ultrasonography and abdominal CT examinations were performed during the first diagnosis. It was decided that the PET-CT examination was unnecessary because the patient did not have any additional findings. Multiple subcentimeter lung nodules first raised the suspicion of metastatic or multifocal lung adenocarcinoma, hematological malignancy, perilymphatic distribution of sarcoidosis, hypersensitivity pneumonitis, chronic pulmonary embolism, asthma, and follicular bronchiolitis, as seen in the setting of rheumatoid arthritis or Sjögren syndrome. Pulmonology, oncology, and thoracic surgery departments were consulted regarding the utility of a lung biopsy diagnosis and the treatment plan decision. Transbronchial needle aspiration (TBNA) and forceps lung biopsies revealed small peripheral airway neuroendocrine cell proliferation, multiple tumorlets, and no granulomas (Figures 5a and b). If the basement membrane is invaded, tumorlets (<5 mm) or invasive carcinoid tumors (>5 mm) occur (3). In our case, they were called tumorlet foci because no tumor focus exceeded the basement membrane by more than 5 mm. The patient was diagnosed with DIPNECH, which led to metastatic carcinoid tumor formation. DIPNECH treatment must be individualized because it can have a variable prognosis, and the rarity of this condition poses some clinical challenges. Most studies show a good clinical outcome with follow-up and observation (4,5). Treatment is not well established and should be guided by symptoms. Surgical resection is possible if an area progresses to a carcinoid tumor during follow-up. Since the patient did not have a tumoral mass at the time of diagnosis, surgical debulking was not considered. Accordingly, systemic and inhaled glucocorticoids (GCs) were initiated, alternating 12 and 8 mg daily. The patient's condition improved, but he still had symptoms. These worsened when the GC dose was reduced below 8 mg a day. Additionally, several systemic GC side effects, such as cushingoid appearance, parchment skin, and unmanageable diabetes, appeared approximately one-year later.

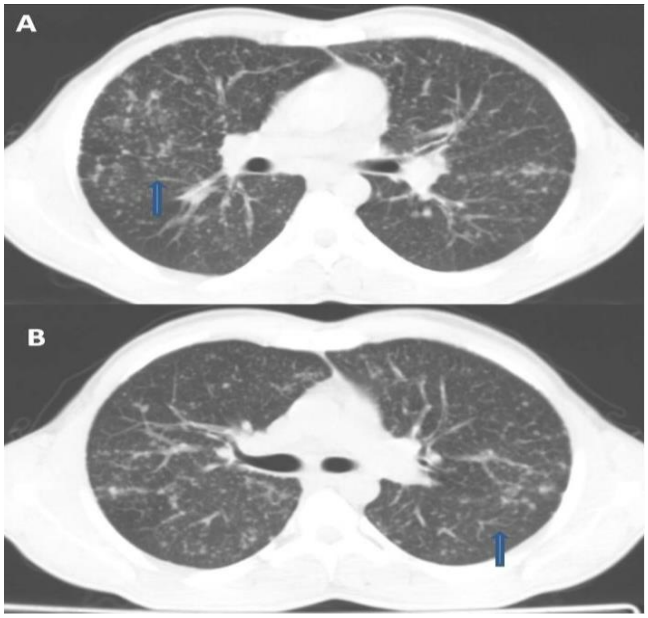

Figure 1: *Unenhanced chest CT axial images show numerous, variable-sized nodules with a noncalcified, centrilobular distribution typical of DIPNECH cases (blue arrowheads)* ***(a-b)***

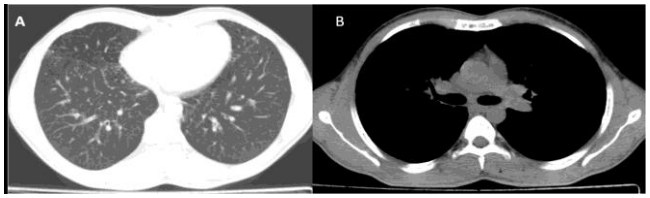

Figure 2: *Axial unenhanced chest CT images show less involvement and preservation of the lower lobes* ***(a)****. Mediastinal lymphadenopathy is not observed* ***(b)***

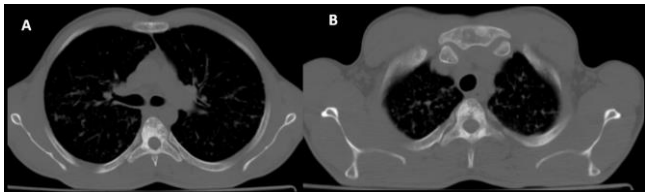

Figure 3: *At the initial diagnosis, sclerotic patchy bone metastases were present in the entire vertebral column, ribs, and sternum*

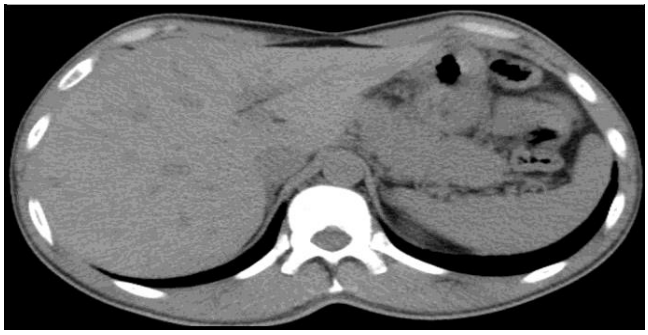

Figure 4: *On chest CT scans, there are a few hypodense, millimeter-sized nodular lesions with unclear edges in the liver*

For this reason, in 2015, the patient was recommended a Somatostatin Analogs (SSA) trial therapy (octreotide 20 mg monthly) with GC treatment discontinuation due to the numerous GC side effects. Octreotide, a somatostatin analog proven to inhibit peptide and neuroamin release, had been utilized successfully, especially in the presence of somatostatin receptors (4). He reported occasional episodes of dyspnea and wheezing at the six-month follow-up appointment, so he additionally took GCs. There is no evidence to support the use of chemotherapy (4). However, Chemotherapy was added to the patient's treatment because of his liver and severe bone involvement at the time of diagnosis. In 2016, two years after the presentation, the patient started to experience stronger episodes of dry cough and wheezing. In the follow-up chest CT, the number and size of the nodules increased significantly. A peribronchial nodular lesion obliterating the right middle lobe bronchus was also discovered to be a new carcinoid tumor (Figure 6 a–d). Apart from the described lesions, nodular solid mass lesions reaching 4 cm also developed in the upper lobes of both lungs (Figure 7). Furthermore, difficult-to-identify millimetric hypodense lesions in the liver were replaced with diffuse hypodense lesions with peripheral dense calcifications (Figures 8a and b). The patient's clinical course began to deteriorate due to these changes. Despite symptomatic treatment, complaints of cough and dyspnea tended to worsen. Complaints of cough and dyspnea tended to increase despite symptomatic treatment. TBNA and forceps lung biopsies were planned again for the patient due to newly developing nodular lesions. A histopathological examination found multiple foci of typical carcinoid tumors, multiple tumorlets, and widespread neuroendocrine cell hyperplasia. Because of the systemic chemotherapy, the patient received during the follow-up period, dense calcification occurred in the lung nodules and metastatic lesions in the liver. The patient's blood calcium values were within normal limits during this period. The blood calcium values measured ranged from 8.7 to 9.2 mg/dl, and no signs of hypercalcemia developed. A nuclear medicine SPECT scan was performed due to suspicion of other metastases. It was reported that infiltrative nodular opacities, which were common in both lung parenchyma and prominent in the upper lobes, increased 18-fluorodeoxyglucose (FDG) uptake to a level equal to the surrounding tissue and mildly increased (SUV max: 4.4). In addition, there was 18F-FDG uptake at the same level as the surrounding tissue in sclerotic areas observed in the skull base, vertebral column, and sternum, bilaterally on the clavicle, scapula, humerus head, multiple ribs, pelvic bones, and proximal femur. Slightly elevated 18F-FDG uptake from the liver parenchyma was observed in multiple hypodense lesions of approximately 1.7 cm in the subcapsular region, the largest of which was located in segment 7 in the right lobe of the liver (SUVmax: 4.1).

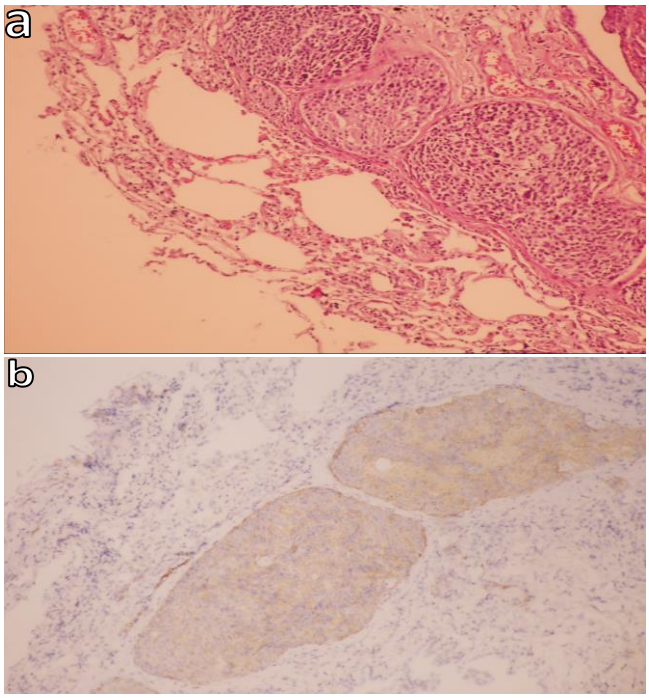

Figure 5: *Tumorlet foci without atypia as solid islands just below the bronchial wall (H&E; x 40)* ***(a)****, NECH and tumorlet foci with positive staining of chromogranin (pale due to staining approximately eight years ago)* ***(b)***

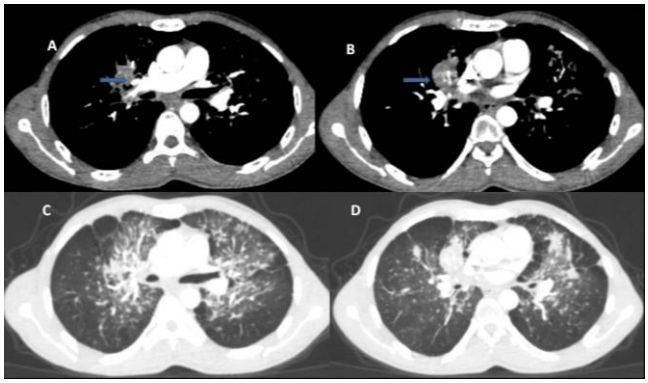

Figure 6: *An unenhanced axial chest CT shows a central carcinoid tumor in the mediastinal window obliterating the right middle lobe* ***(a-b)****, variable sizes of solid masses, and increased size and the number of nodules representing carcinoid tumor and tumorlet* ***(c-d)***

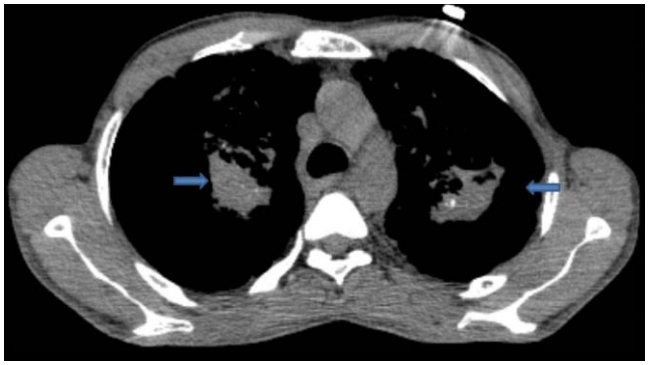

Figure 7: *Solid mass lesions measuring 4 cm in both upper lobes. These carcinoid tumors have developed millimeter-sized calcification foci as a result of chemotherapy treatment*

SSA trial therapy and symptomatic treatments were arranged, and the patient was constantly monitored because surgery would not be beneficial due to the diffusiveness of the lesions and the presence of distant metastases. There have been difficulties in reaching the patient since he was first diagnosed, either because he applied to different centers from time to time or because he failed to come to follow-up examinations. The patient, who applied to the emergency department again with complaints of a sudden cough and hemoptysis during the follow-ups in 2020, was evaluated by interventional radiology. No bronchiectasis was observed on the chest CT since the first diagnosis. Therefore, it was understood that the sudden onset of hemoptysis was caused by hypervascular carcinoid tumors since there was no bronchiectasis or other additional pathology (Figures 9a and b). Due to the hypervascular nature of carcinoid tumors, bilateral hemorrhage foci were embolized with bronchial artery embolization (BAE) (Figure 10 a–c).

The patient has been observed for a year with no signs of relapse. The patient was stable with all imaging abnormalities at the final follow-up chest CT in 2022.

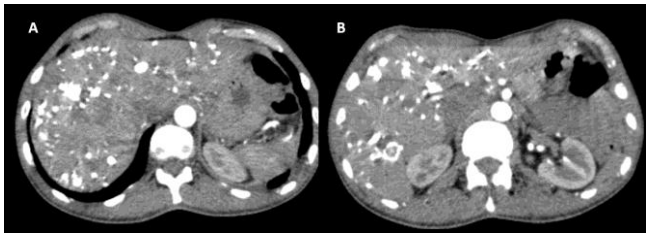

Figure 8: *Multiple calcified, solid metastatic mass lesions in the liver on chest angiography CT sections that go through the abdominal level (a, b)*

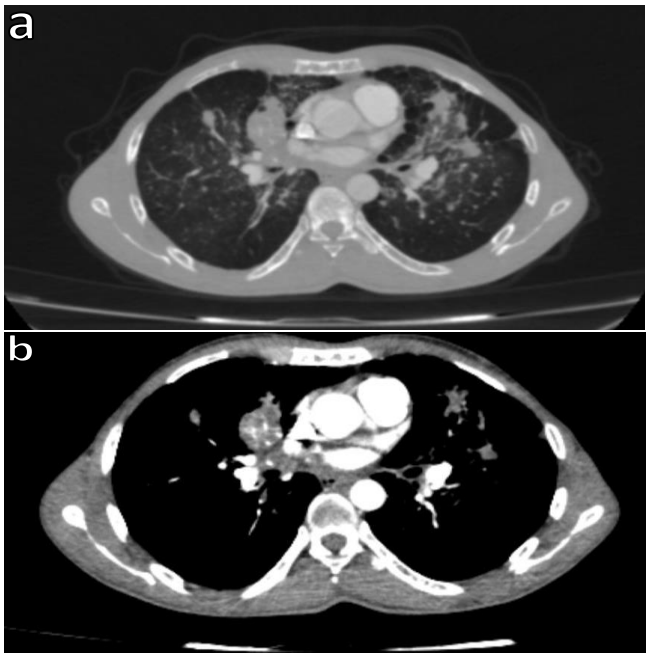

Figure 9: *Bilateral multiple tumorlet foci and peripheral carcinoid tumors are observed in the chest angiography CT of the patient, who was presented to the emergency department with sudden hemoptysis. No bronchiectasis* ***(a–b)***

DISCUSSION

DIPNECH is a rare entity, with only 200 cases reported in the literature, predominantly in case reports and case series (7-9). The diagnosis is usually not apparent from clinical features or pulmonary function tests. Many cases of DIPNECH are hardly understood, and as a result, there is still much to be learned about this rare entity (7). Many questions need to be answered, such as treatment algorithms, clinical presentation, which population is affected more, increasing factors, and the rate and frequency of progression to malignant carcinoid tumors. The prognosis of DIPNECH is variable. Indeed, while most cases follow a chronic, slowly progressive, or stable clinical course, those characterized by marked constrictive bronchiolitis may progress to severe airflow obstruction and respiratory failure requiring lung transplantation. Data on treatment, long-term follow-up, and outcomes in patients with DIPNECH are limited. Therapeutic modalities have included oral and inhaled GCs, SSA, chemotherapy, surgical lung resection, and lung transplantation, as well as clinical

observation alone for mild and stable cases (6).

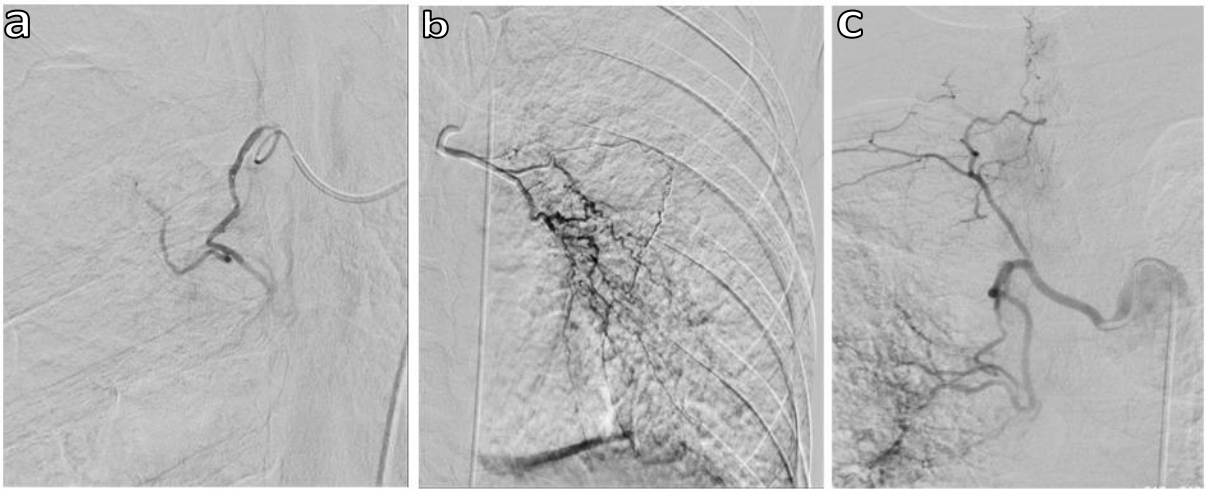

Figure 10: *Orthotopic bronchial arteries pre-embolization digital subtraction angiography (DSA) images* ***(a, b)*** *show selective catheterization of the common bronchial artery, giving rise to the right and left bronchial arteries with parenchymal blush. Postembolization* ***(c)***

We present a DIPNECH case that might be unknown and have different clinical and radiological findings by comparing it with other very limited cases in the literature. As it shows invasive growth kinetics and is a rare case in the literature that requires BAE by causing hemoptysis due to hypervascular hemorrhagic foci, it is a specific example for surveillance planning and change. DIPNECH has been used to define two different types of patient groups. One group is clinical, radiological, and pathological, while the other is asymptomatic and based only on histological presentations (6). People with this diagnosis may have no apparent symptoms or exhibit features of airway disease, such as a chronic, nonproductive cough and wheezing. Symptomatic DIPNECH, included in the second group, consists mainly of middle-aged to elderly women (a female-to-male ratio of approximately 10:1) and nonsmokers who showed small pulmonary nodules that were well-defined, round without calcification, mosaic attenuation, and bronchiectasis in chest CT (8–10). Small, bronchocentric, circumscribed solid nodules typically affect all lobes, with the lower zone and peripheral (small airways) being the most affected or having a more diffuse distribution. Lobular or regional air trapping (constrictive bronchiolitis) causes mosaic attenuation in the affected areas. Nodular bronchial wall thickening (cell clusters), mucus plugging, and bronchiectasis are common (11).

Conversely, our case was that of a middle-aged male who smoked. The distribution of nodules and masses tended to be localized mainly in the upper zones, and the lower zones were partially preserved. Mosaic attenuation was not severe. The DIPNECH clinical course generally remains stable; however, progression to carcinoid tumors can occur, and even respiratory failure can develop, requiring lung transplantation (11,12). The clinical course of our patient was highly variable. While more stable disease progression is expected in DIPNECH cases, many carcinoid tumors developed, and tumorlet foci became widespread in our case. In addition, there was diffuse sclerotic bone and liver involvement in several foci at the time of diagnosis. Diffuse calcification developed demonstratively in all treatment-related lesions, including metastases.

The rate and frequency of conversion to carcinoid tumors are yet unknown and vary. DIPNECH studies also did not contain obvious temporal comparisons in nodule size and number between chest CTs. Little et al. (9) discovered a steady increase in the size and number of nodules in a study of 32 patients with DIPNECH. They also found a characteristic centrilobular distribution with nodules concentrated on the small airways, frequently at the center of lobular air trapping. Sun et al. (7) found that 8 of 73 (11.6%) patients with DIPNECH and tumorlets eventually developed carcinoid tumors based on radiographic criteria, with a median follow-up time of 4.7 years. These patients were finally pathologically diagnosed with carcinoid tumors. Within two years of diagnosis, the number of all nodules, hilar, and parenchymal nodular mass lesions were carcinoid tumors, making the clinic situation worse. Diagnosis of DIPNECH in a timely and accurate manner would prevent patients from having particularly ineffective asthma treatment and will increase their comfort in life, for example, with SSA and other right symptomatic therapies.

CONCLUSION

Most DIPNECH cases are misdiagnosed or undetected due to their vague clinical and radiological presentation. We hope to raise awareness of DIPNECH and its typical and atypical clinical and radiological manifestations with this clinical case. In contrast to our smoking middle-aged male patient, DIPNECH typically affects nonsmoking females in their sixth decade of life. DIPNECH should

also be considered in cases with several noncalcified centrilobular random pulmonary nodules and mosaic attenuation patterns on chest CT. The majority of patients have stable or slowly progressing illnesses. The symptoms usually guide treatment, and the prognosis is quite diverse. The clinical course of the patient, who developed tumorlet foci in number and size and peripheral carcinoid tumors relatively rapidly since the first diagnosis, was variable in correlation with these findings. Responses to symptomatic GCs and SSA trial treatment were variable. There was no clinical progression in distant organ metastases (bone and liver). The clinical condition and radiological findings of the patient who underwent BAE have been stable since hemoptysis developed from a bleeding carcinoid tumor focus. The nature of carcinoid tumor development in this context should be understood, and monitoring should be planned.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - L.D., S.S.; Planning and Design - L.D., S.S.; Supervision - L.D., S.S.; Funding -; Materials -; Data Collection and/or Processing - L.D., S.S.; Analysis and/or Interpretation - L.D., S.S.; Literature Review - L.D., S.S.; Critical Review - L.D., S.S.

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