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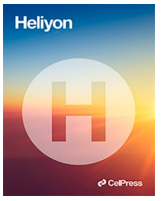

Case report

Coexistence of DIPNECH with pulmonary adenocarcinoma: Coincidence or by design?

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ABSTRACT

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) coexisting with pulmonary adenocarcinoma (ADC) is rare. Herein, we report a new case and review the cases published previously in the English literature. The clinicopathological features of similar cases reported in the English literature were summarized, and a putative association between DIPNECH and pulmonary ADC was suggested.

Among the 22 cases studied, the majority of patients were female and older adults. DIPNECH lesions were usually recognized beyond the lobe or segment in which the ADC was located. Most ADCs were of a low- or intermediate-grade. DIPNECH and pulmonary ADC were interspersed in six patients. In particular, two cases of ADC showed neuroendocrine differentiation.

We consider that DIPNECH accompanied by ADC is not coincidental, and that the two lesions may have a causal relationship. Analogous to the tumor histogenesis association of large cell neuroendocrine carcinoma/small cell carcinoma with ADC, we hypothesized that DIPNECH may also arise from a multipotent precursor cell and associate with a subgroup of ADC. However, further studies are required to explore this possibility.

1. Introduction

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare disease characterized by multifocal hyperplasia of pulmonary neuroendocrine cells associated with tumorlets. It was not fully described until 1992 [1], and was recognized by the World Health Organization (WHO) in 2001. DIPNECH coexisting with pulmonary adenocarcinoma (ADC) is even rarer. To date, 21 cases have been described in the English literature. Herein, we report a new case and describe the clinicopathological features of the disease. We further reviewed previous literature and attempted to speculate on the association of tumor histogenesis with DIPNECH and pulmonary ADC.

1.1. Case report

A 63-year-old woman presented with gradually worsening constipation for seven years. She was not a smoker, but she had been exposed to smoking for thirty years because her husband was a smoker. She experienced slight breathlessness when exposed to smoking, and a little sputum was found in the morning for nearly four years. Otherwise, the patient had no coughing, wheezing, or

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other respiratory symptoms.

Laboratory analyses showed an obviously higher gastrin-releasing peptide precursor (ProGRP) level of 260.60 pg/mL (normal range: 28.3–74.4 pg/mL) and a slightly higher neuron specific enolase (NSE) level of 16.31 g/L (normal range: 0.0–16.3 g/L). The levels of CEA, CA125, CA19-9, CA72-4, CA15-3, and squamous cell carcinoma (SCC) were all within normal ranges.

Endoscopy and tomographic scanning of the lungs were performed for the diagnosis. After gastroscopy, colonoscopy and biopsy, the patient was diagnosed with chronic gastritis, conventional colorectal adenoma, and functional constipation. Tomographic scanning revealed multiple dispersed lesions in both lungs. The largest one, a solid nodule, measuring 13 × 8 mm, was located in the left lower lobe. The rest of the lesions were small ground-glass nodules measuring 1–3 mm in diameter (Fig. 1A).

Smectite and berberine were administered to treat gastritis and chronic functional diarrhea. Left lower lobe lung resection was performed to remove the lung nodules.

1.2. Pathological findings

The lower lobe of the left lung, measuring 16 × 8 × 3 cm, was used for pathological examination. Gross view showed a nodule, with a diameter of 1.3 cm, located in the pulmonary parenchyma, 1.5 cm beneath the pleura. The cut surface of the nodule was homogenous and white-grey in color. No other lesions were observed.

Histopathologically, the white-grey nodule was diagnosed as moderately differentiated pulmonary ADC, with acinar and papillary ADC accounting for 60 % and 40 % of the overall lesion, respectively (Fig. 1B).

In addition to ADC, there was widespread proliferation of pulmonary neuroendocrine cells (PNCs), as highlighted by immunolabeling (Fig. 1C). These lesions produced a miliary pattern in the lungs. The PNCs were round, oval, or spindle-shaped, with a moderate amount of eosinophilic cytoplasm and round-to-oval nuclei with salt-and-pepper chromatin. Mitosis was not visible. The earliest lesions comprised an increased number of individual cells, small groups, or nodular aggregates confined to the bronchial or bronchiolar epithelium. Larger lesions bulged into the lumen as nodular or papillary growth but did not breach the subepithelial basement membrane. These features were sufficient for the diagnosis of DIPNECH.

In more advanced lesions, local invasion occurred as the proliferating PNCs broke through the basement membrane, developing a conspicuous fibrous stroma to form ‘tumorlets’ (1–3 mm in diameter). Some tumorlets were accompanied by mild chronic lymphocytic inflammation (Fig. 1D). Some bronchiolar walls were slightly fibrotic. Interestingly, two tumorlets were mixed with lung ADC, one measuring 3 mm in diameter and located in the middle, and the other measuring 2 mm in diameter and located at the border of the tumor area (Fig. 1E). There were no chronic inflammatory diseases such as bronchiectasis or chronic lung abscesses in the surrounding lung.

Immunohistochemically, both DIPNECH and lung ADC were positive for CK7, and the staining was strong in lung ADC and weak in DIPNECH (Fig. 1F). The lung ADC was positive for TTF-1 and Napsin A; and negative for CD56, chromogranin (CgA), and synaptophysin (Syn). DIPNECH was positive for CD56, CgA, and Syn; and negative for TTF-1 and Napsin A. The proliferative index (Ki-67) was 3 % in the lung ADC, while almost no cells expressed Ki-67 antigen in DIPNECH.

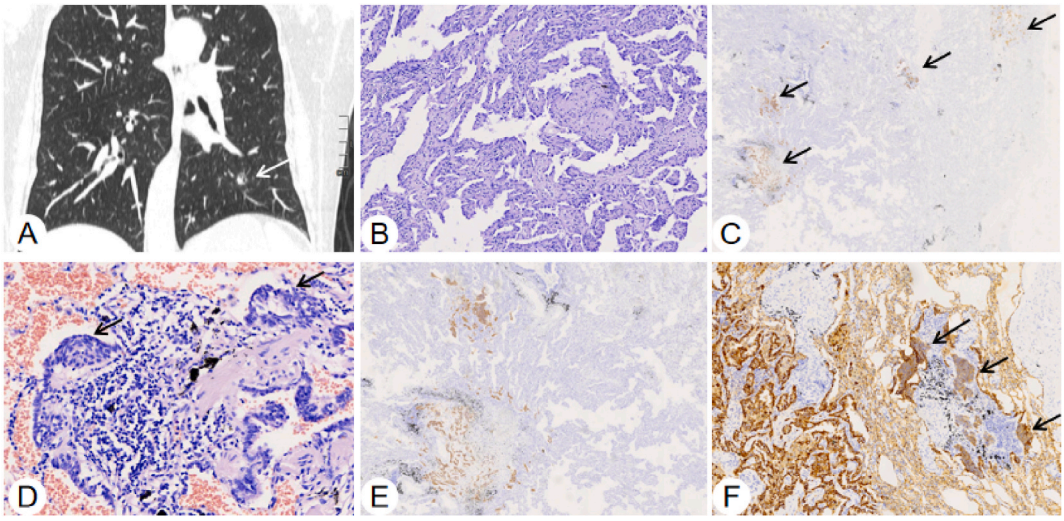

Fig. 1. DIPNECH accompanied by pulmonary adenocarcinoma. **A** Tomographic scanning showed multiple nodules dispersed in both lungs, the largest of which was located in the left lower lobe (arrow). **B** Pulmonary adenocarcinoma was composed of acinar adenocarcinoma and papillary adenocarcinoma (H&E, 200 ×). **C** Widespread proliferation of pulmonary neuroendocrine cells were highlighted by immunolabeling of Syn (arrows) (En Vision, 100 ×). **D** Proliferating PNCs bulged into the lumen as nodular or papillary growths, and broke through the basement membrane to form tumorlets. Some tumorlets were accompanied by chronic lymphocytic inflammation (arrows) (H&E, 200 ×). **E** Two tumorlets (highlighted by Syn immunohistochemical staining) were mixed with lung adenocarcinoma. **F** For CK7 expression, the staining was strong in lung adenocarcinoma while it was weak in DIPNECH (arrows) (En Vision, 200 ×).

1.3. Prognosis

Diarrhea significantly improved after one month of treatment. The patient did not undergo postoperative chemotherapy for lung cancer. Follow-up tomographic scanning was performed one year postoperatively. There was no recurrence of lung cancer and no significant progression of other pulmonary nodules was observed. As of October 2023, the patient has survived for 18 months and is in good condition.

1.4. Review of the literature

We present a new case of DIPNECH by with pulmonary ADC. To explore the putative relationship between these two lesions, we reviewed reports previously published in the English literature and summarized the clinical and pathological characteristics of DIPNECH with ADC (Table 1).

The first case of DIPNECH accompanied by ADC was reported by Warth in 2008 [2], and a total of 21 cases have been reported overall [2–12]. Our presentation is the 22nd case report. In conclusion, most patients were female (11/13) and of older age (median age, 68 years, range 55–81 years). DIPNECH lesions were usually diffused beyond the lobe or segment where the ADC was located. In most cases, the DIPNECH and ADC were separated from each other. However, two lesions were interspersed with each other in six cases. Most ADCs were well- or moderately-differentiated (13/14). In particular, two ADC cases showed neuroendocrine differentiation, as verified by CD56 or NSE expression.

Clinically, most patients presented with cough, expectoration, shortness of breath, and obstructive symptoms. Of the 21 cases reported previously, six patients mentioned their smoking status; four of six were smokers, and our patient was a second-hand smoker. Most patients showed a good response. Eight cases were described with prognosis, there was no recurrence after 10 months–65 months of follow-up [2–12].

2. Discussion

DIPNECH is a slowly progressive condition with a benign course that spans many years. It may occur at any age but typically

Table 1
The clinical and pathological characteristics of DIPNECH with ADC.

Author	Cases number	Sex	Age	ADC size (cm)	ADC grade	ADC location	ADC with neuroendo-crine differation	DIPNECH location	Location of ADC and DIPNECH
Warth [2]	1	F	60	3.5*3*2.8	/	right upper lobe	yes	right middle and lower lobes	separate
Mireskandari [3]	1	M	72	3*1.5*1.4	G2	right upper lobe	no	right upper lobe	separate
	2	F	69	2.5*2.4*1.5	G1	left lower lobe	yes	left lower lobe	related
	3	F	70	2.0*2.0*1.5	G1	right middle lobe	no	right middle lobe	related
	4	F	55	2.8 in diameter	G1	right upper lobe	no	right middle lobe	related
Al-Ayoubi [4]	1	F	81	1.5 in diameter	/	right lower lobe	/	right lower lobe	separate
Marchevsky [5]	three in total	/	/	/	/	/	/	/	/
Baniak [6]	1	F	76	/	/	/	/	both the upper and lower lobes	separate
Trisolini [7]	five in total	/	/	/	AIS, MIA, G1, G2, G3	/	no	/	2/5 related
Gorospe [8]	1	F	66	1.2 in diameter	G1	right lower lobe	/	both lungs	/
Pelosi [9]	1	F	69	1.5 in diameter	G2	left lower lobe	/	/	/
Jin [10]	1	F	64	2.5 in diameter	/	right upper lobe	/	/	/
	2	M	61	/	/	left lower lobe	/	/	/
Inomata [11]	1	F	72	3.8 in diameter	G2	right upper lobe	/	both lungs	/
Hayes [12]	1	/	/	/	G1	/	/	/	/
Our case	1	F	63	1.3 in diameter	G2	left inferior lobe	no	both lungs	related

M, male; F, female; DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; ADC, pulmonary adenocarcinoma; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; G, histological grade.

presents in the fifth or sixth decade and is possibly more common in women [1,13–15]. Nodular proliferations of PNCs invading beyond the bronchiolar wall are diagnosed as carcinoid tumorlets/tumors. The distinction between the two lesions is based on size: tumorlets measure <5 mm, whereas tumors measure ≥5 mm.

Histopathologically, DIPNECH must be distinguished from the limited reactive reversible hyperplasia of PNCs, which may accompany a variety of pulmonary conditions, particularly chronic inflammatory diseases. A previous study revealed that proliferating PNCs expressed Ki-67 at all stages and showed earlier expression of p16 [16] in DIPNECH, unlike proliferation secondary to pulmonary injury. In our case, there were no chronic inflammatory diseases in the surrounding lungs, unlike reactive PNC hyperplasia. Proliferation of PNCs can also be seen in carcinoid tumors, but is limited to the immediate vicinity of carcinoids.

Occasionally, DIPNECH has been reported to coexist with ADC. Is this a coincidence or is there a relationship?

Several studies have investigated the association between DIPNECH and ADC. In a large study of 1090 cases of lung neoplasms, none of the DIPNECH cases was associated with ADC or SCC [17]. Mireskandari et al. also reviewed 82 cases of lung carcinoma and found no foci for PNCs proliferation [3]. Both studies indicated that ADC accompanied by DIPNECH are rare.

In a review of the 22 available cases of DIPNECH accompanied by ADC, we observed that the two lesions interspersed with each other in six cases, and ADCs were prone to be of low- and intermediate-grade, exhibiting better prognosis than conventional lung ADC [2,3]. These observations implied a causal relationship between DIPNECH and a subgroup of ADC.

DIPNECH is considered a pre-invasive lesion in a subset of pulmonary carcinoids, mostly typical carcinoids [18,19]. One study found that 40 % of DIPNECH cases were accompanied by carcinoid tumors [19]. Genetically, allelic imbalance in the 11q13 region, which closely approximates the MEN1 tumor suppressor gene, is present in the majority of carcinoid tumors and occasionally appears in tumorlets [20].

However, its pathogenesis remains unclear. No predictive histological or genetic data are available for DIPNECH. One possible route is from an uncommitted precursor cell stimulated by unknown factors to differentiate along the neuroendocrine line. Similarly, little is known about the pathogenic association between DIPNECH and ADC.

The association between lung cancer and high-grade neuroendocrine tumors has been described extensively in many studies. Definitive large cell neuroendocrine carcinoma (LCNEC)/small cell carcinoma (SCLC) admixed with ADC/SCC/large cell carcinoma is classified as combined LCNEC/SCLC. Studies have revealed that some genetic alterations are common in LCNEC/SCLC and contiguous bronchial epithelium. These observations suggest that LCNEC/SCLC shares the same endodermal origin with other lung cancers, arising from a multipotent precursor cell [21]. This theory is supported by studies using mouse models [22–25].

In the cohort of patients with DIPNECH with ADC diseases (Table 1), ADCs showed neuroendocrine differentiation in two cases. In one study, Mireskandari observed that the cytological features of ADC cells and DIPNECH foci were quite similar; in particular, a morphological transition was observed in these two cells in one case [3].

Accordingly, we hypothesized that, similar to the tumor histogenesis association between LCNEC/SCLC and ADC, DIPNECH may also arise from a stem cell progenitor and have a relationship with a subgroup of ADC. However, more data are required before definitive conclusions can be drawn.

3. Summary

DIPNECH is a preneoplastic lesion of typical and atypical carcinoids. DIPNECH accompanied by ADC is rare. Herein, we report a new case and review previous reports. We considered that the coexistence of DIPNECH and ADC may not be coincidental and proposed that DIPNECH and a subgroup of ADC may arise from the same stem cell progenitor.

We speculated that DIPNECH may not only be a precursor to carcinoid tumorlets/tumors, but also be associated with some other diseases, such as lung adenocarcinoma. Our case indicated that some ADCs, especially those with higher levels of neuroendocrine markers, may be accompanied by DIPNECH. Since our conclusions are primarily based on histopathological and IHC results, there are some limitations. Further studies, such as analysis of the molecular changes in the two lesions, are needed to explore our hypothesis in the future.

CRediT authorship contribution statement

Xiaoyu Song: Writing – original draft. **Qinghua Cao:** Validation. **Wei Liu:** Visualization. **Yanan Zhang:** Formal analysis. **Junmei Hao:** Writing – review & editing, Project administration.

Ethics statement

All the studies were conducted in accordance with the Declaration of Helsinki, written informed consent was obtained from the patient.

Data availability statement

No data was used for the research described in the article.

Additional information

No additional information is available for this paper.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] S.M. Aguayo, Y.E. Miller, J.J. Waldron, R.M. Bogin, M.E. Sunday, G.J. Staton, W.R. Beam, T.J. King, Brief report: idiopathic diffuse hyperplasia of pulmonary neuroendocrine cells and airways disease, NEW ENGL J MED 327 (1992) 1285–1288.
[2] A. Warth, E. Herpel, A. Schmähl, K. Storz, P.A. Schnabel, Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) in association with an adenocarcinoma: a case report, J. Med. Case Rep. 2 (2008), 21-21.
[3] M. Mireskandari, A. Abdirad, Q. Zhang, M. Dietel, I. Petersen, Association of small foci of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) with adenocarcinoma of the lung, Pathol. Res. Pract. 209 (2013) 578–584.
[4] A.M. Al-Ayoubi, J.S. Ralston, S.R. Richardson, C.E. Denlinger, Diffuse pulmonary neuroendocrine cell hyperplasia involving the chest wall, Ann. Thorac. Surg. 97 (2014) 333–335.
[5] A.M. Marchevsky, E. Wirtschafter, A.E. Walts, The spectrum of changes in adults with multifocal pulmonary neuroendocrine proliferations: what is the minimum set of pathologic criteria to diagnose DIPNECH? Hum. Pathol. 46 (2015) 176–181.
[6] N.M. Baniak, B. Wilde, R. Kanthan, Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)—an uncommon precursor of a common cancer? Pathol. Res. Pract. 212 (2016) 125–129.
[7] R. Trisolini, I. Valentini, C. Tinelli, M. Ferrari, G.M. Guiducci, S.N.F. Parri, G. Dalpiaz, A. Cancellieri, DIPNECH: association between histopathology and clinical presentation, Lung 194 (2016) 243–247.
[8] L. Gorospe, G.M. Muñoz-Molina, F.E. Farfán-Leal, A. Cabañero-Sánchez, I. García-Gómez-Muriel, A. Benito-Berlinches, Association of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) with lung adenocarcinoma: a radiologist's perspective, Lung Cancer 110 (2017) 77–79.
[9] G. Pelosi, F. Nesa, D. Taietti, S.P. Servillo, N. Papanikolaou, M. Zompatori, A. Meroni, S. Harari, M. Incarbone, Spread of hyperplastic pulmonary neuroendocrine cells into air spaces (S.H.I.P.M.E.N.T.S): a proof for artifact, Lung Cancer 137 (2019) 43–47.
[10] L. Jin, Z. Wang, X. Qi, Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, Medicine 97 (2018) e13806.
[11] S. Inomata, Y. Matsumura, Y. Kobayashi, H. Yamaguchi, M. Watanabe, Y. Ozaki, S. Muto, N. Okabe, Y. Shio, H. Suzuki, Lung adenocarcinoma coexisting with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia manifesting as multiple pulmonary nodules: a case report, Thorac Cancer 13 (2022) 3076–3079.
[12] A.R. Hayes, T.V. Luong, J. Banks, H. Shah, J. Watkins, E. Lim, A. Patel, A.B. Grossman, S. Navalkissoor, D. Krell, M.E. Caplin, Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH): prevalence, clinicopathological characteristics and survival outcome in a cohort of 311 patients with well-differentiated lung neuroendocrine tumours, J. Neuroendocrinol. 34 (2022).
[13] O.A. Armas, D.A. White, R.A. Erlandson, J. Rosai, Diffuse idiopathic pulmonary neuroendocrine cell proliferation presenting as interstitial lung disease, Am. J. Surg. Pathol. 19 (1995) 963–970.
[14] J.S. Lee, K.K. Brown, C. Cool, D.A. Lynch, Diffuse pulmonary neuroendocrine cell hyperplasia: radiologic and clinical features, J Comput Assist Tomo 26 (2002) 180–184.
[15] R.R. Miller, N.L. Muller, Neuroendocrine cell hyperplasia and obliterative bronchiolitis in patients with peripheral carcinoid tumors, Am. J. Surg. Pathol. 19 (1995) 653–658.
[16] J.R. Gosney, I.J. Williams, A.R. Dodson, C.S. Foster, Morphology and antigen expression profile of pulmonary neuroendocrine cells in reactive proliferations and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), Histopathology 59 (2011) 751–762.
[17] E. Ruffini, M. Bongiovanni, A. Cavallo, P. Filosso, R. Giobbe, M. Mancuso, M. Molinatti, A. Oliaro, The significance of associated pre-invasive lesions in patients resected for primary lung neoplasms1, EUR J CARDIO-THORAC 26 (2004) 165–172.
[18] S.J. Davies, J.R. Gosney, D.M. Hansell, A.U. Wells, R.M. du Bois, M.M. Burke, M.N. Sheppard, A.G. Nicholson, Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: an under-recognised spectrum of disease, Thorax 62 (2007) 248–252.
[19] A.A. Nassar, D.E. Jaroszewski, R.A. Helmers, T.V. Colby, B.M. Patel, F. Mookadam, Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, AM J Resp Crit Care 184 (2011) 8–16.
[20] S.D. Finkelstein, T. Hasegawa, T. Colby, S.A. Yousem, 11q13 allelic imbalance discriminates pulmonary carcinoids from tumorlets, Am. J. Pathol. 155 (1999) 633–640.
[21] I.I. Wistuba, J. Berry, C. Behrens, A. Maitra, N. Shivapurkar, S. Milchgrub, B. Mackay, J.D. Minna, A.F. Gazdar, Molecular changes in the bronchial epithelium of patients with small cell lung cancer, Clin. Cancer Res. 6 (2000) 2604–2610.
[22] D.G. McFadden, T. Papagiannakopoulos, A. Taylor-Weiner, C. Stewart, S.L. Carter, K. Cibulskis, A. Bhutkar, A. McKenna, A. Dooley, A. Vernon, C. Sougnez, S. Malstrom, M. Heimann, J. Park, F. Chen, A.F. Farago, T. Dayton, E. Shefler, S. Gabriel, G. Getz, T. Jacks, Genetic and Clonal dissection of murine small cell lung carcinoma progression by genome sequencing, Cell 156 (2014) 1298–1311.
[23] R. Meuwissen, S.C. Linn, R.I. Linnoila, J. Zevenhoven, W.J. Mooi, A. Berns, Induction of small cell lung cancer by somatic inactivation of both Trp53 and Rb1 in a conditional mouse model, Cancer Cell 4 (2003) 181–189.
[24] K. Park, M. Liang, D.M. Raiser, R. Zamponi, R.R. Roach, S.J. Curtis, Z. Walton, B.E. Schaffer, C.M. Roake, A. Zmoos, C. Kriegel, K. Wong, J. Sage, C.F. Kim, Characterization of the cell of origin for small cell lung cancer, Cell Cycle 10 (2014) 2806–2815.
[25] K.D. Sutherland, N. Proost, I. Brouns, D. Adriaensen, J.Y. Song, A. Berns, Cell of origin of small cell lung cancer: inactivation of Trp53 and Rb1 in distinct cell types of adult mouse lung, Cancer Cell 19 (2011) 754–764.