PATHOLOGICA 2015;107:37-42

Case report

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) and multiple pulmonary epithelioid hemangioendothelioma (PEH): a case report

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Key words

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia • DIPNECH
Epithelioid hemangioendothelioma • PEH • Bilateral microcalcifications • Lung

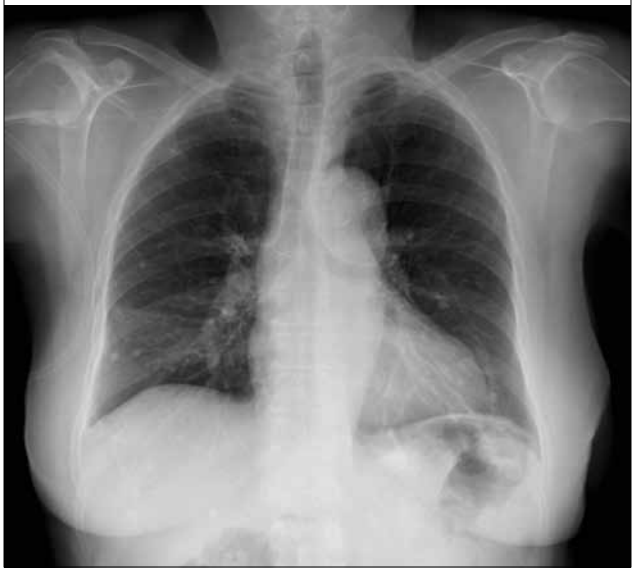
Summary

We report a case of a 76-year-old female with multiple lung nodules (Fig. 1 Rx). Pathologic evaluation of the lower left video-assisted thoracoscopic surgery (VATS) lobectomy VATS-lobectomy showed four nodules that were described as pulmonary epithelioid hemangioendothelioma (PEH); the immunohistochemical stains showed that the neoplastic cells expressed CD31, a variable expression for factor VIII and a low expression of CD34. In the remaining parenchyma of the lobe, multiple nests of neuroendocrine cells were observed with immunohistochemical confirmation, and the diagnosis was diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). To our knowledge, the association between PEH and DIPNECH has never been described in the literature.

Introduction

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare condition, with under 100 cases described in literature [1]. According to the World Health Organization (WHO) DIPNECH is considered as a proliferation of scattered single cells, small nodules (neuroendocrine bodies), or linear proliferations of pulmonary neuroendocrine cells in the mucosa and submucosa of the small bronchi and bronchioles [2]. The patients often have no significant clinical symptoms, sometimes they present an obstructive lung disease, but the condition is usually diagnosed accidentally during general examination. Most commonly, women in the fifth and sixth decades of life are affected. However, the disease may develop at any age. DIPNECH is considered to be a precursor of tumorlets and some of the well (G1) and moderately differentiated (G2) neuroendocrine tumors of the lung (carcinoids and atypical carcinoids) [3 4].
Pulmonary epithelioid hemangioendothelioma (PEH) is a vascular tumor with an intermediate malignant potential,

Fig. 1. Rx: The frontal chest radiograph shows multiple small nodules in both lungs, having a lower lobe predominance.



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and is categorized into a borderline or low-grade malignancy [5]. This tumor is very rare in the lung parenchyma, and most of the previously reported cases have been asymptomatic. Pulmonary epithelioid hemangioendothelioma is also of multicentric origin, and extrapulmonary lesions arise from liver, bone, soft tissue, and skin [6].
Herein we describe a case with concomitant PEH and DIPNECH.

Case report

A 76-year-old woman presented with persistent dry cough, a decline in exercise tolerance. Past medical history was significant for hypertension, dyslipidemia, chronic coronary artery disease. Pulmonary function tests and bronchoscopy revealed no significant abnormalities. High-resolution computed tomography (HRCT) showed a nodule (18 x 14 x 15 mm) in the inferior lobe of the left lung (Fig. 2A), and diffuse bilateral microcalcifications: eleven right and eight on the left lung (Fig. 2B). 18F-Fluoro-2-deoxy D-glucose-positron emission tomography (FDG-PET)/CT revealed increased FDG accumula-

Fig. 2. CT: The major nodule (18 mm) is located in the left lower lobe (posterior basal segment) and shows spiculated borders (2A). The chest computerthomography (axial plane) confirms the presence of multiple small lung nodules with calcifications (2B).

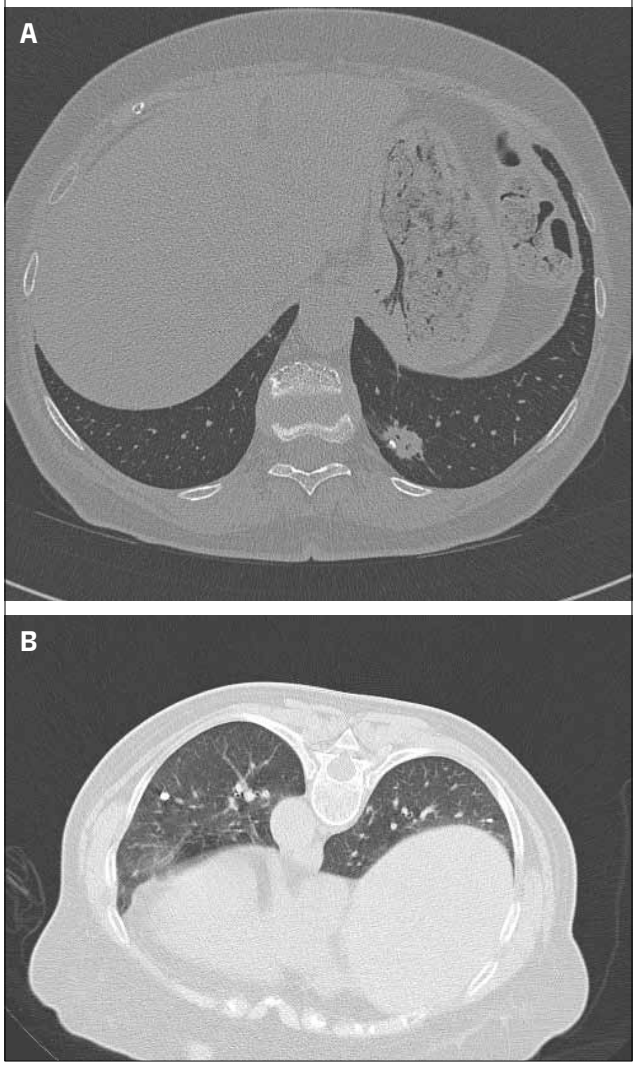
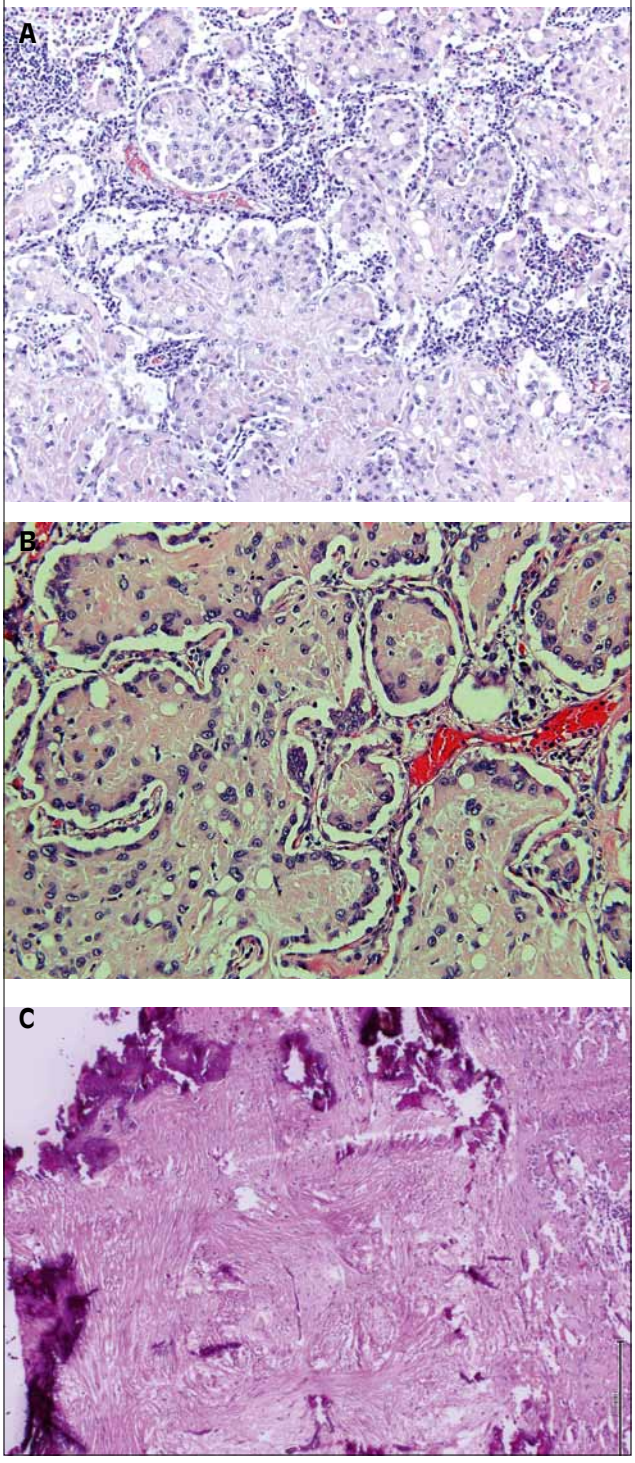


Fig. 3. PEH microscopic findings: The neoplastic cell population was composed of plump epithelioid cells with abundant eosinophilic cytoplasma (3A), sometimes containing intracytoplasmic vacuoles (3B); diffuse fibrosis and calcifications as neoplastic regression are present (3C).



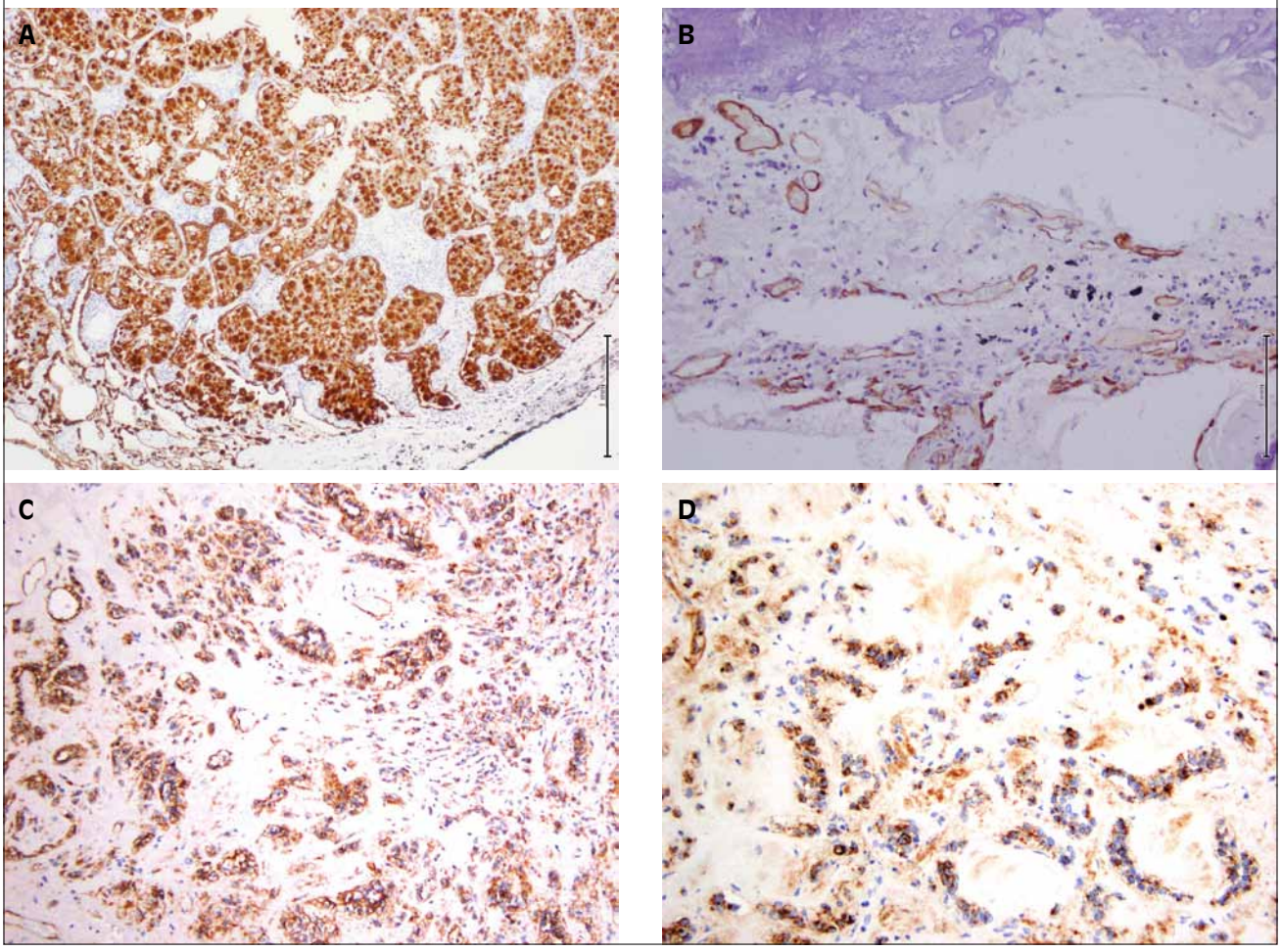
tion in the nodule. The patient performed a transthoracic CT guided needle biopsy of the major nodule which initially been diagnosed a non-small cell lung carcinoma, not otherwise specifed (NSCLC-NOS).

By immunohistochemistry, the neoplastic cells were negative for p63, cytokeratin 7, TTF-1, chromogranin-A, HMB-45, Ber-Ep4, Napsin-A; cells were immunoreactive for cytokeratin CAM5.2.

The patient underwent lower left VATS-lobectomy. Macroscopically, a round, grey tumor, with circumscribed margins, measuring 19 mm in the major axis was described in the posterior basal segment of the left lower lobe; the lesion closely abutted the pleura. Multiple small nodules, with hard consistency, measuring 2-3 mm in diameter, were discernible throughout the remaining lung parenchyma.

Microscopically, the major nodule revealed multiple smaller oval nodular structures with sclerotic hypocellular centers, surrounded by a rim of more cellular areas. The neoplastic cell population was composed of plump epithelioid cells with abundant eosinophilic cytoplasma, sometimes containing intracytoplasmic vacuoles, a fact that suggested us the possibility of endothelial differentiation. In the same lesion, diffuse fibrosis and calcifications were observed and this was attributed to neoplastic regression; therefore the neoplasia was interpreted as multicentric with nodules in different stages, some of them with abundant sclerosis totally replacing neoplastic cells, others with more cellular neoplastic component. Overall we considered four neoplastic nodules in the following different progression stages: 1) In two nodules was predominant cellularity over sclerosis and/or calcification, 2) in one nodule there was 50% cellularity 50% sclerosis or calcification, 3) in one nodule there was more sclerosis or calcification than cellularity (Fig. 3). Neoplastic infiltration of arterioles, venules and lymphatics was not evident. The surgical resection margins and the pleura were free of tumor cells. The immunohistochemical stains showed that the neoplastic cells expressed CD31, a variable expression for factor VIII and a low expression of CD34 (Fig. 4); therefore the hypothesis of endothelial differentiation was confirmed (Tab. I). The diagnosis was epithelioid hemangioendothelioma of the lung without atypia or necrosis, with a 3% of Ki67/MIB-1. Considering the radiological analysis, we noticed that probably there are the same lesions also in the right lung.

Fig. 4. PEH Immunohistochemistry: The neoplastic cells were immunoreactive for cytokeratin CAM5.2 (4A), low expression for CD34 (4B), CD31 (4C) and variable expression for factor VIII (4D).



Tab. I. Immunohistochemical stains in the pulmonary epithelioid hemangioendothelioma (PEH) lesions.

Pulmonary epithelioid hemangioendotelioma	CD31: +
	CD34: -/+
	Fact. VIII: +/-
	Cytokeratin CAM 5.2: +
	Vimentin: +
	EMA: +/-
	HMB-45: -
	Estrogen Receptor (ER): -
	Synaptophysin: -
	Cytokeratin 34betaE12: -
	TTF-1: -
	p63: -
	Protein S-100: -
	Ber-Ep4: -
	CD15: -
	Napsin-A: -
	Cytokeratin 7: -
	Thyreoglobulin: -
	Ki67/MIB-1: 3%

Fig. 5. DIPNECH microscopic findings: Nests of neuroendocrine cells organized in tumorlets centred on small airways (5A). The cells were uniform and oval, showing finely granular chromatin and amphophilic cytoplasm (5B).

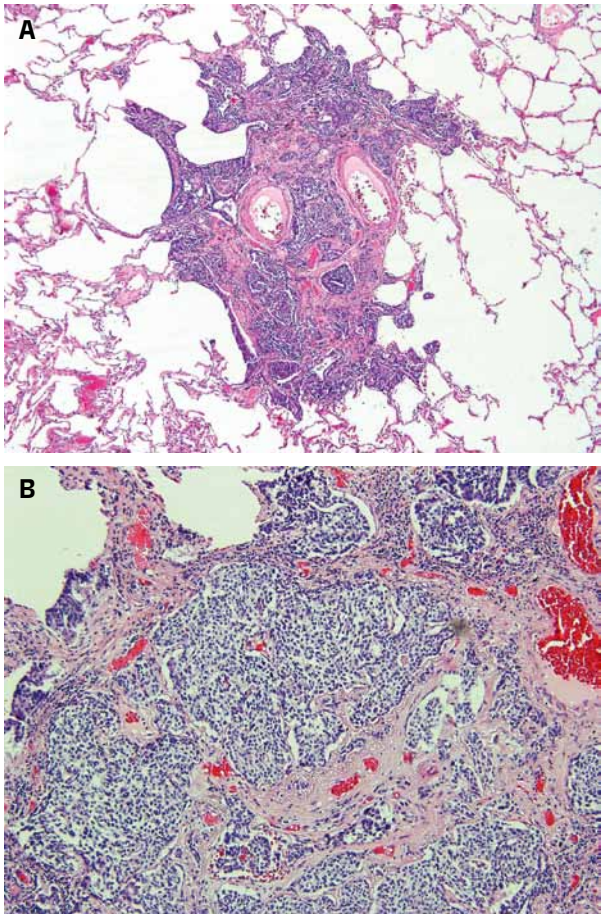
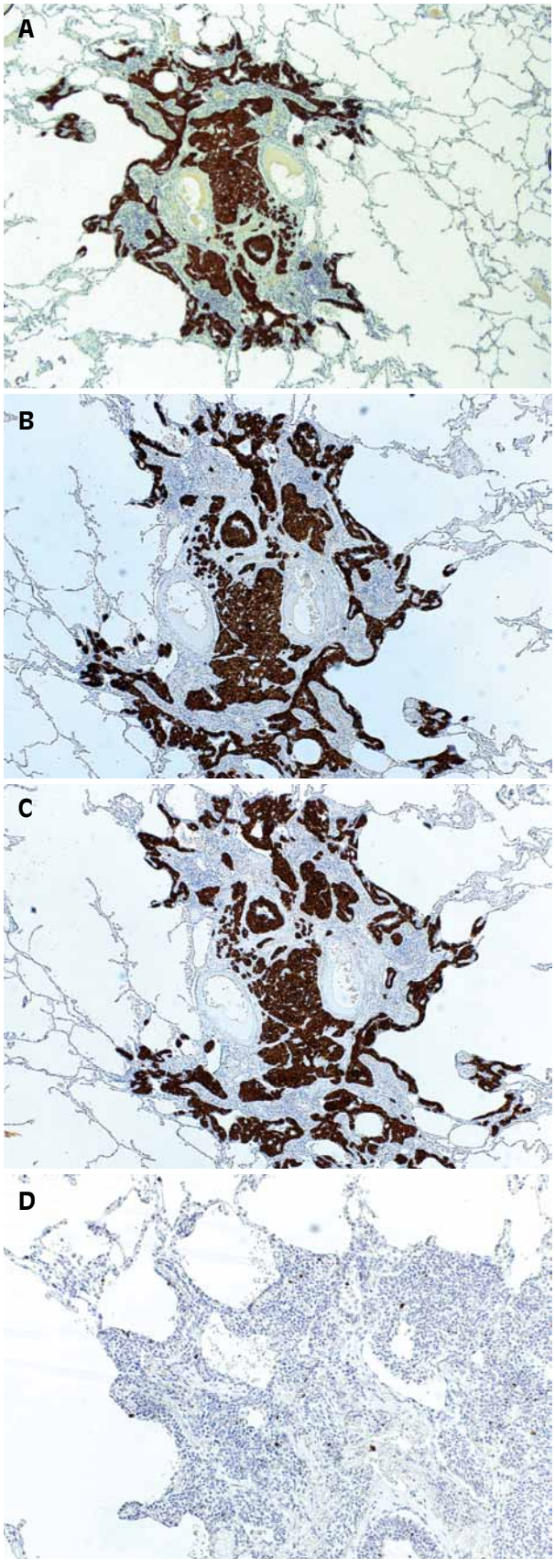


Fig. 6. DIPNECH Immunohistochemistry: The cells expressed cytokeratin 7 (6A) and the neuroendocrine markers chromogranin-A (6B), synaptophysin (6C), and MIB1-Ki67 (6D).



Tab. II. Immunohistochemical stains in the diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) lesions.

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	Cytokeratin 7: +
	TTF-1: +
	Chromogranin-A: +
	CD56 (NCAM): +
	Synaptophysin: +
	Somatostatin: +
	Serotonin: +
	Glucagon: +/-
	Gastrin: -
	PP (pancreatic polipeptide): -
	Insulin: -
	Protein S-100: -
	Ki67/MIB-1: 2%

In the remaining parenchyma of the lobe, nests of neuroendocrine cells centred on small airways were observed. The cells were uniform and oval, showing finely granular chromatin and moderate amounts of amphophilic cytoplasm; they were sometimes organized in tumorlets measuring 2-4 mm diameter. The nests were associated with variable amounts of fibrosis and compression of adjacent bronchioles (Fig. 5).

Neither mitotic figures nor necrosis were seen. Immunohistochemical stains showed that lesional cells expressed neuroendocrine markers, such as chromogranin-A and synaptophysin, CD56 (NCAM); cells were also immunoreactive for cytokeratin 7, somatostatin, serotonin, with variable expression of glucagon. Protein S100 was negative (Fig. 6). The histological and immunohistochemical features were diagnostic for diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) (Tab. II).

Discussion

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)

The recent WHO classification considers DIPNECH a precursor of carcinoid tumorlets and carcinoid tumors. DIPNECH occurs most commonly as a reactive neuroendocrine cell hyperplasia located in the small bronchi and bronchioles [2]. When proliferation of neuroendocrine cells exceeds the confines of small airways, the cells form discrete nodules that are called tumorlets: When the nodule is > 5 mm, it is considered a carcinoid tumor [7].

DIPNECH was first described in the early 1950s, but was not fully recognized and named until 1992, when Aguayo, Miller and colleagues described six patients with diffuse hyperplasia and dysplasia of pulmonary neuroendocrine cells, multiple carcinoid tumorlets, and peribronchiolar fibrosis obliterating small airways. They suggested that it is possible that hyperplastic neuroendocrine cells are involved in the pathogenesis of bronchopulmonary dysplasia [8].

DIPNECH mostly occurs in middle aged or older adults with an average age of diagnosis of 58 years but the reported age range varies from 22 to 79 years. There is a female predilection (F:M 4:1) and most patients are nonsmokers [9]. Clinical presentation is often insidious, with slow onset of dry cough and breathlessness, however, some patients are asymptomatic. Symptoms are secondary to an obstructive lung function profile and consist of a nonproductive cough and dyspnea. HRCT often shows small airways obstruction evidenced by inspiratory mosaic attenuation and expiratory air trapping. The coexistence of multiple pulmonary nodule is the best clue to the diagnosis of DIPNECH [10]. The second mode of presentation is in asymptomatic patients through surgical referral, typically for resection of pulmonary nodule or nodules that have been found incidentally on imaging [11]. The diagnosis of DIPNECH requires histopathological confirmation of pulmonary neuroendocrine cell proliferation confined to the epithelium of large and small airways. The gold standard remains surgical lung biopsy, especially with the increased practice of minimally invasive thoracic surgical procedures [12]. DIPNECH is an indolent and non progressive disorder, with 83% of symptomatic patients being alive at 5 years. Most cases remain stable over many years, although a few patients progress to severe airflow obstruction [11].

Pulmonary epithelioid hemangioendothelioma (PEH)

In 1975 Dail and Liebow reported the first cases of an unusual pulmonary neoplasm that they called "intravascular bronchioloalveolar tumor" (IVBAT). This name reflected their original hypotesis that the lesion in question was an epithelial tumor: specifically, a bronchioloalveolar carcinoma variant showing prominent vascular invasion [13 14]. Four years thereafter, Corrin et al. proposed an endothelial origin for this tumor based on the results of ultrastructural studies.

Subsequent evaluations by other authors have confirmed the vascular histogenesis of the "IVBAT" [13 15]. In 1982 Weiss and Enzinger described a series of soft tissue tumors that were histologically identical to IVBAT, and these authors were the first to use the term "epithelioid hemangioendothelioma" (PEH) [13 16]. In addition to the lungs and soft tissues, EH also primarily occurs in the bone and liver. Among the rare cases of PEH reported in literature the lungs are rarely involved [17].

Pathologically the tumor shows nodules ranging in shape from round to oval, and they tipically have a central sclerotic, hypocellular zone and a cellular peripheral zone and even papillary patterns. The tumor cells are round with abundant eosinophilic cytoplasm and intracytoplasmic vacuolization having a signet ringlike appearance [13]. Spindle -shaped tumor cells are occasionally seen and the presence of tumor cells with high mitotic activity has been reported to be an even worse prognostic factor. Other adverse prognostic factors include prominent symptoms at the time of presentation, radiographic demonstration of extensive intravascular, endobronchial, or pleural spread of the tumor [18]. No specific treatment regimen exists. Because pulmonary epithelioid hemangioendothelioma may express estrogen

and progesterone receptors, a potential role for hormone therapy has been suggested [18]. Watanabe and colleagues used the 18-FDG-PET/CT as an indicator for resection of pulmonary EH, the FDG uptake reflects the activation of pulmonary EH tumor cells, resulting in progression of the disease [19]. Fujita and collegues described long term follow -up of a case of pulmonary epithelioid hemangioendothelioma and indicated that the 5-year survival probability was 60% (range 47%-71%) and only a few cases with long term follow-up over 10 years were reported [20].

Conclusion

Herein we reported a case with the association between PEH and DIPNECH; to our knowledge, this association has never been described in the literature. Both PEH and DIPNECH are rare conditions. The concomitant presence of both lesions in a same patient and in a same lobe is also a potential diagnostic pitfall in evaluating a bilateral and calcified multinodular lung disease, especially if only small biopsies are under examination. Accurate sampling of lung surgical specimen together with appropriate clinico-radiological correlations may help in correctly reveal both conditions.
The patient, because of DIPNECH syndrome, remains in close clinical follow-up functional-radiology. Persists even after surgery dry cough that is treated symptomatically. We believe that this symptom is connected to DIPNECH syndrome. The ventilatory function is its preservation within normal limits.

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