

# An Unusual Finding of Tumorlet Carcinoid and Endobronchial Hamartoma in the Lobar Bronchus

Hallazgo Inusual de Tumorlet Carcinoide y Hamartoma Endobronquial en el Bronquio Lobar

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**SUMMARY:** Neuroendocrine lung tumours are a group of different tumours that have similar morphological, immunohistochemical and molecular characteristics, and represents 1-2 % of all malignant lung tumours. Tumorlet carcinoids represent the nodular proliferation of hyperplastic neuroendocrine cells that is smaller than 5 mm in size. In this study, we reported the unusual finding of tumour carcinoid and endobronchial hamartoma in the same bronchus. A 49-year-old male patient with symptoms of prolonged severe cough and fever, and was treated for pneumonia. Since he did not adequately respond to antibiotic therapy lung CT scan was performed which showed middle lobe bronchus obstruction. Bronchoscopy revealed a lobulated whitish tumour which was biopsied and histopathological diagnosis was hamartoma. Tumour could not be completely removed during bronchoscopy, it was decided to surgically remove it. On serial section, during gross examination in the same bronchus, an oval yellowish area with a diameter of 3 mm was found along the bronchial wall. According to gross and histomorphological characteristics and immunophenotype of tumour cells, the diagnosis of tumour carcinoid was set. Diagnosis of carcinoids of the tumorlet type is usually an accidental finding and it can be seen on CT in the form of subcentimeter, single or multiple, nodular changes. Considering that the clinical picture is nonspecific, they should always be kept in mind as a possible differential diagnosis.

**KEY WORDS:** Carcinoid tumorlet; Bronchus; Pulmonary hamartoma.

## INTRODUCTION

About 25 % of neuroendocrine tumours are localized in the respiratory tract, which represents 1-2 % of all malignant lung tumours (Caplin *et al.*, 2015). The incidence of these tumours is increasing and is estimated at 1.35 cases per 100,000 per year (Oberg *et al.*, 2012).

Neuroendocrine lung tumours are a heterogeneous group of different tumours that have similar morphological, immunohistochemical and molecular characteristics. According to the World Health Organization categorization, neuroendocrine lung tumours include 4 histological entities: small cell carcinoma (SCLC), large cell carcinoma with neuroendocrine morphology (LCNEC), atypical (AC) and typical carcinoid (TC) (WHO/Travis *et al.*, 2015). Small

cell lung cancer is diagnosed in 20 % of all lung cancers, followed by large cell carcinoma with neuroendocrine morphology, while the diagnosis of typical carcinoid and atypical carcinoid accounts for 2 % and 1 % of all lung cancers, respectively (International Agency for Research on Cancer, 2021).

Tumorlet carcinoids include tumours that are similar in histomorphological characteristics to carcinoids and represent the nodular proliferation of hyperplastic neuroendocrine cells that is smaller than 5 mm in size (Hage *et al.*, 2003). Hereby, we reported the unusual finding of tumour carcinoid and endobronchial hamartoma in the same bronchus.

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## CASE REPORT

A 49-year-old male patient with symptoms of prolonged severe cough and fever, and was treated for pneumonia. Since he did not adequately respond to antibiotic therapy lung CT scan was performed. CT scan showed middle lobe bronchus obstruction and complete atelectasis of the parenchyma. A bronchoscopy revealed lobulated whitish tumour which was biopsied. On histology exam, there were fragments of tumour tissue composed of portions of hyaline cartilage, adipose tissue and myxomatous altered connective tissue, surrounded with respiratory epithelium (Fig. 1A-C). The final diagnosis was endobronchial hamartoma.

Whereas the tumor could not be completely removed during bronchoscopy, it was decided to surgically remove it. The cardiovascular status was normal, and from the

cardiovascular point of view, there were no contraindications for the planned operation. After appropriate preoperative preparation of the patient, thoracotomy was performed. After resection of the bronchus for the middle lobe, endoluminal tumour was verified and completely extracted and sent for pathohistological analysis. The specimen measured 1.7x1.4x1 cm in diameter and histologically corresponded to the previously diagnosed endobronchial hamartoma. During further operative work, a significant amount of pus content was expelled from the bronchus for the middle lobe. After interventional bronchoscopy, it was concluded that the bronchus for the middle lobe is passable, but the middle lobe does not inflate. Due to that situation, the operator decides to perform a lobectomy.

On gross examinations of the surgical specimen the pleura was thin, shiny and smooth, and the lung parenchyma of markedly reduced airiness. On serial sections, there was

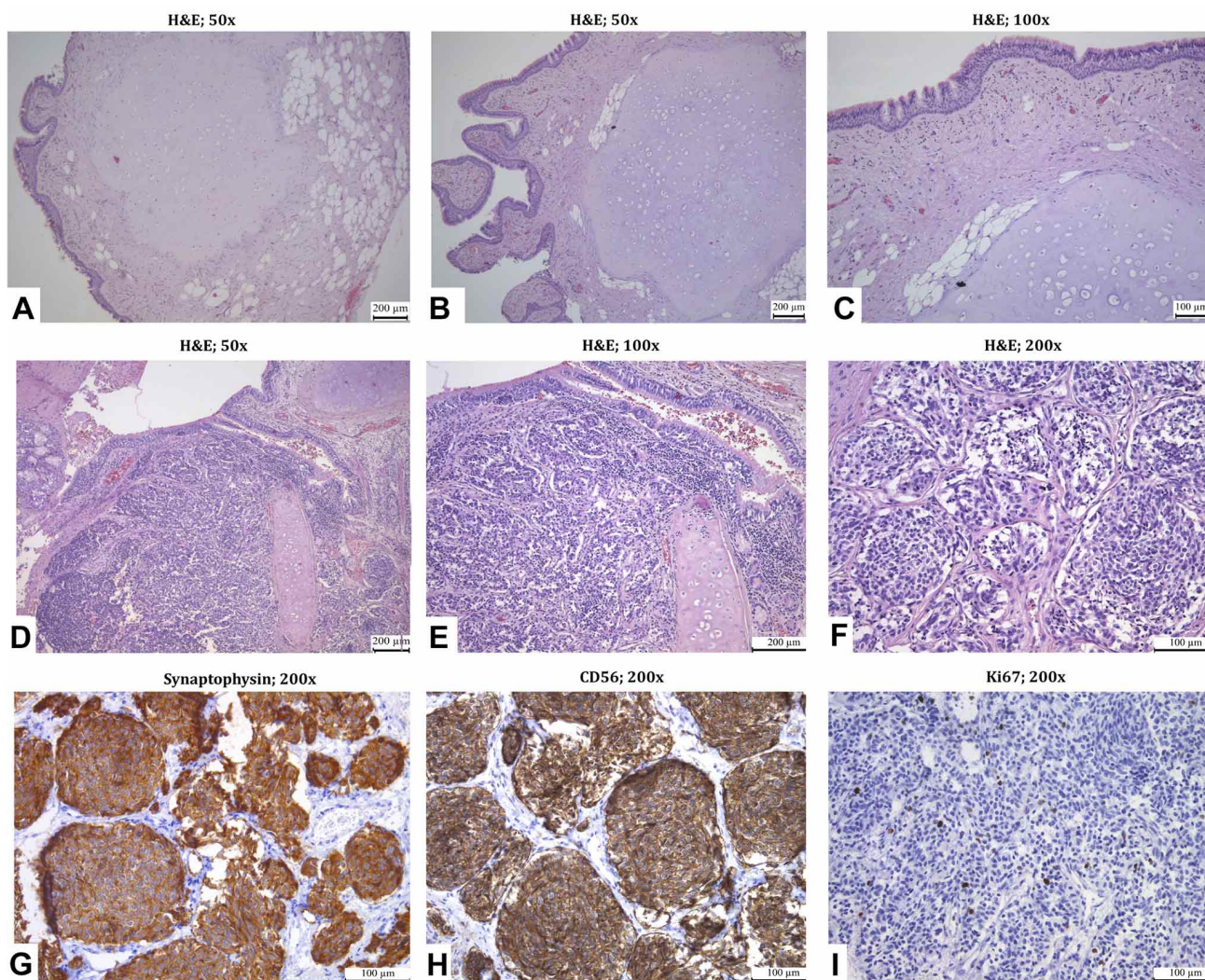


Fig. 1. Photomicrograph of endobronchial hamartoma and tumourlet carcinoid: A-C) Histological structure of a hamartoma diagnosed in the bronchus for the middle lobe; D-I) Histological and immunohistochemical characteristics of tumourlet carcinoid.



no tumour in the lumen of the bronchus for the middle lobe (it was completely removed at the beginning of the surgical procedure), while an oval yellowish area with a diameter of 3 mm was found along the bronchial wall. Histological specimens showed tumour consisted of round and polygonal cells with eosinophilic cytoplasm and round to oval nuclei with "salt and pepper" chromatin. No necrosis and no mitosis was evident (Fig. 1 D-F). Immunohistochemically tumour cells were positive for CD56 and synaptophysin, and Ki-67 levels were <1 % (Fig. 1 G-I). According to gross and histomorphological characteristics and immunophenotype of tumour cells, the diagnosis of carcinoid tumour was determined.

## DISCUSSION

Neuroendocrine tumors can be found in: thymus, lungs, trachea, gallbladder, pancreas, small and large intestine. They arise from the proliferation of neuroendocrine cells, and the largest number is diagnosed in the small intestine (about 30 %), and then in the lungs, where they occupy a share of about 25 % (Taal & Visser, 2004; Bertino *et al.*, 2009).

The histological characteristic of the respiratory epithelium, which lines the airways, is the existence of neuroendocrine cells (known as Kulchitsky cells). Neuroendocrine cells within the epithelium can be found singly or in the form of smaller intraepithelial structures, ie groups of 4 to 10 neuroendocrine cells. Thus grouped cells represent neuroepithelial bodies. According to histomorphological characteristics, neuroendocrine cells are similar to basal cells, and at the electron microscopic level, the cytoplasm of these cells is filled with numerous granules, the content of which may consist of biogenic amines and peptide hormones (Linnoila, 2006).

According to Travis' classification, the proliferation of neuroendocrine cells can be in the form of: diffuse idiopathic neuroendocrine hyperplasia, tumorlet-type carcinoids and typical and atypical carcinoids (International Agency for Research on Cancer, 2021).

Tumorlet carcinoids represent peribronchial nodular proliferation of neuroendocrine cells of the airway mucosal

epithelium, which is smaller than 5 mm in size (Vuitch *et al.*, 1997). They have the same histomorphological characteristics as typical carcinoids, and size is the only criterion that separates them (tumors over 5 mm are considered typical carcinoids). Carcinoids (typical, atypical and tumorlet) are characterized by an organoid growth component (cells are arranged in rosettes, trabeculae, ribbons, nodular nests or are arranged palisade). Tumor cells are, as in the described case, round and polygonal in shape, eosinophilic cytoplasm, round, regular nuclei whose chromatin is granulated - looks like "salt and pepper" (Fig. 1 A-C).

These neoplasms, due to their neuroendocrine origin, show diffuse and strong positivity to immunohistochemical markers: synaptophysin, chromogranin A, neuronspecific enolase, CD56 (Aslan *et al.*, 2005). In the present case, antibodies to synaptophysin and CD56 were applied, and the described tumor cells showed strong positive staining for both markers (Fig. 1 G-H).

In last, 5th WHO classification of Thoracic tumors role of Ki67 proliferative index in lung neuroendocrine neoplasm (NENs) is discussed. Numerous studies have shown that the Ki67 proliferative index in the classification and diagnosis of TC and AC cannot be consistently applied. As some of the reasons are given different staining methodology and interpretation of Ki67 proliferative index, difficult determination of cut off points, indeterminate predictive and prognostic role. The major diagnostic criteria for distinguishing TC from AC on lung resection is number of mitoses per 2 mm<sup>2</sup> and presence or absence of necrosis (Table I). WHO suggest that tumors with a Ki67 proliferative index up to 5 % are TC, those with Ki67 index >5 % are AC, and those with Ki67 index >30 % are SCLC or LCNEC (Table I) (International Agency for Research on Cancer, 2021). In the presented case, Ki67 positive tumor cells were seen in small number and percentage of Ki67 positive tumor cells was 1 %.

Epidemiological studies conducted in the United States revealed an increase in the prevalence of these neoplasms from 14.6 cases per million in 2009 to 28.5 in 2014 (Broder *et al.*, 2018). Neuroendocrine tumours are most often diagnosed in Caucasians, women (in about 65 % of cases), and half of those diagnosed are between the ages of 55 and 64 (Cai *et al.*, 2016).

Table I. Diagnostic criteria for lung NENs.

	TC	AC	LCNEC	SCLC
Mitoses (per 2 mm <sup>2</sup> )	< 2	2-10	> 10	> 10
Necrosis	-	focal	+	+
Ki67	up to 5 %	up to 30 %	30-100 %	30-100 %

According to data from the literature, the occurrence of tumorlet type carcinoids is often associated with changes in the lungs in the form of fibrosis and bronchiectasis, although a clear association between the occurrence of tumorlet carcinoids and these changes has not yet been confirmed (Miller *et al.*, 1978; Dewan *et al.*, 2000). The findings of adenocarcinoma and tumorlet carcinoids in the same lobe of the lung, but without changes in the form of inflammation and fibrosis, have been presented in the literature (He *et al.*, 2012). In a patient with previously diagnosed breast cancer, bronchiectasis and the presence of tumorlet carcinoids have been demonstrated within pulmonary sequestration (Ye *et al.*, 2013). By searching the available literature, the association of the occurrence of benign changes such as hamartoma and carcinoid tumorlet has so far been described in only one case. In this case, the patient was a 65-year-old man, a former smoker with surgically treated rectal adenocarcinoma (Cavazza *et al.*, 2006). Six months after operation, CT scan revealed a subpleural nodule of a lower lobe of the right lung, 1 cm in diameter. Histopathologically the majority of the tumor had features of hamartoma, but at the periphery presented a neuroendocrine proliferation with features of typical carcinoid (TC)/tumorlet, 0.6 cm in diameter (Cavazza *et al.*, 2006).

Hamartoma with endobronchial localisation is usually symptomatic. It may present with various symptoms including chronic cough, shortness of breath, hemoptysis, chest pain and obstructive pneumonia (Cosío *et al.*, 2002). In this case, the patient is a former smoker with symptoms of chronic cough that lasts for months and fever, initially treated for pneumonia.

The treatment for endobronchial hamartoma should be individualized. Usually, bronchoscopic electrocautery resection is used, and surgical management is also legitimised particularly in lesions that could not be differentiated from malignancy (Guo *et al.*, 2008).

## CONCLUSION

Pathohistological diagnosis of carcinoids of the tumorlet type is usually an accidental finding. Since these neoplasms show an increase in prevalence, that can be seen on CT in the form of subcentimeter, single or multiple, nodular changes, as well as that the clinical picture is nonspecific, they should always be kept in mind as a possible differential diagnosis. During the pathohistological examination of the material, it is necessary to pay special attention to them, because they are histomorphologically identical to typical carcinoids, and the size of the change is the only criterion that separates them at the moment.

**POPOVIC, M.; TEGELTIJA, D.; POPOVIC, A.; KASIKOVIC LECIC, S. & LOVRENSKI, A.** Hallazgo inusual de tumorlet pulmonar carcinoides y hamartoma endobronquial en el bronquio lobar. *Int. J. Morphol.*, 40(4):991-994, 2022.

**RESUMEN:** Los tumores neuroendocrinos de pulmón son un grupo de tumores de diferentes características morfológicas, inmunohistoquímicas y moleculares similares, y representan el 1-2 % de todos los tumores malignos de pulmón. Los carcinoides tumorales representan la proliferación nodular de células neuroendocrinas hiperplásicas de tamaño inferior a 5 mm. En este estudio reportamos el hallazgo inusual de tumor carcinoides y hamartoma endobronquial en el mismo bronquio. Un paciente varón de 49 años con síntomas de tos severa prolongada y fiebre fue tratado por neumonía. Al no responder adecuadamente a la terapia con antibióticos, se realizó una tomografía computarizada de pulmón que mostró obstrucción del bronquio del lóbulo medio. La broncoscopia reveló una tumoración blanquecina lobulada de la cual se tomó biopsia y el diagnóstico histopatológico fue hamartoma. No fue posible extirpar el tumor por completo durante la broncoscopia y se decidió extirparlo quirúrgicamente. En la sección seriada, durante el examen macroscópico en el mismo bronquio, se encontró un área amarillenta ovalada de 3 mm de diámetro a lo largo de la pared bronquial. De acuerdo a las características macroscópicas e histomorfológicas y de inmunofenotipo de las células tumorales, se estableció el diagnóstico de tumor carcinoides. El diagnóstico de carcinoides de tipo tumorlet suele ser un hallazgo accidental y se observan en la TC en forma de cambios nodulares subcentimétricos, únicos o múltiples. En consideración de que el cuadro clínico es inespecífico, siempre debe tenerse en cuenta como posible diagnóstico diferencial.

**PALABRAS CLAVE: Tumorlet carcinoides; Bronquio; Hamartoma pulmonar.**

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