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Case Report
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First Description of an Enteric-Type Adenocarcinoma with a High-Grade Neuroendocrine Component of the Lung

*Irene Moya-Horno[1], Rodolfo Posada[2], Clara Mayo[3], Miguel Ángel Molina[3], María Teresa Fernández-Figueras[2,4], Manel Esteller[5,6,7,8] and Eva Musulén[2,5]**

[1]Department of Medical Oncology, Instituto Oncológico Dr Rosell, Hospital Universitari General de Catalunya Grupo Quironsalud, Barcelona, Spain

[2]Department of Pathology, Hospital Universitari General de Catalunya-Grupo Quironsalud, Sant Cugat del Vallès, Barcelona, Spain

[3]Laboratory of Oncology, Pangaea Oncology, Hospital Universitari Quirón Dexeus, Barcelona, Spain

[4]Universitat Internacional de Catalunya (UIC), Sant Cugat del Vallès, Barcelona, Spain

[5]Josep Carreras Leukaemia Research Institute (IJC), Badalona, Barcelona, Spain

[6]Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain

[7]Physiological Sciences Department, School of Medicine and Health Sciences, University of Barcelona (UB), Barcelona, Spain

[8]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain

Abstract

Background: Pulmonary Enteric-type Adenocarcinoma (PEAC) is a rare variant of Non-Small Cell Lung Cancer (NSCLC) characterized by similar morphology and immunohistochemical expression to primary colon adenocarcinoma.

Case Report: A 58-year-old smoker female was submitted to a complete lobectomy due to a mass without lymph node involvement. The resected tumor was a PEAC with a biphasic histologic morphology with one component of glands with a cribriform and acinar pattern with luminal necrosis, and the other component with cells with eosinophilic or clear cytoplasm and round nuclei with prominent nucleoli appearing in a solid growth pattern. The gland cells expressed markers of lung and enteric differentiation such as TTF-1, Cytokeratin 20 (CK20), and CDX2, while the solid component cells showed expression of CK20 and synaptophysin with a Ki-67 proliferation index of 65% defining them as a high-grade Neuroendocrine Carcinoma (NEC). The neoplasm metastasized first to the left clavicle and rapidly spread to multiple bones, cerebellum and pancreas at the expense of the NEC component resulting in the patient's death twelve months after diagnosis of the lung neoplasm. Both PEAC and clavicle tumor shared *KRAS* p.G12V and *TP53* c.375+1G>C mutations but CDK6 amplification, a frequent genetic alteration of neuroendocrine differentiation, was only found at the metastasis.

Conclusion: We describe in this study the first case of Pulmonary Enteric-type Mixed Adenoneuroendocrine Carcinoma (PEMANEC) in analogy to colon neoplasms, where an adenocarcinoma with a high-grade neuroendocrine component is defined as a Mixed Adenoneuroendocrine Carcinoma (MANEC).

Keywords: Pulmonary enteric-type adenocarcinoma; Neuroendocrine carcinoma; Pulmonary enteric-type mixed adenoneuroendocrine carcinoma

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Correspondence:
Eva Musulén, Department of Pathology, Hospital Universitari General de Catalunya-Grupo Quironsalud, Sant Cugat del Vallès, Josep Carreras Leukaemia Research Institute (IJC), Badalona, Barcelona, Spain, E-mail: eva.musulen@quironsalud.es

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Introduction

Pulmonary Enteric-type Adenocarcinoma (PEAC) is a rare variant of Non-Small Cell Lung Cancer (NSCLC) with almost 300 cases described [1,2]. First described in 1991 by Tsao and Fraser [3], PEAC is defined as an adenocarcinoma that resembles the adenocarcinoma arising in the colorectum in ≥ 50% of tumor, with expression of at last one intestinal marker such as Caudal-type homeobox 2 (CDX2) and/or Cytokeratin 20 (CK20), HNF4α, or MUC2, and clinical exclusion of metastatic CRC (mCRC) [4].

We report a PEAC with a component of high-grade Neuroendocrine Carcinoma (NEC) that rapidly spread to multiple locations conferring to the tumor a very aggressive and lethal course.

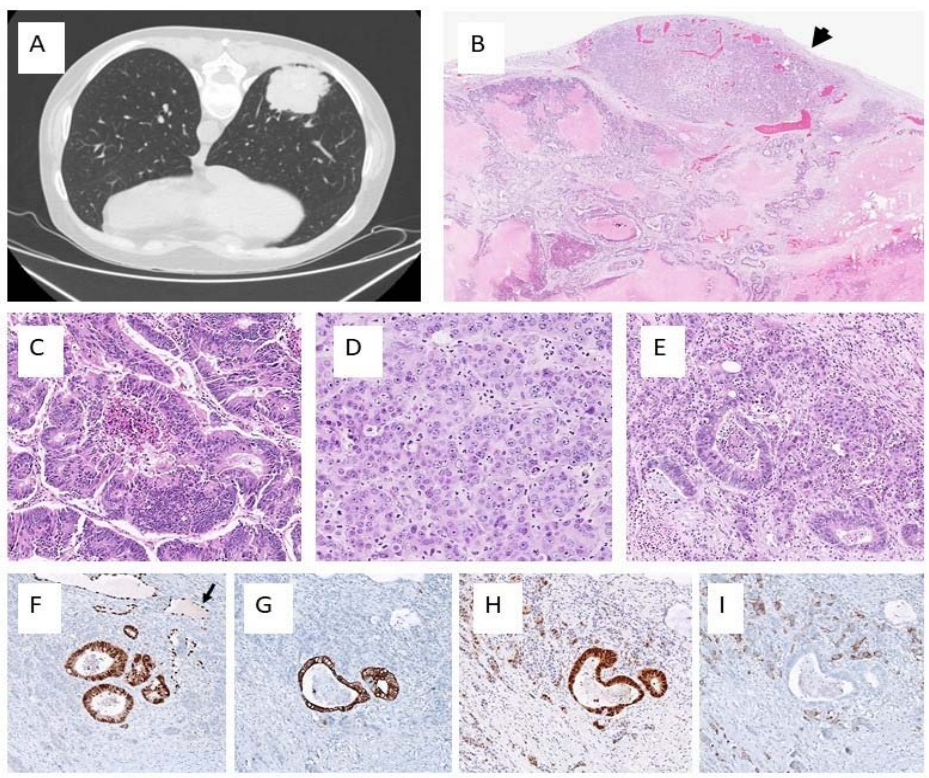

Figure 1: CT image, microscopic appearance and immunohistochemical profile of the lung neoplasm. A) Peripheral lung mass in the right upper lobe on chest CT before transthoracic biopsy. B) The tumor was mostly composed of glands with extensive necrosis but in some areas there was solid growth (arrowhead). C) The glands showed a cribriform pattern with dirty necrosis in the lumen. D) In the poorly differentiated areas the cells showed an eosinophilic cytoplasm and a round nucleus with prominent nucleolus. E) In some sections the two components were merged. F) TTF-1 was expressed in neoplastic glands and in some residual lung parenchymal cells that served as a positive internal control (arrow). G) CK20 was only expressed in glandular cells. H) CDX2 was diffusely expressed in the glandular component and only a few positive nuclei were present among the cells of the solid clusters. I) Synaptophysin was only positive in the high-grade neuroendocrine component.

In CRC a mixed adenocarcinoma that shows a NEC component is designed as Mixed Adenoneuroendocrine Carcinoma (MANEC) now under the umbrella category of MiNENs (Mixed Neuroendocrine-non-Neuroendocrine Neoplasms) in the last WHO classification of digestive system tumors [5]. Compared with CRC, MANEC is an aggressive neoplasm with poorer outcomes. Median overall survival of colorectal MANEC is around one year and depends on stage and Ki-67 proliferation index.

Although in other lung cancers such as in high-grade fetal adenocarcinoma, a combination with NEC has been reported in around 20% of cases [6-8], to the best of our knowledge, this is the first time that a NEC component is described in a PEAC.

Therapeutic strategies for PEAC essentially derive from recommendations for the treatment of lung adenocarcinoma as NSCLC and specific guidance is lacking. Oncogenic driver mutations in PEAC have been reported in case reports and small case series, being the *KRAS* mutation the most frequently detected in these tumors [9-18]. Wide use of Next Generation Sequencing (NGS) may reveal molecular signatures of PEAC to guide treatment options [15,17,19].

Herein we report a PEAC with a NEC component as the first primary PEMANEC of the lung.

Case Presentation

A 58-year-old smoker female with family history of colorectal adenomas was referred to hospital with shortness of breath and cough for over two months. Past medical history was remarkable for dyslipidemia and endoscopic removal of a left CRC with sub mucosal invasion (pT1) with low-grade histology, no lymphovascular invasion and negative margins five years ago. Chest X-ray and contrast-enhanced Computed Tomography (CT) showed a peripheral lung mass in the right upper lobe without mediastinal lymph node involvement. On Positron Emission Tomography (PET)-CT, the mass presented as a unique lobulated lesion measuring 46 mm × 59 mm and high 18F-FDG uptake. A percutaneous transthoracic CT-guided core biopsy of the mass resulted non-conclusive due to necrosis (Figure 1). The patient underwent thoracic surgery and a complete lobectomy with mediastinal lymph node dissection was performed.

Lobectomy showed a 10 cm tumor with pleural retraction. On section, the tumor was poorly demarcated and with extensive necrosis. Microscopically, the neoplasm presented a biphasic histologic morphology with a component of glands in a cribriform pattern with dirty luminal necrosis and other poorly differentiated component having cells with eosinophilic or clear cytoplasm and round nuclei with prominent nucleoli appearing in a solid growth pattern (Figure 1). In some sections these solid nests merged with the glands. No lymphovascular or perineural invasion was identified and the visceral pleura was not infiltrated. Neoplastic gland cells showed expression for TTF-1, CK20, CDX2, and SATB2 while CK7 was negative (Figure 1 and Table 1).

Table 1: Immunohistochemical markers used for the diagnosis of the resected lung primary tumor and both the clavicle and the pancreatic metastases.

Marker	Lung		Clavicle	Pancreas
	Epithelial component	NE component		
CK7	-	-	-	-
CK20	+	-	-	-
TTF-1	+	-	-	-
Napsin A	-	-	-	-
CDX2	+	+	+	+
SATB2	+	-	-	-
Synaptophysin	-	+	+	+

Abbreviations: NE: Neuroendocrine; +: Positive; -: Negative

The diagnosis was PEAC with no mediastinal lymph node involvement, stage pT4N0 and free margins. PD-L1 expression resulted negative <1% and no microsatellite instability was observed. Analysis by NGS detected *KRAS* p.G12V (43%) and *TP53* c.375+1G>C (65%) mutations.

After a postoperative surveillance period free of complications, the patient was referred to a digestive endoscopy unit to exclude lung metastases of colorectal origin. A complete rectocolonoscopy identified a tattoo in the left colon marking previous endoscopically resected pT1 colon adenocarcinoma, with no tumor recurrence at this site on histological examination.

Patient initiated follow-up visits with a chest CT showing postoperative changes and no evidence of thoracic recurrence.

Three months later the patient consulted for a progressive swelling in the left shoulder causing pain and functional impairment. A hard fixed mass was palpable on physical exam and a Magnetic Resonance Imaging (MRI) identified soft tissue infiltration overlying a 40 mm × 37 mm in size lytic lesion of the left distal clavicle (Figure 2).

Performed core biopsy demonstrated infiltration by poorly differentiated carcinoma staining negative for TTF-1, CK20, CK7, and napsin A, and positive for CDX2 and synaptophysin (Figure 2). At that time, synaptophysin immunostaining was performed on the poorly differentiated component of PEAC, resulting positive with a Ki-67 proliferative index expression of 65%, confirming the presence of a NEC component (Figure 1 and Table 1). NGS was performed on the clavicle tumor detecting the same mutations as in PEAC, with acquisition of *CDK6* amplification (Table 2).

Table 2: NGS findings within the resected lung primary tumor and metastases.

Gene	Lung	Clavicle	Pancreas
KRAS G12V	+	+	NP
TP53 c.375+1G>C	+	+	NP
CDK6 amplification	-	+	NP

Abbreviations: +: Positive; -: Negative; NP: Not Performed

At this point, workup with body CT, bone scintigraphy, PET-CT and brain MRI revealed coexisting metastasis in the left cerebellum and in many other bone structures. A pancreatic mass with locoregional lymph node spread was also detected (Figure 2). There was no evidence of disease recurrence in lung and blood levels of tumor markers CEA and CA19-9 were not raised. Pancreatic tissue biopsy obtained by endoscopic ultrasound-guided fine needle aspiration confirmed malignant infiltration by poorly differentiated carcinoma, with an immunohistochemical profile comparable to the clavicle metastasis (Figure 2), supporting the diagnosis of bone and pancreatic metastatic PEAC at the expense of NEC component (Table 1).

The patient underwent brain stereotactic radiosurgery and left shoulder radiotherapy for antalgic purpose. Platinum-based chemotherapy with pemetrexed in combination with pembrolizumab was also initiated. The evaluation of tumor response after the first two cycles of chemoimmunotherapy was consistent with progressive disease with clinically relevant abdominal pain caused by larger involvement of peripancreatic lymph node metastasis. Given the poor performance status, the patient was offered best supportive care alone. Death occurred twelve months after the detection of the lung tumor.

Discussion

PEAC is a rare entity of NSCLC whose diagnosis implies the exclusion of a mCRC. The patient we presented had a low-grade pT1 CRC resected endoscopically five years prior to the appearance of

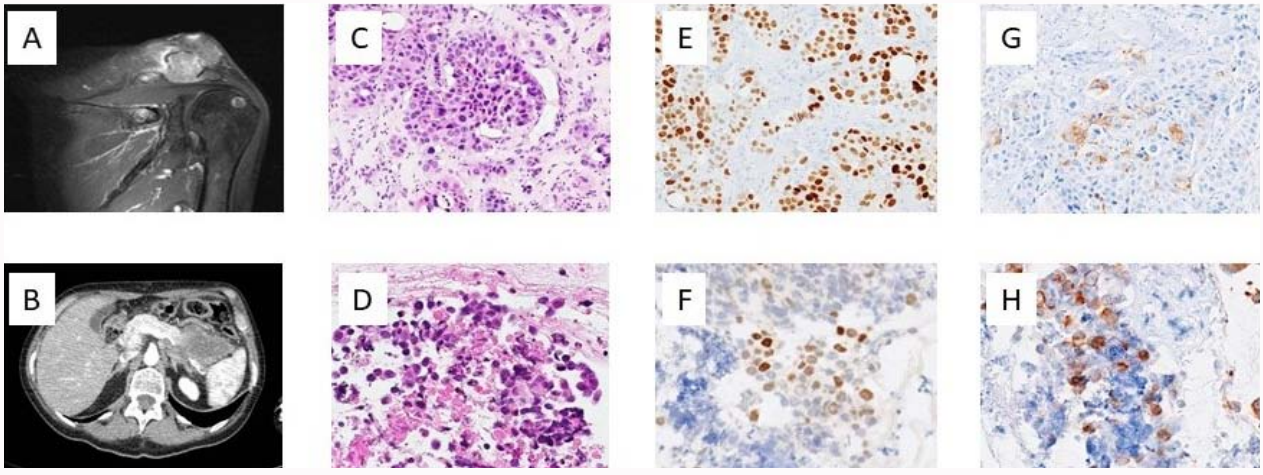

Figure 2: Radiologic and histological findings of clavicle and pancreatic metastasis. A) MRI showing left distal clavicle metastasis with soft tissue infiltration. Additionally, a benign cystic lesion in the humeral head is noted. B) Abdomen CT showed a pancreatic mass with locoregional lymph node metastasis. C, D) Tumor cells from both the clavicle and the pancreas tumors showed similar histological characteristics. E, F) Similar CDX2 immunoexpression was observed in the metastasis. G, H) Synaptophysin was positive in tumor cells of the clavicle and pancreas metastasis.

the pulmonary tumor. However, the possibility of mRCC to the lung was ruled out due to the absence of histologically confirmed local recurrence and the absence of other distant lesions.

For the diagnosis of PEAC it is recommended to use an immunohistochemical panel including pulmonary and enteric markers and that at least one of the enteric is positive among CDX2, CK20, HNF4α, or MUC2 and desirably with co-expression of TTF1 or CK7 [4]. Our case was positive for TTF-1, CK20, and CDX2. Although CK7 characterizes lung cells and is the most frequently expressed marker in PEAC [9,10,12-19], in our case it was negative like other reported cases [20,21]. In addition, other new markers such as cadherin-17, SATB2, and β-catenin have proven useful in the differential diagnosis between PEAC and mCRC [12,18]. In particular, SATB2 has been very effective in recognizing mCRC among lung adenocarcinomas [22]. We found that expression of the enteric marker CDX2 was observed in both glandular and NEC components, whereas SATB2 was expressed only in the epithelial component. This is consistent with current knowledge on SATB2 expression in neuroendocrine tumors: Intense SATB2 expression is observed in well-differentiated neuroendocrine tumors of the lower gastrointestinal tract but among NEC it is only strongly expressed in Merkel's carcinoma [23]. Recently, other methods such as DNA methylation profiling have been proven to be a powerful tool to distinguish PEAC from mCRC [14].

To the best of our knowledge, a NEC within a PEAC has not been previously described in the literature. Among other rare related cases reported we have found a rare case of CK7/CK20 negative PEAC with transformation to a conventional pulmonary carcinoma [24]. Considering that in CRC the presence of two cell lines, one glandular and the other NE, defines a MANEC, we have estimated the diagnosis of PEMANEC of the lung for the present neoplasm.

Currently, no specific recommendations for the treatment of PEAC exist, even less in the context of a NEC component as in our case. NGS can provide a better understanding of the molecular landscape of PEAC and serve as a guiding tool for treatment selection [16,18,20]. As PEAC is histologically regarded as a lung adenocarcinoma, treatment options apply as for non-squamous NSCLC. In the metastatic setting without an actionable oncogenic driver, first-line treatment with platinum-based doublet chemotherapy in combination with immunotherapy should be considered [25].

KRAS mutations are detected in 40% to 50% of PEACs, being the most frequent molecular alteration in these tumors, associated with tobacco use [26] and shorter survival [27]. Recently sotorasib has shown anticancer activity in patients with previously treated *KRAS* p.G12C-mutated NSCLC [28]. The fact that the tumor showed *CDK6* amplification in metastatic progression could open new therapeutic opportunities. *CDK4/6* inhibitor therapies have shown antitumor activity in hormone receptor-negative HER2-negative advanced metastatic breast cancer and are already approved by the FDA in this setting [29]. The role of cyclin inhibitors in patients with *CDK4/6*-amplified lung cancer remains an area of investigation.

Prognosis of PEAC is dismal and survival rates for stage IV disease treated with chemotherapy range from 2 to 12 months [1]. Our particular case followed an aggressive behavior with distant metastasis at 3 months and the patient's death occurred 12 months after the diagnosis of the lung tumor.

Conclusion

We report the first description of a PEMANEC applying the same criteria as in CRC, where the presence of two cell lines in a neoplasm, one glandular and the other neuroendocrine, defines a MANEC.

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