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Case report

Mixed mucoepidermoid carcinoma and adenocarcinoma of the lung: Two cases with unusual histologic features

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ABSTRACT

We herein report two cases of non-small cell lung cancer with unusual histologic patterns, comprising mixed mucoepidermoid carcinoma and adenocarcinoma. Both cases presented identical genetic mutations in each histologic component of the tumor; specifically, one case possessed an ALK-rearrangement and the other case presented a deletion in exon 19 of the *EGFR* gene. The two current cases, as well as an additional case that we previously reported, were all identified as being a specific type of mixed lung cancer with driver mutations typically encountered in conventional lung adenocarcinomas. Our findings support the supposition that different histological components in mixed-histology lung cancer are clonally related. Accordingly, extensive tissue sampling is necessary to avoid overlooking minor adenocarcinomatous components, as patients with mixed lung cancer could potentially benefit from treatment with tyrosine kinase inhibitors.

1. Introduction

Lung cancer is the leading cause of cancer-related mortality in the world. Mutations in epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) genes are routinely tested to identify lung adenocarcinoma patients who could benefit from treatment with target therapies, such as tyrosine kinase inhibitors (TKIs). Specifically, guidelines outlined by the College of American Pathologists recommend that *EGFR* and *ALK* tests be conducted on patients with adenocarcinomas or mixed lung cancers that include an adenocarcinomatous component [1]. We previously reported a case of mixed mucoepidermoid carcinoma (MEC) and adenocarcinoma of the lung with identical *EGFR* mutations in both histologic components [2]. In this paper, we report two additional cases of this specific mixed lung cancer presenting *ALK* and *EGFR* mutations, respectively.

2. Case report

2.1. Case 1

A 43-year-old woman was experiencing chronic cough for a period of six months. Chest X-rays and computed tomography (CT) scans revealed a single 3 cm mass in the left hilum, involving the upper and lower lobes. A bronchoscopic biopsy revealed an adenocarcinoma with extracellular mucin production. Following neoadjuvant chemotherapy using gemcitabine and cisplatin, the patient underwent left pneumonectomy and systemic lymph node dissection. Pathologic examination revealed a mixed mucoepidermoid carcinoma and adenocarcinoma of the lung in a pathologic stage pT2N0M0, stage IB. Microscopically, the bronchus was occupied by a typical MEC, comprising a mixture of mucin-producing cells, intermediate cells, and epidermoid cells (Fig. 1A). The MEC stained negative for TTF-1 and napsin-A, while epidermoid cells were immunoreactive to p63 and p40 (Fig. 1A and C). No keratinizing squamous cell carcinoma (SCC) component was found. A minor adenocarcinomatous component found adjacent to the MEC presented a predominant acinar pattern, abundant mucin production, and immunoreactivity to TTF-1 and napsin-A (Fig. 1B). Seven years after the first operation, the patient developed new symptoms involving abdominal pain and elevated serum carcinoembryonic antigen. Abdominal CT scans revealed a single 3 cm pancreatic tumor with para-aortic lymphadenopathy.

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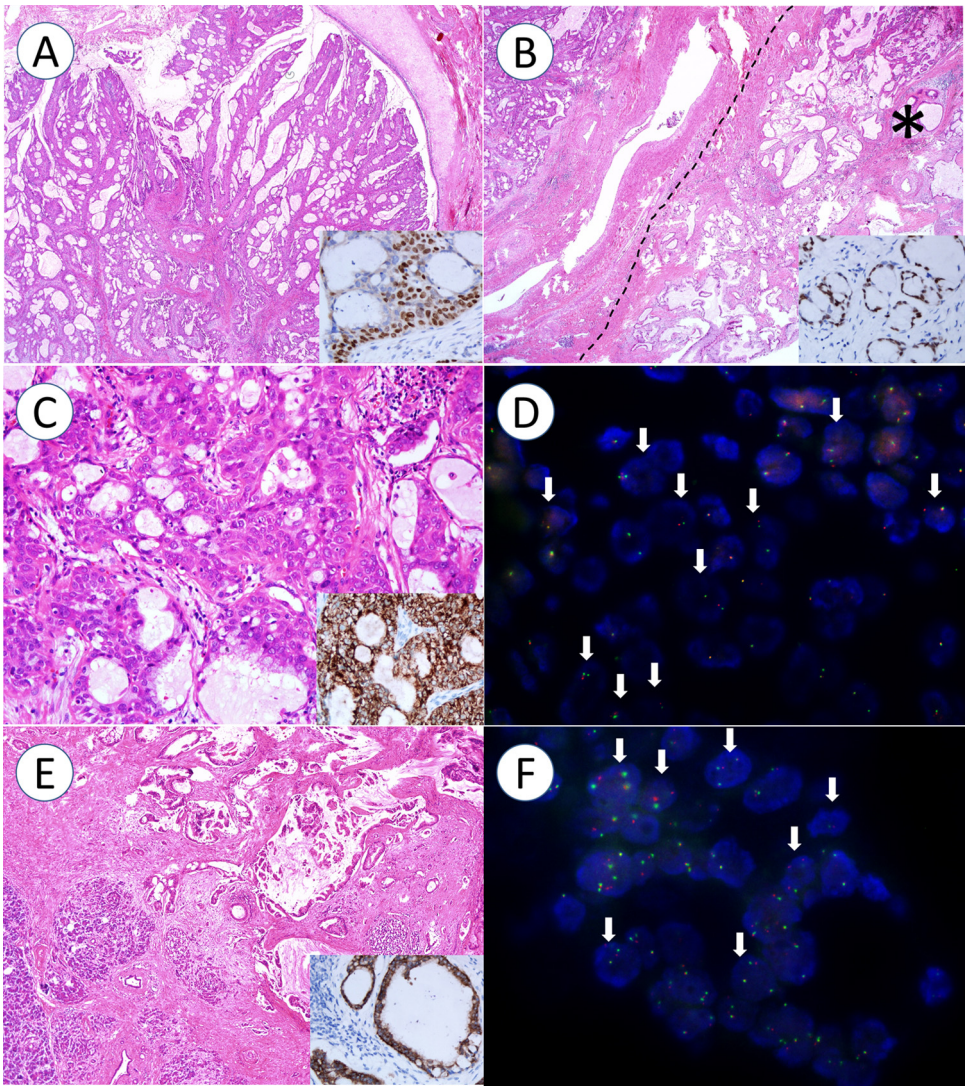

Fig. 1. Case 1 (A) MEC component in the bronchus (original magnification 20×) showing mixed papillary and cystic structures (inset: p40+ epithelioid cells, original magnification 200×); (B) adenocarcinoma (*) found adjacent to the MEC (original magnification 20×) with immunoreactivity to TTF-1 (inset, original magnification 200×); (C) MEC showing mixed mucus-secreting, intermediate, epithelioid cells, and immunoreactivity to ALK (inset, original magnification 200×); (D) *ALK* rearrangement in the major MEC part of primary lung tumor confirmed by FISH showing separated red and green signals (arrows) (original magnification 1000×); (E) Pancreatic metastatic carcinoma presenting an adenocarcinoma without MEC (original magnification 40×) and immunoreactivity to ALK (inset, original magnification 200×); (F) ALK FISH showing separated red and green signals (arrows) in pancreatic metastatic adenocarcinoma (original magnification 1000×). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The patient thus underwent distal pancreatectomy to excise the tumor. Subsequent pathologic examination revealed a metastatic adenocarcinoma with a predominant acinar pattern, abundant mucin production, and immunoreactive to TTF-1 (Fig. 1E). No MEC component was found at the metastatic site. These findings are consistent with metastatic lung adenocarcinoma. Paraffin sections were used for genomic DNA isolation and mutation analysis. Areas containing adenocarcinomatous and MEC components were carefully separated by manual microdissection. No classical mutations in *EGFR*, *KRAS*, or *BRAF* genes were identified in either the adenocarcinoma or the MEC. ALK (D5F3, Ventana, Tucson, AZ) immunohistochemical staining showed both primary lung cancer (MEC and adenocarcinoma) and pancreatic metastatic adenocarcinoma exhibiting strong, diffuse cytoplasmic granular stains (Fig. 1C and E); *ALK* rearrangement was further confirmed by fluorescence in situ hybridization (FISH) using Vysis LSI ALK Break Apart Rearrangement Probe Kit (Abbott Molecular Inc., Des Plaines, IL) (Fig. 1D and F).

2.2. Case 2

A 71-year-old woman underwent a health examination, and chest X-rays found a mass in the right lower lobe. CT scans revealed a 2.1 cm mass with speculated margins, and a CT-guided biopsy identified this as an adenocarcinoma. The patient underwent a right lower lobe lobectomy and systemic lymph node dissection. Pathologic examination revealed a mixed MEC and adenocarcinoma (Fig. 2A). The MEC showed papillary and cystic structures involving the bronchus and its small branches, but no keratinizing SCC component. Immunohistochemical analysis revealed that MEC was negative for TTF-1/napsin-A and that epidermoid cells were immunoreactive to p63/p40 (Fig. 2B). The adenocarcinomatous component showed a predominant acinar pattern and immunoreactivity to TTF-1 (Fig. 2C). Lobar lymph nodes were invaded directly by the MEC and the adenocarcinoma. The pathologic stage was pT1bN1M0, stage IIA. Paraffin sections were used for mutation analysis, and areas containing adenocarcinomatous and