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Case Report

Double the trouble: pulmonary enteric adenocarcinoma with synchronous contralateral pulmonary adenocarcinoma

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Abstract

Pulmonary enteric adenocarcinoma (PEAC) is a rare subtype of non-small cell lung cancer with morphological and immunohistochemical features that are nearly indistinguishable from those of metastatic colorectal carcinoma. Owing to these overlapping features, diagnosis and treatment of PEAC can present a clinical challenge. We report the case of a 78-year-old man with synchronously diagnosed locally advanced pulmonary adenocarcinoma of the left lower lobe and localized right lower lobe PEAC. These malignancies exhibited distinct tumor molecular profiles and differed in their kinetic response to chemoimmunotherapy. We describe plausible mechanisms by which two distinct pulmonary malignancies are present in the contralateral lobes. To the best of our knowledge, this is the first reported case of synchronous invasive pulmonary adenocarcinoma and PEAC.

Keywords: pulmonary enteric adenocarcinoma; enteric features; adenocarcinoma; contralateral; colorectal; synchronous

Introduction

Pulmonary enteric adenocarcinoma (PEAC) is a rare subtype of non-small cell lung cancer (NSCLC) characterized by histopathological features that mimic colorectal adenocarcinoma [1]. The World Health Organization criteria for PEAC include: (1) a predominant (>50%) histologic enteric morphology, (2) expression of at least one intestinal tumor marker such as cytokeratin (CK) 20, caudal-type homeobox (CDX) 2, or mucin 2, and (3) exclusion of primary colorectal malignancy [2]. With features nearly indistinguishable from lung metastatic colorectal carcinoma, PEAC can be challenging to diagnose. The optimal treatment regimen for PEAC has not been established, but many clinicians follow principles for treating more common NSCLC variants [3].

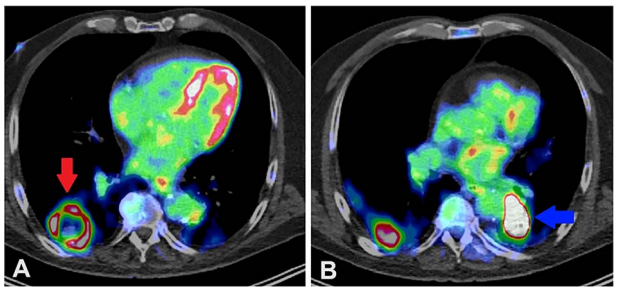

Figure 1. Whole body positron emission tomography (PET) imaging showing 4.6 × 4.6 cm right lower lobe spiculated mass with max standard uptake value (SUV) of 7.1 and central necrosis (panel A, arrow). On the left lobe, there is a 4.8 × 2.7 cm spiculated mass with max SUV of 17.6 that abuts the descending thoracic aorta (panel B, arrow). Of note, there is no increased lymph node or gastrointestinal avidity reported in this study.

Case report

The patient was a 78-year-old male smoker (half-pack per day for 50 years) who presented with progressive cough, dyspnea, and hemoptysis. Computed tomography (CT) and whole-body positron emission tomography (PET) imaging revealed 4.6 × 4.8 cm right lower lobe (RLL) and 4.8 × 2.7 cm left lower lobe (LLL) spiculated masses with increased avidity (Fig. 1). Axillary and mediastinal lymph nodes, including subcarinal nodes, were normal in size and avidity. CT-guided percutaneous core needle biopsy of the RLL mass was performed. Histopathological examination revealed an invasive adenocarcinoma composed of acini lined with tall columnar epithelium with focal cribiforming and luminal necrosis (Fig. 2A). These cells were strongly reactive with CK-20 and CDX-2, moderately reactive with CK-7, and nonreactive with thyroid transcription factor (TTF)-1/napsin-A, which was concerning for gastrointestinal metastasis (Fig. 2B-E). Further evaluation

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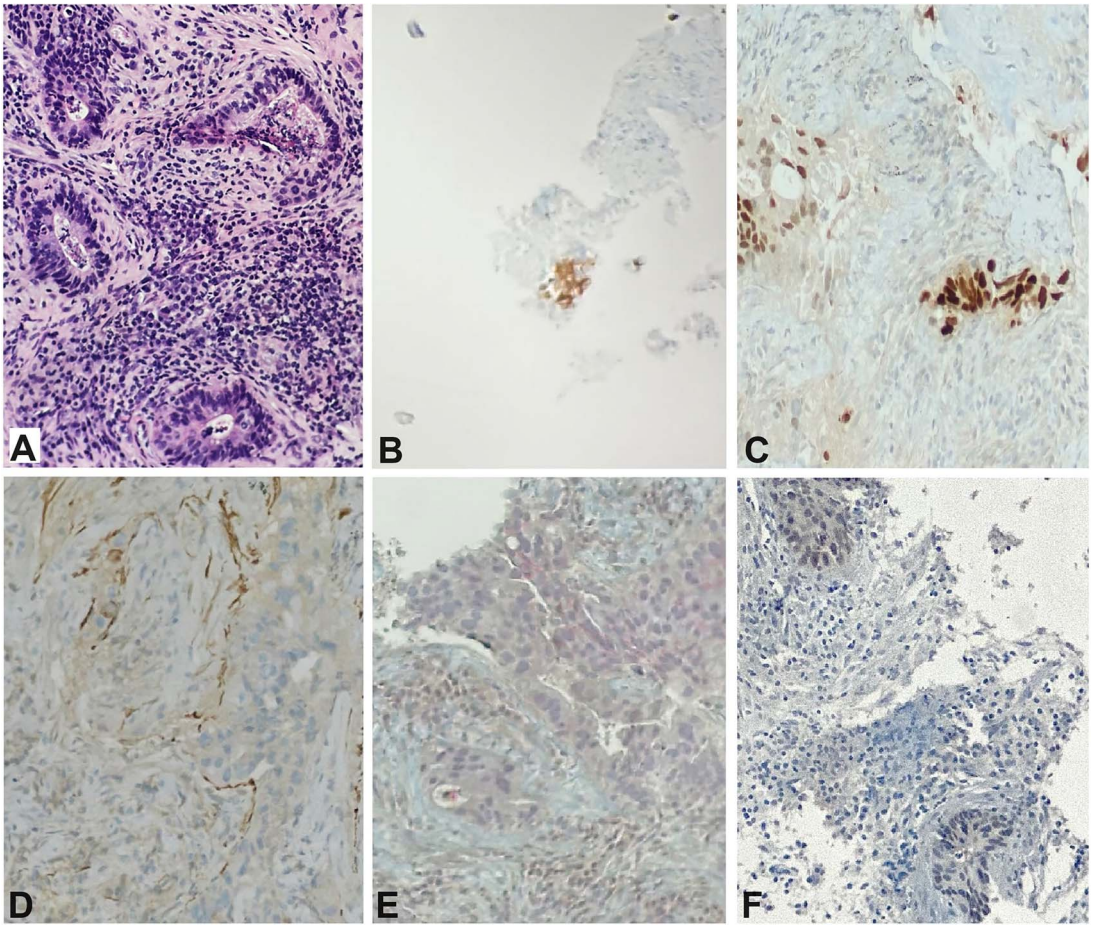

Figure 2. Histopathological specimen of 0.4 cm × 0.1 cm right lower lobe lesion obtained by CT-guided percutaneous core needle biopsy. Hematoxylin and eosin stain at 200x magnification shows invasive adenocarcinoma composed of acini lined by tall columnar epithelium with focal cribiforming and luminal necrosis (A). Immunohistochemical staining at 200x was strongly reactive with CK-20 (B), CDX-2 (C), and moderately reactive with CK-7 (D). Notably, the RLL mass was also nonreactive with TTF-1/napsin-a dual stain (E) and SATB2 (F). These findings were consistent with a diagnosis of pulmonary enteric adenocarcinoma.

with esophagogastroduodenoscopy, colonoscopy, and whole-body PET was unrevealing for gastrointestinal primary. Special AT-rich sequence-binding protein 2 (SATB2) staining of the RLL mass was also nonreactive (Fig. 2F).

Endobronchial ultrasound (EBUS) was subsequently performed to complete mediastinal staging, which demonstrated a concerning level 7 subcarinal lymph node that had previously been undetected on CT/PET imaging. Transbronchial needle aspiration was performed on the LLL mass and the level 7 lymph node. Histopathological examination of both specimens revealed neoplastic cells with abundant cytoplasm and large hyperchromatic nuclei with prominent nucleoli (Fig. 3A). In contrast to the RLL, these cells were immunoreactive to TTF-1/napsin-A, and nonreactive to p40 and p63 antibodies, indicating a primary conventional lung adenocarcinoma (Fig. 3B). Next-generation sequencing (NGS) also revealed discordant profiles. The RLL mass had an intermediate tumor mutational burden (19 mutations/Mb), programmed death ligand-1 (PD-L1) tumor proportion score of 0%, KRAS wild type, and mutations in CDKN2A, NOTCH1, and TP53. NGS of the LLL adenocarcinoma demonstrated EGFR amplification, an intermediate tumor mutational burden (11 mutations/Mb), loss of CDKN2A/B, and mutations in RBM10 and TP53.

After completion of mediastinal staging, the patient was diagnosed with pulmonary enteric adenocarcinoma of the right lobe (T2bN0M0) and conventional adenocarcinoma of the left lobe (T2bN2M0). He received palliative intent chemoimmunotherapy with carboplatin, pemetrexed, and pembrolizumab leading to complete response of the RLL PEAC (Fig. 4) and a partial response of the LLL adenocarcinoma (Fig. 5) at 6 months post-diagnosis.

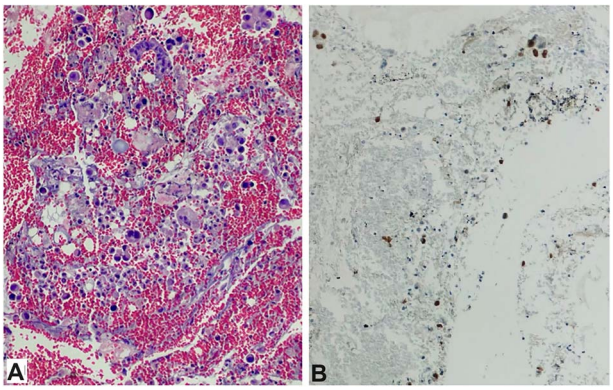

Figure 3. Histopathological specimen of left lower lobe lesion obtained by transbronchial needle aspiration. Hematoxylin and eosin stain at 200x magnification shows neoplastic cells with abundant cytoplasm and large hyperchromatic nuclei with prominent nucleoli (A). IHC stain of the LLL tissue sample was reactive to TTF-1/Napsin-A dual stain (B), indicating a primary conventional lung adenocarcinoma.

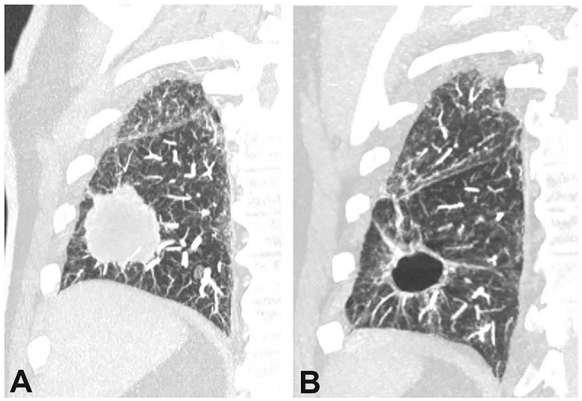

Figure 4. Computerized tomography (CT) scan with coronal view showing right lower lobe spiculated mass measuring 4.5 × 4.6 × 4.8 cm (A). Diagnostic evaluation was consistent with pulmonary enteric adenocarcinoma. Repeat CT scan after therapy with carboplatin, pemetrexed, and pembrolizumab shows large cavity lesion where right lower lobe pulmonary enteric adenocarcinoma used to be. This lesion predominantly consists of an air cavity measuring 3.1 × 3.5 × 3.3 cm.

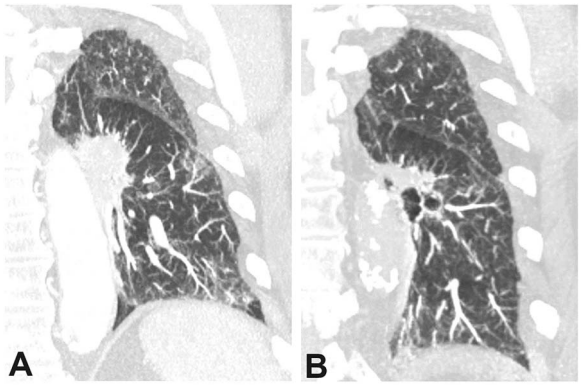

Figure 5. Computerized tomography (CT) scan with coronal view showing left lower lobe spiculated mass measuring 3.7 × 2.7 × 3.6 cm (A). Subsequent histopathological testing was consistent with conventional pulmonary adenocarcinoma. Repeat CT scan after therapy with carboplatin, pemetrexed, and pembrolizumab shows partial response of left lower lobe mass, with residual tumor measuring roughly 50% of the original mass (B).

Discussion

The case reported herein presented diagnostic difficulty given the synchronous presentation of two distinct pulmonary malignancies. After imaging and RLL biopsy, the working diagnosis initially favored a metastatic gastrointestinal primary. However, esophagogastroduodenoscopy and colonoscopy excluded primary colorectal malignancy. Response assessments with whole-body PET at 0, 6, 12, 18, and 24 months after initial diagnosis did not reveal any 18F-fluorodeoxyglucose-avid colorectal lesions. The RLL mass was nonreactive to SATB2, a marker highly specific for colorectal carcinomas and is rarely expressed in primary lung tumors such as PEAC [4]. CDX-2 and CK-7 positivity further supported the diagnosis, as retrospective studies have suggested that this combination may be sensitive and specific for PEAC [5]. Notably, there was a discrepancy between initial CT/PET imaging and endobronchial ultrasound regarding the locally metastatic level 7 lymph node, highlighting the role of EBUS in mediastinal staging of lung cancer.

One theory for this synchronous presentation is the development of two independent primary malignancies. With improved screening and diagnostic modalities, the detection of multiple primary lung cancers is becoming increasingly common [6]. Field cancerization, the process by which large areas of tissue are exposed to carcinogenic alterations, would generate the progressive mutations of tumor oncogenes that drive lung carcinogenesis [7]. In this case, chronic exposure of the respiratory tract to tobacco smoke may provide a substrate for the development of multiple primary tumors over time.

Another plausible explanation is lobe-to-lobe metastasis, followed by metaplasia from one immunohistochemical profile to another. Pulmonary invasive mucinous adenocarcinoma has a predisposition for intrapulmonary spread to contralateral lobes [8]. Additionally, pluripotent cancer stem cells in the lungs are known to self-regenerate, metastasize, and differentiate into different cancer lineages [9]. This presentation may be attributed to pluripotent cancer stem cells metastasizing to the contralateral lobe and undergoing differentiation into new molecular profiles. The patient had a level 7 subcarinal lymph node that was immunohistochemically identical to the LLL adenocarcinoma and may represent the initial site of metastasis. This theory is consistent with the hypothesis that PEAC is derived from the presence of common cancer stem cells in the gastrointestinal mucosa and lower respiratory tract [10]. This could also explain the significant immunohistochemical variability described in PEAC [1, 5]. Finally, this would lend additional credence to the proposal that PEAC shares similar origins with pulmonary invasive adenocarcinoma [2].

The optimal treatment for PEAC is not well established, but strategies like those of other lung adenocarcinomas are frequently employed [1]. The role of immunotherapy remains controversial because retrospective studies have been contradictory regarding PD-L1 expression, tumor mutational burden, and tumor-infiltrating lymphocytes [10]. Most patients with nonoperable PEAC have been treated with standard platinum doublet chemotherapy, with or without immunotherapy [3, 10].

Our patient responded to a three-drug regimen containing carboplatin, pemetrexed, and pembrolizumab, with a compete response of the right lobe PEAC and a partial response of the left lobe adenocarcinoma. Despite reported tumor proportion score of < 1% for PD-L1 on NGS, the RLL PEAC demonstrated a complete response to pembrolizumab-containing therapy. This suggests that PEAC with a higher tumor mutational burden may respond to pembrolizumab-containing therapy, regardless of PD-L1 status.

This is the first report of a patient with synchronous pulmonary enteric adenocarcinoma and contralateral lobe conventional pulmonary adenocarcinoma. Through discussion of the diagnostic evaluation, plausible mechanisms for synchronous presentation, and treatment response, this case contributes important insights into the evaluation and management of these rare pulmonary malignancies.

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Conflict of interest

No conflicts of interest. The views expressed herein are those of the author(s) and do not necessarily reflect the official policy or position of the Defense Health Agency, Brooke Army Medical

Center, the Department of Defense, nor any agencies under the U.S. Government.

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Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. A portion of this manuscript has been presented at CHEST 2023 and the abstract was published in the CHEST 2023 Annual Meeting Abstracts. The abstract may be viewed here: https://doi.org/10.1016/j.chest.2023.07.2918.

Consent

The patient's surviving wife, as his legal next of kin, provided written informed consent on 3 February 2024 for the publication of this case report and accompanying images.

Guarantor

The guarantor of the paper is Dr. Joshua Fenderson.

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