Lung Cancer 122 (2018) 187–191

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

# Synchronous primary lung adenocarcinomas harboring distinct MET Exon 14 splice site mutations

Samantha X.Y. Wang[a], Li Lei[b], Haiwei H. Guo[c], Joseph Shrager[d], Christian A. Kunder[b], Joel W. Neal[a,*]

[a] Department of Medicine, Division of Oncology, Stanford University School of Medicine, Stanford, CA, United States
[b] Department of Pathology, Stanford University School of Medicine, Stanford, CA, United States
[c] Department of Radiology, Stanford University School of Medicine, Stanford, CA, United States
[d] Department of Cardiothoracic Surgery, Stanford University School of Medicine, Stanford, CA, United States

ARTICLE INFO

*Keywords:*
MET exon 14
Multiple synchronous primary lung cancers
Next generation sequencing
Tumor evolution
Subsolid pulmonary nodule

ABSTRACT

When a patient is found to have multiple lung tumors, distinguishing whether they represent metastatic nodules or separate primary cancers is crucial for staging and therapy. We report the case of a 79-year-old patient with two surgically resected synchronous left upper lobe adenocarcinomas initially pathologically staged as T3 (IIB), indicating adjuvant chemotherapy should be recommended. However, the tumors appeared radiographically distinct, so next-generation sequencing was performed on each nodule. Each tumor harbored a different mesenchymal-to-epithelial transition (*MET*) exon 14 skipping mutation, an emerging targetable mutation, suggestive of distinct clonality. While the in frame protein deletion was the same in each tumor, the nucleotide base substitutions were different. Thus, the patient was down-staged to having two separate IA tumors, spared of adjuvant chemotherapy, and routine surveillance was recommended. This case highlights the utility of using molecular analysis in diagnosing and treating multifocal lung tumors, and the process of convergent molecular evolution toward a common oncogenic driver mutation. This is the first case of multiple synchronous lung tumors each harboring a distinct MET exon 14 splice site mutation.

## 1. Introduction

Patients with lung cancer can present with multiple synchronous lung tumors. Distinguishing whether these tumors are multiple synchronous primary lung cancers (MSPLC) or intrapulmonary metastases is paramount for staging, therapy, and prognosis. The current standard relies on histopathologic criteria to make this distinction [1]. However, unrelated tumors may arise independently in response to environmental risk factors, and tissue evaluation alone may be inconclusive [2]. Several studies have used genomic profiling to classify multifocal tumors, and differences in oncogenic "driver mutations" - such as epidermal growth factor receptor (EGFR) - are suggestive of distinct clonality [3–5].

Mutations in the exon 14 splice site of the mesenchymal-to-epithelial transition (*MET*) gene are an emerging target in non-small cell lung cancer (NSCLC) [6,7]. We describe the first case of a patient with two lung nodules, each with a distinct mutation in exon 14 of the *MET* gene, allowing clinical determination that the two tumors were independent primary lung cancers.

## 2. Case report

A 79-year-old male with a 20-pack year smoking history presented with new dyspnea in 2017. A chest CT scan showed two left upper lobe subsolid nodules (Fig. 1B&D), both with mild[18] FDG uptake on positron emission tomography (PET) scan. Brain MRI was negative for metastasis. He underwent mediastinoscopy and lingula-sparing left upper lobe lobectomy. Pathologic analysis showed two nodules of lepidic-predominant adenocarcinoma with a central invasive component showing the acinar pattern. There was no contiguity between the tumors, and no lymphovascular invasion was identified (Fig. 1 E–H). He was initially diagnosed with pathologic stage IIB (pT3N0M0) lung adenocarcinoma, and adjuvant chemotherapy was considered. Previously, the patient had undergone CT imaging for pneumonia 18 months prior to presentation, and images from the earlier CT were compared with the current CT. The tumors appeared radiographically distinct and showed temporal evolution. Nodule #1 enlarged from 1 cm to 1.7 cm, with increased solid and ground glass components (Fig. 1A–B). Nodule #2 enlarged from a 0.6 cm purely ground glass

* Corresponding author at: Stanford Cancer Institute, 875 Blake Wilbur Dr, CC 2220, MC 5826, Stanford, CA, 94305, United States.
*E-mail address:* jwneal@stanford.edu (J.W. Neal).

https://doi.org/10.1016/j.lungcan.2018.06.019
Received 29 January 2018; Received in revised form 19 May 2018; Accepted 13 June 2018

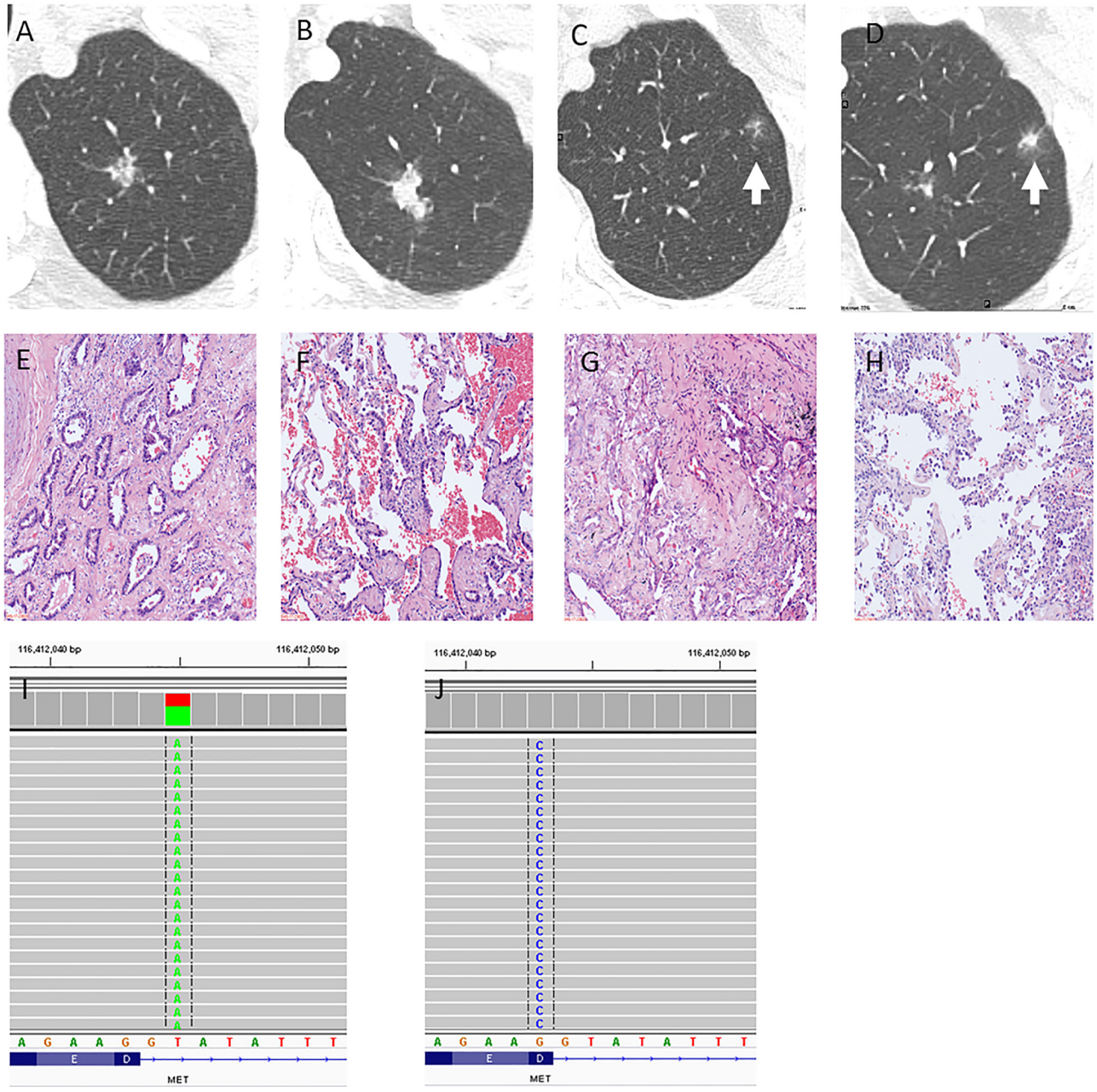


**Fig. 1.** Radiographic, pathologic, and molecular findings of synchronous nodules.
Axial CT images through the left upper lobe show temporal evolution of synchronous lung cancers. Nodule #1 was initially visualized as a 1 cm predominantly ground glass nodule with spiculated margins located in the apical left upper lobe (panel A), and over the next 18 months, enlarged to 1.7 cm with predominantly solid components and increased spiculation, reflecting enlarging invasive components of adenocarcinoma (panel B). Nodule #2 initially appeared as a 0.6 cm subtle groundglass nodule also in the left upper lobe, located inferior-anterolaterally to the first nodule (arrow, panel C), and grew to become a 1 cm subsolid nodule with 0.6 cm solid component, reflecting evolution from a predominant lepidic growth pattern to frank invasion (arrow, panel D).
Both tumors showed invasive components (nodule #1, panel E; nodule #2, panel G) with primarily lepidic (70%) and secondarily acinar (30%) morphologies [hematoxylin-eosin, nodule #1 (panel F); nodule #2 (panel H)]. Sequencing shows the two tumors carried distinct *MET* exon 14 skipping mutations, c.3082 + 2T > A in nodule 1(panel I) and c.3082G > C in nodule 2 (panel J) [IGV pileup at the same position of *MET* gene].

nodule to a 1 cm subsolid nodule with invasive features (Fig. 1C–D). Molecular testing was performed before chemotherapy was started. Specimens were analyzed using an institutionally-developed, hybrid capture-based next-generation sequencing assay targeting 130 genes entirely or in part, which detects single nucleotide variants, short insertions and deletions, selected fusions, and selected amplifications in solid tumors, with tumor-only sequencing [8]. Sequencing demonstrated distinct *MET* exon 14 skipping mutations in each tumor (Fig. 1I-J), without other shared tumor genomic variants. One tumor harbored the chr7:g.116412043 G > C nucleotide base substitution, while the other tumor harbored the chr7:g.116412045T > A base substitution, both functionally resulted in the same in frame deletion of exon 14 and protein product (Table 1). Changes at both of the altered positions have been shown to cause exon 14 skipping at the RNA level and are highly recurrent in lung cancer [5,9,10].

Thus, based on the two tumors' distinct imaging evolution and genetic mutational features, the patient was down staged to having separate IA primary lung adenocarcinomas, and the recommendation was revised to undergo regular surveillance scans without adjuvant