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Case Report

Synchronous Primary Lung Cancers Containing Discrete Driver Mutations in a Never-Smoker: Case Report

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Keywords

Synchronous multifocal primary lung cancer · Synchronous non-small cell lung cancer · Case report · Anaplastic lymphoma kinase · Epidermal growth factor receptor

Abstract

Although most lung cancer patients present with one primary cancer, some present with multiple lung cancers of different clonal origin. Timely recognition of synchronous multifocal primary lung cancer (MPLC) enables distinct treatment regimens that reflect the unique genotypic makeup and location of each cancer. However, recognition of synchronous MPLCs is challenging given the prevalence of multifocal disease. Here, we report a case of a patient diagnosed with anaplastic lymphoma kinase, termed *ALK*, positive metastatic lung adenocarcinoma whose follow-up computerized tomography (CT) imaging identified one lesion, present since the patient's initial presentation, with a distinctly different response to treatment than other lesions. Biopsy results showed a distinct MPLC, an epidermal growth factor receptor (*EGFR*)-positive adenocarcinoma with no evidence of an *ALK* mutation. The *EGFR* lesion was treated with curative intent via surgical resection while the *ALK* disease was managed with palliative intent via targeted therapy. To our knowledge, there have been no other reports of two synchronous MPLCs of an adenocarcinoma subtype with completely distinct *EGFR* and *ALK* driver mutations. This case highlights the importance of serial follow-up imaging, combined with biopsy of lesions with atypical treatment responses, as a method for identifying synchronous MPLCs and adjusting treatment to optimize patient outcomes.

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Introduction

Lung cancer is the primary cause of cancer mortality worldwide, responsible for 18% of cancer deaths [1]. After diagnosis with lung cancer, a patient's prognosis and treatment plan are guided by staging via imaging, morphologic analysis, and more recently, by genomic analysis. Evidence of multifocal pulmonary lesions on initial imaging necessitates the need for the treatment team to distinguish metastatic disease from one primary lung cancer versus the presence of multiple primary lung cancers with distinct clonal origin, termed synchronous multifocal primary lung cancer (MPLC). Providers should note that adenocarcinoma non-small cell lung cancer (NSCLC), which this case report discusses, is the most common synchronous MPLC [2].

When synchronous MPLC is suspected, biopsy should be obtained if possible to enable genomic analysis and guide treatment. Two relevant loci are the epidermal growth factor receptor (*EGFR*) mutation and the echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (*ALK*) translocation. The *EGFR* mutation's epidemiology varies by demographic group but is found more frequently in adenocarcinomas and is more commonly seen in East Asians, non-smokers, and females [3, 4]. Notably, the *ALK* mutation is present in approximately 5% of adenocarcinoma patients (mostly non-smokers) [5]. Genomic analysis allows for more targeted and effective treatment for both *EGFR+* and *ALK+* NSCLC with therapies such as osimertinib and alectinib [6, 7]. A therapeutic strategy is less clear when providers encounter multiple distinct genetic targets present in only a subset of a patient's lesions [7, 8]. Co-mutation of both *EGFR* and *ALK* in one lesion is described in the NSCLC literature, with studies reporting between 0.1% and 1.6% of *EGFR* mutations in non-squamous NSCLC also harboring a concomitant *ALK* rearrangement. To our knowledge, however, there are no cases reported of synchronous MPLC adenocarcinomas demonstrating *ALK* mutation in one cancer and *EGFR* in another [9, 10]. Case reports in the scientific literature can provide prior therapeutic context for such clinical scenarios as well as chronicle the epidemiology of particular gene mutational combinations.

Once lung cancer therapy has been initiated, post-therapy imaging is crucial to evaluate efficacy, and any discrepancy in response to therapy between lesions should prompt consideration of oligoprogression versus distinct metachronous or undiagnosed synchronous primary malignancy. Here, we report a case of synchronous primary lung adenocarcinomas with distinct driver mutations.

Case Report

A 59-year-old never-smoker presented with an unrelenting cough and hematuria, prompting an abdominal and pelvic CT scan and follow-up abdominal magnetic resonance imaging (MRI), which revealed hepatic metastatic disease (see Fig. 1 for clinical timeline). Chest CT imaging 4 months later showed two left lower lobe (LLL) lesions, a 32-mm spiculated cavitary mass, and a 29-mm satellite nodule. Additional findings included a pulmonary left upper lobe (LUL) 21-mm lesion with ground glass opacity and possible adenopathy. Core needle biopsy of a hepatic lesion confirmed pulmonary adenocarcinoma, and fluorescence in situ hybridization (FISH) testing determined an *EML4-ALK* rearrangement with no evidence of other driver mutations, including *EGFR* mutation. Brain MRI showed 4 sub-centimeter supratentorial lesions, suspicious for metastasis. The patient was diagnosed with stage 4 *ALK* NSCLC, and ceritinib treatment was initiated due to its activity against *ALK* malignancy and its central nervous system penetration. The patient subsequently developed a

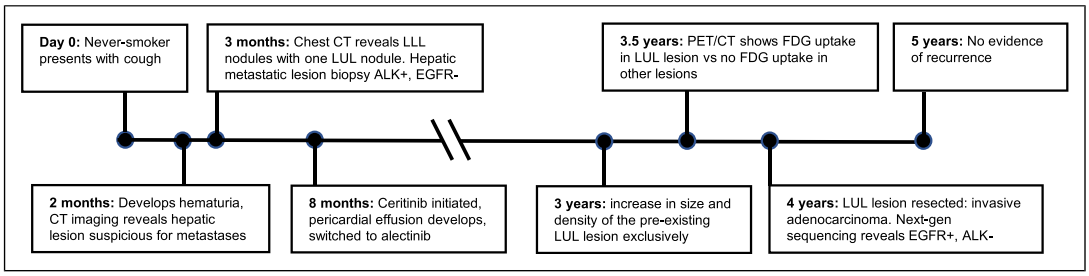

Fig. 1. Clinical timeline of diagnosis and treatment of each MPLC.

pericardial effusion and tamponade, which required a pericardial window procedure, which prompted shifting therapy to alectinib.

Routine follow-up CT imaging every 3–4 months was initiated, and 3 years and 5 months after initial presentation, CT imaging revealed a slight increase in size and density of the pre-existing LUL lesion, while all other lesions decreased in size (Fig. 2). Position emission tomography (PET)/CT scan obtained 4 months later showed further increase in size of this LUL lesion with minimal F-fluorodeoxyglucose (FDG) uptake in the LUL lesion but no FDG uptake in other lesions. The differential for this solitary lesion's progression included oligoprogression of a metastatic lesion, a distinct primary lung cancer, and residual disease.

After multidisciplinary discussion at the thoracic tumor board, the left upper lobe nodule was resected. Pathology revealed invasive moderately differentiated adenocarcinoma with a predominant acinar pattern and papillary and lecidic patterns, measuring 1.8 cm with lymphovascular visceral pleural invasion. Positive identification of markers suggestive of pulmonary adenocarcinomas, thyroid transcription factor-1 (TTF-1) and napsin A protease, supported a primary pulmonary origin. Next-generation sequencing of the LUL lesion revealed an *EGFR p.L858R c.2573T>G* mutation and was notably negative for fusion transcripts involving *ALK*. Given the early stage of this malignancy, the patient did not require adjuvant treatment post-surgery and has no evidence of recurrent or progressive tumor as of 1-year post-surgery.

Discussion

This case report demonstrates that when patients are being treated for lung cancer and present with multiple pulmonary nodules at follow-up imaging, clinicians must consider the possibility of synchronous or metachronous MPLCs, even though metastatic clonal disease is more likely. In fact, MPLCs are becoming more common clinically [11]. Prior research has demonstrated that patients who develop synchronous MPLC carcinomas often have significant tobacco exposure, but this case demonstrates the importance of also considering MPLCs in never-smokers as well [12].

Vigilance for MPLCs is particularly important in today's therapeutic era because many patients are seeing increased overall survival compared to previous decades, thanks to the advent of new generations of therapies. Studies show when immunotherapies are included in treatment regimens, patients with NSCLC experience prolonged overall survival and more patients achieve complete responses [13, 14]. Additionally, therapies which are targeted at specific genetic mutations are leading to longer progression-free survival [6, 15, 16]. With more durable and targeted therapeutic regimens, a patient's second primary lung cancer is given more time and thus more opportunity to grow, to mutate, and to unmask itself.

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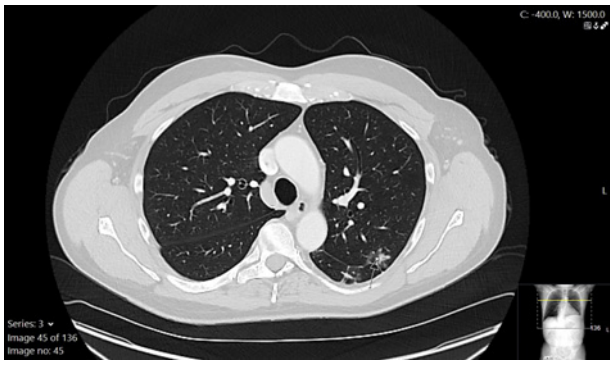

Fig. 2. Routine follow-up CT imaging demonstrates a slight increase in size and density of the pre-existing LUL lesion (arrow), while all other lesions decreased in size.

Our work suggests that upon detection of heterogenous responses to therapy among a patient's tumor burden, a careful review by a multidisciplinary tumor board is recommended, and biopsy sample should always be obtained when possible and genotypic analysis performed [17]. Clinical suspicion with a low threshold for biopsy is warranted because a second primary lung cancer may be susceptible to therapeutic approaches distinct from the first primary lung cancer. As shown in this case, malignancies driven by different mutations can present simultaneously even after one has metastasized. These biopsy findings can have treatment-guiding implications because awareness of the distinct "driver" mutations present in different lesions, even if the lesions are both adenocarcinomas, is predictive of targeted therapy efficacy and valuable in consideration of future lesions that may arise in the patient [7].

A clinician's plan towards treatment of MPLC takes one of three approaches: turning to a treatment modality which targets both primary lung cancers, focusing treatment on the more aggressive cancer, or considering two distinct treatment plans. In this case, one curative treatment plan, surgery, was pursued while the other treatment plan, alectinib, remained palliative.

This case demonstrates that follow-up imaging functions not just as a measure of treatment efficacy but also as a test of a clinician's original assumptions about the clonality of the different lesions a patient presented with. As follow-up imaging modalities continue to improve and as future tumor analysis (such as whole-exome sequencing) provides broader information about a tumor's genotypic makeup and potential susceptibility to different therapies, clinicians will be armed with both more information and more therapeutic options.

Conclusion

Lung cancer clinicians should strongly consider biopsy whenever follow-up imaging detects heterogenous response to treatment amongst tumors or pulmonary lesions that have characteristics of primary lung cancers. Discordance in "driver" mutation may both explain discrepancies in treatment response and suggest new distinct treatment approaches – such as different systemic regimens, surgery, or radiation. This warranted caution allows the treatment team to continually evaluate their initial diagnosis and enables a therapeutic pivot to provide the best outcomes for their patients. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533892).

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Statement of Ethics

The authors confirm that written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. Ethical approval is not required for this report in accordance with local and institutional guidelines.

Conflict of Interest Statement

The authors declare the following financial interests/personal relationships which may be considered potential competing interests: Christine Ciunci reports honoraria relationships with Imedex and Merck & Co., Inc. and reports funding grant relationships with Celgene AB, Merck & Co., Bristol Myers Squibb Co., and Macrogenics Inc.

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Author Contributions

Andrew Davis: writing – original draft, draft preparation, and editing. Sophia Jarrar: writing. Christine Ciunci: supervision, reviewing, and editing.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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