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Case Report

Rare Synchronous Lung Cancers in a Nonsmoker with Epidermal Growth Factor Receptor and Mesenchymal-Epithelial Transition Alterations: A Case Report

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Mesenchymal-epithelial transition alteration · Synchronous non-small cell lung cancer · Capmatinib · Targeted therapy

Abstract
Introduction: Lung cancer is the second most common cancer; however, synchronous lung cancer is rare and challenging to treat. ***Case Presentation:*** We report the case of an 80-year-old female patient who presented with two lung lesions with primary tumor characteristics, which revealed squamous cell carcinoma and synchronous adenocarcinoma after histological sampling. Next-generation sequencing (NGS) analysis revealed a MET Exon 14 skipping mutation in squamous cell carcinoma and an epidermal growth factor receptor mutation in adenocarcinoma. Capmatinib and stereotactic radiotherapy were initiated for the adenocarcinoma with a good clinical response. Capmatinib treatment had to be discontinued because of stage 3 edema of the lower limbs, after which a left lobectomy was performed. Currently, the patient is considered to be in remission. ***Conclusion:*** This case highlights the need for histological analysis of every lung lesion with primary tumor characteristics, as well as for NGS analysis in search of specific mutations enabling the introduction of targeted therapies. mesenchymal-epithelial transition.

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Introduction

Lung cancer represents the leading cause of cancer-related deaths worldwide [1]. There are two main histological subtypes: non-small cell lung cancer (NSCLC) that accounts for roughly 80–85% of all the cases and small cell lung cancer that accounts for 15–20% [2]. The former comprises three main histological subtypes: adenocarcinoma (60%), squamous cell carcinoma (35%), and large cell carcinoma (5%); each subtype has a distinct molecular presentation [3]. The carcinogenesis of adenocarcinomas is driven by known oncogenic alterations, and numerous of these oncogenic drivers have now been identified and could be treated with targeted agents.

Here, we describe the case of an 80-year-old nonsmoking patient diagnosed with synchronous multiple primary lung cancers (sMPLCs), MET-dysregulated advanced squamous lung cancer, and localized adenocarcinoma with epidermal growth factor receptor (EGFR) mutation. Treatment included capmatinib and radiotherapy, respectively, with cessation of systemic therapy owing to adverse event. Surgery permitted then a complete resection. The patient has since been in remission.

To our knowledge, no similar cases involving two sMPLCs with different targetable alterations have been reported. Data in the literature are scant, hence the importance of collecting and reporting these situations. This case highlights the need for rigorous imaging analysis to discuss whether bilateral lesions are synchronous or metastatic and intense pathological sampling and molecular analysis, especially in nonsmoking patients, as they are more likely to be in possession of molecular alterations, thus allowing targeted therapies to be received.

The CARE Checklist has been completed by the authors for this case report and is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538019).

Case Report

An 80-year-old nonsmoking woman consulted the emergency department for exacerbation of chronic cough and hemoptysis, for which bacterial and mycobacterial infections were ruled out. Thoracic computed tomography (CT) scan showed two morphologically different bilateral lesions: a cystic left apical lesion measuring 6.1 cm × 5.3 cm × 4.5 cm with hilar ipsilateral necrotic lymphadenopathyc (Fig. 1) and a peribronchovascular centimetric solid retractile lesion associated with ground glass opacities (GGO) of 3 cm in the right upper lobe (Fig. 2). Brain MRI and abdominal CT scan did not reveal any lesions.

Given the morphological aspect of the lesions, suggestive of primary lesions with cystic features for the left one and retractile with ground glass for the right one, cytological and histological samples were collected from both sites through bronchoscopy. The apical excavated left lesion showed squamous cell carcinoma, whereas the right upper lobe lesion was adenocarcinoma. Next-generation sequencing (NGS) analysis was performed for both lesions and revealed a mesenchymal-epithelial transition (MET) gene deletion with exon 14 skipping in squamous carcinoma and an epidermal growth factor receptor (EGFR) gene mutation in exon 21 (L858R) in adenocarcinoma (Fig. 3). Reverse transcription polymerase chain reaction confirmed MET alterations.

After discussing the case at a multidisciplinary team meeting, the surgical approach was suggested but declined by the patient. Because of the locally advanced stage of the squamous left lesion with 10 L lymph node (cT3N1, stage IIIA, according to the 8th TNM classification), systemic treatment was initiated with capmatinib, a tyrosine kinase inhibitor approved for metastatic NSCLC harboring MET exon 14 skipping mutations [4]. In parallel, for the localized right adenocarcinoma cT1N0 stage IA3, stereotactic radiotherapy with 60 Gy (eight fractions

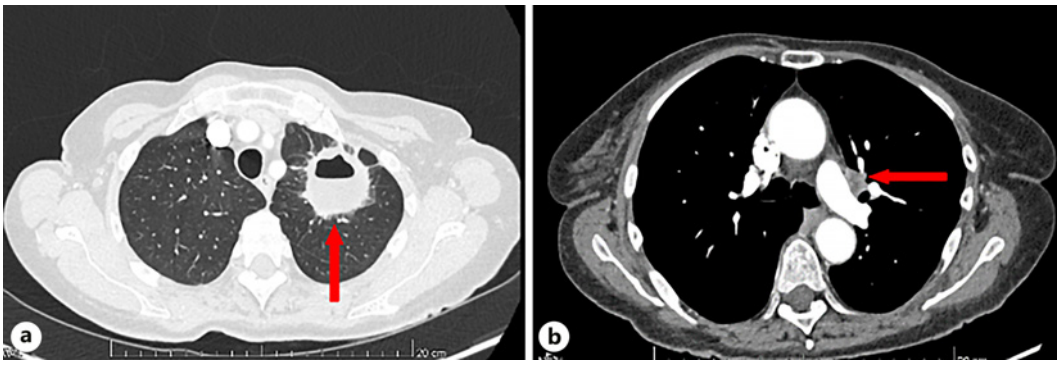

Fig. 1. a Left apical lung lesion with cystic appearance. **b** Hilar ipsilateral necrotic lymphadenopathy (10 L).

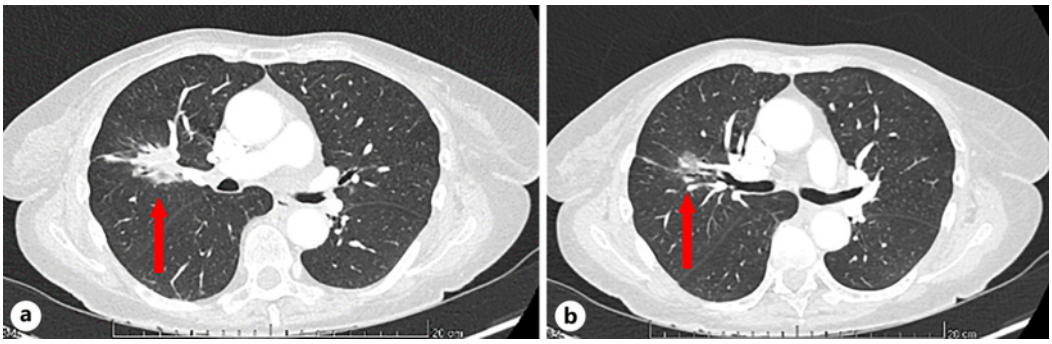

Fig. 2. Right upper lobar lesion with mixed components: solid (**a**) and ground glass (**b**).

of 7.5 Gy) was delivered. Thoracic CT scan after 2 months of treatment showed a partial response with a decrease in the size of the left lesion (40%) and 10 L adenopathy (50%), as well as a good local response after radiotherapy of the right lesion (30%). After developing grade 3 edema of the lower limbs, a known side effect of capmatinib, treatment was stopped. One month after discontinuation, a new thoracic CT scan revealed an increase in the size of the left upper lesion (75%) and the adenopathy (40%). After multidisciplinary discussion, left upper lobectomy was proposed and accepted by the patient. The final histology showed traces of squamous cell carcinoma in the parenchyma but not tumor cells in the resected lymph nodes, including the 10 L area (final staging ypT1 N0). More than 9 months after surgery, patient is considered to be in remission of both NSCLC and is currently under a quarterly radiological and clinical follow-up. The main clinical events are summarized in Figure 4.

This case highlights the importance of rigorous pathological sampling and molecular analysis of lung cancer with possibly advanced stage on radiology, especially in nonsmoking patients. This population is well known to be more likely to have molecular alterations [5], thus allowing targeted therapies to be received.

Discussion

Lung cancer is one of the most common cancers and the leading cause of cancer-related deaths worldwide [6]. The incidence of sMPLC ranges from 0.2–8% [7] and has tended to increase. This may be explained by the popularization of low-dose CT, high-resolution CT, and

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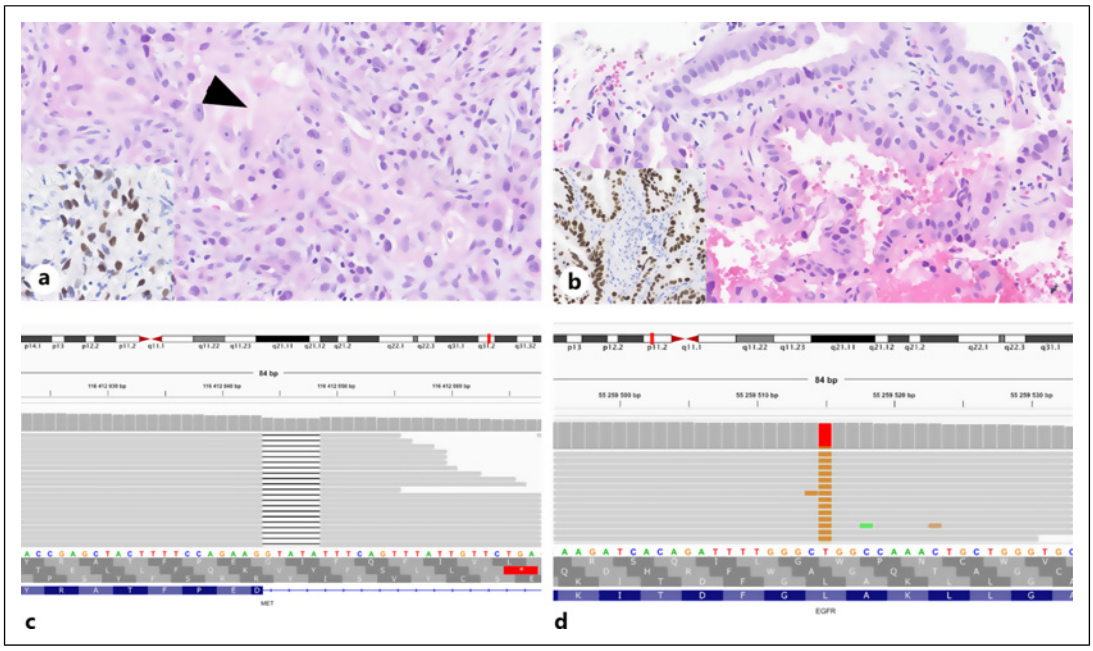

Fig. 3. a Squamous cell carcinoma. Arrow indicates intercellular bridge supporting a squamous differentiation (×200). Inset: p40 immunohistochemistry on the resected lung specimen, confirming the diagnosis of squamous cell carcinoma. **b** Lung adenocarcinoma (×200). Inset: TTF1 immunohistochemistry (×200). **c** Deletion c.3028+1_3028+5del in the splicing donor site of *MET* gene, leading to the splicing of exon 14 in *MET* gene in the squamous cell carcinoma (IGV viewer). **d** c.2573T>G mutation in *EGFR* gene, leading to a p.Leu858Arg amino acid change (IGV viewer) in the lung adenocarcinoma.

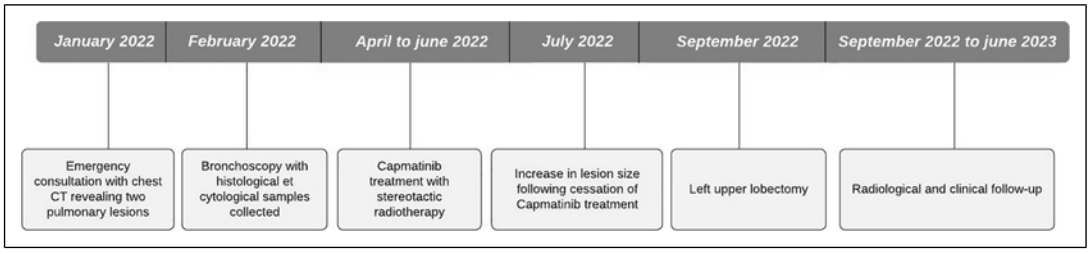

Fig. 4. Timeline of main clinical events.

the promotion and application of early lung cancer screening. Its incidence is higher in women, people with a history of malignant disease, and those with COPD. Female sex and lack of smoking are independent risk factors for sMPLC [8].

It can be difficult for physicians to distinguish between a second primary tumor and intrapulmonary metastasis. The distinction is, however, crucial as the stage of the disease would differ with significant changes in management and outcomes. Previous studies have shown that the overall survival of patients with MPLC is significantly better than those with metastatic tumors [9]. Discrimination is usually obtained by lung or lymph node biopsies or surgical procedures. Nevertheless, a meticulous analysis of radiology, particularly CT, may suggest the presence of different synchronous cancers and guide the preferred method for pathological sampling.

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The criteria for the diagnosis of MPLC were first established by Martini and Melamed [10] and later developed by the American College of Chest Physicians [11]. Both criteria are based on clinical, pathological, and radiological features. However, in recent years, incorporating molecular and histological profiles has suggested their superiority in distinguishing between sMPLC and intrapulmonary metastasis [12].

For patients with two synchronous primary NSCLC who are considered for curative surgical resection, invasive mediastinal staging and extra-thoracic imaging are recommended. A thorough search for extra-thoracic primary cancer to rule out the possibility that both lung lesions represent metastases is recommended [11].

Reports have shown that sMPLC have a high incidence of driver mutations, such as EGFR mutations [13]. However, the discrepancy rate of driver mutations in sMPLC is relatively high, ranging from 72 to 92% [14].

CT is the preferred method for localizing lesions and for providing diagnostic information. Tumors in patients with sMPLC have different appearances, and diagnosis is often difficult due to the poor understanding of these findings. Nonuniform cyst walls, septation within the cyst, wall nodules, GGO around the cyst, irregular margins, and pleural retraction are highly indicative of cancer [15].

However, until now, there has been no consensus regarding the optimal management of patients with NSCLC with multiple pulmonary nodules. Suh et al. established a new method for the diagnosis of MPLC by combining the standard uptake value from PET-CT with the radiological features on CT, including GGO, spicule sign, and air bronchogram [16].

In a study aiming to explore the distinct features of single multiple adenocarcinomas, the strategy was not able to reach a definite diagnosis solely on the basis of CT images for 85 patients with multi-solid tumors and needed pathologic assessment. Twenty-two percent harbored different subtypes, suggesting independent malignancy [17].

Histological analysis is mandatory for establishing a definitive diagnosis. In our case, they revealed two sMPLC for which NGS, fusion testing, and reverse transcription polymerase chain reaction were performed, especially for squamous cancer, as no mutations are usually linked to this subtype [18].

From our point of view, reporting these complex cases with personalized management and the use of recent treatments, such as tyrosine kinase inhibitors, is important. This opens up possible therapeutic approaches for the future, as well as documents possible side effects, as was the case with our patient. We may also be able to identify factors influencing response to treatment and the occurrence of side effects, as in the case of a possible reduced response to checkpoint inhibitors in NSCLC patients on PPIs [19].

Conclusion

Our patient presented an unusual case of synchronous double primary NSCLC with MET gene deletion and exon 14 skipping in squamous cell carcinoma resulting in increased MET expression, which encodes the receptor for hepatocyte growth factor, which functions in cell proliferation, survival, invasion, motility, and metastasis [20], and an EGFR gene mutation exon 21 in adenocarcinoma, resulting in activation of transmembrane receptor receptors without ligand-induced stimulation, thus promoting cell proliferation, survival, and dissemination [21].

There are two main findings. First, the right peribronchiolar retractile lesion was not a metastasis from the mass in the left upper lobe. Second, treatment-naive squamous cell

carcinoma and adenocarcinoma occurring together in the same patient are rare, highlighting the need to explore bilateral lesions with radiological primary malignant characteristics and the widespread use of NGS.

Acknowledgment

We would like to thank the patient for providing consent to publish clinical information and data.

Statement of Ethics

Ethical approval is not required for a case report in accordance with our local and national guidelines (Commission Cantonale d'éthique de la recherche sur l'être humain" (https://www.ge.ch/ccer-obtenir-autorisation-recherche-medicale-etre-humain). The patient was informed orally about this case report project and provided written informed consent for publication and her medical history, including pathological and radiological images.

Conflict of Interest Statement

A. Addeo reported receiving personal fees for attending advisory from Bristol-Myers Squibb, AstraZeneca, Roche, Pfizer, Merck Sharp and Dohme, Astellas, Eli Lilly, and Boehringer Ingelheim and receiving fees for speaking bureau for Eli Lilly, AstraZeneca, Merck Sharp and Dohme for work performed outside of this article. The other authors have no conflicts of interest to declare.

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Author Contributions

Xavier Baer was the first author to contribute to this manuscript. Mathieu Chevallier contributed to the writing of the manuscript and served as a supervisor. Juliana Rey Cobo contributed to the drafting of the manuscript and to the investigations. Jérôme Plojoux took part in the investigations. Claudio De Vito took, analyzed, and interpreted the histological data and contributed to the histological figure. Alfredo Addeo took part in the investigations and proofreading of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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