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CASE REPORT

Case Report: A Metabolic Complete Response to Upfront Osimertinib in a Smoker Non-Small Cell Lung Cancer Patient Harbouring *EGFR* G719A/V769M Complex Mutation

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Abstract: Complex *EGFR* mutations are rare in non-small cell lung cancer (NSCLC). Limited clinical evidence is available on the efficacy of *EGFR* tyrosine kinase inhibitors (TKIs) in patients with NSCLC harbouring these uncommon *EGFR* mutations. Here, we reported the case of a complete metabolic response in a patient with advanced NSCLC carrying the uncommon *EGFR* G719A/V769M complex mutation treated with the first-line osimertinib.

Keywords: non-small cell lung cancer, *EGFR* complex mutations, osimertinib

Introduction

The treatment of NSCLC patients carrying sensitizing *EGFR* mutations has been revolutionized by *EGFR*-targeted therapies. *EGFR* exon 19 deletions and exon 21 L858R substitutions are the most frequent, covering about 80% of all mutations in NSCLC and resulting in a strong sensitivity to tyrosine kinase inhibitors (TKIs) as oncogenic drivers.[1] Other *EGFR* mutations are defined uncommon and represent a heterogeneous group of molecular alterations including exon 18 point mutations, exon 20 insertions and combined complex mutations.[2] Retrospective studies, reports of clinical cases and few prospective data showed inconsistent clinical activity of *EGFR*-TKIs in patients carrying these rare mutations.[3,4]

Moreover, smoking status is a well-known negative predictive clinical factor for *EGFR*-TKIs activity as never smokers have been found to be more sensitive to *EGFR*-TKIs than former or current ones.[5] Intriguingly, while common mutations are mostly found in never smokers, those defined uncommon are frequent in patients with smoking history.[6]

Osimertinib, a third-line generation *EGFR*-TKI, is a novel upfront treatment option for patients affected by NSCLC with sensitizing alterations.[7] However, limited clinical data of osimertinib are available to define the predictive role of uncommon *EGFR* mutations as the large prospective trials enrolled only NSCLC patients carrying common sensitive mutations (exon 19 deletion + exon 21 L858R).[7,8] A small Phase II trial conducted on 36 NSCLC patients with uncommon *EGFR* mutations and treated with osimertinib demonstrated encouraging response rates with manageable toxicities.[9]

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Here, we report a case of excellent disease response in a smoker patient with advanced NSCLC harbouring uncommon complex *EGFR* mutation treated with osimertinib as first-line therapy.

Case Presentation

A Caucasian 69-year-old housewife with a smoking history of 40 pack-years and no significant environmental exposures underwent right upper lobectomy in February 2015 for a stage IIb lung adenocarcinoma. The patients received three cycles of adjuvant chemotherapy with cisplatin and gemcitabine and subsequent standard follow-up. She had no other relevant morbidities, nor family history of cancer. During follow-up, a Computed Tomography (CT) scan performed in November 2019 and a Positron Emission Tomography CT (PET-CT) scan in December 2019 showed disease recurrence in multiple small lung nodes and mediastinal para aortic, aorto-pulmonary and left paravertebral lymph nodes (Figures 1A and 2A). A molecular analysis looking for genetic alterations of *EGFR* (exon 18, 19, 20 and 21), *ALK* and *ROS-1* genes and *PDL-1* immunohistochemistry (ICH) expression were performed in the primary tumor as a new biopsy was not technically feasible. Uncommon complex *EGFR* mutation (exon 18 G719A and exon 20 V769M) was detected using the polymerase chain reaction (PCR)-based Sanger sequencing. No additional alterations other than *EGFR* mutations were found as DAKO *ALK* and *ROS-1* D4D6 ICH were negative. DAKO *PDL-1* ICH 22 C3 was also negative (Tumor Proportion Score 0%).

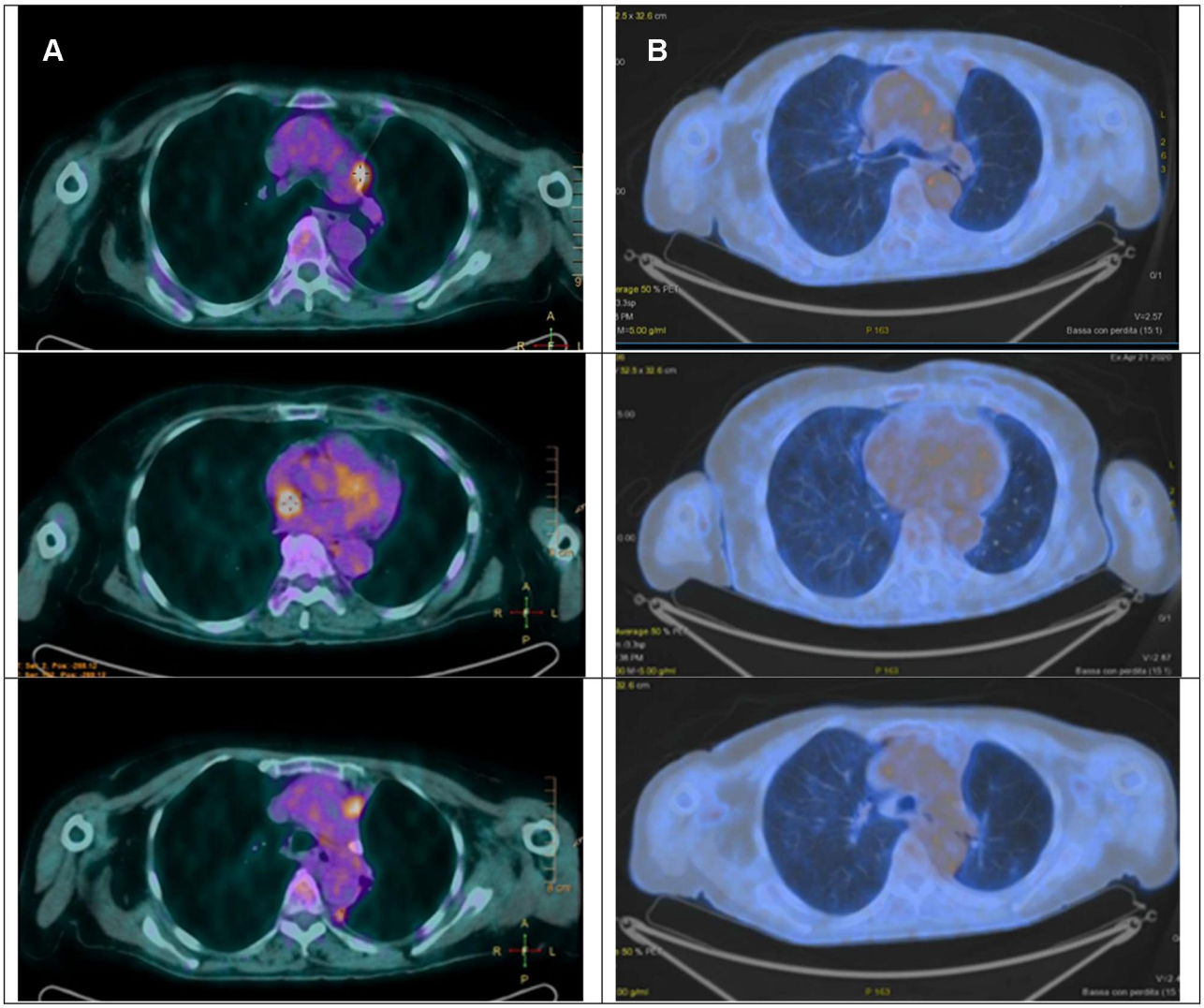

Figure 1 PET CT scan of the chest-mediastinal window. Neoplastic aorto-pulmonary, mediastinal para aortic and left paravertebral lymph nodes. (**A**) Baseline disease. (**B**) Complete disease response after 12 weeks of therapy with osimertinib.

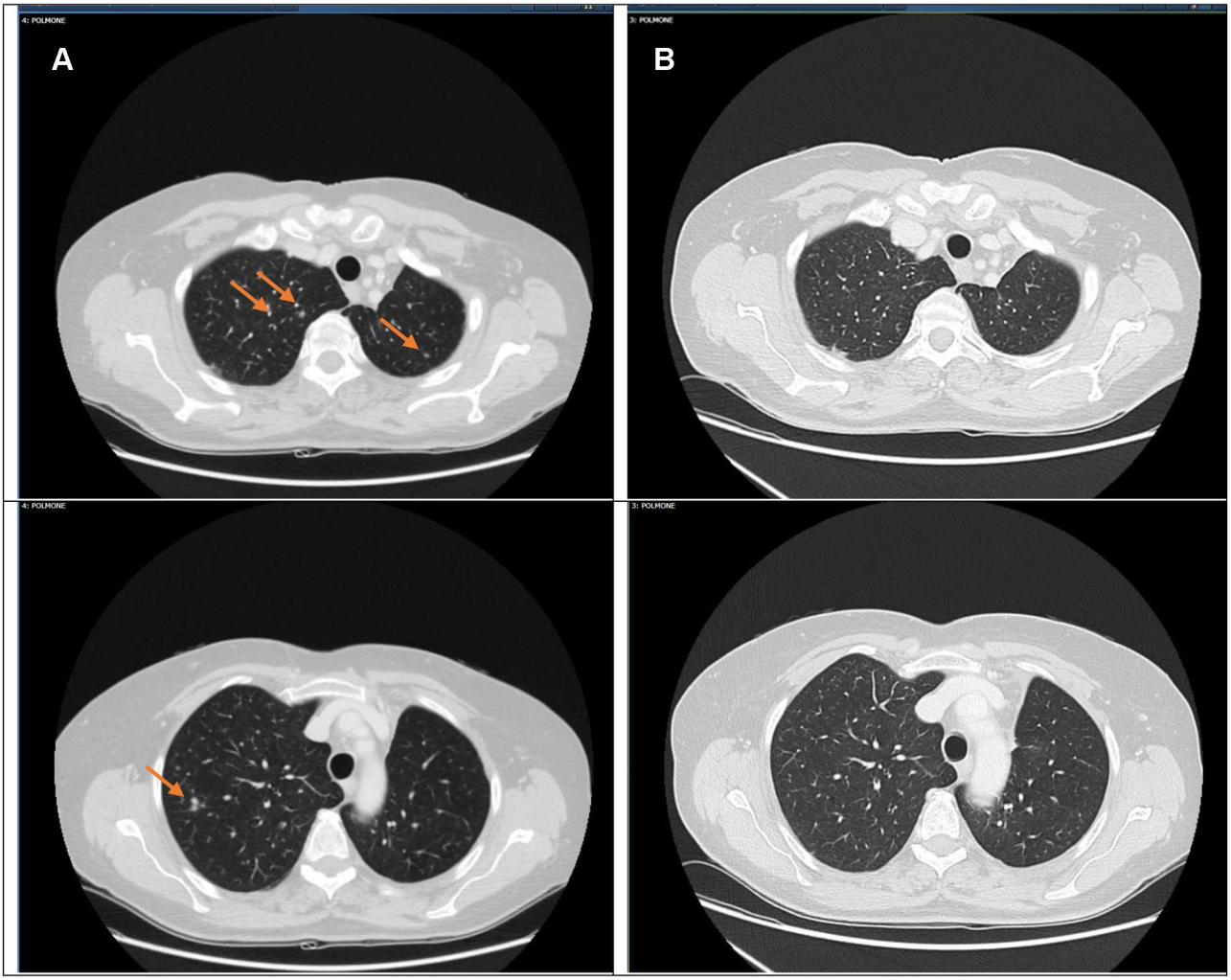

Figure 2 Chest CT scan. (**A**) Baseline disease in multiple small lung nodes. (**B**) Complete disease response after 12 weeks of therapy with osimertinib.

The patient started first-line osimertinib 80 mg/day on the 2nd of February 2020. The treatment was well tolerated with no adverse events. On the 21st of April 2020, a restaging PET CT scan demonstrated a disease complete response to osimertinib (Figures 1B and 2B). The patient is still on treatment at full dose (last follow-up was on 12th October 2020).

A written informed consent was provided by the patient to have the case details and radiological images published. No institution approval was required to publish the case details.

Discussion

Nowadays, TKIs treatment is considered the gold standard in NSCLC harbouring classic *EGFR* mutation. In particular, TKIs demonstrated superior efficacy than standard chemotherapy in several randomized trials.[7,10,11] Moreover, new clinical data suggested poor and unpredictable activity of immunotherapy in this molecular setting.[12]

However, limited clinical evidence is available on the efficacy of *EGFR*-TKIs in patients with NSCLC harbouring uncommon *EGFR* mutations. Intratumoral heterogeneity with the presence of different subpopulations resistant to targeted therapy is thought to be one reason of intrinsic drug resistance in some of these patients.[13] In particular, tumors with high metastatic burden may be related to higher intratumoral heterogeneity and worst outcome to TKIs than oligometastatic ones.

Large retrospective analyses suggested that *EGFR*-TKIs have unpredictable activity in patients with tumours harbouring these uncommon mutations than the common ones.[3] Complex *EGFR* mutations account for 3–14% of all *EGFR* mutations. Retrospective analyses suggest that patients carrying specific complex mutations may benefit

from first and second-generation TKIs as patients with classical mutations.[14,15] Moreover, a combined post hoc analysis of three prospective clinical trials of afatinib suggested a potential activity in NSCLC with certain types of uncommon *EGFR* mutations, including complex mutations with exon 18 and exon 21.[4]

In addition, smoking history has been related to a lower incidence of *EGFR* mutations and poor outcome to TKIs in *EGFR* mutant tumors in smokers. However, uncommon and complex mutations are more often in smokers than classic mutations and TKIs activity in these patients has not been clearly defined.[16]

At present, osimertinib is considered one first-line standard of therapy for NSCLC carrying classical mutations. However, its activity in NSCLC with these complex *EGFR* mutations is still unclear, although first clinical data showing promising activity are emerging. In particular, Cho et al reported four cases of complex mutations with significant response rates.[9] None of these patients carried the specific complex mutation detected in our patient. As far as we know, this is the first report of remarkable *EGFR*-TKI antitumor activity in NSCLC carrying complex exon 18 G719A + exon 20 V769M mutation. Tumor assessment was conducted with both CT scan and PET-CT as part of an internal analysis of radiomic phenotyping of these tumors and gave us evidence of the deepresponse to osimertinib.

Certainly, this is a single report of the activity of osimertinib in these rare alterations that cannot be considered conclusive. However, we strongly believe that also single cases are clinically relevant in such a rare molecular setting where a larger series of cases are hard to collect in singular institutions.

Conclusion

Uncommon complex *EGFR* mutations can be present in naïve smoker NSCLC patients and may be associated with disease response to the first-line osimertinib, irrespectively to smoking status. Efforts to describe these rare molecular alterations and their predictive role for a response to *EGFR*-TKIs better in larger series of cases are necessary to guide clinicians to personalize therapeutic strategies for NSCLC patients.

Disclosure

The authors report no conflicts of interest for this work.

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