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Response to trametinib in a nonsmall cell lung cancer patient with osimertinib resistance harboring *GNAS* R201C and R201H mutations: a case report

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Osimertinib, an orally administered third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, is widely approved for the first-line and second-line treatment of advanced non-small-cell lung cancer (NSCLC) with *EGFR* mutations. However, the rapid development of osimertinib resistance renders the unsustainable treatment benefit. Patients with *EGFR*-mutated NSCLC who develop osimertinib resistance, especially those acquiring relatively rare and 'off-target' resistance mutations, still lack effective therapeutic options for postosimertinib therapy. Herein, we reported a 73-year-old woman diagnosed with T1N3M1 lung adenocarcinoma harboring *EGFR* L858R mutation, who acquired two *GNAS* mutations (R201C and R201H) and lost the *EGFR* L858R mutation after progression on icotinib and osimertinib. The patient was subsequently treated with trametinib and there was no obvious tumor increase. Our study revealed that *GNAS* R201 can confer the osimertinib resistance in *EGFR*-positive NSCLC, and present the first report of the prevalence of *GNAS* R201C and R201H mutants in NSCLC which response to trametinib treatment. Our case suggests that trametinib could be a treatment option in NSCLC patients harboring *GNAS*-activating mutations. *Anti-Cancer Drugs* 33: 966–969 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKIs) play an important role in the treatment of activating *EGFR*-mutated advanced non-small-cell lung cancer (NSCLC) [1]. Osimertinib, an orally administered third-generation irreversible EGFR-TKI, is widely approved for advanced NSCLC patients with both EGFR-TKI sensitizing and T790M resistance mutations. With the wide application of osimertinib, more and more resistance mechanisms have been found in the real world. The acquisition of 'on-target' resistance mutations in *EGFR* has been found as the significant cause of resistance to osimertinib [2,3]. On the other hand, resistance mechanisms by activating bypass signaling pathways are also commonly reported [4,5]. Patients who develop osimertinib resistance by acquiring these 'off-target' resistance mutations and relatively rare bypass gene mutations still lack efficient therapeutic options for later-line treatment. Herein, we reported a stage IVB NSCLC patient with *EGFR* L858R mutation, who acquired rare novel *GNAS* R201C and R201H mutations after progression on osimertinib. She subsequently benefited from trametinib, a mitogen-activated protein kinase kinase (MEK) inhibitor. We present the following case in accordance with the CAse REport (CARE) reporting checklist.

Case presentation

In January 2018, a 73-year-old never-smoking woman came into the clinic for a routine medical examination. A chest computed tomography (CT) scan showed a 24 mm nodule in the right lung with enlarged mediastinal lymph nodes (Fig. 1). The abdomen enhanced CT and bone scanning detected no evidence of metastasis in the abdomen, but multiple bone metastases in ribs, thoracic and lumbar spine. Radiographic and pathologic evaluations resulted in a diagnosis of advanced lung adenocarcinoma (T1N3M1, stage IVB). A baseline next-generation sequencing (NGS) assay of the biopsied pulmonary lesion revealed the presence of *EGFR* L858R mutation. No concurrent alterations in other driver mutations were identified at that time.

In Feb 2018, the patient started on icotinib (125 mg Tid) and achieved stable disease (SD) (Fig. 1). We performed

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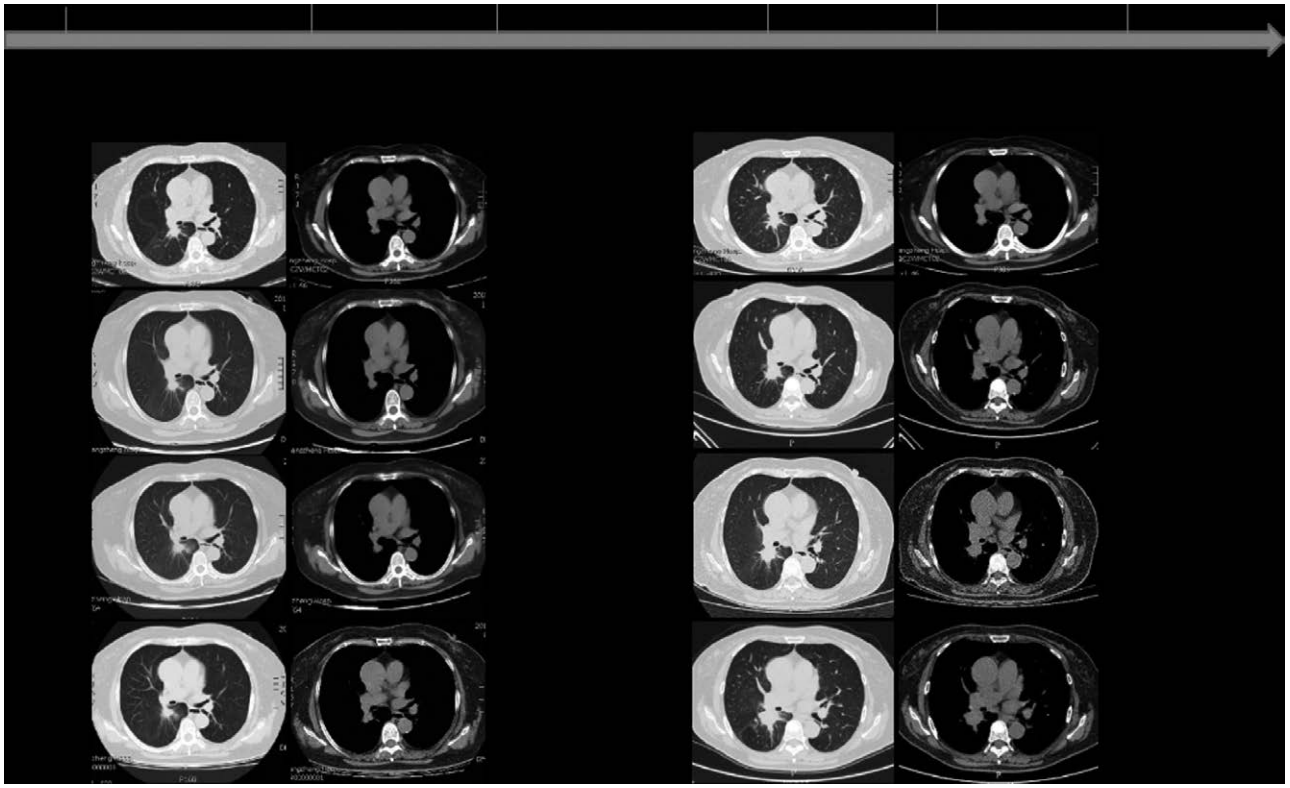
Fig. 1



Radiologic images of the primary lung mass at baseline and at evaluation of treatment response after 2 months of icotinib, after osimertinib, before trametinib, 1 month after trametinib and 3 months after trametinib.

Fig. 2

Schematics showing the timeline of treatment. Integrative Genomics Viewer snapshot of *GNAS* R201C (a) and R201H (b) by next-generation sequencing.

NGS with the plasma sample collected in Aug 2018 using a Guardant360 CDx test (Guardant Health, California, USA) but did not detect any mutation. Subsequently, immune cell therapy was performed five times without shrinkage of the primary mass. In Oct 2018, the patient received osimertinib (80 mg daily) and achieved SD (Fig. 1). From Feb 2019 to Mar 2019, she also received programmed death 1 immune checkpoint blockade therapy but discontinued use for immune-related pneumonia, myocarditis and hepatitis. Osimertinib was kept until July 2019 when disease progression in the primary mass (29 mm in diameter) was revealed by chest CT. Considering the osimertinib resistance and to seek further treatment options, a 10 ml tube of whole blood sample was sent to the laboratory of Jiaxing Yunying Medical Inspection Co., Ltd for targeted sequencing which covers 447 cancer-relevant genes. This revealed two activating *GNAS* mutations: R201C and R201H (allele frequency:1.40 and 0.70%) (Fig. 2a,b). *EGFR* and other mutations were not detected. Previously, it was reported that a patient with appendiceal adenocarcinoma experienced clinical benefits from trametinib treatment harboring a *GNAS* R201H mutation [6]. However, the antitumor efficacy of trametinib for *GNAS* R201C and R201H mutants in NSCLC is still unclear. Nevertheless, the patient still decided to accept trametinib as a life-saving treatment after careful consideration. Trametinib (2 mg Qd) was administered, followed by a routine visit, where no obvious tumor increase was observed (Fig. 1). Considering the progressive increase in carcinoembryonic antigen, the patient received bevacizumab (300 mg Q3w), which resulted in a significant improvement of clinical symptoms. No treatment-related adverse events were observed during the treatment course. The patient had a stable disease for 5 months. Due to coronavirus disease-19, the last follow-up visit occurred in May 2020.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

In the present study, we identified the acquisition of *GNAS* R201C and R201H mutations after osimertinib progression in an *EGFR*-positive NSCLC. The *GNAS* gene is located at chromosome 20q13.3, which encodes the alpha subunit of the stimulatory G protein (Gs-α), a guanine-nucleotide binding protein involved in hormonal regulation of adenylate cyclase. Gs-α is an important component of the cAMP/protein kinase [7]. Mutations in the *GNAS* gene have been described more frequently at codon 201, which leads to the replacement of arginine 201 with histidine (R201H) or cysteine (R201C). These mutations lead to the loss of GTPase activity of the G-stimulatory protein alpha subunit while leaving the adenyl cyclase stimulatory activity intact. The resulting constitutive activation, increased intracellular cAMP levels and constitutive cAMP signaling are associated with excessive proliferation and tumor development [8–10].

Preclinical evidence suggests that tumors with GNAS mutations may be sensitive to mitogen-activated protein kinase (MAPK) and Wingless and int-1 (Wnt) pathway inhibitors [8]. Because *GNAS* activation may affect downstream MAPK and Wnt signaling pathways [8], inhibitors of these pathways may be relevant to tumors with *GNAS*-activating mutations such as R201C and R201H mutations. Trametinib is a reversible, highly selective allosteric inhibitor of MEK1 and MEK2, which was approved in 2013 for the treatment of unresectable or metastatic melanoma with a B-Raf Proto-Oncogene V600E mutation. It was reported that an appendiceal adenocarcinoma patient harboring a *GNAS* R201H mutation, experienced clinical benefits from trametinib treatment [6]. Our NSCLC patient also experienced meaningful, albeit short-lived, clinical benefits – including an improvement in quality of life from trametinib, suggesting that targeted MAPK pathway inhibition was important in inducing tumor response.

To the best of our knowledge, this is the first report on the prevalence of *GNAS* R201C and R201H mutants in NSCLC and their response to trametinib treatment. However, the effect of trametinib on *GNAS* R201C and R201H mutations, especially its side effects, should be further investigated and confirmed in subsequent studies. This report demonstrated the important role of comprehensive genomic analysis by NGS and optimizing the targeted therapeutic strategy based on genetic test results in NSCLC patients.

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The authors have completed the CARE reporting checklist.

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Conflicts of interest

There are no conflicts of interest.

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