



An advanced non-small cell lung cancer patient with *EGFR* and *KRAS* mutations, and PD-L1 positive, benefited from immunotherapy: a case report

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Background: Patients with epidermal growth factor receptor (*EGFR*)-sensitive mutations have great opportunity to benefit from *EGFR*-tyrosine kinase inhibitors (TKI) in non-small cell lung cancer (NSCLC). Although the presence of Kirsten rat sarcoma virus (*KRAS*) mutations is predictive of lack of benefit from *EGFR*-tyrosine kinase inhibitor (TKI) therapy for NSCLC, patients with *KRAS* mutations could be more sensitive to programmed cell death 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors. However, the application of immunotherapy in *EGFR* mutated NSCLC patients is still controversial.

Case Description: In this study, we reported the case of a 56-year-old NSCLC patient who harbored the mutations of *EGFR* L858R and *KRAS* G12D, with a high tumor mutational burden value and positive PD-L1 expression. Considering the *EGFR* sensitive mutation, gefitinib combined pemetrexed was administered; however, the disease progressed soon after. The patient then underwent combined treatment of bevacizumab (400 mg), camrelizumab (200 mg), and pemetrexed (0.8 mg), and partial response was observed after 4 months. When chemotherapy was removed from the combined treatment, liver metastasis was detected. Interestingly, the disease was well controlled when the combined treatment of bevacizumab, camrelizumab, and pemetrexed was resumed. Overall, the patient benefits lasted more than 17 months.

Conclusions: Our results indicated that immunotherapy may be a potential choice in NSCLC with *EGFR* and *KRAS* mutations, and combined chemotherapy may effectively increase therapeutic efficiency during combined immunotherapy.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (*EGFR*); programmed death-ligand 1 (PD-L1); immunotherapy; case report

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Introduction

Lung cancer is a disease with high rates of incidence and mortality worldwide (1). Most patients are diagnosed at stages III and IV. The factors related to the staging and prognosis of non-small cell lung cancer (NSCLC) include age, overall health, lifestyle such as smoking and drinking, immune and genetic markers of cancer, family history, and so on. Traditional treatments for lung cancer include surgery,

chemotherapy, and radiotherapy (2). In the past few years, with the continuous progress of molecular tissue detection technology, the development of targeted therapy has been greatly promoted. The survival of advanced NSCLC patients with sensitive epidermal growth factor receptor (*EGFR*) mutation has been significantly improved (3). However, the majority of NSCLC patients with *EGFR*-tyrosine kinase inhibitor (TKI) mutations have no response

Table 1 Patient genomic variations information

Gene name	Amino acid variation	Variation site	Variation type
<i>EGFR</i>	L858R	Exon 21	SNV
<i>KRAS</i>	G12D	Exon 2	SNV
<i>NOTCH1</i>	M771I, T772A	Exon 14	SNV
	K814*	Exon 15	SNV
<i>CTNNA2</i>	K873N	Exon 18	SNV
<i>DNMT3A</i>	A572S	Exon 15	SNV
<i>FAM135B</i>	E515A	Exon 13	SNV
<i>GRIN2A</i>	P1053S	Exon 14	SNV
<i>LRP1B</i>	H42Q	Exon 2	SNV
	G3378V	Exon 64	SNV
<i>MTAP</i>	–	–	Deletion
<i>PIK3CG</i>	E415Q	Exon 2	SNV
<i>RBM10</i>	L454Sfs*31	Exon 13	InDel
<i>TNFRSF19</i>	E82*	Exon 4	SNV
<i>TRIO</i>	S1948F	Exon 38	SNV

*, Stop codon. SNV, single nucleotide variant; InDel, short insertion/deletion.

or early resistance to EGFR-TKI (4,5). The mutation of EGFR T790M is a common resistance mechanism of TKI. Bypass activation such as *MET* and *HER2* activation, downstream pathway including *BRAF* and *PI3K*, and histological exchange such as NSCLC transformation to small cell lung cancer, are all potential resistance mechanisms (6,7).

Programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) immunotherapy is another effective treatment option for lung cancer patients, and the combination of chemotherapy, radiotherapy and immunotherapy can effectively improve the efficiency and clinical prognosis of various solid tumors, including lung cancer (8). In a study, only 20% of the unselected patients responded to immunotherapy (9). The expression of PD-L1 and tumor mutational burden (TMB) are biomarkers for the prediction of response to immunosuppressants (10). The heterogeneity of expression of PD-L1 existed in patients with NSCLC. Among them, 33.7% of patients with PD-L1 positive expression $\geq 1\%$ and 10.8% of patients with PD-L1 positive expression $\geq 50\%$ (11). Previous study also showed that the expression of PD-L1 is associated with type of tumor sample, resection versus biopsy samples, and biopsies

of primary versus metastatic cancers (12). Clinical trials have shown that pembrolizumab or nivolumab combination therapy can significantly improve patient prognosis (13). However, the efficacy of anti-PD-1/PD-L1 immunotherapy is limited in patients with *EGFR*-sensitive mutations (14). Although the combination of atelizumab, chemotherapy, and bevacizumab is effective in *EGFR* positive patients (15), there have been few reports of camrelizumab in *EGFR* positive patients. Especially in the treatment of patients with *EGFR* and *KRAS* double mutations, there is still controversy about which is more suitable for targeted therapy or chemotherapy (16–18). Immunotherapy in patients with *EGFR* and *KRAS* double mutations is also rarely reported. In this case report, we detailed the case of a male patient with *EGFR* sensitive mutation who benefited from combined immunotherapy. We present the following case in accordance with the CARE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-403/rc>).

Case presentation

All procedures performed in this study 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 patient 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.

In October 2019, a male patient was diagnosed with NSCLC and invasive lung adenocarcinoma, with tumor stage of IVA (cT3N2M1b). Next generation sequencing-based genomic detection was performed and the results showed that the patient harbored the mutations of EGFR L858R and KRAS G12D (Table 1). Meanwhile, the TMB was evaluated as 12.7 muts/Mb, which was considered TMB-high, and the expression of PD-L1 was also evaluated as positive (22C3 TPS: positive, 50%; 28-8 TPS: positive, 80%). According to the EGFR L858R mutation, gefitinib combined with pemetrexed was used for 4 months, but the tumor progressed. The diameter of the tumor was 77 mm \times 56 mm. On 20 March 2020, considering the level of TMB and PD-L1 expression, the combined treatment of bevacizumab (400 mg), camrelizumab (200 mg), and pemetrexed (0.8 mg) was administered. After 2 months of this treatment, the adrenal nodule found at the beginning of admission had disappeared, and the diameter of the

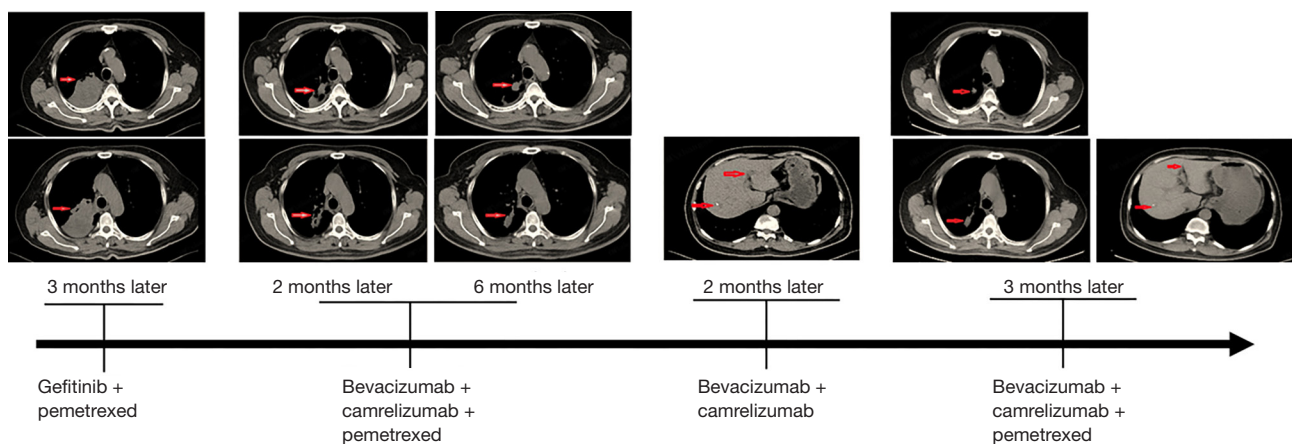


Figure 1 Details of the pathological images and treatments during the course of the disease. Red arrows indicate tumor lesions or nodules.

tumor had decreased to 56 mm × 25 mm (*Figure 1*). The treatment duration was 4 months, the diameter of the tumor continued decreased to 49 mm × 25 mm, and the curative effect was evaluated as partial response (PR). After 6 cycles of chemotherapy, the combined treatment of bevacizumab (400 mg) and camrelizumab (200 mg) was continued for 2 months. On 4 November 2020, liver metastasis was detected upon reexamination (*Figure 1*). We attempted to continue the combined treatment of bevacizumab (400 mg), camrelizumab (200 mg), and pemetrexed (0.8 mg), and interestingly, we found that both the primary and metastatic tumors were diminished for 3 months. To date, the patient has continued to benefit from the combination of the 3 drugs for more than 17 months (the last follow-up time was August 2021).

Discussion

With the development of next generation sequencing technology, the targeted therapies based on oncogenic mutations greatly increase the selection of treatment of advanced NSCLC. The *EGFR* activation mutation, which is approximately almost 50% in the Asian population and nearly 15% in Caucasians, is a hot spot mutation widely used in targeted therapy (4,5,19). The most common mutations are exon 19 deletion and exon 21 L858R point mutation, accounting for nearly 85% of *EGFR* mutated NSCLC (20). *KRAS* is another commonly mutated gene and is approximately 8-12% in Chinese NSCLC patients (21,22). Previous study showed that *EGFR* and *KRAS* mutations are mutually exclusive in NSCLC, however, the *KRAS* mutations are probably a resistance mechanism of

first-generation *EGFR*-TKI (23). Jia *et al.* also reported that *KRAS* mutation is a negative predictive factor in advanced NSCLC patients (24). Although studies have shown that *KRAS* mutations do not affect the responses of *EGFR*-TKI (16,17,25), low efficiency was observed, with the short disease-free survival (DFS) (26). Considering the mutation of *EGFR* L858R, we tried to administer gefitinib combined with chemotherapy, however, the patient was not sensitive to gefitinib, which may have been the cause of *KRAS* mutation. Studies have shown that different driving gene mutations have different effects on the efficacy of immunotherapy (27,28). When treated with immunotherapy, patients with *EGFR* sensitive mutations have a poor prognosis, while those with *KRAS* mutations may have a longer progression-free survival (PFS) (29,30). In this study, the patients carried both *EGFR* sensitive mutation and *KRAS* mutation, and high TMB and high PD-L1 expression (≥50%) were also detected. Patients with PD-L1 expression higher than 50% showed improved objective response rate (31). These results support the possibility of benefit from immunotherapy. Although there has been a precedent of TKI combined with immunotherapy (32), considering the rapid progress of the patient while receiving gefitinib, treatment was switched to combined immunotherapy, anti-vascular inhibitor, chemotherapy, and they continued to benefit for 4 months. It is suggested that immunotherapy can potentially be selected for patients with both *KRAS* and *EGFR* mutations.

Generally, the TMB of patients with general *EGFR* mutation in lung adenocarcinoma is low, which may be related to the microenvironment of lung adenocarcinoma, and leads to poor prognosis of immunotherapy (14). Low TMB represents a lack of killer T cells. When the

dominant tumor cells are inhibited and other non-dominant tumor cells are enriched, TMB may be increased and promote the infiltration of killer T cells, so as to increase the opportunity of immunotherapy. Chemotherapy may play a key role in this process. So far, the treatment of NSCLC patients with *EGFR* and *KRAS* mutations is still under exploration. Zhuang *et al.* concluded that patients harboring co-alterations tend to benefit more from TKI therapy than from chemotherapy (16). Lee *et al.* also showed that NSCLC patients with *EGFR* and *KRAS* mutations achieved partial responses after receiving targeted therapy with EGFR TKI gefitinib and erlotinib, but showed disease progression less than 20 months (17). In contrast, another report suggested that a subgroup of *EGFR* mutated tumors with concomitant driver mutations affected the activity of first-line EGFR TKIs (18). In this case report, chemotherapy may have played a key role in the treatment process, which was manifested as stopping chemotherapy and metastasis occurring, and upon resumption of the combination of 3 drugs, the metastatic and primary lesions effectively responded. The possible mechanism is as follows: first, chemotherapy can kill tumor cells and cause aseptic inflammation, which changes tumor microenvironment and may promote the infiltration of killer T cells; second, chemotherapy has the opportunity to kill immunosuppressive cells, so that immune cells can play a better role in killing tumor cells; and third, chemotherapy can kill tumor cells and release a large number of immune antigens to promote the anti-tumor immunity of the immune system. However, the specific mechanism remains to be further studied.

In conclusion, our patient continued to benefit for 17 months through combined treatment of immunotherapy, anti-vascular inhibitor, and chemotherapy, suggesting that next-generation sequencing based genomic alteration detection is necessary and immunotherapy can be attempted in advanced NSCLC patients with *EGFR* and *KRAS* mutations. Combined chemotherapy may effectively increase efficiency during immunotherapy treatment.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-403/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-403/coif>). XS and SZ are from Shanghai Origimed Co., Ltd. The other authors have no conflicts of interest to declare.

Ethical Statement: 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 this study 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 patient 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.

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