Received: 6 April 2023 | Accepted: 24 April 2023

DOI: 10.1002/rcr2.1155

CASE REPORT

Respirology Case Reports OPEN ACCESS APSR WILEY

PD-L1-negative non-small cell lung cancer harbouring a rare *BRAF* mutation with successful treatment of first-line pembrolizumab plus chemotherapy: A case report and review the literature

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Associate Editor: James C. M. Ho

Abstract

BRAF mutations are uncommon in non-small cell lung cancer (NSCLC), accounting for less than 5% of all NSCLC cases. The utilization of targeted therapies in non-V600E *BRAF* mutant NSCLC is considered controversial, although non-V600E genotype is reported in ~50% of all *BRAF* mutant patients. We document the case of a 63-year-old patient with NSCLC harbouring a rare *BRAF* E501Q mutation, who had prolonged response to immunotherapy combined with chemotherapy in Vietnam. The patient was diagnosed with metastatic PD-L1-negative lung adenocarcinoma and received pembrolizumab plus chemotherapy as first-line treatment. After completing 35 cycles of pembrolizumab and pemetrexed, his disease has remained stable during the treatment-free follow-up period, and he is alive 38 months after treatment initiation at the latest follow-up. Immune-based therapy is an appropriate option for lung adenocarcinoma with rare non-V600E *BRAF* mutation. Further clinical studies are necessary to determine the effectiveness of using immune-based therapy in this specific population.

KEYWORDS

BRAF mutation, immunotherapy, non-small cell lung cancer (NSCLC), non-V600E genotype, pembrolizumab

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality worldwide.[1] It is a common type of cancer with high morbidity and mortality among newly diagnosed cases in Vietnamese population.[2] According to the WHO classification, adenocarcinoma is the most common histological type of NSCLC.[3] In terms of race, epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) driver mutations are more common in Asian than non-Asian populations,[4–8] and these patients benefit from treatment with receptor tyrosine kinase-targeted inhibitors therapy.[9] However, these genetic alterations were not observed in the majority of patients with NSCLC for whom immune-based therapy has become the standard of care in the first- and second-line settings.[9,10] Due to the use of next-generation sequencing (NGS), other rare activating mutations have been identified including the *BRAF* mutations, which occur in less than 5% of all NSCLC cases. Although approximately 50% of patients with *BRAF*-mutation have been reported to have non-V600E genotypes, currently, the use of targeted therapies and immunotherapy in non-V600E *BRAF*-mutated NSCLC remains unclear. We reported here a male patient diagnosed with PD-L1-negative NSCLC with a rare non-V600E *BRAF* mutation. He received a total 35 cycles of first-line pembrolizumab plus chemotherapy.

CASE REPORT

A 63-year-old male patient with no previous medical history presented with symptoms of left chest pain, dry cough and hoarseness 1 month before his admission. His performance status was ECOG 1. He was a heavy smoker with a history of 20 pack-years. The patient was referred to Department of Medical Oncology 1 at Vietnam National Cancer Hospital in February 2020. Chest computed tomography (CT) revealed a left lung mass measuring 30 × 45 mm with

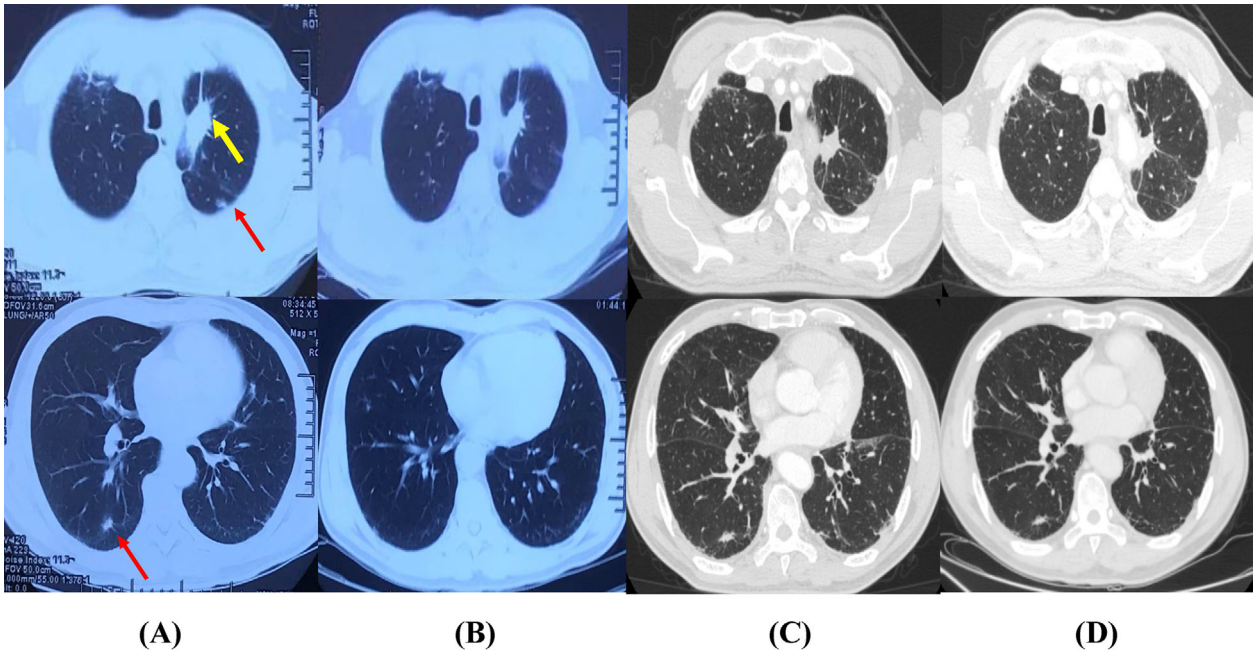

FIGURE 1 Images of CT scans showed a partial response in the primary tumour and bilateral pulmonary nodules after first-line treatment by pembrolizumab plus chemotherapy. (A) Whole-body computed tomography (CT) revealed a left lung mass of 30 × 45 mm with scattered bilateral nodules of up to 25 mm at diagnosis. (B) Partial response to immune-based therapy after 6 cycles.

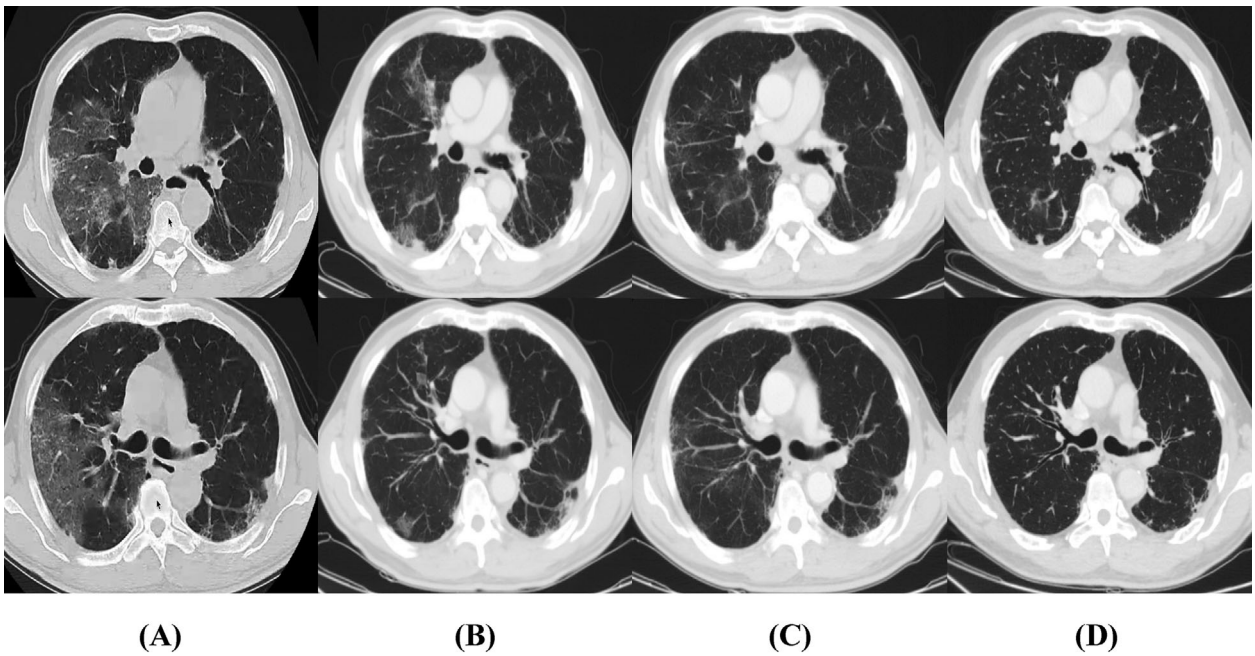

FIGURE 2 COVID-19 pneumonia was evaluated based on the chest CT scans. (A) Bilateral pneumonia with a CT-SS score of 15/25 at the time of COVID-19 disease. (B) One month later, chest CT showed improvement of pulmonary injury. (C) After completion of 35 cycles, chest CT revealed a partial response. (D) One year after completing treatment, his disease has remained stable throughout the treatment-free follow-up.

bilateral scattered nodules of up to 25 mm (Figure 1A). Magnetic resonance imaging (MRI) showed no evidence of brain metastasis. Histopathological findings of core biopsy revealed lung adenocarcinoma that was negative for programmed death-ligand 1 (PD-L1) (TPS <1%) by PD-L1 IHC 22C3 pharmDx Assay (Dako). PD-L1 22C3 clone was stained by a platform of Autostainer Link 48, automatically. NGS test was performed by a platform such as MiniSeq, Illumina, with Massively parallel DNA sequencing by Next Generation Sequencing technology. Gene panel of lung carcinoma includes seven genes such as *EGFR*, *ALK*, *ROS1*, *BRAF*, *KRAS*, *NRAS*, *PIK3CA*. Tumour NGS results showed no mutations in *EGFR*, *ALK*, *ROS1*, *KRAS*, *NRAS*, *PIK3CA* genes, but evidence of *BRAF* E501Q mutation (NM_004333.4:c.1501G > C) with a mutation frequency of 45%. The patient received a combination of pemetrexed, carboplatin and pembrolizumab as the first-line treatment for metastatic NSCLC. After 3 cycles, he experienced a partial response based on CT scan and clinical symptoms improvement. Treatment was continued until a total of six cycles with a partial response (Figure 1B) and pembrolizumab plus pemetrexed were planned up to a total of 35 cycles. However, before the 27th cycle in February 2022, patient was diagnosed with COVID-19 with symptoms of cough, dyspnea, high fever and SpO_2 value between 85% and 90%, and positive for SARS-CoV-2 by RT-PCR. The patient had received two doses of Pfizer vaccine, the last dose being given 3 months ago. Chest CT scans showed bilateral pneumonia with a CT-SS score of 15/25 (Figure 2A).[11] He gradually recovered after receiving antibiotics, corticosteroids and prophylactic anticoagulation. One month later, chest CT showed improvement of pulmonary injury (Figure 2B), and pembrolizumab plus pemetrexed were resumed every 3 weeks until the 35th cycle was given in April 2022. After completion of 35 cycles, CT revealed a partial response. At latest follow-up, his disease has remained stable throughout the treatment-free follow-up (Figures 1C and 2C,D), and the patient is alive 38 months without severe adverse events from start of treatment.

DISCUSSION

BRAF mutations, most of which lead to activation of the MAPK pathway, occur in 2%–4% of NSCLC cases with the most common genotype, V600E. The remaining *BRAF* mutations were non-V600E *BRAF* group, including activating (i.e., G469A/V, K601E, L597R) or inactivating (i.e., D594G, G466V).[12–14]

Male smokers and adenocarcinoma were common characteristics were observed in *BRAF*-mutated NSCLC studies and in our patient.[14,15] A retrospective study by Litvak et al. reported that all of *BRAF*-mutated NSCLC patients were adenocarcinoma, and heavy smokers were observed in 24 of 27 non-V600E BRAF-mutated patients.[16] In a study by Tissot et al., non-V600E BRAF mutations were reported in 38 of 80 patients, with high rates of smoking and adenocarcinoma among these patients (95% and 92%, respectively). It should be noted that non-V600E mutations have been reported more frequently with concomitant *KRAS* mutations (13%) than V600E mutation. In our case, NGS revealed only a rare E501Q genotype as non-V600E mutation (NM_004333.4: c.1501G > C) with a mutilation frequency of 45%. In this genotype, the nucleotide change occurs at position 1501, where a G nucleotide has been replaced by a C nucleotide. This change leads to a change in the amino acid sequence of the *BRAF* protein at position 501, where the amino acid glutamic acid (Glu) is replaced by glutamine (Gln). This variant is referred to as p.Glu501Gln or c.1501G > C.[17] To the best of our knowledge, we first described a NSCLC patient with E501Q genotype.

Recent advances in cancer genetics and targeted therapy have been improved the outcome and safety of advanced NSCLC treatment, especially those with *EGFR*, *ALK*, or c-Ros oncogene 1 mutations (*ROS1*). Several anti-*BRAF* inhibitors have been approved for V600E *BRAF*-mutant melanoma. However, data on the use of anti-*BRAF* inhibitors in NSCLC were still limited. In a phase 2 study by Planchard et al. using dabrafenib plus trametinib in V600E *BRAF*-mutant NSCLC, overall response rate (ORR) was 64% with a high rate of Grades 3–4 toxicities (69%).[18] In Asian population, Ota et al. reported a successful treatment of *BRAF*/MEK inhibitors in a female patient with V600E *BRAF*-mutated lung adenocarcinoma.[19] Another study from Japan also reported the efficacy of dabrafenib combined with trametinib in an 85-year-old patient with V600E mutation.[20] However, the use of targeted therapies in non-V600E *BRAF*-mutated NSCLC was considered controversial although about 50% of all *BRAF*-mutated patients were reported to be non-V600E-genic type.[12]

Chemotherapy has showed limited results in the treatment of previously untreated *BRAF*-mutant NSCLC. In a cohort of advanced NSCLC treated with first-line chemotherapy, Ding et al. showed that patients with *BRAF* mutations had a median progression-free survivals (PFS) of 5.6 months. According to *BRAF* genotypes, the median PFS was longer in non-V600E-mutant patients than V600E-mutant patients (6.2 vs. 5.2 months, respectively), however, there was no significant difference between the two groups ($p = 0.561$).[15] Although immunotherapy has changed the lung cancer treatment landscape over the past decade, data on the use of immunotherapy in *BRAF*-mutant NSCLC remain limited. In the retrospective cohort study by Wang et al., primary *BRAF* mutations were observed in 73 patients with a non-V600E genotypes, accounting for 32.9%. In 29 *BRAF*-mutant patients, immunotherapy plus chemotherapy showed a prolonged response compared with immune-monotherapy, with a median PFS of 14.77 versus 5.0 months, respectively. This was also similar for overall survival.[21] A large study by Mazieres et al. using immunotherapy in 551 patients with activating molecular mutations showed a median PFS and OS of 3 and 13.6 months, respectively in patients harbouring *BRAF* mutations.[22] Interestingly, Dudnik et al. demonstrated that high levels of PD-L1 expression were associated with *BRAF* mutations. In this study, using immunotherapy, median PFS in patients with V600E and non-V600E genotypes

were 3.7 and 4.1 months, respectively. However, PD-L1 expression and *BRAF* genotypes did not affect PFS in this cohort.[23] A study by Negrao et al. showed that the rate of PD-L1 positivity (TPS ≥1%) in V600E genotype (75.4%) was higher than that in non-V600E genotypes (55.8%), particularly the 48.3% of high PD-L1 expression (TPS ≥50%) in V600E *BRAF* group. However, high tumour mutational burden (TMB) was observed in non-V600E *BRAF* mutations. Regarding the results of immunotherapy, median PFS and OS of non-V600E BRAF-mutation patients were lower than those of V600E group, which were 5.42 versus 9.79 months and 14.88 versus 20.83 months, respectively.[24] However, Li et al. reported no differences of PD-L1 expression between *BRAF* mutations and wild-type *BRAF* groups and between two *BRAF* genotypes. Furthermore, patients with advanced NSCLC with V600E and non-V600E *BRAF* mutations had similar OS.[25]

In our study, the patient received pembrolizumab plus chemotherapy based on the demonstrated benefit in the Keynote-189 study.[26] Despite of a 1.5-month interruption due to severe COVID-19 disease, he received a total of 35 pembrolizumab/pemetrexed cycles. After completing 35 cycles, his disease has remained stable during treatment-free follow-up, and the patient is alive 38 months after treatment initiation at latest follow-up. It was found that our patient, diagnosed with PD-L1-negative lung adenocarcinoma with a non-V600E *BRAF* mutation, responded successfully to immune-based therapy without serious adverse events. Our result was similar to those reported by Rittberg et al. that demonstrated a prolonged disease control over 4 years with nivolumab monotherapy in a 61-year-old patient with advanced NSCLC harbouring a de novo *BRAF* G469A mutation. However, in this case, PD-L1 > 50% was observed.[27]

In conclusion, we reported a patient with PD-L1-negative NSCLC carrying a rare non-V600E *BRAF* mutation, who had prolonged response to immunotherapy plus chemotherapy. Further clinical studies are necessary to determine the effectiveness of using immune-based therapy in this specific population.

AUTHOR CONTRIBUTIONS

Kien Hung Do should be considered the major author. He participated directly in diagnosis, treatment, and follow-up of the patient, performed the literature review, and assisted in drafting of the components of the case report, and assisted in formatting the presented material. Phuong Nguyen Thi Bich and Gia Hoang Nguyen took part in the diagnostic and treatment consultant and assisted in literature review. Tai Van Nguyen performed follow-up of the patient, took illustrated figures, literature review, assisted in drafting of the components of the case report. Chu Van Nguyen performed the diagnostic consultant of the HE stains and immunohistochemical staining and testing of gene mutation, literature review and assisted in drafting of the components of the case report and assisted in formatting the presented material.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

All data analysed during this case report is in this article.

ETHICS STATEMENT

Ethical approval is not required for this study in accordance with local guidelines. The authors declare that appropriate written informed consent was obtained from the patient for publication of details of his medical cases and any accompanying images.

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How to cite this article: Do KH, Nguyen TV, Nguyen Thi Bich P, Nguyen GH, Nguyen CV. PD-L1-negative non-small cell lung cancer harbouring a rare *BRAF* mutation with successful treatment of first-line pembrolizumab plus chemotherapy: A case report and review the literature. Respirology Case Reports. 2023;11:e01155. https://doi.org/10.1002/rcr2.1155