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Case Report

Response to ABCP Regimen in a ROS1-Rearranged Lung Adenocarcinoma Patient with Brain Metastases and High PD-L1 Expression: A Case Report

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Abstract

Background: C-ROS oncogene 1 (ROS1) rearrangement is rare in non-small-cell lung cancer (NSCLC) while the ROS1 tyrosine kinase inhibitors (TKIs) have shown remarkable anti-tumor activity. However, drug resistance is inevitable. The next generation of targeted therapy or chemotherapy is a standard treatment recommended by the NCCN guidelines. Although the populations of high programmed cell death ligand 1 (PD-L1) expression (PD-L1>50%) were reported approximately 20.3%-60% in ROS1 rearranged NSCLC, there were few clinical trials focus on the immunotherapy among NSCLC patients with ROS1 rearrangement, and the efficacy is still controversial in the posterior line.

Case Description: We report a case of a 42-year-old female with ROS1-rearranged NSCLC and high PD-L1 expression treated with atezolizumab (1200 mg) / bevacizumab (7.5 mg/kg) / carboplatin (AUC 5) / pemetrexed (500 mg/m^2) (ABCP) regimen after failure of targeted therapy. After 2 cycles, she achieved partial response (PR) and confirmed PR after 4 cycles of ABCP regimen not only in the primary lung lesion, but also in multiple metastatic lesions of the brain. Then the maintenance treatment of atezolizumab (1200 mg) / bevacizumab (7.5 mg/kg) / pemetrexed (500 mg/m^2) (ABP) was continued to have benefit. Moreover, the levels of serum tumor markers all showed a downward trend during treatment. During the treatment, the major adverse events (AEs) observed were nausea, dazzling and headache that were tolerable.

Conclusion: This case reminds us of new possibilities for further line therapy among NSCLC patients with ROS1-rearranged. The treatment of immune-chemotherapy plus antiangiogenic therapy may be a potential treatment option for advanced ROS1-rearranged NSCLC especially with high PD-L1 expression after ROS1-TKI failure.

Keywords: ROS1 rearrangement; Lung adenocarcinoma; Immunotherapy

Introduction

The overall prevalence of ROS1 rearrangement is approximately 1-2% in NSCLC [1]. Crizotinib, demonstrated by PROFILE 1001 trial, has shown an objective response rate (ORR) of 72% (95% CI, 58–83), a median progression-free survival (mPFS) of 19.3 months (95% CI, 15.2–39.1) and a median overall survival (OS) of 51.4 months (95% CI, 29.3–not reached) among patients with ROS1 rearrangement [2]. Due to the remarkable antitumor activity of crizotinib, it has been recommended as standard first-line therapy in NSCLC patients with ROS1 rearrangement. The next generation targeted agents or systemic therapies such as chemotherapy were recommended by the national comprehensive cancer network (NCCN) guidelines for NSCLC patients with ROS1 rearrangement who have failed first-line targeted therapy [3]. PD-L1 is a predictor of immunotherapy, and whether to add immunotherapy is based on its expression. The expression status of PD-L1 in ROS1-rearranged NSCLC patients have been reported in several previous studies as approximately 20.3%-60% patients were with high PD-L1 expression (PD-L1>50%). Though the proportion of PD-L1 high expression was more than that in patients with EGFR mutation or ALK fusion NSCLC [4-8], there were few studies on ROS1 rearranged NSCLC patients received immunotherapy, and thus the efficacy is still controversial. However, in our case, we challenged the combination regimen of chemo-immunotherapy and antiangiogenic therapy on a ROS1-rearranged NSCLC patient after resistance to first-line targeted therapy.

Case report

The patient, a 42-year-old female who was a never smoker, presented with neck pain. The chest computed tomography (CT) revealed a 68x52x77 mm lesion in her right upper lung with metastases to multiple mediastinal lymph nodes (LNs), the first and the second cervical vertebral body. Positive electron emission tomography (PET) - CT showed a strong fluorodeoxyglucose (FDG) accumulation in the primary lung lesion (SUVmax 22.3). Fortunately, the brain magnetic resonance imaging (MRI) was normal at baseline. The right supraclavicular LN biopsy showed poorly differentiated lung adenocarcinoma（Figure 1A) with immunohistochemistry (IHC) staining results as TTF-1 (+), CK (+++), CK7 (-), Napsin A (-), CK5/6 (-) and P40 (-) with the tumor proportion score (TPS) of PD-L1 (22C3, TPS) was 80% (Figure 1B). The next-generation sequencing (NGS) of the LN biopsy specimen and blood samples obtained at baseline revealed CD74-ROS1 rearrangement, TP53 mutation and TERT mutation. She was enrolled in a clinical trial of second-generation ALK and ROS1 tyrosine kinase inhibitor (TKI) SAF-189s. She achieved a partial response (PR) according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) after 1 month and confirmed PR at 3 months after the treatment of TKI and radiotherapy of the cervical vertebrae with 42Gy/14F.

However, after 10 months of TKI therapy, she underwent progressive disease (PD) due to the enlarged primary lung lesion and multiple brain metastases. Then, the lumbar puncture was performed, without any tumor cells in the cerebrospinal fluid (CSF). However，PD-L1 of lung tissue in second biopsy reduced from 80% to 70%（Figure 1D). And the lung biopsy showed poorly differentiated carcinoma (Figure 1C). NGS of blood and CSF still showed CD74-ROS1 rearrangement, TP53 mutation and TERT mutation. Besides, a FGFR3 amplification was found in CSF but not in blood (Table 1).

Figure 1. Pathology images of HE staining and IHC (×200).

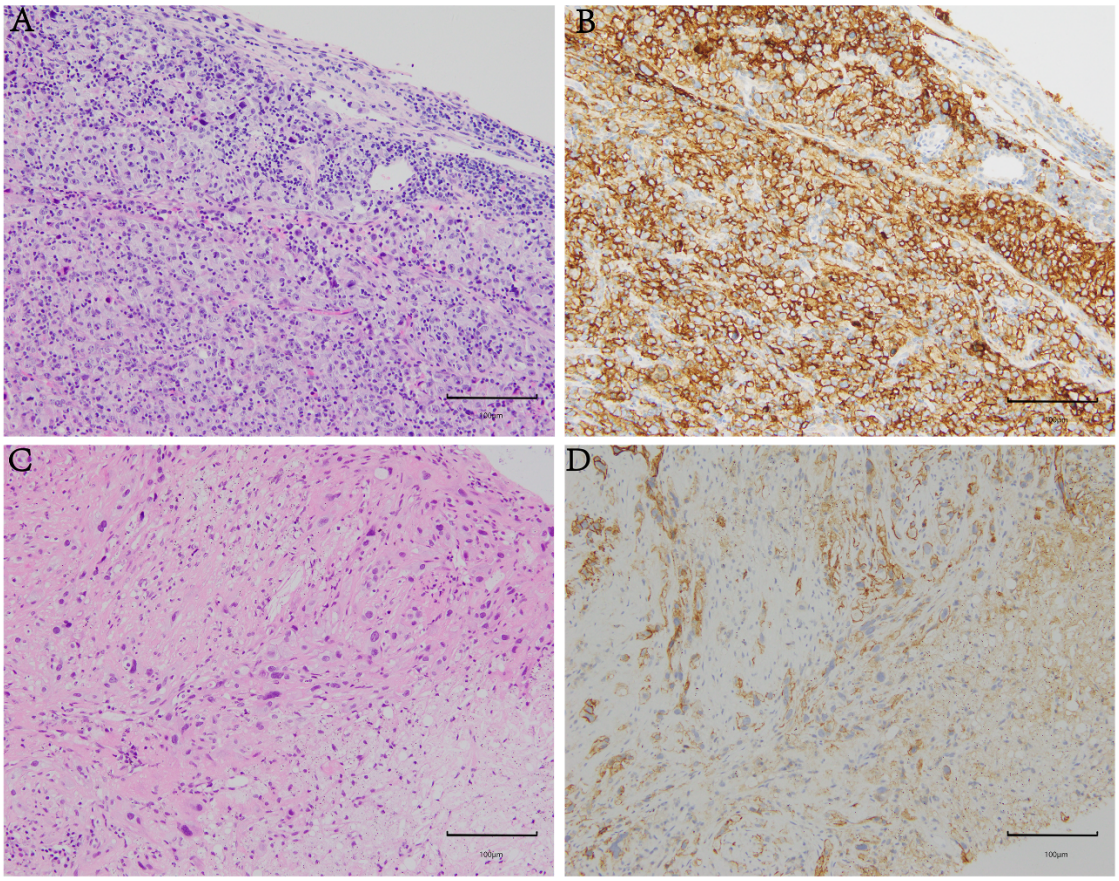

Figure 1. A: HE-staining result of LN as poorly differentiated lung adenocarcinoma at baseline. B: IHC staining of PD-L1 (TPS) was 80% at baseline. C: HE-staining result of lung lesion after first line TKI treatment failed. D: IHC staining of PD-L1 (TPS) was 70% after failure of first line TKI treatment. Scale bar: 100 μm.
Abbreviations: HE: hematoxylin and eosin; LN: lymph node; IHC: immunohistochemistry; PD-L1: programmed death ligand 1; TPS: tumour proportion score.

Date	Sample type	Gene	Variant type	cDNA	Amino Acid	Variable frequency
Oct/2020	Tissue	ROS1	Fusion	CD74- ROS1	CD74: exon7~ ROS1: exon34	25.70%
Oct/2020	Tissue	TERT	Mutation	c.-146C>T		11.89%
Oct/2020	Tissue	TP53	Mutation	c.853G>A	P. E285K	20.07%
Oct/2020	Plasma	ROS1	Fusion	CD74- ROS1	CD74: exon7~ ROS1: exon34	1.53%
Oct/2020	Plasma	TERT	Mutation	c.-146C>T		0.40%
Oct/2020	Plasma	TP53	Mutation	c.853G>A	P. E285K	1.79%

Aug/2021	Plasma	ROS1	Fusion	CD74- ROS1	CD74: exon7~ ROS1exon34	0.99%
Aug/2021	Plasma	TERT	Mutation	c.-146C>T		0.45%
Aug/2021	Plasma	TP53	Mutation	c.853G>A	P. E285K	1.24%
Aug/2021	CSF	ROS1	Fusion	CD74- ROS1	CD74: exon7~ ROS1exon34	37.18%
Aug/2021	CSF	TERT	Mutation	c.-146C>T		16.28%
Aug/2021	CSF	TP53	Mutation	c.853G>A	P. E285K	29.81%
Aug/2021	CSF	FGFR3	Amplification			CN:5.5
The NGS results of tissue and plasma when diagnosed lung adenocarcinoma showed ROS1 (+), TERT (+), TP53 (+). After first-line TKI treatment failed, the NGS results of plasma showed ROS1 (+), TERT (+), TP53 (+) and that of CSF showed ROS1 (+), TERT (+), TP53 (+), FGFR3 (+). Abbreviations: NGS: next-generation sequencing; ROS1: c-ros oncogene 1; TERT: telomerase reverse transcriptase; TKI: tyrosine kinase inhibitor; CSF: cerebrospinal fluid; FGFR3: fibroblast growth factor receptor 3.						

Table 1: The NGS results when diagnosed and first-line treatment failed.

Due to the high PD-L1 expression, we challenged a combined treatment of immunochemotherapy and antiangiogenic therapy consisting of atezolizumab (1200 mg) / bevacizumab (7.5 mg/kg) / carboplatin (AUC 5) / pemetrexed (500 mg/m^2) (ABCP). And after two cycles' treatment, not only the primary lung lesion, but also the multiple brain metastases lesions were evaluated as PR (Figure 2). However, the patient had some central nervous system symptoms, including nausea, dazzling and headache after 1 cycle treatment. And after 4 cycles, the lung primary lesion and brain lesions were assessed as confirmed PR with chest CT and brain MRI. The lung lesion was evaluated PR while the brain metastases lesion in frontal lobe a little bit enlarged by brain MRI after 2 more cycles maintenance treatment of atezolizumab (1200 mg) / bevacizumab (7.5 mg/kg) / pemetrexed (500 mg/m^2) (ABP), the overall evaluation was PR. The level of carcinoembryonic antigen (CEA), neuron-specific enolase (NSE) and cytokeratin fragment antigen 21-1 (CYFRA21-1) all showed a downward trend in the course of treatment (Figure 3). Until now, the patient had received 4 cycles ABCP regimen and 2 cycles ABP regimen treatments and will receive whole brain radiotherapy before next cycle of treatment.

Figure 2. The chest CT and brain MRI scans during the period of treatment.

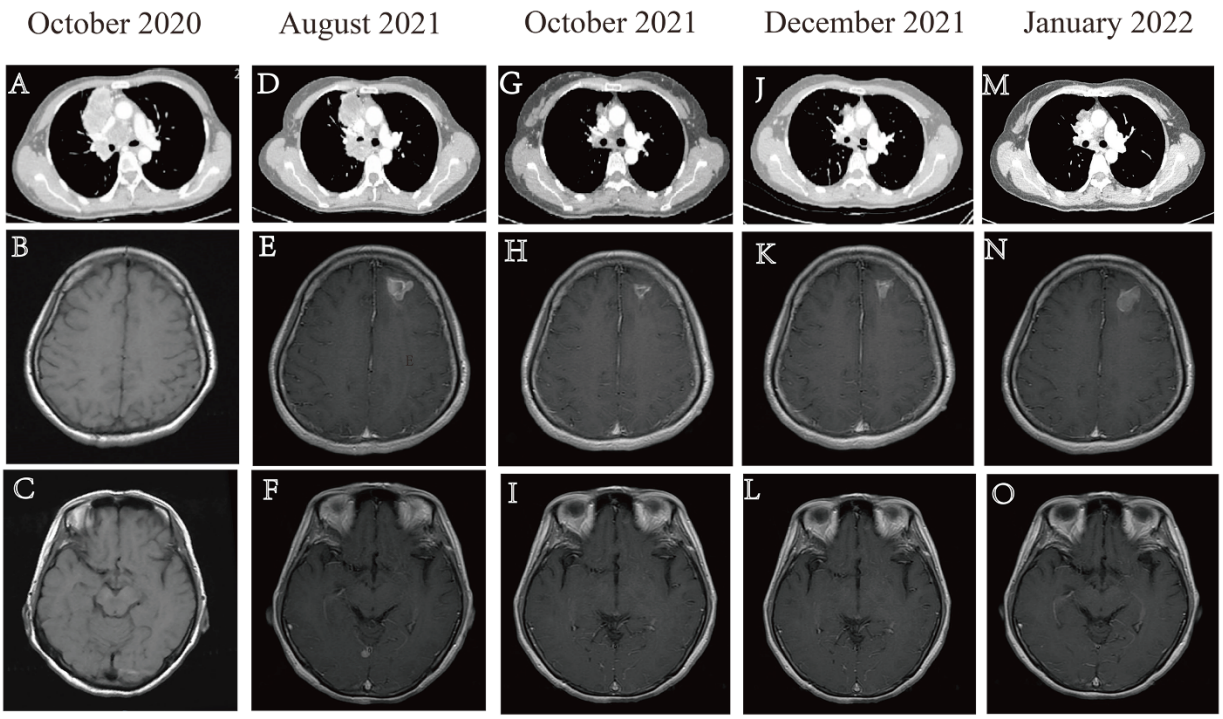

Figure 2. Chest CT revealed a lung lesion in the right lobe(October 2020) (A) and brain MRI revealed that there was no lesion in the brain at baseline (October 2020) (B,C) ; chest CT scan revealed the right lobe lesion PD after first-line TKI treatment (August 2021)(D) and brain MRI revealed multiple brain metastasis after first-line TKI treatment (August 2021) (E,F) ; chest CT and brain MRI showed PR after 2 cycles (October 2021) (G,H,I), confirmed PR after 4 cycles (December 2021) (J,K,L) second-line ABCP regimen, chest CT revealed the lung lesion continued PR(January 2022) (M), however the brain MRI revealed the brain lesion of frontal lobe was local progression (January 2022) (N,O), the overall evaluation was PR.

Abbreviations: MRI: magnetic resonance imaging; CT: computed tomography; PD: disease progression; TKI: tyrosine kinase inhibitor; PR: partial response;

ABCP: atezolizumab/ bevacizumab /carboplatin /pemetrexed.

Figure 3. The dynamic changes on levels of serum tumor markers.

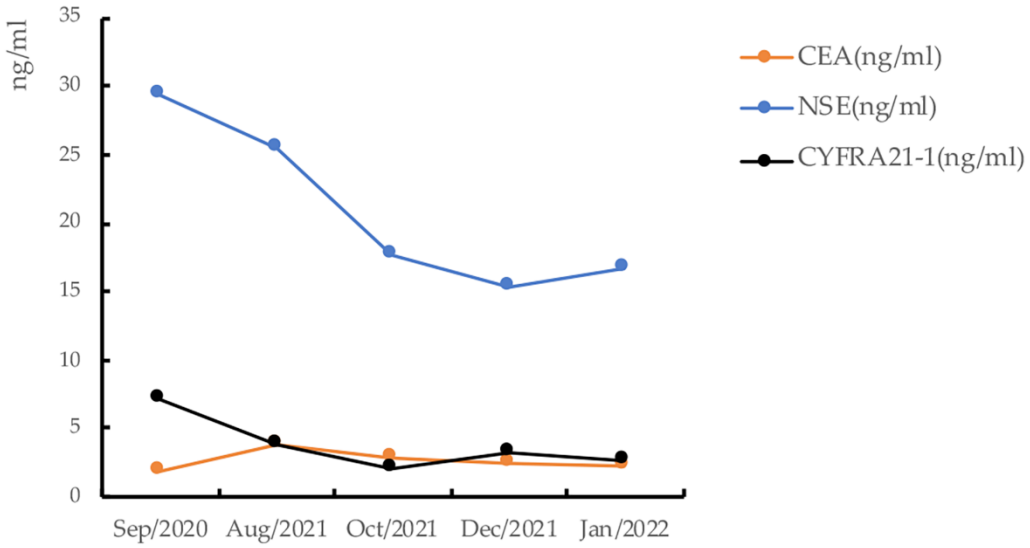

Figure 3. The levels of CEA, NSE and CYFRA21-1 were 283.53 ng/ml, 29.42 ng/ml and 1.89 ng/ml, respectively at baseline. After the failure of first line TKI therapy in August 2021, the levels of CEA, NSE and CYFRA21-1 were 3.86 ng/ml, 25.52 ng/ml and 3.82 ng/ml, respectively. And after 2 cycles, 4 cycles ABCP regimen and 2 cycles maintenance treatment of ABP regimen as the second line therapy, the level of NSE was increased from 17.7 to 15.38 and then to 16.64, while the levels of CEA and CYFRA21-1 were within normal range.
Abbreviations: CEA: carcinoembryonic antigen; NSE: neuron-specific enolase; CYFRA21-1: cytokeratin fragment antigen 21-1; ABCP: atezolizumab/bevacizumab /carboplatin /pemetrexed; ABP: atezolizumab/ bevacizumab /pemetrexed.

Discussion

This case of ROS1-rearranged NSCLC with high PD-L1 expression was treated with ABCP regimen after the failure of TKI therapy and achieved efficacy not only in the primary lung lesion, but also in brain metastases. However, no systematic study has shown response to the chemo-immunotherapy plus antiangiogenic therapy in ROS1 -rearranged NSCLC patients with brain metastases.

The incidence of brain metastases for untreated ROS1-rearranged NSCLC patients was reported as 36% according to Patil T et al., which was higher than wild-type NSCLC [9]. Many current studies and clinical trials have demonstrated that some targeted therapies not only have a certain effect on lung lesions but also have better control on brain metastases, and the intracranial efficacy of TKIs therapy has been evaluated. For instance, the intracranial ORR of lorlatinib was 64% (95%CI, 31-89) in TKI-naive patients and 50% (95%CI, 29-71) in crizotinib-pretreated patients [10]. The intracranial ORR of brigatinib achieved 50.0% (95%CI, 11.8-88.2) in crizotinib-pretreated patients as well [11]. Thus, the further-line treatment of ROS1-rearranged NSCLC patients with intracranial progression still mainly focuses on targeted therapy, especially the next-generation TKIs. Whereas the patient in our study refused to receive the next-generation ROS1-TKI due to financial problem. Considering the high PD-L1 expression, she was likely to be sensitive to immunotherapy. Although the effects of chemotherapy have been demonstrated by several studies [12-13], there were fewer studies to illustrate the efficacy of chemo-immunotherapy plus antiangiogenic therapy on ROS1-rearranged patients.

As for Immune-Checkpoint Inhibitors (ICIs) monotherapy in ROS1 rearrangement patients, the previous studies all showed a poor efficacy, the IMMUNOTARGET showed an ORR of only 16.7% (1 out of 6, median PFS was not estimated) in ROS1-rearranged NSCLC patients with PD-L1>20% after the treatment of single-agent ICI [14]. Another multi-institutional retrospective study also had suboptimal results that the ORR was 13% in ROS1 fusion-positive NSCLCs after ICI monotherapy [15]. Thus, the ICI

monotherapy maybe not indicated for ROS1-rearranged NSCLC. And the regimen of chemo-immunotherapy plus antiangiogenic therapy, it was not reported in NSCLC with other driver genes except for EGFR mutation. As in the subgroup analyses of IMpower150 study, the atezolizumab/bevacizumab /carboplatin/ paclitaxel regimen had an improvement in PFS compared with the bevacizumab/carboplatin/paclitaxel regimen in NSCLC patients with EGFR mutation [16]. Furthermore, a phase 2 single-arm study also demonstrated good efficacy of modified ABCP regimen in metastatic EGFR-mutated NSCLC after TKI failure [17]. Surprisingly, we found that such a case with ROS1 rearrangement and high PD-L1 expression also showed anti-tumor activity in both lung tumors and brain metastases with ABCP regimen.

In conclusion, the successful treatment of immune-chemotherapy plus antiangiogenic therapy in this case provided a potential treatment option for advanced ROS1-rearranged NSCLC with high PD-L1 expression after ROS1-TKI failure. Nevertheless, further studies of immune-chemotherapy plus antiangiogenic therapy are warranted in a larger sample size of ROS1-rearranged NSCLC patients. Additionally, further studies on how the immune microenvironment influenced by immunotherapy in ROS1 positive NSCLC patients are also needed.

Declarations

Consent for publication: Written informed consent was obtained from the patient for using tissue samples.

Ethical approval: Ethical approval was obtained from Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences.

Declaration of Competing Interest: All the authors declare that they have no competing interest. This article has not been published previously.

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CRediT authorship contribution statement

Quan-Quan Tan: Data collection, writing the paper. Yu-Qing Chen: Methodology, writing the paper. Ming-Ying Zheng: Investigation, reviewing the paper. Yu-Fa Li: Data collection. Ke-Jun Liu: Validation. Jun-Wei Su: Validation. Hua-Jun Chen: Study concept, validation. Jin-Ji Yang: Study concept, Supervision.

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