Int J Clin Exp Pathol 2025;18(1):37-41
www.ijcep.com /ISSN:1936-2625/IJCEP0149919

Case Report

Complete response to anti-PD1 therapy and chemotherapy in a patient with ALK-rearranged non-small cell lung cancer

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Received March 1, 2023; Accepted October 4, 2024; Epub January 15, 2025; Published January 30, 2025

Abstract: Targeted therapies are effective in non-small cell lung cancer (NSCLC) patients with driver gene mutations. Chemotherapy combined with immunotherapy is also a common treatment strategy in lung cancer. However, in previous studies, patients with ALK (Anaplastic Lymphoma Kinase) rearranged had a low response to immune checkpoint inhibitor (ICI) and the role of immunotherapy in ALK-positive NSCLC patients is unclear. Here, we report a case of a young man with ALK rearranged who demonstrated a complete response to anti-PD1 combination with chemotherapy, which suggests some ALK-rearranged patients with high expression of PD-L1 may permanently benefit from immunotherapy.

Keywords: Non-small cell lung cancer, ALK rearrangement, immunotherapy, PD-1, PD-L1, chemotherapy

Introduction

Anaplastic lymphoma kinase (ALK) rearrangements are found in 3-7% of non-small cell lung cancers (NSCLC). As a tumor driver gene, ALK fusion gene is essential for the occurrence and development of NSCLC [1]. For patients with stage IV NSCLC harboring ALK rearrangement, ALK tyrosine kinase inhibitors (TKIs) are preferred as the initial treatment option and have demonstrated superior efficacy compared to chemotherapy in terms of progression-free stage. However, previous research has indicated that immune checkpoint inhibitor (ICI) monotherapy yielded limited objective response rates and short median progression-free survival in patients with advanced ALK-rearranged NSCLC [2]. While ALK-rearranged NSCLC exhibits high sensitivity to ALK-targeted therapy, it commonly exhibits resistance to immunotherapy [3]. In this case report, we present a patient with advanced ALK-rearranged NSCLC who achieved a complete response (CR) following a combination of immunotherapy and chemotherapy.

Case report

A 35-year-old man was diagnosed with adenocarcinoma of the right lung with intracranial metastasis stage IVa (cT2bN1M1b) on February 2021. Percutaneous lung biopsy was performed. Pathological diagnosis was adenocarcinoma, EGFR gene test disclosed that no mutation was found. ALK-V (D5F3) (+), ROS-1 was negative by PCR. PD-L1 expression level was TPS 71-80%, CPS 80% (**Figure 1A-D**). He received palliative radiotherapy for intracranial metastases (radiotherapy dose GTV 45 Gy/15 F), and the first cycle (pemetrexed 885 mg D1 + carboplatin 400 mg D1) of chemotherapy on 26th February 2021. On 12th March 2021, the patient completed had palliative radiotherapy, and re-examination MRI showed that the intracranial lesions shrank.

On April 20th, from the second cycle of treatment, the patient started additional immunotherapy (pemetrexed 885 mg D1 + carboplatin 400 mg D1) chemotherapy + camrelizumab 200 mg immunotherapy. The results of re-

https://doi.org/10.62347/XWHW6190

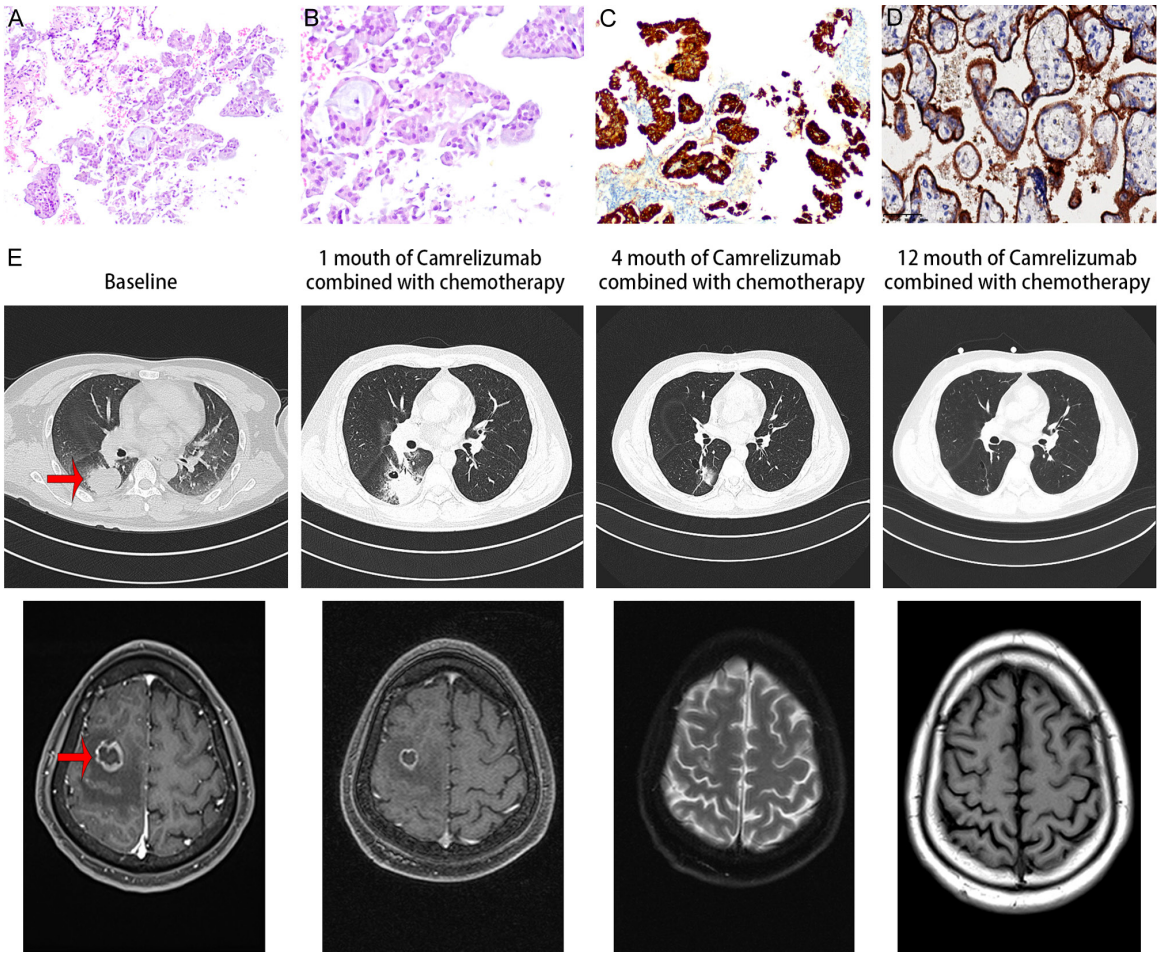

Figure 1. A, B. Immunohistochemical staining of lung adenocarcinoma. Hematoxylin and eosin staining showing lung adenocarcinoma cells (magnification ×100, magnification ×200). C. Immunohistochemical staining for the ALK protein showing diffuse cytoplasmic expression (magnification ×200). D. Immunohistochemical staining for the PD-L1 protein showing 80% of tumor cells expressing PD-L1 (magnification ×200). E. Chest and cranial CT imaging at diagnosis, during treatment, and post-treatment.

examination of the lesions of the head and lungs in the patient are shown after 1 month of chemotherapy combined with immunotherapy showed a partial response (PR) (**Figure 1E**). We re-examined the lesions, and the efficacy was evaluated as PR when the patient was treated with 6 cycles of AC chemotherapy, and 4 cycles of camrelizumab 200 mg (after 4 months of chemotherapy combined with immunotherapy) (**Figure 1E**). Follow-up treatment was started with pemetrexed maintenance chemotherapy (pemetrexed 885 mg D1) combined with camrelizumab 200 mg immunotherapy on August 19th. After the patient continued to receive 5 cycles of pemetrexed chemotherapy and 7 cycles of immunotherapy, we reassessed the lesions (For the full course of treatment for this patient refer to **Figure 2**). It was surprising to find that both the lung lesions or an intracranial lesions reached a CR (complete response); that is, the lesions disappeared on imaging.

Discussion

While immune checkpoint inhibitors (ICIs) have shown significant efficacy in various cancers such as non-small cell lung cancer (NSCLC), melanoma, renal carcinosarcoma, and gastric cancer, their effectiveness in ALK-positive patients has generally been poor. Previous studies have indicated that NSCLCs harboring ALK rearrangements exhibit low objective response rates and short median progression-free survival (PFS) to PD-1/PD-L1 inhibitors,

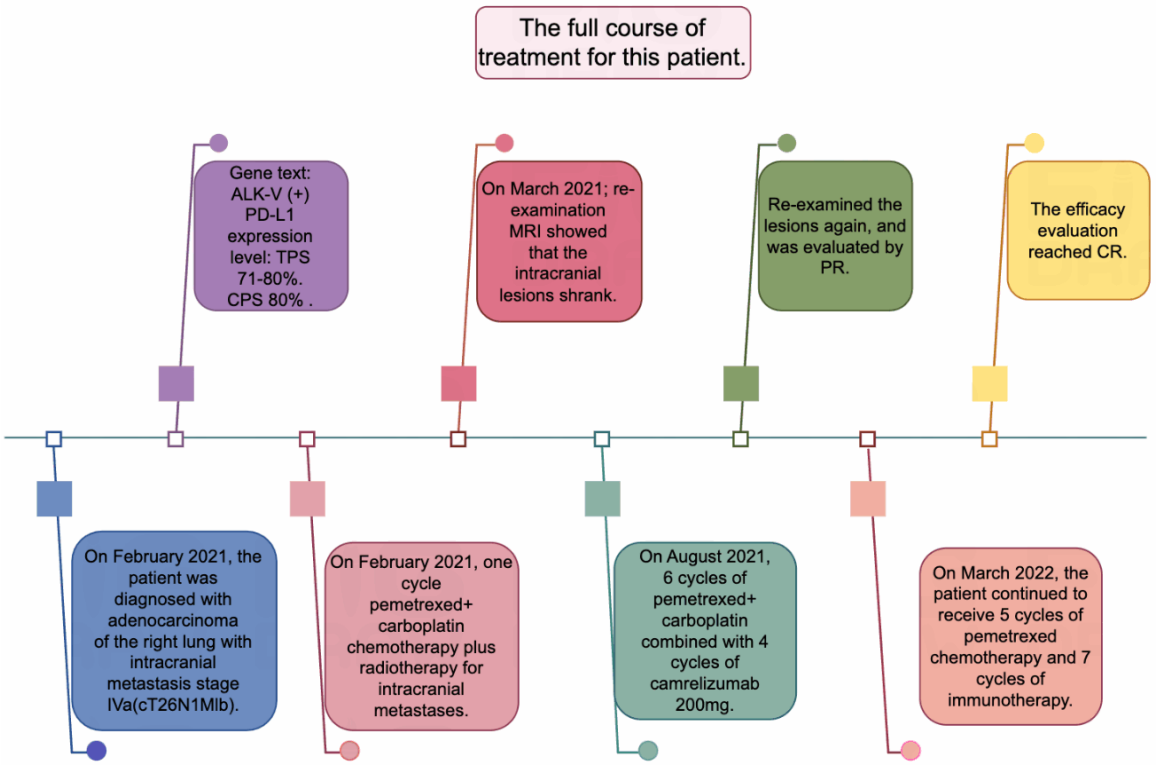

Figure 2. The full course of treatment for this patient.

and PD-L1 expression was not considered a critical biomarker for ICI treatment in patients with gene mutations [4, 5]. In addition, patients with ALK rearrangements have been routinely excluded from phase III trials of PD-L1 inhibitors and chemotherapy outside of 2 trials: IMpower130 and IMpower150. The addition of atezumab to bevacizumab plus chemotherapy significantly improved progression-free survival and overall survival in patients with metastatic non-squamous NSCLC, in spite of PD-L1 expression and EGFR or ALK gene alteration status [6].

The IMpower150 trial showed a remarkable improvement in PFS and OS with atezolizumab plus chemotherapy (carboplatin + paclitaxel) compared to the bevacizumab plus chemotherapy (carboplatin + paclitaxel) standard in patients with ALK- and EGFR-positive patients. However, only 11 ALK-positive patients were included in the trial [7]. In Checkmate 057, the benefit of nivolumab was found to be poorer to that of docetaxel in patients with EGFR mutations. However, there is little data on the efficacy of immunotherapy for patients with ALK rearrangement [8].

Consistent with these studies, subgroup analyses from IMpower130 showed no clinical benefit of the addition of atezolizumab to carboplatin and nab-paclitaxel among ALK-positive NSCLC patients [9]. There are some clinical reports that indicated that ALK rearrangements are associated with PD-L1 overexpression [10], with PD-L1 staining in up to 78% of ALK-rearranged patients [11]. However, the low number of ALK-positive patients in these studies limits the ability to derive firm conclusions about this subgroup of patients. Randomized controlled studies assessing ICI in NSCLC either did not involve patients with ALK rearrangement or did not have adequate numbers to offer meaningful subgroup analyses. Immunotherapy plays an important role in non-small cell lung cancer, and a proportion of patients could benefit from immunotherapy to achieve longer-term survival. It is very rare to find a patient with advanced NSCLC harboring ALK rearranged who achieves a complete response in both lung and brain lesions after chemotherapy combined with immunotherapy. There are few data on the efficacy of immunotherapy for ALK-rearranged NSCLC. However,

this case suggests that under certain conditions, these patients may still benefit from immunotherapy. We believe the reasons for the failure of previous methods may include the tumor microenvironment in ALK-positive patients possibly inhibiting effective immune responses and the inadequate activation of the immune system due to the sole application of immunotherapy in prior studies. The patient in this study had a high PD-L1 expression level (TPS 71-80%, CPS 80%), which could be a crucial factor contributing to the favorable response to immunotherapy. The combination with chemotherapy might have further enhanced the immune response. Additionally, we noted that the patient did not experience severe complications throughout the treatment process, contrasting with the severe toxic side effects reported in the CheckMate 370 study [12]. The CheckMate 370 study employed a combination treatment strategy different from that used in our case. By comparing these approaches, we aim to gain a deeper understanding of the benefits and risks associated with various treatment regimens in ALK-rearranged NSCLC patients. Moreover, the severe toxicities observed in the CheckMate 370 study underscore the importance of monitoring and managing adverse effects throughout the course of cancer treatment. Additionally, the differences in treatment responses observed across various studies and cases highlight the necessity of developing individualized treatment strategies to optimize efficacy while minimizing adverse reactions. This case suggests that the safety and efficacy of the combined treatment regimen might be associated with specific individual characteristics. Therefore, for ALK-positive NSCLC patients with high PD-L1 expression, a combination of chemotherapy and immunotherapy could be a feasible option. However, further clinical trials and biomarker studies are needed to validate our findings.

In summary, this case provides an example of a complete response achieved with combined chemotherapy and immunotherapy in an ALK-positive NSCLC patient, highlighting the possible efficacy of this combined treatment strategy under certain conditions. Future research should continue to explore and validate this approach.

Acknowledgements

Written informed consent has been obtained from the patient for publication of this case report (including all data and images). The authors thank the patient for his agreement to the publication of the report.

Disclosure of conflict of interest

None.

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