Clinical Oncology: Case Reports

Case Report

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Remarkable Effect of Atezolizumab in Advanced Non-Small Cell Lung Cancer with PD-L1 Negative but Genome Instability is Increased: Case Report

Nozomu Motono[1*], Yo Niida[2], Sohsuke Yamada[3] and Hidetaka Uramoto[1]

Abstract

Immune checkpoint inhibitors have become important paradigms for treating non-small cell lung cancer patients. Although several biomarkers indicating the efficacy of immune checkpoint inhibitors have been reported, these markers sometimes are not accurate concerning the therapeutic effect. A 63-year-old man without a smoking history was diagnosed with lung adenocarcinoma pathological stage IVB without an epidermal growth factor receptor mutation or anaplastic lymphoma kinase translocation, rearrangement of ROS1, or expression of programmed death-ligand 1 (PD-L1). Although cytotoxic anticancer therapies were administered, carcinoembryonic antigen (CEA) gradually became elevated, and the lesions progressed. Atezolizumab was administered as third-line chemotherapy, after which CEA normalized. After atezolizumab therapy was started, the Tumor Mutation Burden (TMB) and Microsatellite Instability (MSI) were analyzed in this patient's samples. The TMB was identified at 16.1 mutations per megabase by next-generation sequencing. MSI was analyzed by a Bethesda panel assay, and three microsatellite loci (D2S123, D5S346, D17S250) were positive. Therefore, this patient was defined as TMB-high and MSI-high (MSI-H).Although this patient had negative PD-L1 expression, atezolizumab showed remarkable efficacy. PD-L1, TMB, and MSI are considered new predictive biomarkers for selecting patients that benefit from immune checkpoint inhibitors.

Keywords

Programmed death-ligand 1; Tumor mutation burden; Microsatellite instability; Immune checkpoint inhibitor; Non-small cell lung cancer; Prognosis

Abbreviations

NSCLC: Non-small Cell Lung Cancer; PD-L1: Programed Death-Ligand 1; CEA: Carcinoembryonic Antigen; TMB: Tumor Mutation Burden; MSI: Microsatellite Instability; CT: Computed Tomography; FDG: Fluoro-Deoxy-Glucose; PET: Positron Emission Tomography; EGFR: Epidermal Growth Factor Receptor; ALK: Anaplastic Lymphoma Kinase; MMR: Mismatch Repair

Introduction

Lung cancer remains the main cause of cancer-related mortality worldwide [1], and outcomes for patients diagnosed with advanced Non-small Cell Lung Cancer (NSCLC) are poor [2]. Patients with previously treated lesions or advanced or metastatic NSCLC are difficult to treat. Docetaxel has been the gold standard for second- or third-line treatment. The new development of antibodies that target the Programmed Death 1 (PD-1) and Programmed Death-ligand 1 (PD-L1) pathways resulted in an important advance in the management of advanced NSCLC, and PD-1 inhibitors showed overall survival benefits compared to docetaxel. The POPLAR and OAK trials revealed that atezolizumab significantly improved survival compared to docetaxel in patients with previously treated NSCLC and showed prognostic improvement correlated with the PD-L1 expression on the tumor cells and tumor-infiltrating immune cells [3,4]. However, while a prognostic improvement correlated with the PD-L1 expression was noted in the POPLAR trial, even patients with low or undetectable PD-L1 levels in the OAK trial showed improved survival with atezolizumab.

Similar to the PD-L1 expression, Microsatellite Instability (MSI) and the Tumor Mutation Burden (TMB) are considered new predictive biomarkers for identifying patients likely to benefit from immune checkpoint inhibitors [5-14]. However, the overlap between the TMB, MSI, and PD-L1 differs among cancer types, and only 0.6% of cases were positive for all three markers in NSCLC [15].

We herein report a remarkable response to atezolizumab in a patient with previously treated advanced NSCLC who had TMB-high and MSI-high status and negative PD-L1 expression.

Case Presentation

A 63-year-old man without a smoking history was aware of left shoulder pain. Chest Computed Tomography (CT) showed a mass in the apex of the left lung that was suspected of infiltrating being the left subclavian artery and aortic arch (Figure 1A). ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) Positron Emission Tomography(PET) showed a high uptake of FDG in the mass, mediastinal lymph nodes, left 9th rib, and right adrenal gland (Figure 1B). The patients underwent a biopsy of pleural dissemination, and a pathological examination confirmed a poorly differentiated adenocarcinoma (Figure 1C). The pathological stage was pT4N2M1c, stage IVB, without Epidermal Growth Factor Receptor (EGFR) mutation or Anaplastic Lymphoma Kinase (ALK) translocation, rearrangement of ROS1, or expression of PD-L1. The patient received four Cycles of Chemotherapy with Cisplatin (CDDP), Pemetrexed (PEM), and Bevacizumab (BEV), followed by PEM and BEV maintenance therapy. However, Carcinoembryonic Antigen (CEA) was gradually elevated, and CT showed enlargement of the lesion at the left upper lung (Figure 2). Four cycles of Docetaxel and ramucirmab as second-line chemotherapy were administered. After

***Corresponding author:** Nozomu Motono, Department of Thoracic Surgery, Kanazawa Medical University, 1-1 Daigaku, Uchinada, Ishikawa, 920-0293, Japan, E-mail: motono@kanazawa-med.ac.jp

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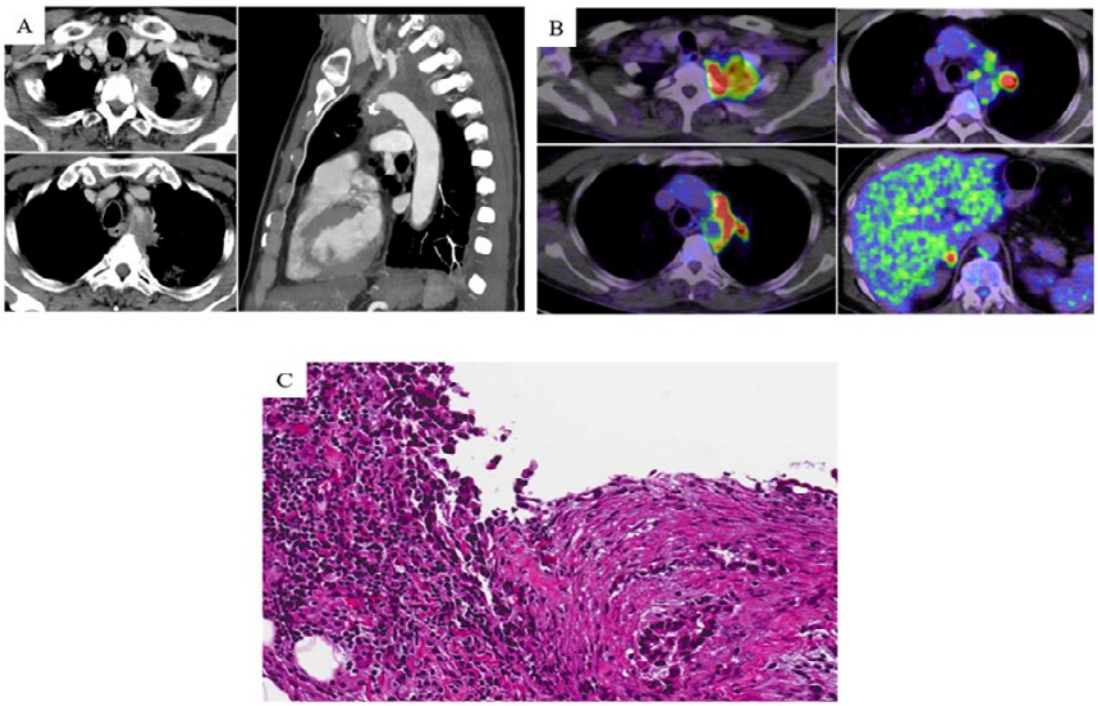

Figure 1: (A): Chest CT showed a mass in the apex of the left lung which suspected of infiltrating the left subclavian artery and the aortic arch; **(B):** FDG-PET showed high uptake of FDG in the mass, mediastinal lymph nodes, and right adrenal gland; **(C):** Pathological examination diagnosed a poorly differentiated adenocarcinoma.

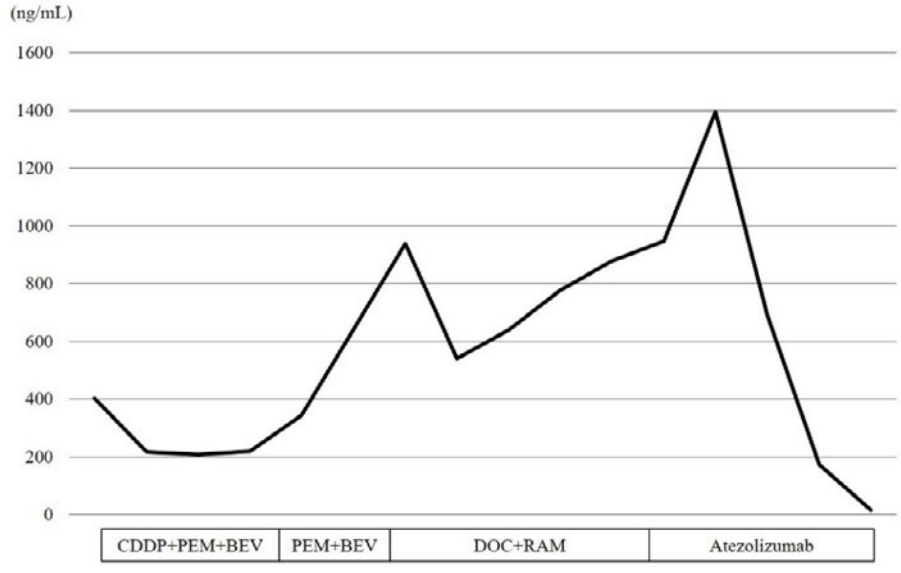

Figure 2: Transition of CEA.

that, CEA was further elevated (Figure 2), and PET showed the further uptake of FDG in the lesions (Figure 3A and 3B). The patient received atezolizumab as third-line chemotherapy. After eight cycles of atezolizumab, CEA was normalized (Figure 3C).

After starting atezolizumab therapy, the TMB and MSI were analyzed in this patient's pleural biopsy samples. The TMB was identified to be 16.1 mutations per megabase (mut/Mbp) by Next-generation Sequencing (NGS). The MSI was analyzed by the Bethesda

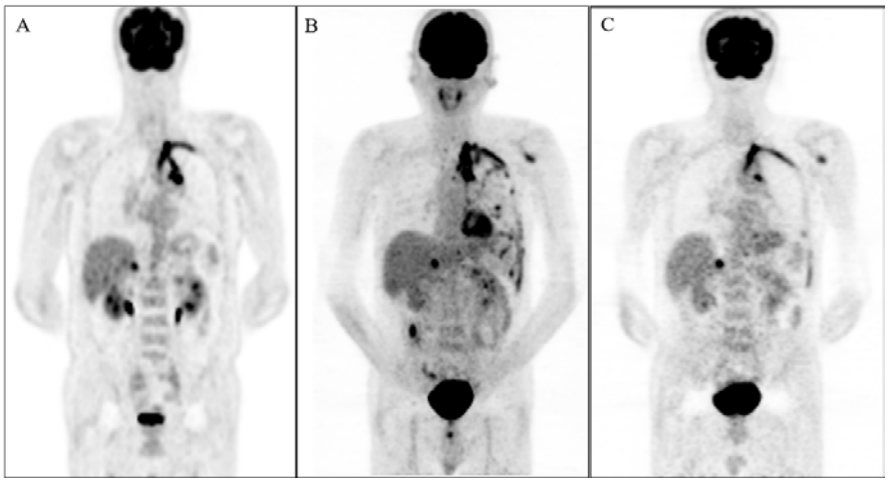

Figure 3: FDG-PET showed progression of uptake of FDG in lesions. **(A and B):** Before chemotherapy; **(C):** After 2nd line chemotherapy.

panel assay, three microsatellite loci (D2S123, D5S346, D17S250) were MSI positive. Therefore, this patient was defined as TMB-high and MSI-high (MSI-H) [16-18].

Discussion

Treatment of advanced NSCLC has evolved rapidly, and immunotherapy is a relatively new paradigm. The PD-1 receptors of activated T-cells are engaged by the tumor-expressed ligands PD-L1 and PD-L2 to reduce T-cell activation and facilitate tumor immune escape [5,18,19]. PD-1 and PD-L1 inhibitors for the treatment of advanced NSCLC are currently available and have demonstrated anti-tumor activity [3-6,20-22]. PD-1 and PD-L1 inhibitors significantly improved the Overall Survival (OS), Progression-Free Survival (PFS), and Objective Response Rate (ORR) in advanced NSCLC patients with PD-L1 expression. Furthermore, high PD-L1 expression was likely to be associated with increased benefits. However, PD-1 and PD-L1 inhibitors have also been reported to improve the OS in the population with PD-L1 <1% [22].

This discrepancy may be attributable to other biomarkers associated with the efficacy of PD-l and PD-L1 inhibitors. The TMB was recently confirmed to be a biomarker of the efficacy of PD-1 and PD-L1 inhibitors [8-11,23,24]. The TMB is defined as the total number of somatic mutations of the genomic coding area and associated with the emergence of neoantigens that trigger anti-tumor immunity [8]. The TMB is calculated based on the number of nonsynonymous somatic mutations identified by NGS. Although objective cut-off points for the TMB are not universally established, the cut-off points have been set at around 10 mut/Mbp in previous studies. Therefore, our case, which showed a TMB of 16.1 mut/Mbp, was defined as TMB-high [3,8,11].

MSI is also considered an independent predictive biomarker of immune checkpoint inhibitors [12-14,24]. MSI is the condition of genetic hypermutability and represents the phenotypic results of Mismatch Repair (MMR) deficiency. The five microsatellite loci (BAT-25, BAT-26, D2S123, D5S346, and D17S250) were amplified in a single multiplex Polymerase Chain Reaction (PCR). Cancers with instability at two or more of these loci are defined as MSI-H, while those with instability at a single locus are defined as MSI-low (MSI-L), and those with no instability at any of these loci are defined as Microsatellite Stable (MSS). In our case, three microsatellite loci (D2S123, D5S346, D17S250) were recognized, so the patient was defined as MSI-H.

In addition to the PD-L1 expression, TMB, and MSI are considered predictive biomarkers for selecting patients likely to benefit from immune checkpoint inhibitor.The overlap rates between PD-L1, TMB, and MSI are reportedly low in NSCLC [15]. TMB-high and MSI-H are found in 0.5%, TMB-high and PD-L1 positivity in 7.7%, MSI-H and PD-L1 positivity in 0.4%, and positivity in all 3 markers in 0.6% of NSCLC cases. Of note, most MSI-H patients had TMB-high (30/31) in a recent analysis of 5895 lung cancer tumors [25].

TMB-high and the neoantigen burden in tumors with MMR deficiency are associated with a favorable response to immune checkpoint inhibitors. A previous study reported an ORR of 53% and a 64% 2-year survival rate in cases of MMR deficiency or MSI-H tumors treated with pembrolizumab in a range of different cancer types, but this study did not include NSCLC patients.Although the efficacy of immune checkpoint inhibitors for NSCLC with TMB-high and neoantigen burden in tumors with MMR deficiency is uncertain, the present data showed that atezolizumab was markedly effective for NSCLC with TMB-high and MSI-H in the present case.

Conclusion

While PD-L1, TMB, and MSI can help identify patients who may benefit from immune checkpoint inhibitors, they are not complete predictors of favorable response in NSCLC. In the future, an analysis of the relationship among these biomarkers associated with the efficacy of immune checkpoint inhibitors is desired.

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Author Affiliations

Top

[1]*Department of Thoracic Surgery, Kanazawa Medical University, Ishikawa, Japan*

[2]*Division of Genomic Medicine, Department of Advanced Medicine, Medical Research Institute, Kanazawa Medical University, Ishikawa, Japan*

[3]*Department of Clinical Pathology, Kanazawa Medical University, Ishikawa, Japan*