Multiple Sclerosis and Related Disorders 37 (2020) 101447

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Case report

Neuromyelitis optica spectrum disorder after treatment with pembrolizumab

Tomoyo Shimada, Yasunobu Hoshino, Taiji Tsunemi*, Anri Hattori, Emi Nakagawa, Kazumasa Yokoyama, Nobutaka Hattori

Department of Neurology, Juntendo University School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo, 113-8421 Japan

ARTICLE INFO

Keywords:
Neuromyelitis optica spectrum disorder
Pembrolizumab
Immune checkpoint inhibitor
Immune-related adverse event
Anti-aquaporin-4 antibody
PD-1 monoclonnal antibody

ABSTRACT

While immune checkpoint inhibitors (ICIs) have contributed to the development of therapeutic treatments for previously incurable advanced malignancies, they may induce immune-related adverse events (irAEs) in many organs including the CNS [1]. Because immune checkpoint molecules are predominantly expressed on T cells, irAEs are largely not B cell-mediated. Here, we report a patient who was treated with pembrolizumab (a PD-1 monoclonal antibody) for lung adenocarcinoma with brain metastasis, and who developed anti-aquaporin-4 antibody (AQP4-Ab) positive neuromyelitis optica spectrum disorder (NMOSD). We hypothesized that PD-1 immune checkpoint blockage might induce a B cell-mediated immune response in CNS resulting in this complication, which was further supported by the observation of a transient increase in plasmablasts in their CSF.

1. Introduction

Recently, prognoses of patients with a variety of malignancies in advanced stages have been considerably improved thanks to the discovery of novel treatments based on immune response targeting tumor-associated antigens or tumor-specific mutations (Yshii et al., 2017). Immune checkpoint inhibitors (ICIs) are meant to activate T cells, and therefore sometimes induce immune-related adverse events (irAEs) that result in neurological complications with the prevalence rate between 2.4% to 4% by monotherapies (Spain et al., 2017; Zimmer et al., 2016; Eggermont et al., 2015) but 14% by combination therapies (Spain et al., 2017). Here, we report a case of anti-AQP4 antibody positive myelitis that occurred as an irAEs.

2. Case report

A 63-year-old Asian woman, who has well-controlled Sjogren's syndrome, was diagnosed as having lung adenocarcinoma at stage IV, cT2aN1Mib. She received gamma knife radiation against brain metastasis, resulting in a partial improvement. While being negative for both epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), more than 80% of her malignant cells were positive for programmed cell death–ligand 1 (PD-L1). At two weeks after the first cycle of intravenous administration of pembrolizumab, a humanized PD-1 monoclonal antibody, she found that she had lost temperature sensation in both lower extremities. Then a week after, her bilateral hands trembled, and a weakness of her lower extremities with bladder and rectal disturbance appeared. Neurological examination revealed a weakness and sensory loss in all, but predominantly lower extremities, and was positive for bilateral Hoffman's sign and Babinski's sign and sphincter atonia. While the brain metastasis did not alter in size, sagittal T2-weighted MRI images of spinal cord revealed T2 high intensity lesions between C4 and Th1 that were enhanced with gadolinium, suggesting longitudinal myelitis causing her symptoms [Fig. 1A]. While AQP4-Ab was detected in the serum by both enzyme-linked immunosorbent assay (ELISA) and cell-based assay (CBA), anti-myelin-oligodendrocyte glycoprotein antibody was not. Cerebrospinal fluid (CSF) revealed increased protein value (48 mg/dl), negative for oligoclonal bands and normal myelin basic protein value. CSF showed a slight increase in monocytes (9 cells/μl) without malignant cells. The results from flow cytometry of her CSF cells revealed increased plasmablasts ($CD19^{+}$, $CD20^{-}$, $CD27^{hi}$, $CD180^{-}$, $CD38^{hi}$) [Fig. 1B,D] while regulatory T-cells (Tregs) were not promoted (data not shown). She was diagnosed with NMOSD that presented as pembrolizumab-mediated irAEs. However, three days-intravenous methylprednisolone of 1000 mg per day followed by oral prednisolone 0.5 mg/kg/day was effective for her neurological symptoms. Subsequent treatment of plasma exchange (Good-Jacobson et al., 2010) further abbreviated her symptoms and led to an improvement in spinal lesions without exacerbation of either lung carcinoma or brain metastasis. At three

* Corresponding author.
E-mail addresses: t-tsunemi@juntendo.ac.jp, t-tsunemi@juntendo.ac.jp (T. Tsunemi).

https://doi.org/10.1016/j.msard.2019.101447
Received 14 July 2019; Received in revised form 4 October 2019; Accepted 13 October 2019

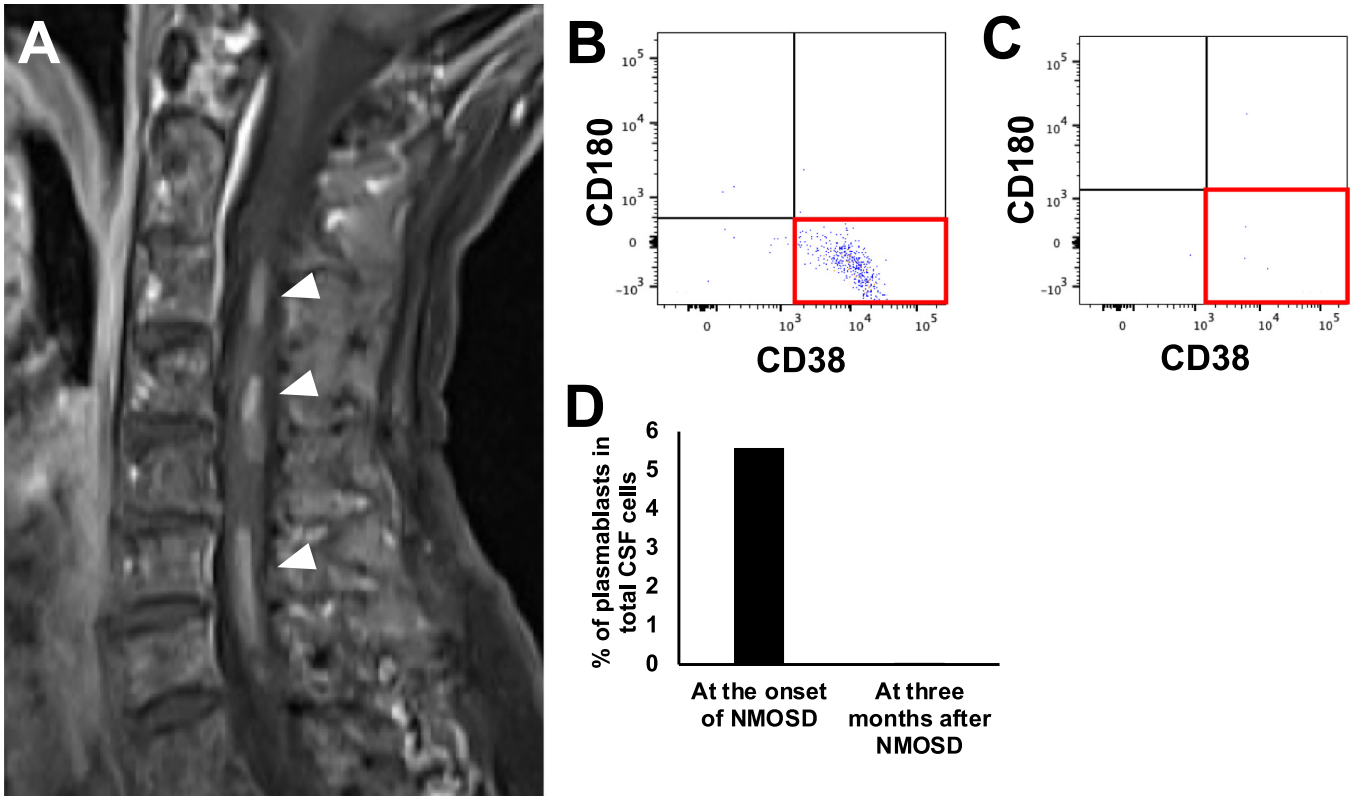

Fig. 1. A Gadolinium-enhanced T1 weighted MRI revealed longitudinal myelitis (arrowheads) in cervical spinal cord. **BC** Fluorescence-activated cell sorting detected plasmablasts ($CD19^{+}$, $CD20^{-}$, $CD27^{hi}$, $CD180^{-}$, $CD38^{hi}$) from cerebrospinal fluid (CSF). Plasmablasts at the onset of (**B**) and at three months after NMOSD (**C**). **D** The alternation of plasmablasts in CSF at the onset of and at three months after NMOSD.

months after the initial symptom, repeated flowcytometry of CSF cells revealed a reduction of the number of plasmablasts [Fig. 1C,D], suggesting that the transient induction of plasmablasts in CSF was caused by the immunological reaction of the administration of pembrolizumab.

3. Discussion

We have experienced a patient who developed anti AQP4-Ab positive NMOSD after the first cycle of pembrolizumab, an immune checkpoint inhibitor.

Immune-mediated adverse effects caused by ICIs have been increasingly documented with the widespread use of ICIs. Since ICIs target cytotoxic T-lymphocyte associated antigen 4 (CTLA4) and programmed cell death 1 (PD-1), most ICIs-mediated neurological complications, like Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, aseptic meningitis, limbic encephalopathy and cerebellitis, present without diseases-specific antibodies, whereas disorders positive for anti-*N*-methyl-D-aspartate receptor, anti-contactin-associated protein-like 2 or anti-Hu antibodies have also been reported (Wilson et al., 2018; Martins et al., 2019). Myelitis was a rare compilation with only a couple of cases being reported thus far (Wilson et al., 2018; Narumi et al., 2018). The first case was a 35-year old male, who at one week after the second cycle of pembrolizumab treatment for Hodgkin lymphoma developed longitudinally extensive transverse myelitis (Wilson et al., 2018). While he was neither anti AQP4-Ab nor MOG positive, the result of flow cytometry of peripheral blood revealed decreased Tregs, which was stained positively by human IgG, indicating that remaining Tregs were targeted by pembrolizumab, leading to the activation of a B-cell mediated immune response. Extensive immunotherapy was effective for clinical symptoms and MRI lesions. The other previously reported patient was a 75-year old male, who at one month after the nivolumab treatment for lung squamous cell carcinoma, developed transverse myelitis and was positive for anti AQP4-Ab. While steroids were not effective, plasmapheresis improved his symptoms (Narumi et al., 2018). In contrast to these previous patients, our patient has primary Sjogren's syndrome that is known to be associated with NMOSD (Kahlenberg, 2011). NMOSD as a paraneoplastic syndrome has also been reported due to high expression levels of AQP4-Ab in many malignant cells (Pittock and Lennon, 2008). It may be possible, therefore, that NMOSD in our patient occurred in association with Sjogren's syndrome or lung adenocarcinoma, but a transient increase in the number of plasmablasts in CSF indicates that the treatment with pembrolizumab induced AQP4-Ab producing-B cells [Fig. 1B,C].

Although ICIs are meant to activate T cells, irAEs sometimes occur as immunological diseases with specific antibodies. While the mechanism behind this remains unclear, recent studies provide the evidence of T cell involvement in the antibody production, in which the PD-1/PD-1 L pathway plays a pivotal role (Good-Jacobson et al., 2010). In germinal centers, follicular helper T cells (T_{FH} cells), on which PD-1 is highly expressed, are important for positioning and maturation of B-cells, on which PD-1 L is highly expressed, showing PD-1/PD-1 L interaction to be necessary for proper differentiation of B-cells into antibody-producing plasmablasts/plasma cells (Shi et al., 2018). Indeed, certain autoimmune diseases, like systemic lupus erythematosus, are linked to inappropriate signals from T_{FH} cells to B cells, resulting in autoimmune antibody production (Martins et al., 2019). Hence, it is tempting to speculate that improper blockage of PD-1 may generate aberrant B cells. While most of irAEs require several cycles of ICI administration, the appearance of NMOSD in all three cases after a relatively short time period after the initiation of ICIs may support this hypothesis. Further studies are thus required to clarify the mechanism of the antibody production caused by the administration of ICIs.

In summary, this case highlights that antibody-mediated immune

complications happen as irAEs. Analysis of the characteristics of the CSF cell population may thus help understand the immune status of the patients. Clinicians should be further mindful since prompt discontinuation of ICIs followed by the initiation of immune therapy will lead to a complete remission.

Declaration of Competing Interest

The authors declare no conflicts of interest associated with this manuscript and received no specific funding.

Acknowledgement

We would like to thank Yvette Wong for proofreading the manuscript.

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