CASE REPORT

Immune checkpoint inhibitor-associated paraneoplastic cerebellar degeneration in a case of extensive-stage small-cell lung cancer with pre-existing anti-SOX1 antibody

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Abstract : Neurological immune-related adverse events can manifest as paraneoplastic neurological syndrome (PNS), especially in patients with small-cell lung cancer (SCLC). We herein report a 73-year-old man with SCLC treated with an immune checkpoint inhibitor (ICI) combined with chemotherapy. Although the chemo-immunotherapy induced a favorable response to SCLC, he later developed acute cerebellar ataxia. He was diagnosed with paraneoplastic cerebellar degeneration associated with anti-Sry-like high mobility group box 1 (SOX1) autoantibody. The antibody was also identified in serum collected at the diagnosis of SCLC and before ICI administration, which retrospectively suggested that the patient was at risk of ICI-induced PNS. J. Med. Invest. 72 : 172-176, February, 2025

Keywords **:** *small-cell lung cancer, immune checkpoint inhibitors, paraneoplastic cerebellar degeneration, anti-SOX1 autoantibody*

INTRODUCTION

Cancer immunotherapy with immune checkpoint inhibitors (ICIs), such as anti-programmed cell death-1 (PD-1) or anti-programmed cell death ligand-1 (PD-L1) antibodies, has transformed the treatment paradigm for several malignancies including small-cell lung cancer (SCLC). Although SCLC, which accounts for approximately 15% of lung cancer, generally presents aggressive phenotype and poor prognosis, anti-PD-L1 antibodies, such as atezolizumab or durvalmab, in combination with either cisplatin or carboplatin plus etoposide have recently shown the superior therapeutic efficacy to chemotherapy alone in patients with extensive-stage (ES)-SCLC (1, 2). On the other hand, ICIs are known to induce not only favorable therapeutic efficacy but also several inflammatory side effects, termed immune-related adverse events (irAEs) in multiple organs (3).

Neurological irAEs are rare complications which represent approximately 3% of patients who were treated with ICIs (4). Although central nervous system (CNS) irAEs, such as encephalitis, meningoencephalitis, or cerebellitis, are less common than neuromuscular complications, such as myositis, myasthenia gravis (MG), or peripheral neuropathy, the CNS irAEs can sometimes be severe and fatal (5). Neurological irAEs can manifest as paraneoplastic neurological syndromes (PNSs), especially in patients with the types of cancer that are most frequently associated with these disorders, such as SCLC (6).

Here, we report a case where ICI was associated with paraneoplastic cerebellar degeneration (PCD) in a patient with ES-SCLC who had pre-existing anti-Sry-like high mobility group box 1 (SOX1) antibody.

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CASE PRESENTATION

A 73-year-old man with a severe smoking history of 80 pack-year was referred to our hospital with abnormal thoracic opacity. He had hypertension, hyperlipidemia, and carotid artery stenosis as comorbidities. Chest X-ray showed a mass shadow in the right upper lung field. Chest computed tomography (CT) revealed a mass shadow in the right upper lobe along with mediastinal lymph node swelling (Fig. 1A). Based on the transbronchial biopsy and imaging studies, we diagnosed him with ES-SCLC (cT4N3M1c stage IVB) with liver metastasis (Fig. 1B).

We started to treat him with carboplatin (area under the curve [AUC] = 5) and etoposide (100 mg/m^2) combined with durvalmab (1500 mg/body) every three weeks for four cycles followed by durvalmab monotherapy every four weeks. This treatment induced a partial response, however, he developed brain metastases in the right parietal lobe and cerebellum six months after the initiation of chemo-immunotherapy (Fig. 2A and B). We treated him with stereotactic radiotherapy (total 43 gray) and kept durvalmab monotherapy because tumor regions in the body trunk were regulated. At seven months after radiotherapy, which corresponded to 13 months after the initiation of chemo-immunotherapy, he was admitted to our hospital because of severe nausea, vomiting, and gait disturbance.

On admission, he was unable to keep standing and sitting positions, which was later attributed to truncal ataxia. His consciousness was alert, extraocular movement was intact, without nystagmus, and no dysarthria was observed. Muscle strength and deep tendon reflex were normal. Limb ataxia was not apparent. Five days after admission, he developed diplopia. Two days later, neurological examination revealed horizontal gaze nystagmus and slurred speech. Laboratory examinations showed normal blood cell count and blood chemistry including vitamins and endocrine function. Pro-gastrin-releasing peptide, which was initially elevated at diagnosis, was also normal. CT scan revealed that the primary and metastatic tumor nodules, in the lung and liver respectively, remained in remission (Fig.

1C and D). While magnetic resonance imaging (MRI) showed no evidence of recurrent brain metastasis, leptomeningeal carcinomatosis, ischemia, hemorrhage, or abnormal contrast enhancement (Fig. 2C-E), brain perfusion scintigraphy with N-isopropyl-[^{123}I]-p-iodoamphetamine revealed increased perfusion in the cerebellum (Fig. 2F). Cerebrospinal fluid (CSF) analysis showed a slight lymphocytosis (7/μL) with normal protein and glucose levels but no evidence of leptomeningeal carcinomatosis or infection. Neurophysiological tests including electromyogram did not show any abnormal findings.

Based on these findings, we suspected him of having PNS and identified anti-SOX1 autoantibody in the serum by a screening test for onconeural antibodies against amphiphysin, CV2, PNMA2 (Ma2/Ta), Ri, Yo, Hu, recoverin, SOX1, titin, zic4, GAD65, and Tr (delta/notch-like epidermal growth factor-related receptor : DNER) (BML, Inc., Tokyo, Japan). Furthermore,

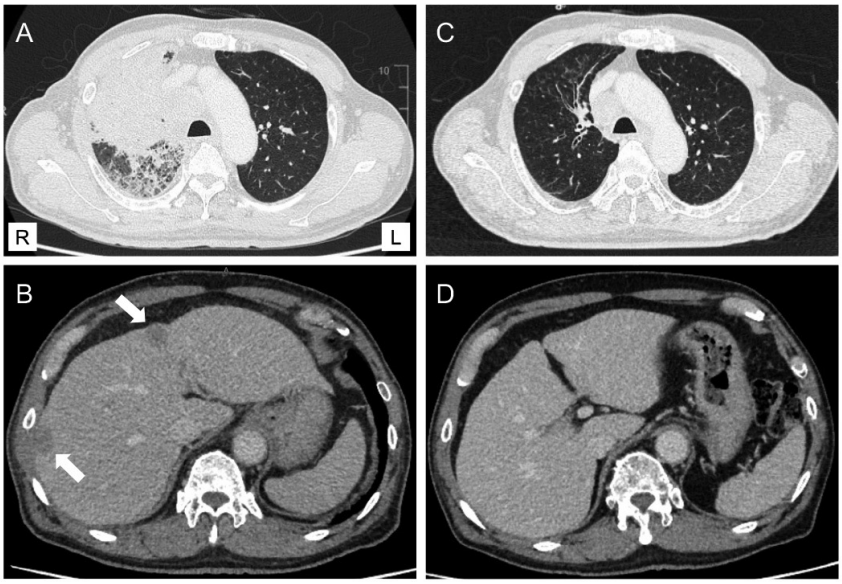

Figure 1. Computed tomography findings. The images at diagnosis showed a mass shadow in the right upper lobe (A) and multiple liver metastases (white arrows) (B). The images when he developed paraneoplastic cerebellar degeneration showed that the primary and metastatic tumor nodules remained in remission (C, D).

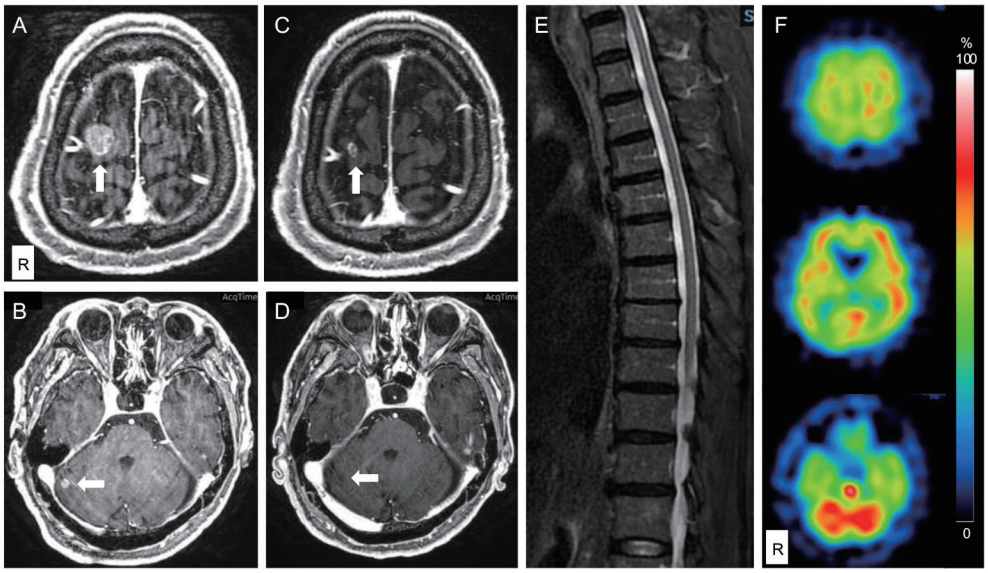

Figure 2. The imaging studies for the central nervous system. The contrast-enhanced magnetic resonance imaging (MRI) revealed brain metastases in the right parietal lobe (A) and cerebellum (B) six months after the initiation of chemo-immunotherapy. MRI showed no evidence of recurrent brain metastasis (C, D) or leptomeningeal carcinomatosis (E) when he developed paraneoplastic cerebellar degeneration. Brain perfusion scintigraphy revealed increased perfusion in the cerebellum compared to cerebral hemisphere (F).

we retrospectively analyzed the serum at the time of cancer diagnosis and identified the same antibody. As he had no symptoms of cerebellar disorder before the initiation of chemo-immunotherapy, we finally diagnosed him with PCD triggered by the administration of durvalmab based on the diagnostic criteria (7, 8).

We terminated the administration of durvalmab and introduced methylprednisolone pulse (1 g/day for three days) followed by oral prednisolone (0.5 mg/kg/day). Although the induction steroid therapy showed some efficacy, the severity of cerebellar ataxia evaluated by the Scale for the Assessment and Rating of Ataxia (SARA) score remained high (slightly improved from 16 before treatment to 14 on day 7 from the initiation of steroid) (9). Therefore, we introduced intravenous immunoglobulin (IVIG) 0.4 g/kg/day for 5 days and tapered the oral steroid. Subsequently, the symptoms were improved (SARA score was 8 on day 75 from the initiation of steroid) and he was transferred to a hospital nearby.

Two months later, the tumor relapsed with severe multiple liver metastases, however, the severity of cerebellar ataxia was stable (SARA score was 8). As the second-line chemotherapy with four cycles of carboplatin plus etoposide introduced tentative therapeutic efficacy, we treated him with second cycle of IVIG. However, his liver metastases re-progressed rapidly one months after the treatment of IVIG. Although we treated him with third-line chemotherapy with amrubicin (40 mg/m^2), he died due to tumor progression two years after the initiation of chemo-immunotherapy, which corresponded to 9 months after the development of PCD (Fig. 3).

DISCUSSION

PNSs are remote disorders associated with cancer that can affect any part of the nervous system. Although PNSs present in less than 1% of cancer patients, these disorders can worsen their quality of life. SCLC, followed by ovarian cancer, breast cancer, and non-small cell lung cancer (NSCLC) are mostly associated with PNSs (10). PNSs are induced by cross-reactive autoimmune responses against shared antigens between cancer and neural tissues (onconeural antigens) (11). Several autoantibodies targeting onconeural antigens are associated with PNSs, and the PNSs with autoantibodies targeting intracellular antigens, such as SOX1, show poor response to immunosuppressive therapy (12). In a prospective study with 264 consecutive patients with SCLC, 24 (9.4%) patients had PNSs, most frequently Lambert-Eaton myasthenic syndrome (LEMS, 3.8%). No patient with PCD was identified in this cohort (13). Another retrospective study of 116 SCLC patients demonstrated that 71 (61.2%) patients manifested any neurological symptoms, most frequently peripheral neuropathy (31%). Cerebellar ataxia was identified in 12%. Anti-SOX1 antibody was the fourth most frequent autoantibody (16.9%) detected in this cohort (14). Furthermore, another case report demonstrated an ES-SCLC patient with anti-SOX1 antibody who developed paraneoplastic sensory polyneuropathy after the treatment with chemo-immunotherapy (15). These results suggest that PCD associated with anti-SOX1 antibody is rarer than other PNS–antibody combinations.

PCD is characterized by rapidly progressive cerebellar syndrome, such as limb and truncal ataxia, dysarthria, and nystagmus. It was first reported in an ovarian cancer patient who developed cerebellar ataxia in 1919. Subsequently, the association between PCD and an antibody against Purkinje cells, also known as Yo antibody, was identified (8). Recently, further antibodies for intracellular targets, such as Hu, Ri, and Ma2, and extracellular targets, such as DNER, have been reported to be associated with PCD. Although anti-SOX1 antibody is rarely characterized in the association with PCD, a previous study demonstrated that the presence of anti-SOX1 antibody has a specificity of 100% and a sensitivity of 49% in patients of SCLC with cerebellar ataxia (16). On the other hand, a systematic review of patients with cerebellar syndromes that were induced by ICIs has recently revealed that 26 out of 46 (61.9%) patients

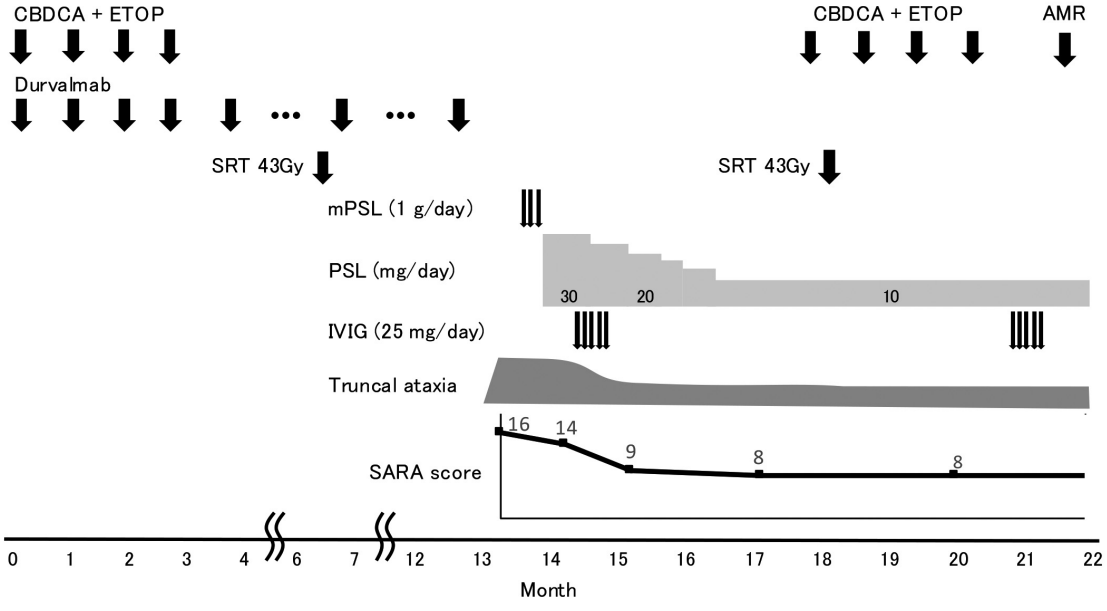

Figure 3. Clinical course of the patient after the initiation of chemo-immunotherapy. CBDCA, carboplatin ; ETOP, etoposide ; AMR, amrubicin ; SRT, stereotactic radiotherapy (for brain metastasis) ; mPSL, methylprednisolone ; PSL, prednisolone ; IVIG, intravenous immunoglobulin ; SARA, scale for the assessment and rating of ataxia.

were positive for any autoantibodies, however, anti-SOX1 antibody was not identified in any patients (17). To our knowledge, this is the first report of anti-SOX1 antibody-associated PCD that was induced by ICIs.

SOX proteins family consists of 20 proteins of DNA-binding transcriptional factors (18). Among them, SOX1 is expressed in neuronal precursor cells in the developing CNS and plays an important role in early neurogenesis. As SOX1 was originally identified in nuclei of cerebellar Bergmann glia cells as an antigen of anti-glial nuclear antibody in patients with LEMS associated with SCLC, anti-SOX1 antibody is consequently regarded as one of the autoantibodies for PNSs (19-21). Although LEMS is mostly associated with anti-SOX1 antibody, several neurophysiological examinations showed no evidence of LEMS in this patient. Therefore, we diagnosed him with pure PCD associated with ICI.

It is still unknown whether pre-existing autoantibodies against onconeural antigens can be risk factors for ICI-induced PNSs. Several papers have recently reported that new PNS symptoms can be induced or pre-existing neurological symptoms can be worsened by the administration of ICIs (7, 22, 23). Although no prospective study has shown the association of the incidence of PNSs or neurological irAEs with pre-existing autoantibodies in patients treated with ICIs, theoretically ICIs may increase the development of PNSs in patients with pre-existing autoantibodies. In our patient, anti-SOX1 antibody was detected in the serum at diagnosis of cancer before the ICI administration and PCD development. The screening assay for onconeural antibodies is just semi-quantitative, however, the titer of anti-SOX1 antibody seemed to be slightly elevated after the ICI administration (from 2+ to 3+). This result suggests the possibility that ICI enhanced the immune response against onconeural antigens, resulting in the development of PCD. We therefore consider that pre-existing autoantibodies may be biomarkers to evaluate the risk of ICI-induced PNSs. This may facilitate early diagnosis and treatment of PNSs in patients who are treated with ICI.

PCD is clinically diagnosed based on the criteria that consist of cerebellar symptoms, autoantibodies, and presence of cancer (7, 8). Although the imaging studies are often performed, they are not incorporated in the diagnostic criteria. Among them, brain MRI, which is the gold standard imaging modality for PNSs, shows no abnormal findings in most cases, especially in acute phases (8, 24, 25). However, it sometimes shows transient diffuse cerebellar hemispheric enlargement or cortical meningeal enhancement with eventual cerebellar atrophy. On the other hand, ^{18}F-fluorodeoxyglucose positron-emission tomography (FDG-PET) is reported to show cerebellar hypermetabolism in an acute phases or cerebellar hypometabolism in chronic phases in some patients (8, 24). Some reports also demonstrated the utility of brain perfusion scintigraphy to detect cerebellar hypermetabolism in patients with PCD (26). In our patient, while FDG-PET was not performed, brain perfusion scintigraphy revealed cerebellar hypermetabolism, suggesting that it is helpful for the diagnosis of PCD. The optimal timing for imaging tests including brain perfusion scintigraphy needs to be further considered in future studies.

The treatment of ICI-induced PCD is still challenging. Corticosteroids and ICI discontinuation were reported to be the two most frequent therapeutical options (17). Although half of the patients with ICI-induced PCD received only steroids in one study, the remaining patients required more aggressive immunosuppressive therapies (17, 27). Furthermore, other reports showed that patients with pre-existing seropositive PNSs presented severe progression after ICI administration, and their symptoms did not improve after immunosuppressive therapies (22, 23). Our patient responded only partially to the intensive immunosuppressive therapies with high-dose steroids and intravenous immunoglobulin, which was consistent with the previous reports.

In summary, we experienced a case of ES-SCLC with pre-existing anti-SOX1 antibody who developed PCD after the administration of ICI. This case indicates that pre-existing autoantibodies may be associated with the development of ICI-induced PNS.

CONFLICT OF INTEREST

Yasuhiko Nishioka reports lecture fees as honoraria from AstraZeneca K.K., Chugai Pharmaceutical Co., Ltd., and scholarship donation from Chugai Pharmaceutical Co., Ltd. The other authors have declared no conflict of interest to disclose.

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