A Case of Anti-CRMP5 Paraneoplastic Neurological Syndrome Induced by Atezolizumab for Small Cell Lung Cancer

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Abstract:
We herein report a 76-year-old man who developed irritability and forgetfulness 5 months after the introduction of atezolizumab for the treatment of small cell lung cancer (SCLC). Brain magnetic resonance imaging showed lesions of the striatum, and an investigation of the serum revealed a high titer of anti-CRMP5 antibody. After stopping atezolizumab and starting steroid pulse therapy, these clinical features improved. Given these findings, it is considered that CRMP5-associated striatal encephalitis was induced by atezolizumab in this case with SCLC.

Key words: atezolizumab, immune-checkpoint inhibitors, irAE, CRMP5, paraneoplastic neurological syndrome

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Introduction

With advances in cancer immunotherapy, immune checkpoint inhibitors (ICIs) have greatly increased the survival and have become the standard treatment for many malignancies. ICI-therapy enhances anti-tumor immunoreactivity and results in tumor regression but can disrupt immune tolerance to self-antigens and cause autoimmune complications termed immune-related adverse events (irAEs) (1, 2).

Paraneoplastic neurological syndrome (PNS) is a syndrome caused by an immune response to the ectopic expression of neuronal proteins in cancer cells (3, 4). Characteristic clinical syndromes are observed with specific antibodies to intracellular or cell surface antigens (3, 4). ICI therapy is known to be able to induce PNS, particularly in small cell lung cancer (SCLC) (2, 5). However, there has been only one reported case of anti-CRMP5 PNS after ICI therapy for SCLC (6).

We herein report an SCLC case in which anti-CRMP5-associated striatal encephalitis was induced by atezolizumab, an ICI.

Case Report

A 76-year-old man with metastatic SCLC receiving atezolizumab presented with irritability and forgetfulness. Stage IVB SCLC (T4N2M1c) had been diagnosed in August 2019, and he had undergone four courses of chemotherapy consisting of carboplatin, etoposide, and atezolizumab over the following 3 months.

Prior to treatment, chest and abdominal computed tomography (CT) had revealed a 76-mm tumor in the mediastinum and large metastasis in the left iliac bone with bone destruction and invasion of the surrounding muscles (Fig. 1). Bone scintigraphy also revealed right iliac bone metastasis. The treatment was remarkably effective, and the above primary and metastatic lesions had almost disappeared by January 2020 (Fig. 1).

The serum levels of progastrin releasing peptide (ProGRP) decreased significantly from the beginning to the end of the treatment (2,451.3 versus 29.0 pg/mL). Similarly, serum concentrations of neuron-specific enolase (NSE) also improved significantly (66.9 versus 7.9 ng/mL). He was ad-

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mitted to the hospital on January 2020 because of forgetfulness and irritability. He became forgetful in many areas of his daily activity (e.g., what he had eaten the previous day, hospital appointments). He was also irritable towards his wife but not physically violent. He had a 50-pack-year smoking history and a 7-year history of pigmentary degeneration of the retina, leading to blindness in both eyes. He had no history of autoimmune or neurological diseases. The antinuclear antibody titer was 1:40 in August 2019.

On a neurological examination, he was mildly disinhibited. Although he reported being forgetful, his mini-mental state examination (MMSE) score was 23, which was nearly normal (total score of 28 because of his blindness). There were no abnormalities in the cranial nervous system, no paralysis in the extremities, normal tendon reflexes, and no involuntary movements, such as chorea. No other clinical findings, such as a fever or seizures, were observed.

A laboratory investigation showed no abnormalities in serum electrolytes, liver, or the kidney function. Screening for syphilis and HIV were negative. A cerebrospinal fluid analysis revealed pleocytosis (12 cells/μL, 100% monocyte), a normal glucose level, and a mildly elevated protein concentration of 76.4 mg/dL. There were 10 oligoclonal bands present in the cerebrospinal fluid compared to 3 in the serum. A serum analysis showed a high titer of anti-CRMP5 antibody. Other paraneoplastic markers, including anti-Hu antibody, anti-MA2 antibody, anti-Ri antibody, anti-Tr antibody, anti-amphiphysin, anti-Yo, anti-recoverin, anti-SOX-1, antititin, anti-zinc4, anti-GAD65, and anti-NMDA-R antibody, were negative. Brain magnetic resonance imaging (MRI) had shown no abnormalities when performed for surveillance for brain metastasis in August 2019 but showed T2-hyperintensity in the bilateral striatum in January 2020 (Fig. 2). The striatum showed the involvement of the far anterior portion (i.e. the caudate and anterior part of the putamen). Other brain regions, including the amygdala and hippocampus, were preserved. There was no contrast enhancement of the brain or leptomeninges.

Since no irritability or striatal lesions had been observed before atezolizumab administration, it was considered that CRMP5-associated striatal encephalitis had been induced during atezolizumab treatment. Atezolizumab was therefore discontinued, and steroid pulse therapy (mPSL 1,000 mg/day, 3 days) was initiated. After steroid pulse therapy, oral prednisolone (0.5 mg/kg/day) was started and gradually discontinued. His irritability improved, and he regained the same gentle personality as before. On day 9, the findings of striatal T2 hyperintensity on brain MRI improved (Fig. 2).

**Discussion**

In this case, the treatment including atezolizumab was highly effective, and the mediastinal mass and iliac metastasis of SCLC almost disappeared (Fig. 1). Prior to atezolizumab administration, no neurological abnormalities or basal ganglia lesions had been observed, even in the presence of metastatic SCLC. Five months after atezolizumab initiation, irritability developed in association with the striatal lesions.
Various neuropsychological deficits, and these deficits can be caused by the initiation of ICI therapy (11-13). Anti-CRMP5 antibody is often associated with ballism, Parkinsonism, irritability, and memory dysfunction. The onset of CRMP5-associated striatal encephalitis includes chorea, Parkinsonism, irritability, and memory dysfunction (3, 9). Symptoms of CRMP5-associated striatal encephalitis are chorea, ballism, Parkinsonism, irritability, and memory dysfunction (11-13). Anti-CRMP5 antibody is often associated with various neuropsychological deficits, and these deficits can precede chorea (13). In the present case, the symptoms were limited to forgetfulness and irritability without movement disorders. This is probably because the neurological symptoms or irAEs were detected early in this case. Furthermore, the lesions of the basal ganglia were limited to the anterior portion of the striatum (Fig. 2), in contrast to other reports, in which the lesion extended over the entire striatum (11, 12, 14). Limbic lesions were not observed on the brain MRI in this case.

The relationship between the patient’s blindness and his cancer is unknown. Although he had been diagnosed with retinitis pigmentosa, retinal degeneration can also be caused by paraneoplastic retinopathy (16). However, anti-recoverin antibody, which is an anti-retinal antibody (16), was not detected in this case, and there was no deterioration or improvement of his visual symptoms after ICI therapy or steroid pulse therapy.

Recent studies have suggested that the use of ICIs might trigger PNS, particularly in SCLC patients, which is commonly associated with neurological autoimmunity (2, 5). However, to our knowledge, only one case has been reported concerning anti-CRMP5 PNS after ICI therapy for SCLC (paraneoplastic myelopathy) (6). We herein report another case of anti-CRMP5-associated striatal encephalitis induced by the ICI atezolizumab administered for SCLC.

The authors state that they have no Conflict of Interest (COI).

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Ethical Publication Statement
We confirm that we have read the journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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