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【 CASE REPORT 】

CV2/CRMP5-antibody-related Paraneoplastic Optic Neuropathy Associated with Small-cell Lung Cancer

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Abstract:
A 61-year-old woman who had smoked for 41 years developed subacute dizziness, ataxic gait, opsoclonus, and right visual impairment. She had right optic disc swelling and optic nerve gadolinium enhancement on magnetic resonance imaging. She had small-cell lung cancer (SCLC), with CV2/collapsin response mediator protein (CRMP)5 and HuD antibodies in her serum and cerebrospinal fluid. She was diagnosed with paraneoplastic optic neuropathy (PON) accompanied by paraneoplastic opsoclonus-ataxia syndrome. Her symptoms improved after removing the SCLC. Classical PON is rare in Japan. We recommend assaying for CV2/CRMP5 antibodies and searching for cancer in elderly patients with subacute painless visual impairment.

Key words: paraneoplastic optic neuropathy, paraneoplastic opsoclonus-ataxia syndrome, HuD antibodies, CV2/CRMP5 antibodies, small-cell lung cancer

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Introduction

Paraneoplastic neurological syndrome (PNS) is a rare disorder that develops in 0.1-10% of cancer patients (1, 2). Neurological symptoms often precede those of cancer itself, and the cancer is sometimes difficult to detect. PNS has various neurological manifestations, so it is important that it be considered during a differential diagnosis, especially in patients with atypical clinical manifestations, other neurological disorders, and risk factors for neoplastic diseases.

We herein report a patient with CV2/collapsin response mediator protein (CRMP)5 antibody-positive paraneoplastic optic neuropathy (PON) associated with small-cell lung cancer (SCLC). The case was complicated by opsoclonus-ataxia syndrome, and anti-P/Q-voltage-gated calcium channel (P/Q-VGCC) and anti-HuD antibodies were positive as well. PON is one of the rarest form of PNS, but its early detection can result in surgical removal of the underlying cancer and recovery from the neurological deficit.

Case Report

A 61-year-old woman was admitted to our hospital because of subacute progressive dizziness, impairment of the vision in her right eye, dysarthria, and gait instability over the past 9 months. She had had visual impairment and a visual field defect caused by retinochoroidal coloboma in her left eye since childhood and had been smoking 20 cigarettes per day for 41 years.

A neurological examination revealed cerebellar-type dysarthria, visual impairment in both eyes [0.2 (n.c.) OD], opsoclonus, impaired coordination of the extremities, predominantly on the left side, and ataxic gait. There was no decrease in the muscle strength or tendon reflex in the extremities. She had right optic disc swelling but no eye pain.

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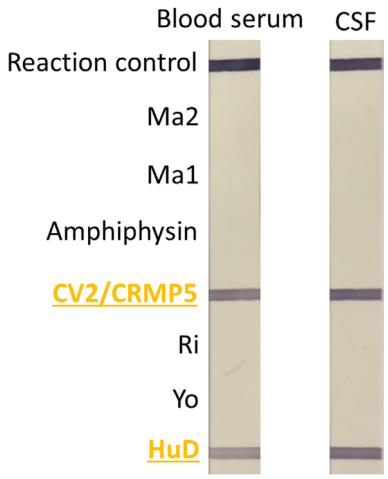

Figure 1. Assay of paraneoplastic neurological syndrome-related antibodies using PNS-Blot® (ravo Diagnostika, Freiburg, Germany). CV2/CRMP5 and HuD antibodies were positive in both the serum and cerebrospinal fluid (CSF). In antibody assays, the patient's serum and CSF were diluted to a total IgG concentration of 62 µg/dL each. Both antibodies showed stronger reactivity in the CSF than in the serum.

Electroretinography showed reduction in all waves, suggesting hypofunction of the rod and cone cells. At admission, the progastrin-releasing peptide level was elevated at 113 pg/mL (normal range <69.9 pg/mL), anti SS-A antibodies were elevated at 1,140.0 U/mL (normal range <6.9 U/mL), anti SS-B antibodies were elevated at 15.5 U/mL (normal range <6.9 U/mL), and anti-thyroglobulin antibodies were elevated at 174 IU/mL (normal range <27 IU/mL). Other markers were within normal ranges for blood cell counts (red blood cells, white blood cells, and platelets), coagulation system (prothrombin time and activated partial thromboplastin time), thyroid hormone, vitamin B1, vitamin E, biochemistry (liver function, renal function, electrolytes), and immune serum (C-reactive protein, erythrocyte sedimentation rate, serologic test for syphilis, *Treponema pallidum* antibodies, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti-thyroid peroxidase antibodies, and thyroid stimulatory hormone receptor antibodies). Anti-aquaporin 4 antibodies were negative (cell-based assay), anti-myelin-oligodendrocyte glycoprotein (MOG) antibodies were positive (1: 512), and anti-P/Q-VGCC antibodies were elevated equivocally at 31.8 pmol/L (normal range <20.0 pmol/L). In the cerebrospinal fluid (CSF), protein was mildly elevated (protein 44.4 mg/dL), and the IgG index was elevated (1.23), but other measurements were normal [opening pressure 13.0 cmH_2O, cell count 5/µL (mononuclear cells 100%), no oligoclonal IgG bands, IL-6 2.9 pg/mL, and progastrin-releasing peptide 33.0 pg/mL]. In tests for PNS-related antibodies, CV2/CRMP5 and HuD antibodies were positive in both the serum and CSF. Antibody titers adjusted to the same IgG concentration (62 µg/dL each) were higher in the CSF than in the serum, suggesting that the antibodies were produced in the central nervous system (Fig. 1). Head magnetic resonance imaging (MRI) did not show atrophy of the cerebellum or tegmentum of the midbrain. Gadolinium-enhanced MRI of the orbit demonstrated relatively well-marked enhancement of the right optic nerve compared with the left optic nerve; non-enhanced MRI of the orbit did not show abnormal signals (Fig. 2). In pattern reversal visual evoked potentials, the major positive peak (P100) latencies were 98.1 ms for the right eye and 120.6 ms for the left eye. Formation of the P100 peak in the right eye was fuzzy compared with the left eye (Fig. 3). Contrast-enhanced chest computed tomography showed a tumor in the hilum of the lower lobe of the right lung (Fig. 4). There was no evidence of distant metastasis. The histopathological diagnosis based on the tumor biopsy was SCLC, which was assessed as cancer stage IIA through a systemic evaluation.

Using the proposed diagnostic criteria for PNS (3), we diagnosed the patient with paraneoplastic opsoclonus-ataxia syndrome and PON based on the following: symptoms such as subacute progressive cerebellar ataxia, opsoclonus, and right visual impairment; right optic disk swelling and gadolinium enhancement of the right optic nerve on MRI; positive results for CV2/CRMP5 and HuD antibodies in serum and CSF; and the presence of SCLC.

The SCLC was no bigger than 4 cm in diameter, and there was no distant metastasis; therefore, surgery was performed for total extirpation followed by adjuvant chemotherapy. Although her ataxic gait temporarily improved with preoperative rehabilitation, after the operation and chemotherapy, her dizziness and ataxic gait gradually improved, and her right visual acuity and optic disc swelling slightly improved (Fig. 5). Anti-MOG antibodies still had a high titer (1:1,024) on day 1,022 after admission.

Discussion

The most frequent forms of PNS with visual loss are cancer-associated retinopathy and melanoma-associated retinopathy, whereas PON is rare (4). PON was reported for the first time by Pillay et al. in 1984 (5). In 2003, Cross et al. reported 16 (8%) cases of optic neuritis among 190 individuals who were positive for CV2/CRMP5 antibodies (6). The age range of the 16 patients was 52-74 years, and the male/female ratio was 7:9. All patients were smokers, and 11 had underlying SCLC. The 16 patients had neurological findings other than visual loss, including five each with cerebellar ataxia or peripheral neuropathy. Furthermore, three patients had optic neuropathy with myelopathy that was difficult to differentiate from neuromyelitis optica. Ten of the 16 cases were positive for other PNS-related antibodies, and 8 of these were complicated with SCLC. In 2001, Yu et al. reported optic neuritis in 7% of 116 cases positive for CV2/CRMP5 antibodies (7). Cross et al. reported optic neuritis in 35% of cases of SCLC positive for CV2/CRMP5 antibodies, and lung cancer associated with CV2/CRMP5-antibody-positive PNS was SCLC in at least 77% of cases (6). Taken together, these findings suggest that PON

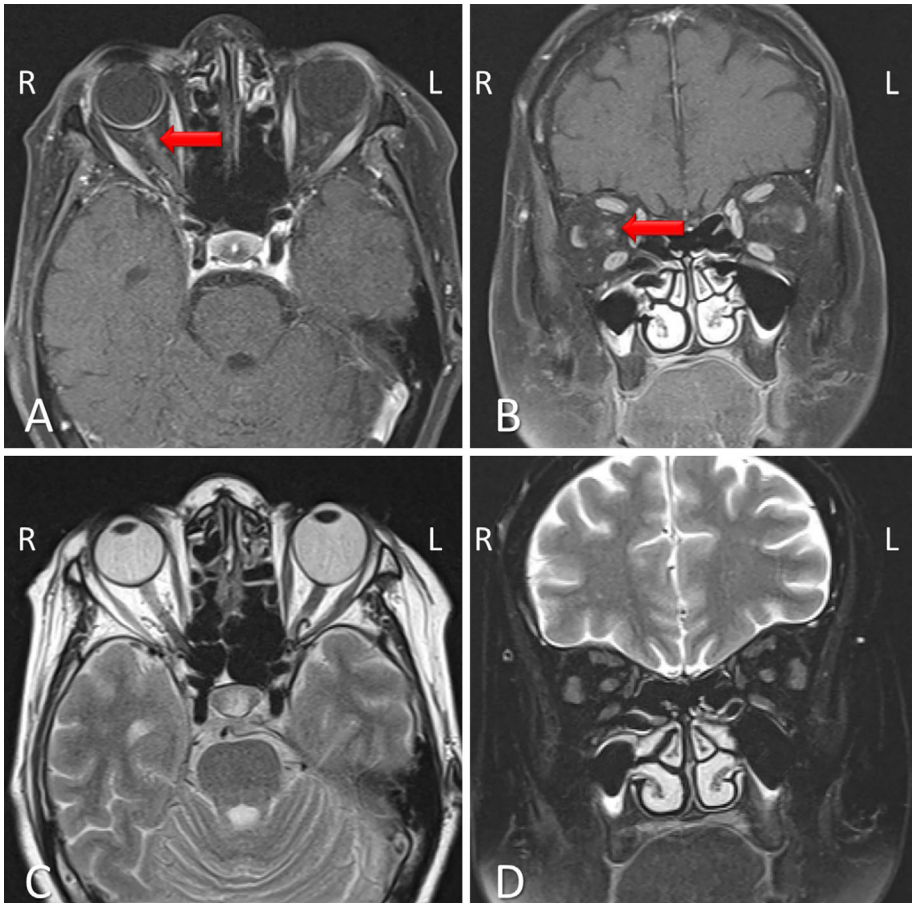

Figure 2. **Axial and coronal orbit magnetic resonance imaging (MRI). Post-contrast T1 MRI demonstrates relatively well-marked enhancement of the right optic nerve (arrows) compared with the left optic nerve (A, B). T2-weighted imaging and short T1 inversion recovery show no abnormal signals (C, D).**

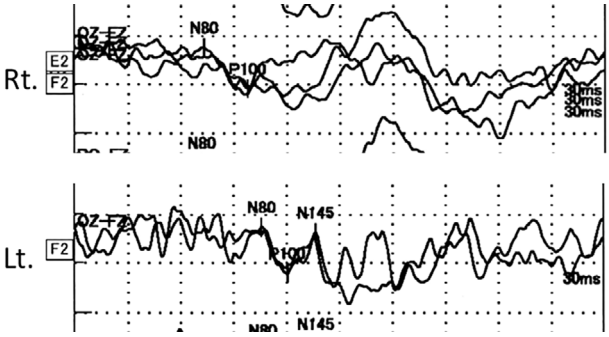

Figure 3. **Pattern reversal visual evoked potentials. The major positive peak (P100) latencies are 98.1 ms for the right eye and 120.6 ms for the left eye. The formation of the P100 peak in the right eye is fuzzy compared with that in the left eye.**

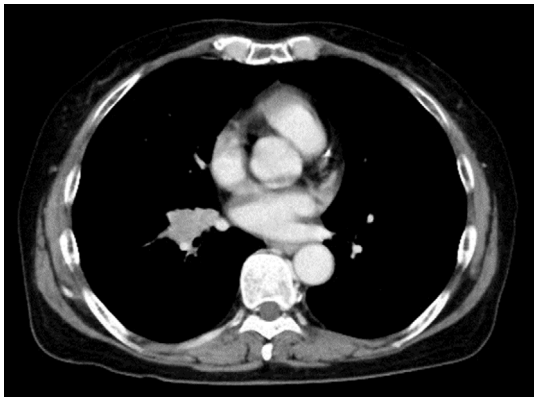

Figure 4. **Contrast-enhanced chest computed tomography. A tumor with non-uniform enhancement at the hilum of the lower lobe of the right lung is present.**

associated with CV2/CRMP5 antibodies is typically related to smoking, subacute optic neuropathy with other neurological findings, and SCLC as the main underlying cancer.

In Japan, 12 cases of PON have been reported (8-14). CV2/CRMP5 antibodies were positive in two of these cases, and the underlying cancer included six cases of lung cancer, with four cases of lung adenocarcinoma and one definitive case of SCLC. Neurological findings other than optic neuropathy were palsy, epilepsy, sensory disorder, consciousness disorder, cerebellar ataxia, and retinopathy. In the two cases with CV2/CRMP5 antibodies, the main neurological manifestation was subacute loss of vision, and neurological findings other than visual loss were epilepsy and retinopathy. With regard to PNS-related antibodies other than CV2/CRMP5 antibodies, only recoverin antibodies were detected

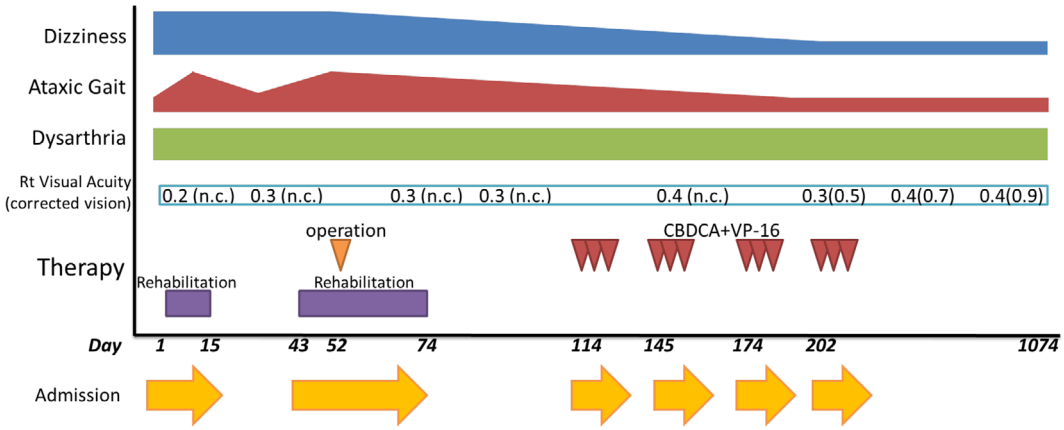

Figure 5. Clinical course after admission. Surgery for small-cell lung cancer was performed on the 52nd day after admission. Ataxic gait temporarily improved with preoperative rehabilitation. Chemotherapy was administered after the operation. Dizziness and ataxic gait gradually improved, and right visual acuity and optic disc swelling slightly improved. CBDCA: carboplatin, VP-16: etoposide

in one case. In the current case, anti-P/Q-VGCC antibodies and anti-Hu antibodies were detected as PNS-related antibodies other than CV2/CRMP5 antibodies. Anti-P/Q-VGCC antibodies might be related to cerebellar ataxia in this case, but the patient did not show clinical features suggesting Lambert-Eaton syndrome. The underlying cancer was lung cancer in both of the aforementioned cases with CV2/CRMP5 antibodies, being SCLC in one and adenocarcinoma in the other. One of the cases received chemotherapy and showed improvement in the visual acuity.

The present case is the third of PON associated with CV2/CRMP5 antibodies in Japan (12, 14). The clinical features of the cases of PON associated with CV2/CRMP5 antibodies in Japan agree with those reported in other countries, including neurological findings other than visual loss, positivity for PNS-related antibodies other than CV2/CRMP5 antibodies, an association with lung cancer, especially SCLC, and the improvement of the visual acuity following anticancer therapy.

CV2 antibodies were first reported in 1996 (15) and are called CRMP5 antibodies because they specifically recognize the 62-kDa CRMP5. CRMP5 is associated with the development and differentiation of brain cells and brain plasticity. It is expressed in the cytoplasm of glial cells as well as in the peripheral nervous system, the retina, and optic nerves (16); given this localization of expression, CV2/CRMP5 antibodies are found in a variety of neurological disorders, including optic neuropathy. It is reported that antibodies for intracellular proteins, such as Hu, Yo, and Ri antibodies, are produced intrathecally (17-19), but they are not regarded as pathogenic factors because experiments using animals failed to give rise to PNS and immunotherapy was not effective for PNS that was associated with these antibodies. PNS associated with antibodies for intracellular protein might be caused by cytotoxic T cell-mediated cell death. PNS-related antigens developing in the tumor may stimulate T cells in the peripheral blood through antigen-presenting cells, such as dendritic cells; B cells then produce antibodies through helper T cells and activate cytotoxic T cells to attack the nervous system (20, 21).

In a study on CV2/CRMP5 antibody-related PON by Cross et al. (6), the IgG index was elevated in three of five cases examined, and CV2/CRMP5 antibodies in CSF were positive in all eight cases measured. There was a higher level in the CSF than in the serum in one case, and a lower level in the CSF than in the serum in five. The levels were not clear in two cases. In the current case, the CV2/CRMP5 antibody titer was higher in the CSF than in the serum when assayed at the same IgG concentration, suggesting that the antibody was produced in the central nervous system. This finding suggests that the CV2/CRMP5 antibodies may be associated with pathological processes in the central nervous system, even though they do not directly cause tissue damage.

Anti-MOG antibodies were reported in anti-aquaporin (AQP) 4 antibody-negative neuromyelitis optica spectrum disorder (22). This suggests that the antibodies might be related to optic neuropathy in the current case. However, visual impairment of PON is usually subacute and painless, as with this case (6), whereas visual impairment of anti-MOG antibody optic neuropathy is acute and frequently accompanied by optic pain (23). It is possible that an immunological condition other than PNS exists, and further consideration must be given to the occurrence of symptoms associated with the antibodies.

CV2/CRMP5 antibodies target intracellular protein antigens, so their effects in terms of immunotherapy for PON remain unclear. In the current case, the patient did not undergo immunotherapy, but her neurological symptoms improved following anticancer therapy. However, the chemotherapy acted via immunosuppression and might have improved her neurological symptoms. Adjunctive systemic immunosuppression may be considered as a treatment option for PON based on its presumed autoimmune mechanism, but

the results of systemic steroid therapy for PON, usually given to supplement cancer therapy, have been variable (24). Intravenous immunoglobulin or plasma exchange plus cyclophosphamide is reportedly effective for Hu or Yo antibody-positive PNS (25, 26). Therefore, adjunctive immunotherapy might have led to further improvement in the neurological symptoms in this case.

In elderly smokers with subacute, bilateral, painless visual impairment and optic disc swelling, PON should be considered as a differential diagnosis. Patients should be examined for PNS-related antibodies, including CV2/CRMP5 antibodies, and for cancer, including SCLC, especially because the neurological condition may be reversible by managing the cancer.

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

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