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【 CASE REPORT 】

CV2/CRMP5-antibody-related Paraneoplastic Neurologic Syndrome Associated with Gastrointestinal Stromal Tumor

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Abstract:
Paraneoplastic neurological syndrome (PNS) is a heterogeneous group of neurological disorders caused by immune-mediated inflammatory mechanisms. We herein report a 77-year-old man with CV2/CRMP5-antibody-related PNS associated with a gastrointestinal stromal tumor (GIST). He was admitted for forgetfulness and delusional behavior. His neurological symptoms were subacute, and a whole-body examination revealed a gastric GIST. Serology showed CV2/collapsin response mediator protein (CRMP)-5 antibodies. Partial gastrectomy was performed for the GIST, and the neurological symptoms and serum CV2/CRMP5 antibodies disappeared. No relapse has occurred since the surgery. PNS should be considered in patients with subacute neurological disorders.

Key words: paraneoplastic neurologic syndrome, gastrointestinal stromal tumor, CV2/CRMP5 antibodies, developed limbic encephalitis

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Introduction

Paraneoplastic neurological syndrome (PNS) is a heterogeneous group of neurological disorders caused by immune disorders or inflammatory mechanisms. PNS of unknown cause is often observed in association with a malignant tumor. There have been reports of PNS in association with gastric cancer (1, 2), but its association with a gastrointestinal stromal tumor (GIST) is extremely rare.

We herein report a case of GIST that developed limbic encephalitis and was positive for anti-CV2/collapsin response mediator protein (CRMP)5 antibodies. This is the first report to describe the improvement in PNS-associated neurological symptoms in a GIST patient after resection of the tumor.

Case Report

A 77-year-old man had undergone resection for a benign tumor in the left shoulder but had no history of neurological disease.

In May 2016, he presented with forgetfulness and delusional behavior. The frequency of forgetfulness had increased beginning in October 2016. One month later, exacerbation and emotional incontinence of symptoms were observed, along with previously unrecognized behavior and the exacerbation of delusional behavior. The symptoms did not improve, and the neurological disorder worsened while the delusional symptoms persisted. He was therefore admitted to our hospital for an examination and treatment in December 2016.

Short-term memory loss and disorientation worsened progressively. His revised Hasegawa's Dementia Scale (HDS-R) score was 13 out of 30 (3, 4). A neurological examination

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revealed no abnormal findings regarding muscle strength, tendon reflexes in the extremities, dysarthria, vision or gait, such as ataxia.

Table 1. Laboratory Findings on Admission.

WBC	8,800 /μL	CRP	0.9 mg/dL
RBC	5.01×10^4 /μL		
Hemoglobin	14.6 g/dL	Vitamin B1	42 ng/mL
Hematocrit	43.7 %	Vitamin B12	308 pg/mL
Platelet	27.1×10^4 /μL	Folic acid	18.0 ng/mL
PT activity	84.0 %		
PT-INR	1.10	TSH	2.43 μIU/mL
APTT	34.7 sec	FT3	3.1 pg/mL
		FT4	1.4 ng/dL
Total protein	6.5 g/dL		
Albumin	3.4 g/dL	CEA	1.3 ng/mL
Sodium	140 mEq/L	CA19-9	8 U/mL
Potassium	4.3 mEq/L	IL-2rec	376 U/mL
Chloride	104 mEq/L		
Calcium	9.2 mg/dL	HBs-Ag	-
BUN	17 mg/dL	HCV-Ab	-
Creatinine	0.57 mg/dL	Herpes IgM	-
AST	14 U/L	CMVC7HRP	-
ALT	12 IU/L	Beta-D Glucan	-
CK	36 IU/L		
LDH	149 IU/L		
T-bilirubin	0.69 mg/dL		
D-bilirubin	0.16 mg/dL		
Glucose	90 mg/dL		

WBCs: white blood cells, RBCs: red blood cells, PT: prothrombin time, PT-INR: prothrombin time international normalized ratio, APTT: activated partial thromboplastin time, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CK: creatinine kinase, LDH: lactate dehydrogenase, CRP: C-reactive protein, TSH: thyroid stimulatory hormone, FT3: free triiodothyronine, FT4: free tetraiodothyronine, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, IL-2 receptor: interleukin-2 receptor

Blood test results for the following were within the normal range: red blood cells, white blood cells, and platelets, prothrombin time and activated partial thromboplastin time, thyroid hormone, vitamins, liver function, renal function, and electrolytes, immune serum values for C-reactive protein, anti-thyroid peroxidase antibodies and thyroid stimulatory hormone receptor antibodies, and tumor markers (Table 1). Cytology from lumbar puncture revealed no signs of a tumor, inflammation or infection.

Magnetic resonance imaging (MRI) of the head did not show atrophy of the cerebellum or tegmentum of the midbrain, and gadolinium-enhanced MRI showed normal signals. Dopamine transporter (DAT) scans revealed a reduced accumulation in the left putamen, indicating a decreased dopamine uptake (Fig. 1A). Enhanced computed tomography (CT) performed for whole-body screening showed a tumor in the gastric wall, about 25 mm in diameter (Fig. 2A). Because the patient had severe neurological symptoms, positron emission tomography (PET)-CT was performed to determine the need for invasive treatment to evaluate malignant lesions. PET-CT showed a tumor [maximum standardized uptake value (SUV_{max})=3.11] in the same localization as on enhanced CT, with no distant metastasis observed (Fig. 2B). Esophageal-gastric endoscopy revealed a submucosal ridge with a smooth surface in the lesser curvature of the gastric body (Fig. 3A). Endoscopic ultrasound (EUS) identified a mass in the fourth layer (Fig. 3B). An EUS-fine-needle aspiration biopsy (FNAB) was performed via the gastric approach with a 22-gauge needle (Acquire; Boston Scientific, Marlborough, USA) (Fig. 3C). The EUS-FNAB specimen revealed a GIST (Fig. 3D).

We suspected PNS based on the progressive neurological symptoms and presence of a tumor. In tests for PNS-related antibodies, CV2/CRMP5 antibodies were positive in serum (Table 2). Using the proposed diagnostic criteria for PNS (5), we diagnosed PNS based on positivity for CV2/

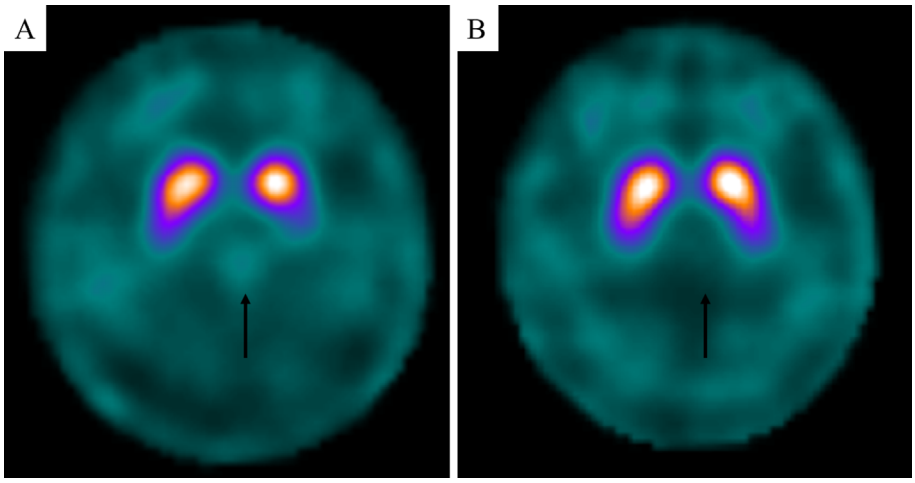

Figure 1. Comparison of dopamine transporter (DAT) scans before and after treatment. (A) A DAT scan shows a decrease in the accumulation, reflecting a decrease in dopamine capture in the left putamen before treatment (arrow). (B) A DAT scan revealed improvement in the same area after treatment (arrow).

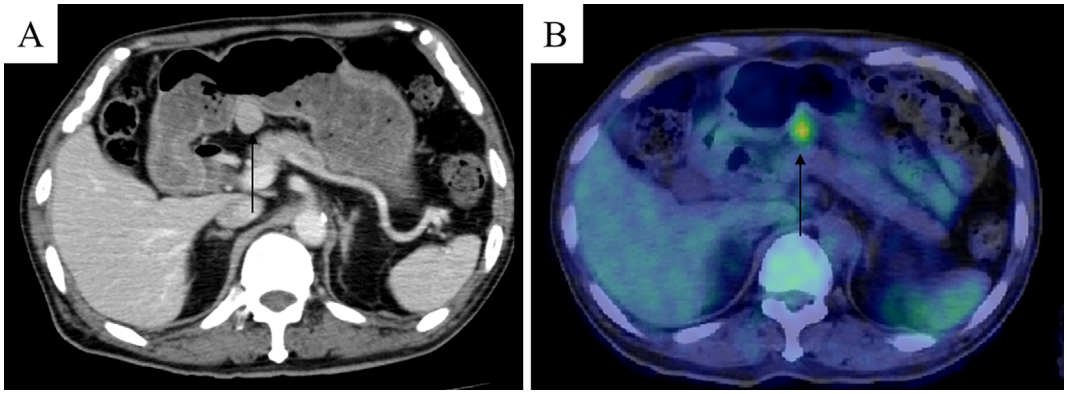

Figure 2. **Computed tomography (CT) and positron emission tomography (PET)-CT findings of the gastric gastrointestinal stromal tumor (A). The tumor (arrow) was 22 mm on enhanced CT (B). PET-CT showed a specific uptake in the same tumor (SUV_{max}=3.11, arrow). PET-CT, positron emission tomography-computed tomography.**

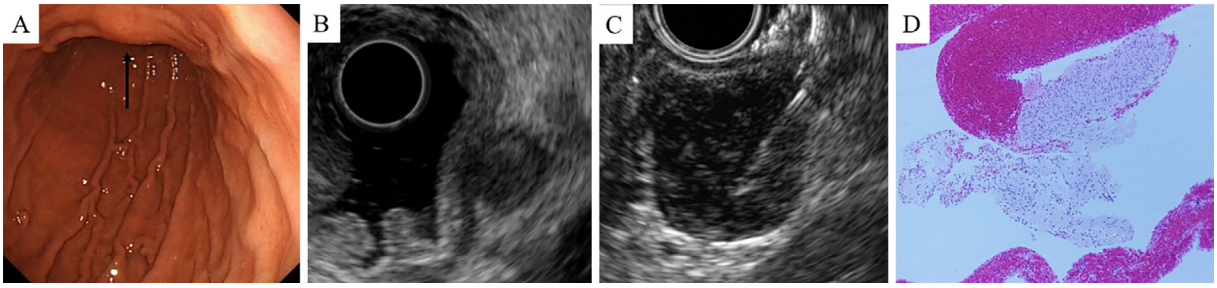

Figure 3. **(A) Esophageal-gastric endoscopy revealed the submucosal ridge with a smooth surface in the lesser curvature of the gastric body (arrow). (B) Endoscopic ultrasound (EUS) findings. EUS via the gastric approach detected a mass 22 mm in diameter located in the fourth layer of the gastric wall showing no obvious calcification. (C) An EUS-fine-needle aspiration biopsy (FNAB) was performed via the gastric approach, and two passes were made using a 22-gauge needle. (D) The EUS-FNAB specimen indicated a GIST (Hematoxylin and Eosin staining, ×40).**

Table 2. **Results of Tests of Paraneoplastic Neurological Syndrome-related Antibodies.**

La	-
Ce	-
Tr	-
GAD65	-
Zic4	-
Titin	-
Soy1	-
Rec	-
Hu	-
Yo	-
Ri	-
Ma2/Ta	-
CV2	+
Amphiphysin	-

CRMP5 antibodies in serum and the presence of the GIST. The lesion was larger than 20 mm in diameter, but there was no distant metastasis; therefore, surgery was performed for total extirpation. The pathological findings of the resected specimen resulted in a diagnosis of GIST, consistent with the FNAB results (Fig. 4).

After surgery the patient's short-term memory loss and disorientation gradually improved, and the HDS-R score improved to 29/30. Serum became negative for CV2/CRMP5 antibodies. Furthermore, DAT scans showed an improvement in the decrease in accumulation in the left putamen (Fig. 1B). The patient's condition progressed without recurrence or metastasis after resection.

Discussion

PNS is infrequent and associated with malignant tumors, comprising a heterogeneous group of neurological disorders affecting various areas of the nervous system. Among the well-known neurological disorders associated with PNS are paraneoplastic encephalomyelitis, sensory neuronopathy, cerebellar degeneration and Lambert-Eaton myotonic syndrome (6). PNS occurs in conjunction with solid malignant tumors in far less than 1% of cases but is most commonly associated with ovarian cancer, thymoma and small-cell lung

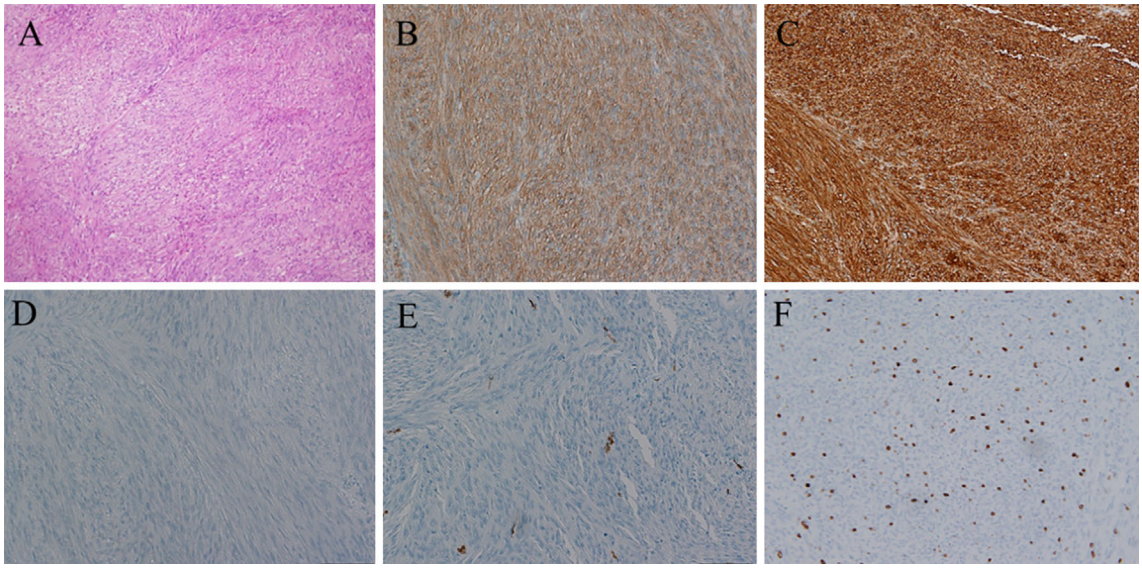

Figure 4. Immunohistochemical characterization of GIST. (A) Composed of a spindle-shaped cell structure (Hematoxylin and Eosin staining, ×100), (B) c-kit positivity (×100), (C) CD34 positivity (×100), (D) S100 protein negativity (×100), (E) SMA positivity (×100) and (F) MIB-1 index 5%. These findings were compatible with the diagnosis of a GIST (×100). GIST: gastrointestinal stromal tumor, CD34: cluster of differentiation 34, SMA: smooth muscle actin

cancer (7). PNS often occurs prior to discovery of the tumors that cause symptoms by weeks or months (8-10).

In our case, neurological impairment was apparent three months before the identification of the GIST. As in this patient, early detection is important for satisfactory neurological and oncological outcomes. Should the diagnosis come late, after the symptomatology has been established, the neuropathy may be unresponsive to treatment, and irreversible neurological damage can occur (1, 11-14).

Recognition of PNS should prompt an immediate search for the causative lesion. We detected paraneoplastic antibodies based on the presence of a subacute neuropathy indicating a neurological syndrome and the tumor. We diagnosed PNS based on the international diagnostic criteria for PNS (3).

After early detection of the causative tumor, resection resulted in disappearance of antigens, and symptoms of PNS were resolved. In most cases of suspected PNS, the tumor is revealed by CT, and whole-body fluorodeoxyglucose PET-CT may be useful for detecting the causative lesion (1, 15, 16). However, for causative lesions in the gastrointestinal tract, the diagnosis may be difficult using these modalities. Methods such as gastrointestinal endoscopy may thus be needed to detect the causative lesion.

In our case, CV2/CRMP5 antibody, which is a PNS-related antibody, was positive. CV2 antibodies were first reported in 1996 (17), and they specifically recognize 62-kDa CRMP5. These antibodies are associated with the development and differentiation of brain cells and brain plasticity and are expressed in the cytoplasm of glial cells, peripheral nervous system, retina, and optic nerves. CV2/CRMP5 antibodies are found in a variety of neurological disorders based on the localization of expression (18). However, the precise pathophysiological role of anti-CV2/CRMP5 antibodies is still unknown.

In addition, a DAT scan was useful in the present case for evaluating the damaged areas of the brain and objectively assessing treatment strategies. DAT imaging is considered a useful modality for differentiation of Alzheimer's dementia (AD) and dementia of Lewy bodies (DLB) with high sensitivity and specificity (19). DAT scans assess the DAT uptake in the basal ganglia. Their utility for discriminating DLB and AD is based on a reduced uptake within the striatum in DLB compared to less marked changes in AD (20). Indeed, the comparison of DAT scans before and after treatment shows a reduced dopamine uptake in the left putamen. In our patient, we recognized an improvement after treatment.

In our case, neurological impairments occurred three months before the detection of the GIST. We were able to consult with a neurologist and performed a systematic evaluation with PNS in mind. The early detection of the lesion contributed to favorable neurological and oncological outcomes in this patient. Therefore, it is important to consider PNS when subacute neurological disorders are observed accompanying a malignant disease, including a GIST.

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

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