

[ CASE REPORT ]

## A Unique Case of Encephalopathy with an Elevated IgG-4 and Extremely High Interleukin-6 Level and Delayed Myelodysplastic Syndrome

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### Abstract:

We herein report a 75-year-old man who developed disturbed consciousness with polynuclear cell dominant pleocytosis and low glucose and extremely high interleukin (IL)-6 levels in his cerebrospinal fluid. The biopsy specimen from his right supraclavicular lymph node showed the infiltration of inflammatory cells positive for IgG, IgG4 and IL-6. Prednisolone and azathioprine administered under suspicion of IgG4-related disease (IgG4-RD) or multicentric Castleman's disease (MCD) successfully remitted the symptoms. However, he developed myelodysplastic syndrome (MDS) and died 18 months later. The extremely high IL-6 may have been related to the rare neurological manifestations and development of MDS in the present case.

**Key words:** encephalopathy, IgG4 related disease, interleukin-6, multicentric Castleman's disease

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### Introduction

IgG4-related disease (IgG4-RD) affects many organs, but only 5% of IgG4-RD patients show the involvement of the central nervous system (CNS) (1). Multicentric Castleman's disease (MCD) usually affects lymph nodes and tissues in the chest or abdomen but rarely involves the CNS. The differentiation of IgG4-RD and MCD is sometimes challenging because both diseases present high IgG4 level (2).

We herein report a very rare encephalopathy case with an elevated IgG4 level and an extremely high level of IL-6 that subsequently developed myelodysplastic syndrome (MDS).

### Case Report

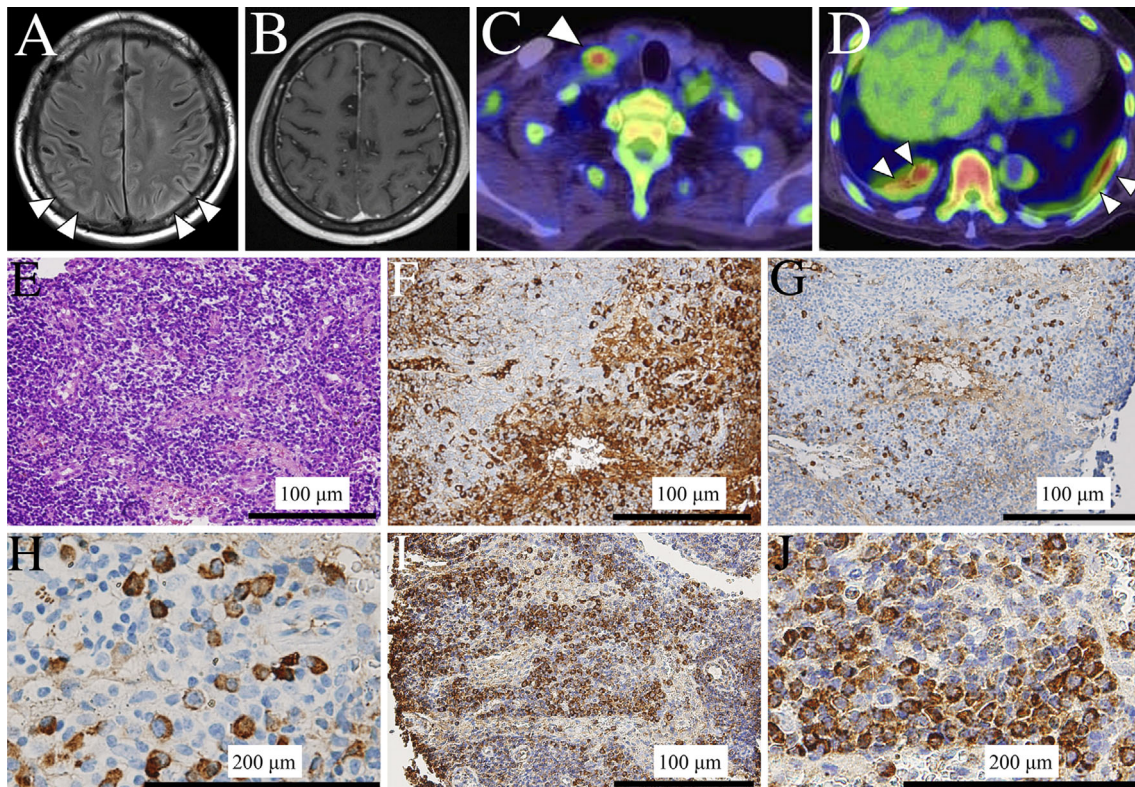
The patient was a 75-year-old man previously treated for chronic pleuritis at 71 years old and for bilateral optic neuritis at 73 years old. He complained of severe persistent malaise, developed disturbed consciousness six months later, and was admitted to our hospital.

A clinical examination revealed mild consciousness disturbance [Glasgow Coma Scale (GCS) score of 12/15 with eye (E) 3, verbal (V) 4, motor (M) 5] and neck stiffness without any other neurologic abnormalities. An analysis of the arterial blood gas revealed acute respiratory alkalosis (pH 7.50, pO<sub>2</sub> 82.4 mmHg, pCO<sub>2</sub> 28.9 mmHg, HCO<sub>3</sub><sup>-</sup> 22.4 mol/L). Laboratory data revealed normal blood cell counts (white blood cells 5,940/μL, red blood cells 4.78×10<sup>6</sup>/μL, hemoglobin concentration 11.9 g/dL and platelets 296×10<sup>3</sup>/μL) with an elevated erythrocyte sedimentation rate (105/119 mm) and increased levels of C-reactive protein (4.23 mg/dL), soluble interleukin (sIL)-2 receptor (1,524 IU/mL; normal 122-496 IU/mL) and interleukin (IL)-6 (24.5 pg/mL; normal <8.0 pg/mL). Immunoglobulin (Ig) G and IgG4 levels were significantly elevated (4,134 mg/dL; normal 861-1,747 mg/dL and 1,670 mg/dL; normal 4.5-117 mg/dL), while rheumatoid factor, SS/A and B, and antinuclear antibodies were negative. A cerebral spinal fluid (CSF) examination revealed an elevated initial pressure (260 mmH<sub>2</sub>O) with a normal terminal pressure (50 mmH<sub>2</sub>O), polynuclear cell-dominant pleocytosis (311/mm<sup>3</sup>, polynuclear cells =

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**Figure.** Magnetic resonance imaging (MRI) showing elevated fluid-attenuated inversion recovery (FLAIR) hyperintense areas on both sides of the parieto-occipital cortex (A, arrowheads) without contrast enhancement (B). (C and D) Computed tomography (CT) showing an enlarged right supraclavicular lymph node (C, arrowhead) and thickened visceral pleura (D, arrowheads) with a significantly elevated uptake in fluorine-18 fluorodeoxyglucose positron emission tomography ( $^{18}\text{F}$ -FDG PET). (E to J) A biopsy specimen from the right supraclavicular lymph node showing extensive infiltration of inflammatory cells on Hematoxylin and Eosin staining (E). These cells were positive for IgG (F). Around 20% of IgG-positive cells were also positive for IgG4 (G and H) and strongly positive for IL-6 (I and J).

73%), high protein level (184 mg/dL) and low glucose level (27 mg/dL, serum 104 mg/dL). The CSF IL-6 content was quite high (5,430 pg/mL). Blood and CSF cultures, polymerase chain reaction testing for herpes simplex virus type 1 and CSF cytology were not informative.

Magnetic resonance imaging (MRI) revealed hyperintense fluid-attenuated inversion recovery (FLAIR) areas on both sides of the parieto-occipital cortex (Figure A, arrowheads) without contrast enhancement (Figure B). Computed tomography (CT) showed an enlarged right supraclavicular lymph node and thickened visceral pleura with a significantly elevated uptake on fluorine-18 fluorodeoxyglucose positron emission tomography ( $^{18}\text{F}$ -FDG PET) (Figure C and D, arrowheads). A biopsy specimen from the right supraclavicular lymph node showed the extensive infiltration of inflammatory cells with Hematoxylin-Eosin staining (Figure E). Those cells were positive for IgG (Figure F). Around 20% of IgG-positive cells were also positive for IgG4 (Figure G, H). The cells were also strongly positive for IL-6 (Figure I, J).

Intravenous methylprednisolone (mPSL) pulse therapy (1 g/day, 3 days) was administered, followed by oral PSL (45

mg/day). Within a few days, the patient became completely alert (GCS score 15 with E4V5M6), and his malaise also diminished. Follow-up laboratory data showed reduced serum levels of IgG (2,251 mg/dL) and IgG4 (677 mg/dL), and a CSF examination revealed the significant improvement of pleocytosis (mono = 6/mm<sup>3</sup>, poly = 0/mm<sup>3</sup>) and the glucose level (72 mg/dL, serum 116 mg/dL). Although the CSF protein level was still high (105 mg/dL), the IgG index and IgG and IL-6 levels were reduced (0.50, 14 mg/dL and 795 pg/mL, respectively). The laboratory data and biopsy specimen findings indicated MCD (2) rather than IgG4-RD (3). However, the patient remitted promptly after PSL administration and thus was suspected of having IgG4-RD, which is more responsive to steroid therapy than MCD (4, 5). He was discharged 2 months after admission but continued oral PSL, gradually tapering the dose to 14 mg/day in 12 months in combination with azathioprine (100 mg/day), without showing any clinical recurrence.

However, the patient developed pancytopenia (white blood cell count 1,690/ $\mu\text{L}$ , red blood cell count  $2.72 \times 10^6$ / $\mu\text{L}$ , hemoglobin concentration 7.3 g/dL and platelet count  $26 \times 10^3$ / $\mu\text{L}$ ) with normal levels of sIL-2 receptor (273 IU/mL) and

**Table. Cerebrospinal Fluid Findings of IgG4 Related Disease Patients with CNS Involvement.**

	Ref. 10)		Ref. 11)			Present case (2020)	
	n		n	Case 1	Case 2		
Demographic and clinical data							
Median age		n.m.	60	53 (19-82)	55	66	74
Male/Female		n.m.		Male 40/Female 20	Male	Male	Male
CNS involvement		n.m.		Brain 81% single brain: n=44 brain and spinal cord: n=5	Spinal cord	Optic nerve	Optic nerve, Brain
CSF examination							
							on admission
Cell number (/ $\mu$ L)	11	14 (1-112)	20	19.5 (0-150)	69	2	311
Lymphocytes count (%)	9	94 (44-100)	18	91.5 (0-100)	95	n.m.	27
Protein (mg/dL)	11	76 (22-260)	20	92.5 (22-417)	196	99	184
Total IgG (mg/dL)	4	18.1 (8.7-38)	10	14.3 (6.29-38.1)	18.7	6.29	50
IgG4 (mg/dL)	3	5.17 (4.94-5.36)	4	0.965 (0.53-1.84)	0.53	0.63	25.7
IgG index	3	1.8 (0.8-1.8)	6	5.225 (4.94-8.5)	n.m.	n.m.	0.789
Oligoclonal band		n.m.	10	positive in 70%	negative	n.m.	negative
Interleukin-6 (pg/mL)		n.m.		n.m.	1923	normal	5,430
CSF glucose (mg/dL)	5	46.5 (30-73)					27
Serum glucose (mg/dL)		n.m.					104

CNS: central nervous system, CSF: cerebrospinal fluid, IgG: immunoglobulin G, n; number of patients with available data, n.m.: not mentioned

IgG (1,577 mg/dL) and slightly elevated levels of IL-6 (9.0 pg/mL) and IgG4 (279.6 mg/dL). An examination of the bone marrow showed a reduced number of hematopoietic cells with the heterozygous deletion of chromosome 7. He was thus finally diagnosed with MDS and treated with azacitidine. Six months later, he died from the transformation of his original MDS into acute leukemia.

## Discussion

IgG4-RD is a polyclonal lymphoproliferative disorder in which IgG4-positive plasma cell proliferation affects the pancreas, salivary glands, lymph nodes or retroperitoneum (6). Although pachymeningitis (7) and neuropathy (8) are well-known neurological manifestations in IgG4-RD, only 5% of IgG4-RD cases involve the CNS (1). MCD is an uncommon lymphoproliferative disorder that manifests as a local or generalized tumor-like condition affecting both lymph nodes and non-nodal tissues, usually in the chest or abdomen (2). MCD rarely involves the CNS, and previously reported cases presented with intracranial meningeal tumors (9). As with the present case, the differentiation of IgG4-RD and MCD is sometimes challenging, as both diseases show high serum levels of IgG4 (2).

The CSF findings of IgG4-RD patients are characterized by mononuclear-dominant mild pleocytosis and elevated IgG4 levels (Table) (10, 11). However, the present case showed polynuclear-dominant (73%) pleocytosis, low glucose levels and extremely high IL-6 levels (5,430 pg/mL) (Table, Present case). There have been no previous reports on the CSF findings of MCD patients.

As IL-6 induces neutrophil invasion into the CSF space (12), polynuclear cell-dominant pleocytosis may be re-

lated to the high IL-6 levels. Neutrophils reportedly consume more glucose than lymphocytes or monocytes (13), so the low CSF glucose level in the present case might be explained by the presence of polynuclear cell-dominant pleocytosis. Furthermore, it was reported that IL-6 itself inhibited the excitation in the cerebral cortex (14). The consciousness disturbance in the present case might be attributed to neutrophil-induced low glucose levels and excessive IL-6 levels in the CSF.

IgG4-RD patients rarely show elevated serum levels of IL-6 (15, 16), whereas MCD patients frequently show elevated IL-6 levels. The association between IgG4-RD and cancer or hematological malignancy (17) as well as the cocurrence of MCD and hematological malignancy (5) have been reported. Furthermore, the relationship between a high IL-6 level and cancer development has also been reported (18), so the extremely high level of IL-6 might also be related to the development of MDS. In the present case, the cumulative azathioprine dose of 26.5 g seemed to be too low to induce MDS (median 146 g) (19).

The present case developed steroid-responsive encephalopathy with high IgG4 and IL-6 levels followed by MDS. Although the differentiation of IgG4-RD and MCD was challenging in this patient, encephalopathy with polynuclear cell-dominant pleocytosis as well as low glucose and extremely high IL-6 levels were the first reported aspects. Extremely high IL-6 levels might indicate atypical encephalopathy and a risk of malignancy development.

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

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