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【 CASE REPORT 】

Intravenous Immunoglobulin in the Treatment of Adalimumab-associated Optic Neuritis

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Abstract:
Optic neuritis (ON) is a rare complication of tumor necrosis factor (TNF)-α inhibitors. The autoantibody serostatus, treatment, and outcome of TNF-α inhibitor-associated ON remain unclear. We herein report a 50-year-old woman with ON following adalimumab therapy. The patient presented with decreasing visual acuity of the right eye, quickly diminishing to light perception. Anti-aquaporin-4 (anti-AQP4) and anti-myelin oligodendrocyte glycoprotein antibodies were negative. Adalimumab was discontinued, and intravenous methylprednisolone and intravenous immunoglobulin (IVIg) were administered. However, her visual acuity improved only up to counting fingers. IVIg may be ineffective depending on the pretreatment severity.

Key words: adalimumab, tumor necrosis factor-α, optic neuritis, aquaporin-4, myelin oligodendrocyte glycoprotein, intravenous immunoglobulin

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Introduction

Tumor necrosis factor (TNF)-α inhibitors are an effective biological therapy for a variety of autoimmune diseases, such as rheumatoid arthritis, uveitis, inflammatory bowel diseases, and ankylosing spondylitis (1, 2). However, demyelinating diseases, such as multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), transverse myelitis, and optic neuritis (ON), can be infrequently induced by TNF-α inhibitor (1). Because of its rarity, the clinical characteristics of TNF-α inhibitor-associated ON remain unclear, especially concerning the serostatus of NMOSD-associated antibodies [anti-aquaporin-4 (anti-AQP 4) and anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies], treatment, and outcome.

We herein report a patient with TNF-α inhibitor-associated ON who was negative for both anti-AQP4 and anti-MOG antibodies and intractable to intensive immunosuppression therapies, including intravenous immunoglobulin (IVIg).

Case Report

A 50-year-old woman with a 2-year history of undifferentiated spondyloarthritis presented with vision loss in her right eye. Two months prior, she had begun therapy with adalimumab (40 mg every 2 weeks). Four days after the fifth cycle of adalimumab, she noticed blurred vision in her right eye (Figure A). After the sixth cycle of adalimumab, she visited our hospital because her vision loss was worsening. A neurological examination showed visual loss and an upper visual field defect in the right eye. Her visual acuity was 0.3 (20/63) in the right eye and 1.2 (20/16) in the left eye, but on the next day, the right eye's vision acutely deteriorated to 0.01 (20/2000). Her cerebrospinal fluid (CSF) cell count, protein, oligoclonal bands, and immunoglobulin G index were normal, but myelin basic protein (MBP) was markedly elevated at 1,290 pg/mL (reference range ≤40 pg/mL). Anti-AQP4 and anti-MOG antibodies were analyzed using a cell-based assay in the serum and CSF and confirmed to be negative.

Brain magnetic resonance imaging (MRI) showed a T2-

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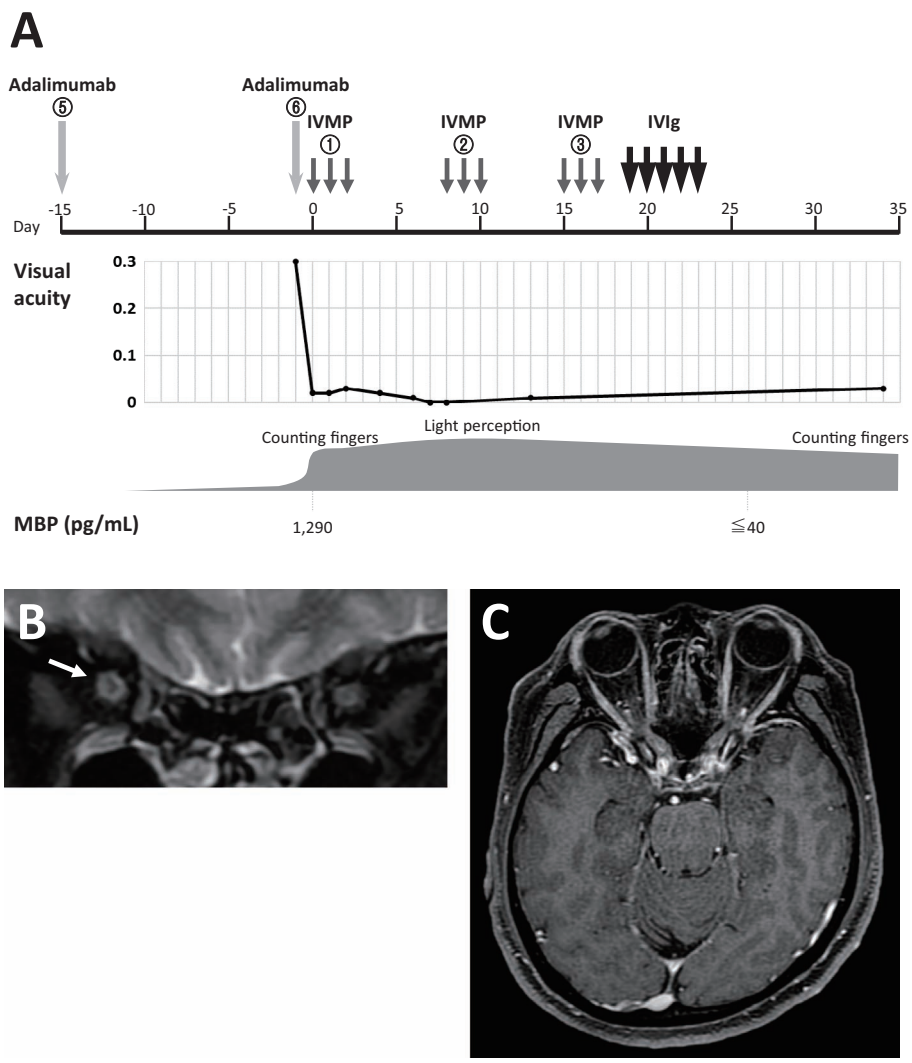

Figure. **(A) Time course of the visual acuity of the right eye and MBP levels in the CSF. (B) High signals in the right optic nerve (arrow) in coronal sections of fat-suppressed T2-weighted imaging. (C) No enhancement in axial sections on gadolinium-enhanced fat-suppressed T1-weighted imaging.**

weighted hyperintensity in the right optic nerve without gadolinium enhancement (Figure B, C) but no other intracranial abnormalities. Spine MRI showed no lesions in the spinal cord. Visual evoked potentials (VEPs) were not detected in the right eye and were normal in the left eye. A fundus examination of the eyes was normal. These findings resulted in the patient being diagnosed with adalimumab-associated acute retrobulbar neuritis.

Adalimumab was discontinued, and three courses of intravenous methylprednisolone (IVMP) were administered (Figure A). However, even after the introduction of IVMP, her right eye visual acuity deteriorated to light perception. Therefore, we added IVIg, but it provided only a small improvement to counting fingers. A follow-up study of the CSF showed a decreased level of MBP (≤40 pg/mL) (Figure A); meanwhile, follow-up brain MRI 10 months later showed no new lesions, and follow-up VEPs showed no improvement. Her right eye visual acuity remained at counting fingers at the 11-month follow-up.

Discussion

The use of TNF-α inhibitors, including adalimumab, has been associated with developing demyelinating diseases, such as ON. However, the incidence of ON among patients receiving adalimumab is low (0.01%) (3). Thus far, 13 patients with adalimumab-associated ON have been described in case reports (Table) (2-13). The patients, 6 men and 7 women, ranged from 32 to 66 years old. Their clinical characteristics included unilaterality (13/13, 100%), retrobulbar neuritis (8/11, 73%), visual field defect (11/11, 100%), and abnormal MRI signals in the optic nerve (6/12, 50%). The treatments included mostly adalimumab cessation (12/13, 92%) and steroids (IVMP and oral prednisolone) (9/13, 69%). IVIg was not used in these patients. The outcome is often complete resolution (9/13, 69%), but among the 4 cases that showed severe pretreatment visual defect (Cases 2, 5, 6, and 13), complete resolution was occasional (1/4, 25%). Altogether, adalimumab-associated ON usually pre-

Table. **Reported Cases of Adalimumab-associated ON.**

	Age/ Sex	Disease	Duration of adalimumab therapy (month)	Duration of ON (day)	Laterality	Location	Visual acuity at pretreatment	Visial field defects	Anti-AQP4-Abs	Anti-MOG-Abs	MRI abnormal findings	Adalimumab cessation	Immunosupressive therapy	Outcome of visual acuity	Reference
1	55/M	Psoriatic arthritis	4	5	Unilateral	Retrobulbar	0.7 (20/30)	+	ND	ND	O	+	IVMP, PSL	CR	3
2	40/M	RA	12	ND	Unilateral	Anterior	0.005 (1/200)	+	ND	ND	O, CNS	-	-	PR (20/30)	3
3	32/F	RA	25	ND	Unilateral	Retrobulbar	ND	ND	ND	ND	CNS	+	IVMP	PR	4
4	60/F	RA	2-6	5	Unilateral	Anterior	0.8 (20/25)	+	ND	ND	-	+	PSL	CR	5
5	39/F	Uveitis	23	2	Unilateral	Retrobulbar	CF	+	ND	ND	CNS	+	IVMP, IFNβ	PR (CF)	6
6	42/F	Uveitis	0.5	ND	Unilateral	Retrobulbar	CF	+	ND	ND	CNS	+	IVMP, PSL	CR	7
7	51/M	RA	5	ND	ND	ND	ND	ND	ND	ND	ND	+	IVMP	CR	2
8	45/F	RA	6	ND	Unilateral	Retrobulbar	ND	+	ND	ND	-	+	-	CR	8
9	48/M	Crohn's disease	12	ND	Unilateral	Retrobulbar	0.4 (20/50)	+	ND	ND	O	+	PSL	CR	9
10	64/M	UC	6	14	Unilateral	Retrobulbar	0.8 (20/25)	+	-	ND	O	+	-	CR	10
11	42/F	UC	2	ND	Unilateral	Retrobulbar	0.2 (20/100)	+	-	-	O	+	IVMP	CR	11
12	61/M	Plaque psoriasis	2	5	Unilateral	Retrobulbar	0.4 (20/50)	+	ND	ND	CNS	+	-	CR	12
13	66/F	RA	60	7	Unilateral	Anterior	LP	+	ND	ND	O, CNS	+	MTX, PSL	PR (20/40)	13
Our case	50/F	Undifferentiated spondyloarthritis	2	11	Unilateral	Retrobulbar	0.01 (20/2000)	+	-	-	O	+	IVMP, IVIg	PR (CF)	

Abs: antibodies, AQP4: aquaporin-4, CF: counting fingers, CNS: central nerve system, CR: complete resolusion, F: female, IFNβ: interferon beta, IVIg: intravenous immunoglobulin, IVMP: intravenous methylprednisolone, LP: light perception, M: male, MTX: methotrexate, MOG: myelin oligodendrocyte glycoprotein, ND: no data, O: optic nerves, ON: optic neuritis, PSL: predonisolone, PR: partial resolution, RA: rheumatoid arthritis, UC: ulcerative colitis

sents as unilateral retrobulbar neuritis, as shown in our case.

The disease etiology of our case was unclear because there was no evidence suggesting MS, and both anti-AQP4 and anti-MOG antibodies were negative. Among the previously reported cases, anti-AQP4 and anti-MOG antibodies were measured only in two cases (10, 11) and one case (11), respectively, with negative findings found in all cases (Table). Interestingly, even after expanding the scope to all demyelinating diseases associated with TNF-α inhibitors, we found no cases with anti-AQP4 seropositivity but did note one case of anti-MOG antibody-positive NMOSD associated with etanercept and adalimumab (14). The etiology of demyelination differs among MS, anti-AQP4 antibody-positive NMOSD, and anti-MOG antibody-positive NMOSD (15). Although the relapse rate of MS is increased by TNF-α blockade (16), whether TNF-α inhibitors induce or exacerbate other demyelinating diseases as frequently as MS is unclear. Additional cases should be accumulated to confirm the prevalence of anti-AQP4 and anti-MOG antibodies in cases of TNF-α inhibitor-associated ON.

In our case, IVIg had only a small effect of improving the patient's visual acuity, although the demyelinating process had subsided as inferred from the decreased level of MBP. We assume the severe visual acuity at pretreatment to be the reason for the patient's poor responsiveness to IVIg.

As described above, in the previously reported cases with a severe visual defect at pretreatment, the complete resolution rate was low, suggesting that pretreatment severity may predict a less-than-satisfactory outcome of adalimumab-associated ON. Notably, our case showed apparent deterioration within one day following the re-administration of adalimumab (sixth cycle) 10 days after the onset of the ON. The cessation of TNF-α inhibitors is required as soon as possible if a neurological event develops (4). In our case, the continuation of adalimumab, after the onset of ON, may have worsened the disease severity.

The influence of the double-seronegativity for anti-AQP4 and anti-MOG antibodies on the poor visual outcome after IVIg was unclear. A large-scale cohort study showed that double-seronegative ON and anti-MOG antibody-positive ON had a better visual recovery after treatments, including steroids and plasmapheresis, than anti-AQP4 antibody-positive ON (17). In contrast, IVIg has been proven to have no significant effect on treating ON (18), although a recent clinical trial showed the efficacy of IVIg in treating anti-AQP4 antibody-positive ON patients (19). The etiologies of anti-AQP4 antibody-negative ON might be refractory to IVIg. However, if autoimmune pathogenesis and refractoriness to IVMP are assumed, IVIg may be a candidate treatment for anti-AQP4 antibody-negative ON. Immunotherapy regimens should be considered individually for anti-AQP4 antibody-negative ON cases. Further research is required to clarify the effect of IVIg on TNF-α inhibitor-associated ON.

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

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