

[CASE REPORT]

Aseptic Meningitis-retention Syndrome Associated with Tocilizumab in a Patient with Idiopathic Multicentric Castleman Disease

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Abstract:

This is the first report of tocilizumab-associated meningitis-retention syndrome in a patient with idiopathic multicentric Castleman disease. A 57-year-old man presented with headache, nuchal rigidity, impaired consciousness, pyramidal tract signs and urinary retention. A cerebrospinal fluid examination revealed increased cell counts and protein levels. These symptoms were improved by intravenous methylprednisolone. Tocilizumab-associated meningoencephalitis has been reported in patients with rheumatoid arthritis and juvenile idiopathic arthritis but not with multicentric Castleman disease. This case presents evidence of the increased probability of meningitis as a neurological complication of tocilizumab administration.

Key words: aseptic meningitis, meningitis-retention syndrome, tocilizumab, idiopathic multicentric Castleman disease

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Introduction

Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody targeting the interleukin-6 (IL-6) receptor that effectively treats multiple autoimmune diseases, including rheumatoid arthritis (RA) (1) and juvenile idiopathic arthritis (JIA) (2), which are chronic systemic inflammatory diseases caused by the overexpression of several cytokines, including IL-6.

Furthermore, TCZ has been approved for treating idiopathic multicentric Castleman disease (iMCD) (3), which is a systemic lymphoproliferative disease characterized by a fever, multiple arthritis, and multiple lymphadenitis. Its pathogenesis is considered to involve the overproduction of IL-6 by B cells in the germinal centers of hyperplastic lymph nodes.

There have been two recent cases of meningoencephalitis and recurrent meningitis following TCZ administration (4), with RA and JIA as the underlying conditions. However,

cases with iMCD have not been reported. This case report describes a patient with iMCD who presented with meningitis-retention syndrome (MRS) following TCZ administration and suggests the increased probability of meningitis as a complication of TCZ administration.

Case Report

We herein report a 57-year-old man with iMCD. The disease onset had occurred at 53 years old, involving a fever, multiple arthritis, and multiple lymphadenitis. Fluorodeoxyglucose-positron emission tomography revealed an abnormal accumulation in the lymph nodes. A biopsy was performed for an inguinal lymph node. A diagnosis of iMCD (plasma cell type) was made based on the presence of plasma cell infiltration with a preserved lymph node structure as well as negative HIV and HHV-8 immunoreactivity. Considering the possibility of multiple organ involvement and a high disease activity, TCZ (8 mg/kg/month) was introduced with a sufficient treatment response; furthermore,

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Table 1. Laboratory Findings in This Case.

WBC ($\times 10^3/\mu\text{L}$)	6.8	IgA (mg/dL)	145	CSF examination	
RBC ($\times 10^4/\mu\text{L}$)	498	IgM (mg/dL)	65	Cell counts ($/\mu\text{L}$)	37
Hemoglobin (g/dL)	15.8	C3 (U/mL)	95	Lymphocyte ($/\mu\text{L}$)	34
Platelet ($\times 10^4/\mu\text{L}$)	26.5	C4 (U/mL)	16.0	Monocyte ($/\mu\text{L}$)	3
Albumin (g/dL)	4.4	CH50 (U/mL)	37	Total protein (mg/dL)	84
BUN (mg/dL)	12.6	Anti-nuclear antibody	-	Glucose (mg/dL)	48 (serum 132)
Creatinine (mg/dL)	0.69	Anti-SS-A antibody	-	Albumin (mg/dL)	46.4
AST (U/L)	20	Anti-SS-B antibody	-	IgG (mg/dL)	5.3
ALT (U/L)	37	MPO-ANCA	-	IgG index	0.54
LDH (U/L)	239	PR3-ANCA	-	Cytology	Class II
HbA1c (NGSP) (%)	5.6	CMV-IgG/IgM	-/-	Culture	-
Na (mEq/L)	127	HSV-IgG/IgM	-/-		
K (mEq/L)	4.1	VZV-IgG/IgM	+/-		
CRP (mg/dL)	<0.30	EBV-IgG/IgM	-/-		
ESR (mm/hr)	1	T-SPOT	-		
IgG (mg/dL)	936	β -D glucan	-		

WBC: white blood cell, RBC: red blood cell, BUN: blood urea nitrogen, AST: aspartate amino-transferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, Na: sodium, K: potassium, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, Ig: immunoglobulin, C3: Complement component 3, C4: Complement component 4, CH50: 50% hemolytic complement activity, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibodies, PR3-ANCA: proteinase-3-anti-neutrophil cytoplasmic antibodies, CMV: Cytomegalovirus, HSV: herpes simplex virus, VZV: varicella zoster virus, EBV: Epstein-Barr virus, CSF: cerebrospinal fluid

oral prednisolone 10 mg/day (0.15 mg/kg/day) was added to treat the remaining lymphadenitis and arthritis. Oral prednisolone was gradually reduced to 2 mg/day for the subsequent 3 years, with the TCZ dose being maintained. The patient received TCZ for three years, and the final TCZ administration had been performed two weeks before admission.

The patient presented with a fever $>38^\circ\text{C}$, and fatigue lasting for a few days. To avoid relative corticosteroid insufficiency, oral prednisolone was increased to 15 mg/day. Intravenous meropenem (0.5 g every 8 hours) was administered as a probabilistic treatment for 5 days. Moreover, celecoxib (400 mg/day) was introduced for antifebrile purposes. However, the patient showed a poor response. Headache, nuchal rigidity, and urinary retention appeared, so a urinary catheter was introduced. Since central nervous system involvement was suspected, the patient was transferred to our department.

In addition to headache and fatigue, a neurological examination revealed nuchal rigidity, mild disturbance of consciousness (JCS I-3, E4V4M6), pyramidal tract signs (increased tendon reflexes of extremities, positive Babinski and Chaddock signs), and urinary retention. A serum examination did not reveal autoimmune or infectious diseases. A cerebrospinal fluid (CSF) examination demonstrated increased cell counts ($37/\mu\text{L}$) with lymphocyte predominance (91%), increased protein levels (84 mg/dL), and mildly decreased glucose levels (48 mg/dL, 132 mg/dL in serum). The IgG index was 0.54. Cytology and bacteriological examination results were unremarkable (Table 1).

There were no abnormal brain or spine findings on contrast-enhanced Magnetic resonance imaging. Electroen-

cephalography showed diffuse θ waves that were predominant in the parieto-occipital region. Truncal computed tomography revealed no mass lesions, including swollen lymph nodes.

Probabilistic treatment was continued using intravenous acyclovir (625 mg every 8 h) and ceftriaxone (2 g/day) for 10 days, with the patient showing a poor response. Nuchal rigidity and unconsciousness gradually worsened. A CSF examination 10 days after admission revealed an increased protein level (147 mg/dL) and IgG index (0.75), with slightly decreased cell counts ($18/\mu\text{L}$).

Because an immune-mediated mechanism was suspected, intravenous methylprednisolone therapy (500 mg/day for 3 days and 1,000 mg/day after 1 week for 3 days) was started. The patient showed a sufficient response with rapid improvement of his fatigue, headache, and nuchal rigidity; in addition, his consciousness became clear. A CSF examination revealed decreased protein levels (76 mg/dL) and a reduced IgG index (0.63). The α waves were predominant in the electroencephalogram. The patient became able to urinate on his own.

Following the introduction of an increased oral prednisolone dose (30 mg/day), the patient was discharged without neurological deficits (Figure). His iMCD has remained well controlled for two years since his discharge without TCZ administration.

Discussion

We encountered a patient with MRS following TCZ therapy for iMCD. There were several possible causes of the meningitis in our patient.

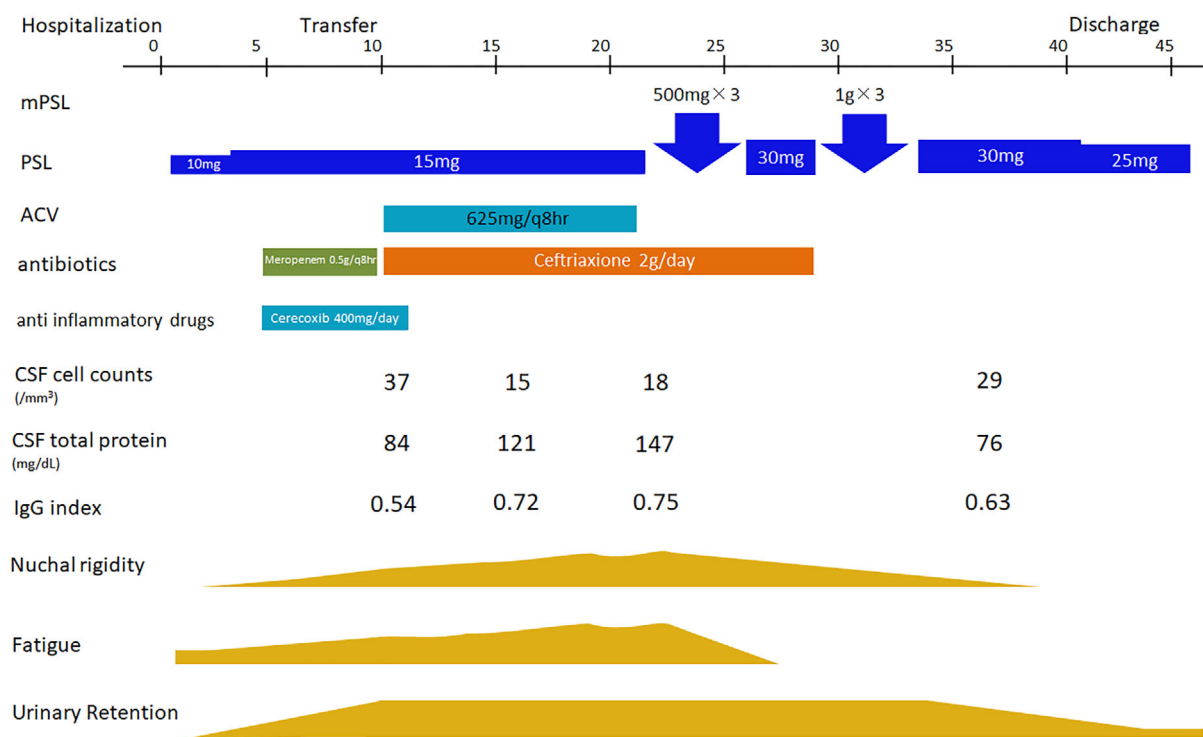


Figure. Clinical course of the patient. mPSL: methylprednisolone, PSL: prednisolone, ACV: acyclovir, CSF: cerebrospinal fluid

First, the most common cause of aseptic meningitis is infection, including herpes simplex virus or varicella-zoster virus infection. However, these causes were excluded through serological examinations. In addition, other infectious causes were unlikely although not completely ruled out, given the remarkable response to intravenous methylprednisolone therapy. Second, there was the possibility of immune-mediated mechanisms, including systemic collagen diseases or paradoxical TCZ reactions involving drug-induced systemic lupus erythematosus. However, laboratory examination findings did not support any of these possibilities. Third, regarding iMCD itself, some case reports have indicated cerebrovascular involvement, including ischemic stroke (5) and subarachnoid hemorrhaging (6); however, there have been no reports of the involvement of meningitis.

Drug-induced aseptic meningitis (DIAM) seemed most plausible cause in the present patient. Causative drugs for DIAM include nonsteroidal anti-inflammatory drugs, antibiotics, immunosuppressive or immunomodulatory drugs, and antiepileptic drugs (7). Recently, monoclonal antibodies, including infliximab (8), which targets tumor necrosis factor, and efalizumab (9), which targets CD11 molecules on the T-cell surface, have been recognized as causative drugs for DIAM (10). Candidate drugs included TCZ, meropenem, and celecoxib. TCZ was selected since it was the only candidate drug prescribed before the meningitis onset, although other drugs may have contributed to the prolongation of the meningitis.

Although MRS has a good prognosis, its prevalence and pathogenesis remain unclear (11), and drug-induced MRS

has been rarely reported (12). Further research on this syndrome is needed, especially concerning cases of drug-induced MRS.

The mechanism underlying the neurotoxicity of TCZ might involve elevated IL-6 levels in the central nervous system. First, TCZ binds to the IL-6 binding site of human IL-6 receptor and competitively inhibits IL-6 signaling. This leads to increased serum levels of IL-6 due to the reduction in its receptor-mediated clearance (13). Second, the IL-6 levels in CNS are elevated by direct transit of IL-6 via production in the periphery and trafficking of activated immune cells to the CNS (14). Third, because in contrast to IL-6, TCZ is not expected to cross the blood-brain barrier (14), the elevated IL-6 levels might activate the inflammatory system in the CNS, leading to neurological manifestations.

A report of two cases (4) described TCZ-associated meningoencephalitis and recurrent meningitis; however, the manifestations markedly differed between the cases. In the first case, the administration of TCZ was initiated, and the duration between the last administration of TCZ and disease onset was only one day. This clinical manifestation indicates an acute immunological mechanism, like allergic responses towards TCZ itself. In contrast, in the second case and our present case, the administration of TCZ was repeated, and the duration between the last administration of TCZ and the disease onset was more than two weeks, indicating an autoimmune mechanism evoked by TCZ, as described above. The disappearance of the meningeal syndrome after TCZ discontinuation and good response to the steroid therapy further supports this mechanism (Table 2). The differences in

Table 2. Clinical Pictures of Tocilizumab-associated Neurological Complications.

	Case 1 ⁴⁾	Case 2 ⁴⁾	This case
Onset age(years)	68	17	57
Sex	F	F	M
Underlying condition	rheumatoid arthritis	JIA	iMCD
Clinical presentation	meningoencephalitis	recurrent meningitis	meningoencephalitis
Fever	N/A	+	+
Focal signs	hemiplegia, aphasia	-	-
Urinary retention	-	-	+
CSF cell counts(/ μ L) and predominance of cell types	48 (98% neutrocytes)	324 (78% lymphocytes)	37 (91% lymphocytes)
CSF protein (mg/dL)	59	63	84
CSF glucose level	N/A	not elevated	slightly decreased
Number of TCZ administration	for the first time	repeated	repeated
Onset from last administration	one day	15 days	18 days
Additional therapy	iv. dexamethasone	none	iv. methylprednisolone
Prognosis	cognitive impairment	no sequelae	no sequelae

JIA: juvenile idiopathic arthritis, iMCD: idiopathic multicentric Castleman disease, CSF: cerebrospinal fluid, TCZ: tocilizumab, iv.: intravenous

the clinical presentation between these cases should be further elucidated.

In addition, despite the differences in the background systemic conditions across these three cases (inflammatory or lymphoproliferative process), the presentation of neurological toxicity is more indicative of the involvement of the immunomodulatory mechanism of TCZ described above than the underlying systemic condition itself.

In conclusion, this case report proves the increased probability of meningitis as a complication of TCZ administration, and more attention should be paid to neurological complications of TCZ.

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

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