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【 CASE REPORT 】

Tocilizumab-induced Leukoencephalopathy with a Reversible Clinical Course

Ryo Sasaki[1], Nozomi Hishikawa[1], Emi Nomura[1], Yoshio Omote[1], Mami Takemoto[1], Toru Yamashita[1], Noriko Hatanaka[2], Yasuto Higashi[2] and Koji Abe[1]

Abstract:

Tocilizumab (TCZ; Actemra/RoActemra) is an anti-interleukin (IL)-6 receptor antibody for the treatment of rheumatoid arthritis (RA) and other autoimmune diseases and cytokine storms. The present case is a 63-year-old female well-controlled RA patient, who presented with a progressive cognitive impairment after 34 months of TCZ administration. Brain magnetic resonance imaging (MRI) showed leukencephalopathy with a lactic acid peak in magnetic resonance spectroscopy (MRS), a decreased blood flow in single photon emission computed tomography (SPECT), and a decreased accumulation in fluorodeoxyglucose positron emission tomography (FDG-PET). The discontinuation of TCZ improved her cognitive function and brain MRI findings at 3 months after drug cessation. The present case suggests that TCZ may sometimes cause leukoencephalopathy after long-term administration, and thus the early discontinuation of TCZ is recommended to achieve a good prognosis.

Key words: tocilizumab, TCZ, leukoencephalopathy, cognitive dysfunction, COVID-19

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Introduction

Tocilizumab (TCZ) is a humanized anti-interleukin (IL)-6 receptor monoclonal antibody for the treatment of moderate to severe active arthritis (RA) patients who are resistant to treatments with steroids, methotrexate (MTX), and tumor necrosis factor (TNF) inhibitors (1). TCZ has also been used for various diseases related to the autoimmune response. Recently, TCZ was reported to be one of the treatments for novel coronavirus disease (COVID-19) by suppressing cytokine storms (2).

The most common adverse events associated with TCZ are infection and abnormalities in laboratory tests including dyslipidemia, neutropenia, thrombocytopenia, and an abnormality of the liver enzymes (3). However, nervous adverse effects including leukoencephalopathy are significantly rare, and thus it is unclear how to prevent or treat such neurological events.

We herein report the first known case of leukoencephalopathy with a progressive cognitive impairment suspected to have been induced by TCZ, who demonstrated a recovery of her symptoms and magnetic resonance imaging (MRI) findings at 3 months after TCZ withdrawal.

Case Report

A 63-year-old woman was admitted to our hospital due to a gradually progressive cognitive impairment. She was previously diagnosed to have RA, and had thus started the administration of prednisolone (PSL) 10 mg/day followed by MTX 6 mg/week at age 58. At age 60, MTX administration was discontinued due to acute interstitial pneumonia, and TCZ 680 mg/month with tacrolimus 2 mg/day was started (Fig. 1). Since the disease activity of RA was controllable, the dose of TCZ was changed to 162 mg/week with tapering of PSL to 8 mg/day at age 62. At age 63, after 34 months from the initial TCZ administration, she developed forgetfulness in regard to taking her daily medicine and also in other daily life events, and therefore she visited to a local neurol-

[1]Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Japan and [2]Department of Neurology, Himeji Central Hospital, Japan
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Correspondence to Dr. Koji Abe, pwag680v@okayama-u.ac.jp

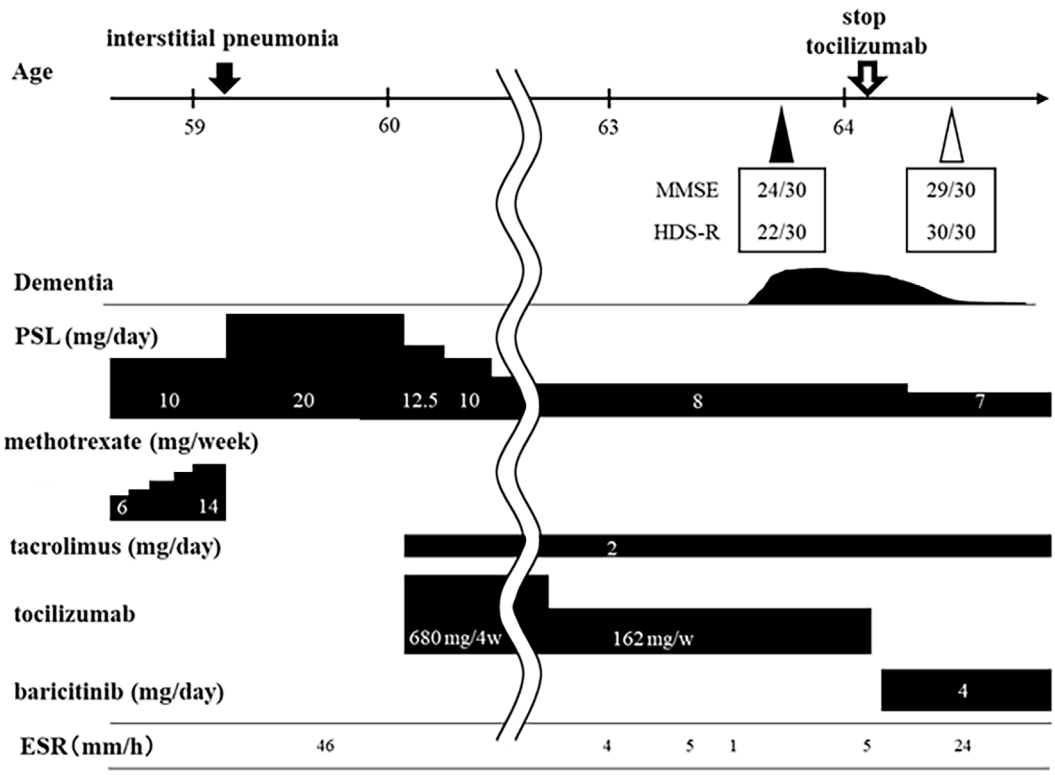

Figure 1. Clinical course of the patient: At age 60, the administration of tocilizumab (TCZ) 680 mg/month with tacrolimus 2 mg/day was started. At age 62, the dose of TCZ was reduced to 162 mg/week with tapering of PSL to 8 mg/day. At age 63, after 34 months from the initial TCZ administration, she presented with progressive dementia which improved 3 months after TCZ discontinuation.

ogy clinic. She showed mild cognitive dysfunction with a score of 24/30 in a mini mental state examination (MMSE), 22/30 in Hasegawa dementia scale-revised (HDS-R), and 15/18 in a frontal assessment battery (Fig. 1, top). MRI showed high intensity lesions with edema in the bilateral temporal, frontal, and parietal lobes on fluid-attenuated inversion recovery images (Fig. 2A-C), where Gadolinium-enhanced T1-weighted MRI showed no enhancement (data not shown). She was therefore admitted to our hospital for further examination.

On admission to our hospital, her blood pressure was 108/76 mmHg with a body temperature of 36.5 °C. Neurological examinations revealed hyperreflexia in all extremities with snout reflex. Her sensory, cerebellar, and autonomic systems were normal. Biochemical analyses showed elevated white blood cells (10,070 /μL, normal 3,300-8,600 /μl), normal C-reactive protein (0.02 mg/dL, normal 0.00-0.14 mg/dL), erythrocyte sedimentation rate (5 mm/hr), and elevated interleukin-6 (IL-6: 69 pg/mL, normal <4.0 pg/mL). Anti-glutamic acid decarboxylase, aquaporin 4, myelin oligodendrocyte glycoprotein, N-methyl-D-aspartate, human immunodeficiency virus, and Human T-cell leukemia virus type 1 antibodies were all negative. A cerebral spinal fluid study showed a normal pressure, slight pleocytosis (9/μL, monocyte 100 %), and an elevated protein level (91 mg/dL, normal 10-40 mg/dL). The IgG index (5.63, normal <0.73) was elevated and an oligo clonal band was present. Bacterial, mycobacterium, and fungal cultures of cerebrospinal fluid (CSF) were negative. Polymerase chain reaction for JC virus DNA was negative. Whole body computed tomography showed no evident feature of malignancy. A follow-up brain MRI after 36 months from the initial TCZ administration showed no remarkable changes compared to the previous findings (data not shown). Magnetic resonance spectroscopy (MRS) revealed a lactic acid peak in the left temporal lobe (Fig. 2D, arrowhead) which was absent on the contralateral side. Radio isotope inspections showed a low accumulation in the left frontal lobe in brain single photon emission computed tomography [SPECT, using N-isopropyl-P-(^{123}I) iodoamphetamine, and analyzed by the graph plot method] (Fig. 2E, arrowhead), and a decreased accumulation in the left frontal lobe lesion on ^{18}F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) (Fig. 2F, arrowhead).

Because TCZ induced leukoencephalopathy was suspected, TCZ was stopped after 37 months from the initial administration. We continued PSL 7 mg/day and tacrolimus 2 mg/day, and newly started baricitinib 4 mg/day. After 3 months from starting the above therapy, the MMSE and HDS-R scores improved to 29/30 and 30/30 (Fig. 1), and the brain MRI findings also improved in the bilateral temporal, right frontal, and right parietal lobe lesions (Fig. 2G-I, arrowheads) without an exacerbation of the RA symptoms.

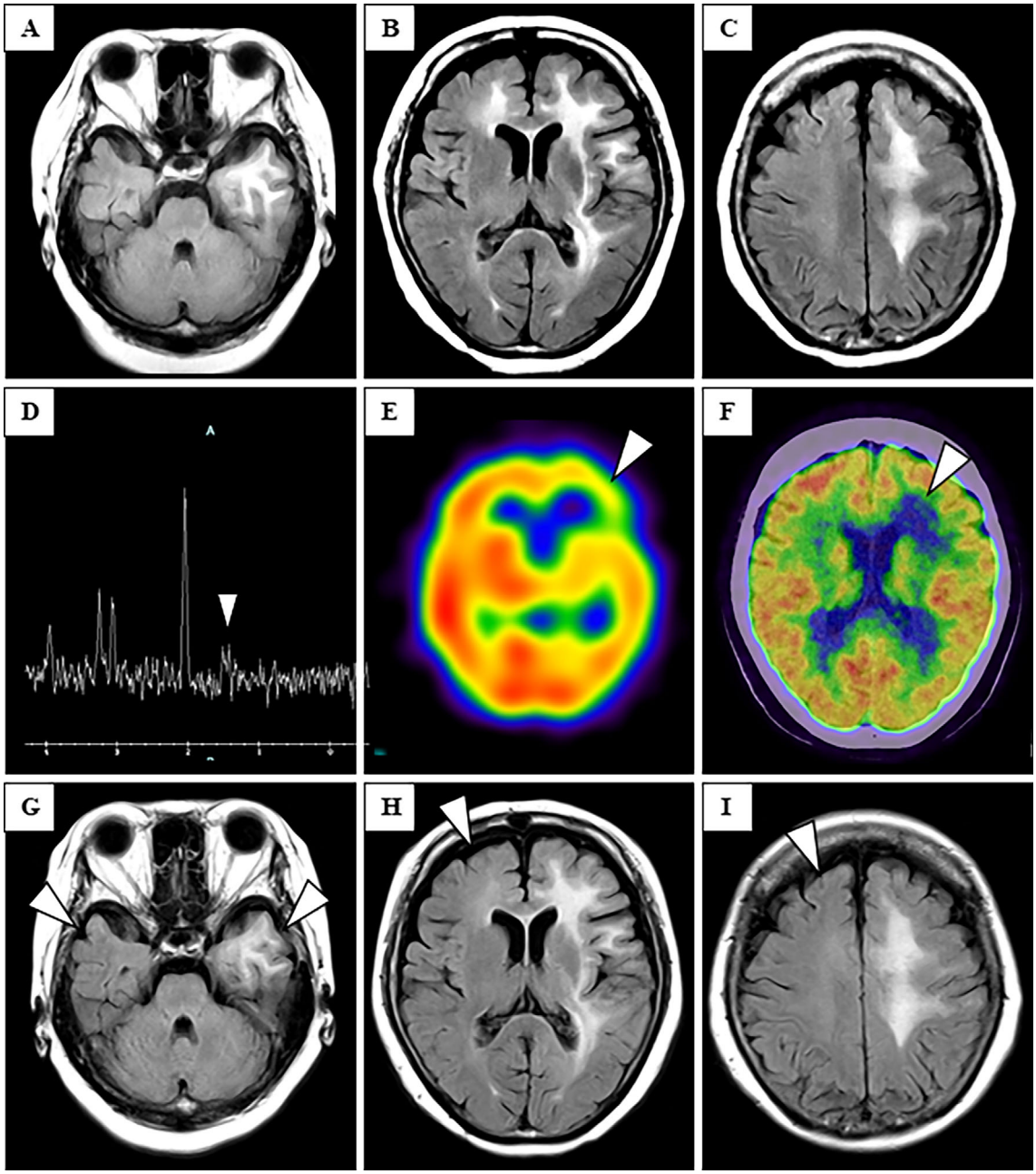

Figure 2. **A brain MRI showed leukencephalopathy in the bilateral temporal, frontal, and parietal lobes (A-C) with a lactic acid peak in MRS (D, arrowhead), a decreased blood flow in SPECT (E, arrowhead) and a decreased accumulation in FDG-PET (F, arrowhead). The brain MRI findings improved at 3 months after TCZ discontinuation (G-I, arrowheads).**

Discussion

The present case was a well-controlled RA patient who presented with a progressive cognitive impairment after 34 months of TCZ administration (Fig. 1). Brain MRI showed leukencephalopathy in the bilateral temporal, frontal, and parietal lobe (Fig. 2A-C) with a lactic acid peak in MRS (Fig. 2D, arrowhead), a decreased blood flow in SPECT (Fig. 2E, arrowhead) and a decreased accumulation in FDG-PET (Fig. 2F, arrowhead). We suspected her to have drug induced leukencephalopathy and therefore stopped TCZ administration. Three months later, both her dementia and the brain MRI findings improved (Fig. 2G-I, arrowheads).

TCZ is an IgG1 class monoclonal antibody against IL-6 receptor, inhibiting the IL-6-mediated cascade of autoimmune cell differentiation and autoantibody production related to the inflammatory response (4). Conversely, IL-6 also works as a neurotrophic or tissue repair mediator regarding neuroprotection (5). Therefore, the inhibition of IL-6 potentially makes the central nervous system vulnerable to various types of damage resulting in leukoencephalopathy. In addition, the combination of tacrolimus administration may worsen the disruption of the blood brain barrier and

thereby increase the toxic effect of TCZ (6). Prior MTX administration may be one of the potential causes of leukoencephalopathy, however, this is thought to be less likely because of the long range from discontinuation of MTX and the symptoms. TCZ induced leukoencephalopathy is rare (7, 8), and this is the first case report that showed an improvement of both the symptoms and in the MRI findings after TCZ withdrawal. Comparing the reported TCZ-induced leukoencephalopathy cases including ours, the common MRI findings may be the diffuse high intensity on fluid-attenuated inversion recovery (FLAIR) with the laterality of the lesions. However, it is unclear that the present case showed improvement of lesions only in the right frontal lobe. The accumulation of further cases, and more frequent MRI or neurological examinations are required to clarify the mechanisms of TCZ-induced leukoencephalopathy.

TCZ has been used for RA (1) and Castleman disease (9), and also showed an efficacy in neuromyelitis optica (10). Recent reports revealed that TCZ could suppress cytokine storm in patients with COVID-19 (2, 11). Although the administration period of TCZ is shorter for COVID-19 patients than for RA patients, the potential adverse effect of TCZ for leukoencephalopathy should also be taken into account.

This is the first report of suspected TCZ induced leukoencephalopathy case who recovered at 3 months after TCZ withdrawal. The present case suggested that TCZ may cause leukoencephalopathy after long-term administration and the early discontinuation of TCZ is therefore recommended for to achieve a good prognosis.

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

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