Multifocal Encephalopathy and Autoimmune-mediated Limbic Encephalitis Following Tocilizumab Therapy

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Abstract

A 63-year-old man with rheumatoid arthritis developed multifocal encephalopathy and limbic encephalitis following therapy with tocilizumab, a humanized anti-interleukin-6 receptor antibody. Anti-glutamate receptor ε2 antibodies were later found to be positive in both the serum and cerebrospinal fluid. This case highlights the possibility of the development of encephalopathy after treatment with tocilizumab, which may also induce autoimmune limbic encephalitis.

Key words: autoantibody, anti-glutamate receptor (GluR), multifocal encephalopathy, limbic encephalitis, tocilizumab, interleukin-6

Introduction

Recently, several emerging biological agents have been increasingly used in the treatment of collagen-vascular and hematological disorders. However, several reports have shown that these agents can induce encephalopathy (1-3), the underlying mechanisms of which are currently unknown. We herein report the case of a patient presenting with multifocal encephalopathy and limbic encephalitis following treatment with tocilizumab, a humanized monoclonal antibody against interleukin (IL)-6 receptor (IL-6R). In this case, autoantibodies against the N-methyl-D-aspartate (NMDA)-type glutamate receptor (GluR) subunit were detected. The GluR antibodies, which were possibly induced by treatment with tocilizumab, may have contributed to the pathogenesis of multifocal encephalopathy and limbic encephalitis.

Case Report

A 63-year-old man with rheumatoid arthritis (RA) was initially prescribed 7 mg/day of oral prednisolone (PSL) and 8 mg/week of methotrexate (MTX) at 60 years of age. Since the disease activity of RA was uncontrollable, he was treated with TNF-α antagonists, including 0.4 mg/kg of etanercept twice a week for five months followed by 40 mg of adalimumab every other week for 13 months, in addition to PSL and MTX. However, these agents were ineffective for treating the RA.

One month after the cessation of adalimumab therapy, the regimen was changed to 8 mg/kg of tocilizumab every four weeks (Fig. 1). Three months after the initiation of tocilizumab, the patient gradually developed cognitive impairment and weakness of the right arm. Total knee joint replacement was planned, and tocilizumab was discontinued. Two months later, he further developed weakness of the right leg and disorientation and his verbal communication progressively deteriorated. The Mini-Mental State Exam score was 4/30. Dysphagia, right-side dominant muscle weakness and rigidity in the extremities were later detected.

Laboratory blood tests showed an elevated C-reactive protein level (5.84 mg/dL) and erythrocyte sedimentation rate (105 mm/hr). The levels of angiotensin-converting enzyme and thyroid hormones were within the normal ranges. Serological tests were negative for syphilis and human immunodeficiency virus. No antinuclear, anti-SS-A, SS-B antibod-
A cerebrospinal fluid (CSF) examination revealed slight lymphocytic pleocytosis (6/μL) and an elevated protein concentration (57 mg/dL). No bacteria were cultured in the CSF, and viral studies were negative, including polymerase chain reaction for herpes simplex virus, human herpes virus-6 and JC virus DNA. No malignancy was detected on esophagogastroduodenoscopy, colonoscopy or a whole-body CT scan.

Fluid-attenuated inversion recovery (FLAIR) MRI of the brain revealed high intensity lesions within the left frontoparietal and bilateral temporal white matter seven months after the administration of tocilizumab (Fig. 2a). These lesions were partially contrasted with gadolinium. 99mTc-ethylcysteinate dimer SPECT showed a decreased uptake in both the lesions observed on MRI and bilateral limbic areas (data not shown).

A needle brain biopsy of the right temporal lobe lesion adjacent to the lateral ventricles showed definitive perivascular lymphocytic infiltration and abundant reactive astrocytes (Fig. 2a, arrow, Fig. 2c). Immunohistochemical staining with lymphocyte markers showed perivascular inflammatory infiltrates of both T- (CD3) and B- (CD20) cells (Fig. 2d, e), while fibrinoid necrosis, characteristic of RA associated angiitis, was absent, thus indicating nonspecific encephalitis. The administration of methylprednisolone pulse therapy (1 g/day for three days) and subsequent oral steroids (PSL, tapered from 40 mg/day) temporarily ameliorated the patient’s symptoms; however, his condition deteriorated (Fig. 1). Furthermore, he experienced recurrent generalized tonic-clonic seizures 16 months after treatment with tocilizumab. An interictal EEG showed periodical lateralized epileptiform discharges in the right hemisphere. MRI performed nine months later demonstrated the disappearance of enhancement in the left parietal and right temporal white matter lesions, although new lesions were observed in the right frontal lobe in addition to marked atrophy in the bilateral mesial temporal areas, suggesting limbic encephalitis (Fig. 2b). Autoantibodies against the N- and C-termini of NMDA type GluRε2 (homologs to NR2B) were detected in both the serum and CSF collected 12 months after the initiation of tocilizumab; the antibody titer was higher in the CSF than in the serum. The IL-6 level was simultaneously elevated (35 pg/mL) in the CSF. However, anti-NMDA receptor (NMDAR) antibodies were negative in the CSF collected 14 months after the administration of tocilizumab using a cell-based assay with human embryonic kidney 293 cells (Fig. 1).

The patient suffered from recurrent infections; therefore, only low-dose PSL (7 mg/day) was continued. He died of aspiration pneumonia 19 months after the introduction of tocilizumab. An autopsy was not allowed.

Discussion

Tocilizumab is a humanized monoclonal antibody against IL-6R that was introduced for the treatment of adult RA in 2008 in Japan, 2009 in Europe and 2010 in the U.S.A. More recently, tocilizumab has been shown to be effective for neuromyelitis optica (NMO) (4). In general, tocilizumab attenuates plasma cell differentiation and subsequent autoantibody production, such as that of aquaporin 4 antibodies in patients with NMO (4, 5). It also suppresses IL-21, which is primarily derived from effector/memory CD4-T cells. IL-21
plays a pivotal role in the differentiation of plasma cells and production of autoantibodies in patients with RA. Tocilizumab also inhibits IgG4 (not IgG1)-class anti-CCP antibodies by blocking the effects of IL-6 on IL-21 production induced by CD4+ T-cells (6). IL-6 exhibits ambivalent effects with respect to inflammation and neurotrophic repair depending on the pathological context in the central nervous system (CNS) (7). Therefore, tocilizumab potentially has both positive and negative effects on the CNS.

Notably, tocilizumab-induced leukoencephalopathy was described in the case of a 72-year-old woman with RA who developed cognitive impairment 40 months after the initiation of tocilizumab (1). FLAIR-MRI demonstrated the dissemination of high-intensity lesions in the bilateral cerebral white matter. The patient’s clinical symptoms and MRI abnormalities persisted for five months after the discontinuation of tocilizumab. Unlike that observed in this reported case, which lacked a pathological study, the present patient exhibited progressive dementia, weakness of the extremities and generalized tonic-clonic seizures. MRI of the brain demonstrated both multifocal encephalopathy lesions and bilateral mesial temporal atrophy.

TNF-α antagonists, such as etanercept and infliximab, may cause demyelinating disorders of the CNS and encephalopathy (8). These drugs were administered before the introduction of tocilizumab in the present case. Although several cases of etanercept-related encephalopathy have been previously reported (2), it is unlikely that etanercept caused encephalopathy after at least 16 months of use in our patient. Furthermore, to our knowledge, no cases of encephalopathy induced by adalimumab have been reported. Therefore, we suspect tocilizumab, the last biological agent used,

Figure 2. An axial view of FLAIR (upper) and T1-weighted contrast (lower) MRI performed at seven months (a) and 16 months (b) after tocilizumab treatment. FLAIR-MRI revealed high-intensity lesions reflecting leukoencephalopathy within the left frontoparietal, right frontal and bilateral temporal areas (a). Gadolinium-enhanced areas on T1-weighted MRI were partially observed within the lesions. Compared to the image obtained at seven months (a), progressive brain atrophy was conspicuous at 16 months, especially in the bilateral mesial temporal areas (b). A needle brain biopsy of the right temporal white matter adjacent to the lateral ventricles performed at 10 months after the initiation of tocilizumab (Fig. 1a, arrow). The microscopic findings of the obtained tissue showed definitive perivascular lymphocytic infiltration (c) with reactive astrocytes (Hematoxylin and Eosin staining) (c, inset). Immunohistochemical staining with T-(CD3) (d) and B-(CD20) cell (e) markers revealed perivascular inflammatory infiltrates of both T- and B-cells. The scale bar indicates 25 μm (c, inset) and 50 μm (d, e).
to be the trigger for the development of encephalopathy in this case (Fig. 1).

Regarding MTX, which was used in the present case in combination with tocilizumab, rare case reports have shown that low doses of this drug can cause blood brain barrier (BBB) disruption and subsequent leukoencephalopathy in RA patients (9). We postulate that MTX disrupted the BBB, which then allowed tocilizumab to exert toxic effects on the CNS.

Furthermore, the detection of autoantibodies against intrathecal GluRe2 in this case warrants comment. Tocilizumab attenuates autoantibody production (4, 10); however, it may also augment serum IL-6 via the suppression of IL-6R signaling (10). Salsano et al. reported a case of autoimmune limbic encephalopathy in which the patient exhibited an upregulated IL-6 level in the CSF and an augmented intrathecal IL-6 level that was not suppressed by tocilizumab treatment (11). On the other hand, the serum IL-6 levels increase in RA patients following the administration of tocilizumab for at least two weeks, while RA symptoms continue to be ameliorated (10). Therefore, the temporally augmented serum IL-6 levels induced by tocilizumab may allow IL-6 to spread into the brain parenchyma via a disrupted BBB, which may subsequently induce the secondary production of intrathecal anti-GluRe2 antibodies and limbic encephalitis.

Among several subtypes of GluRs, NMDA-type GluRs play key roles in synaptic plasticity related to learning and memory. These molecules exhibit a heterotetramer complex structure composed of NR1 and NR2/3 subunits. Antibodies against the glutamate NR1 and NR2A/NR2B subunits of NMDAR, known as anti-NMDAR antibodies, were originally reported in cases of ovarian teratoma-associated limbic encephalitis (12). Because antibodies against GluRe2 (NR2B) are detected in several diseases, including reversible autoimmune limbic encephalitis and other forms of encephalitis/encephalopathy, the presence of GluRe2 antibodies is thought to be less specific than that of NMDAR (13).

Furthermore, cases involving the development of anti-NMDAR encephalitis following TdaP-IPV booster vaccination (14) or Guillain-Barré syndrome (15) have been reported. These examples imply that the production of either anti-NMDAR or anti-GluR antibodies can be induced via host immunomodulatory reactions and by drugs, such as tocilizumab.

To date, biological agents, including tocilizumab, have been increasingly used for the treatment of several inflammatory autoimmune disorders. However, strong suppression of specific cytokine receptors, such as IL-6R, may perturb the balance of the immune system under a disrupted BBB, thus resulting in the development of autoimmune encephalitis/encephalopathy. Therefore, careful attention should be paid to monitoring the development of encephalopathy under treatment with these biological agents due to their possible adverse effects.

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

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References


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