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CASE REPORT

A case of rheumatoid arthritis complicated by demyelination in both cerebral cortex and spinal cord during etanercept therapy

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Abstract Tumor necrosis factor (TNF) antagonists, including etanercept, have been approved for the treatment of rheumatoid arthritis (RA). These agents are not free of adverse events like other antirheumatic agents. Several important adverse events in CNS lesions have been reported. In this paper, we report on one patient with RA that had complications from a demyelinating disorder during TNF-blockade therapy using etanercept at 24 months after initial administration. A 66-year-old Japanese woman was diagnosed with RA in 1959. She received various disease-modifying antirheumatic drugs (DMARDs), but all of these agents were ineffective. She was administered etanercept in June 2005, and stayed well. Twenty-four months after the initial administration of etanercept, she developed palsy of bilateral upper extremities and gait disturbance subacutely, and was then admitted to our institute in August 2007. MRI of her spinal cord revealed a high-intensity lesion from the third through to the seventh cervical (C3–C7) levels. Additionally, T2-weighted MRI images showed disseminated high-intensity lesions in the white matter of brain. She was suspected of having a demyelinating disorder based on these MRI findings. There was no significant finding that pointed to another neurological disorder. High-dose corticosteroid therapy was conducted and was effective for her.

Keywords Adverse event · Demyelination · Etanercept · Rheumatoid arthritis

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Introduction

Tumor necrosis factor (TNF) antagonists, including etanercept, have revolutionized the treatment of several inflammatory diseases globally, such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis. Although these biologics are in widespread use, there is a potential risk of adverse events, such as infection, neoplasm, demyelinating disease and autoimmune disorder, during TNF blockade therapy [1]. Among these adverse events induced by TNF antagonists, demyelinating disease is considered to be very rare; however, it is very serious for the patient [2–5]. In addition, the etiology of demyelination induced by TNF antagonists is still unclear [6].

In this work, we present a case of RA in a female patient who rapidly developed neurological symptoms during treatment with etanercept, and then improved upon being given high-dose corticosteroid therapy.

Case report

A 66-year-old Japanese woman was diagnosed with RA in 1959. Though she had received various disease-modifying

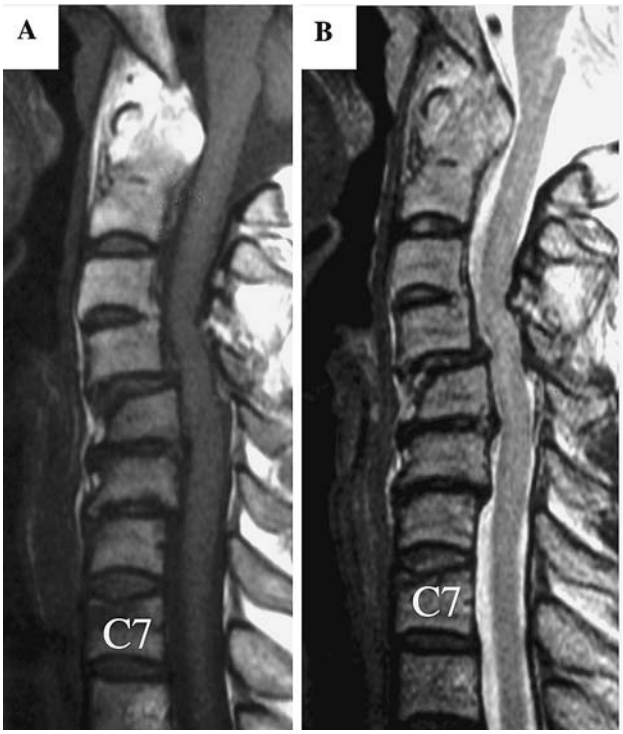

Fig. 1 MRI images at the surgery revealed no findings that suggested demyelinating disorder in her cervical cord. **a** T1-weighted, **b** T2-weighted

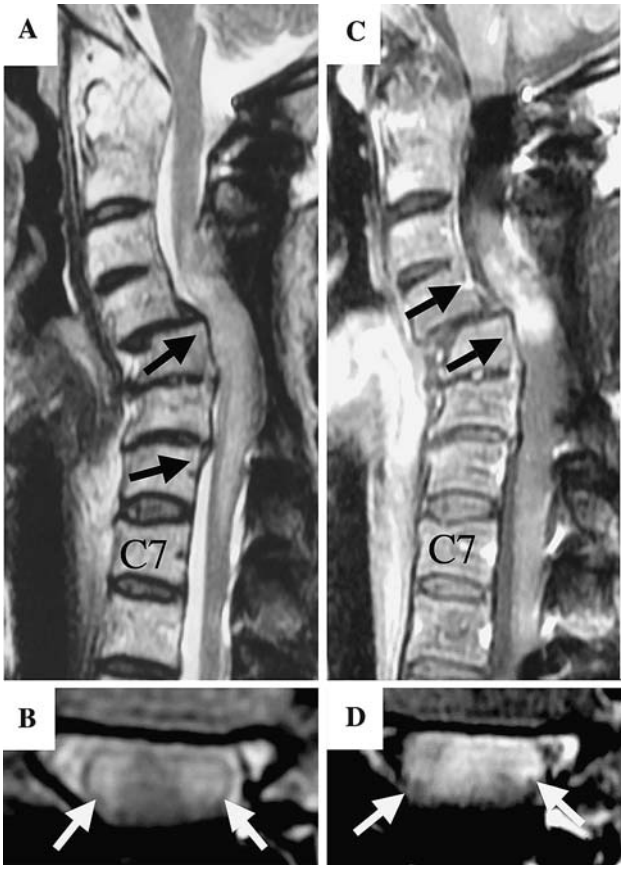

Fig. 2 T2-weighted MRI demonstrating swelling and abnomal signal intensity of the cervical cord (*arrows*): **a** sagittal, **b** axial at the C4 level. T1-weighted postgadolinium MRI demonstrating enhancement of the cervical cord: **c** sagittal, **d** axial at the C4 level

antirheumatic drugs (DMARDs) alone or in combination, joint destruction was gradually progressing, with high disease activity of RA observed. She underwent bilateral total knee arthroplasty (TKA) in 1988, and spinal fusion surgery for spondylolisthesis at the fourth cervical (C4) level in 2004. MRI images upon surgery revealed no findings suspicious for demyelinating disorder in her cervical cord (Fig. 1A,B). Even after treatment with several immunosuppressants, her activity of daily living (ADL) was growing worse. She was administered 25 mg of etanercept twice a week in June 2005. She responded to etanercept therapy, and stayed well. C-reactive protein (CRP) was 0.67 mg/dl (normal range: <0.20 mg/dl, before administration of etanercept: 1.46 mg/dl), anti-nuclear antibody (ANA) was positive (×80 speckled pattern, normal <×40, before administration of etanercept; ×1,280 speckled pattern), Rheumatoid factor (RF) was 217 IU/ml (normal range: <10 IU/ml, before administration of etanercept: 472 IU/ml) and matrix metalloproteinase-3 (MMP-3) was 133.3 ng/ml (normal range: 17.3–59.7 ng/ml, before administration of etanercept: no data). Twenty-four months after the initial administration of etanercept, she developed palsy of the bilateral upper extremities and gait disturbance subacutely, and was then admitted to our institute in August 2007. MRI of the spinal cord revealed swelling from the third through seventh cervical (C3–C7) levels, with a longitudinal high-intensity lesion present in the T2 weighted image (Fig. 2A,B). Although no abnormal signal was detected on T1 weighted MRI images, a high-intensity lesion was apparent with intense contrast enhancement after gadolinium injection at the same cervical lesion (Fig. 2C,D). In addition, contrast-enhanced fluid-attenuated inversion-recovery (FLAIR) MRI of the brain showed high-intensity lesions disseminated bilaterally throughout the white matter, although these were not enhanced after gadolinium injection (Fig. 3). No oligoclonal band formation was found upon examining the cerebrospinal fluid (CSF). The biochemical profiles of CSF were as follows: protein was 62 mg/dl (normal range: 15–45 mg/dl), glucose was 54 mg/dl (normal range: 50–75 mg/dl), cells were 4/μl (normal range: 0–5/μl), myelin basic protein was <40.0 pg/ml (normal range: <102 pg/ml) and the IgG index in CSF was 0.44, in the normal range. Several markers for microorganisms including virus, fungus, or bacteria in sera or CSF were negative. She was suspected of having a demyelinating disorder. There were no findings that pointed to another neurological disorder. Her etanercept treatment was

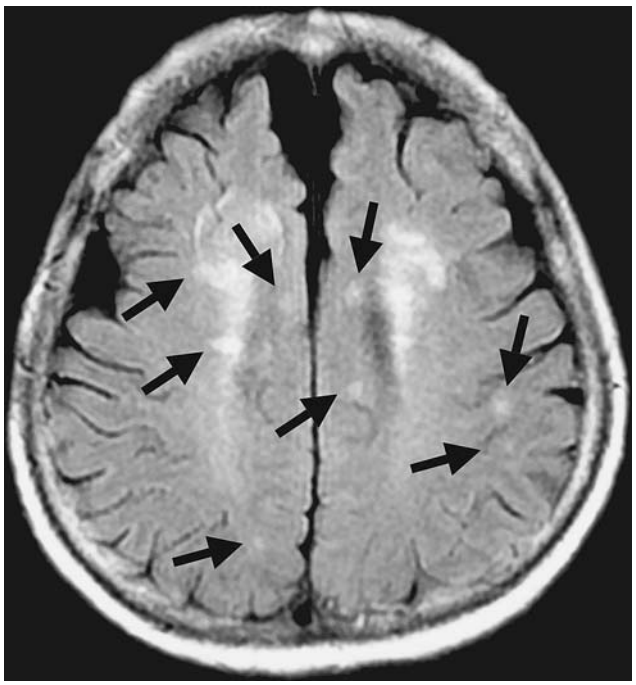

Fig. 3 FLAIR MRI demonstrating high-intensity lesions (*arrows*) that were disseminated bilaterally throughout the white matter of the brain

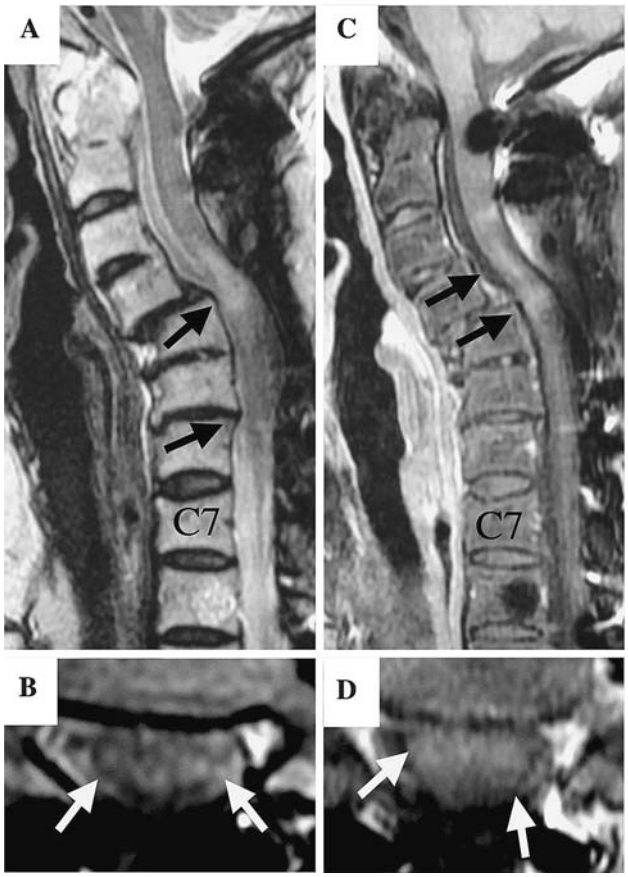

Fig. 4 Abnormal MRI findings of the cervical cord were improved: **a** sagittal, **b** axial at the C4 level. T1-weighted postgadolinium MRI demonstrating enhancement of the cervical cord: **c** sagittal, **d** axial at the C4 level

discontinued, and she received intravenous methylprednisolone pulse therapy (1,000 mg/day, 3 days) four times weekly. After one month, MRI indicated that her cervical cord had improved (Fig. 4). The swelling of the spinal cord had disappeared. The gadolinium-enhanced T1 lesion of the cervical cord was markedly reduced. In addition, her neurological symptoms had almost disappeared by the time of her discharge from our hospital.

Discussion

Etanercept, a fully human fusion protein, is the one of the most effective biologics used in the treatment of RA. The number of RA patients on etanercept therapy has grown rapidly all over the world. Along with the expansion of etanercept therapy, various adverse events have also been increasing in RA patients. Generally, as with other TNF antagonists, there are potential risks of infection, malignancy, demyelinating disorder, or autoimmune disease development during the use of etanercept [1]. In 2001, the Adverse Event Reporting System of the Food and Drug Administration (FDA) reported central nervous system demyelination in 19 patients receiving either etanercept or infliximab [7]. Nevertheless, a cause-and-effect relationship or a mechanism by which the TNF blockade may cause demyelination has not been established [8]. Clinical manifestations of all neurological adverse events varied considerably, and included altered mental status, dysesthesias, paresthesias, optic neuritis, and motor deficits [9]. Our case developed paresthesias, motor deficit without any change in mental status. Based on MRI findings, we suspected demyelinating disorder although no oligoclonal band formation was observed and normal levels of IgG index were present in the CSF profile. Furthermore, we also considered neuromyelitis optica (NMO) as a differential diagnosis, because her abnormal cervical spinal lesion extended across more than three vertebral segments, although she did not develop optic neuritis [10]. Anti-aquaporin 4 antibody, which is a specific marker autoantibody in NMO, was negative. (Anti-aquaporin 4 antibody was measured via human AQP4-transfected cells.)

No laboratory or clinical findings indicated any disorder that causes demyeliation, except for the use of etanercept. Additionally, MRI findings of her cervical spinal cord and brain showed multiple abnormal lesions, and these findings improved with corticosteroid therapy. Accordingly, we diagnosed that this patient had demyeliating disorder associated with etanercept therapy. To our knowledge,

there are only a few reports on demyelinating disorder associated with etanercept in Japanese RA patients. This might be due to the low incidence of deyelinating disorder in Japan compared to that in a foreign country. Additionally, the mechanisms by which the TNF antagonist may cause demyelination are unclear [9, 11].

Although cases of neurological adverse events with TNF blockade therapy are rare, it is an important adverse event for all rheumatologists monitoring RA patients who are receiving TNF antagonist therapy. It is necessary to look for neurological signs and symptoms suggestive of demyelinating disorder in either the central or peripheral nervous system. It is important to elucidate the etiology and predictive markers of demyelination caused by TNF antagonists in patients treated with them. However, discussions of other such cases are also necessary.

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