CASE REPORT

Acute encephalomyelitis with multiple herpes viral reactivations during abatacept therapy

Hideto Nakajima,^{1,2} Ayami Takayama,² Takumi Ito,² Tetsushi Yoshikawa³

¹Department of Internal Medicine, Osaka Medical College I, Takatsuki, Japan
²Department of Internal Medicine, Seikeikai Hospital, Sakai, Japan

³Departments of Pediatrics, Fujita Health University School of Medicine, Aichi, Japan

Correspondence to

Dr Hideto Nakajima,
 in1045@poh.osaka-med.ac.jp

SUMMARY

To describe the case of a patient who had been receiving abatacept, a T-cell costimulatory molecule blocker for rheumatoid arthritis, and developed an acute encephalomyelitis associated with reactivation of the varicella zoster virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV). A 61-year-old woman receiving abatacept therapy for rheumatoid arthritis developed a disturbance of consciousness. MRI indicated multifocal parenchymal lesions in the brainstem, supratentorial areas and cervical spinal cord. Although steroid therapy significantly improved the neurological symptoms and MRI findings, the patient died of sepsis aggravated by coinfection with a fungal infection. Retrospectively, a PCR assay revealed continued systemic reactivation of VZV, EBV and CMV. Acute encephalomyelitis may be associated with VZV, EBV and CMV reactivation during abatacept therapy. Clinicians must be aware of the possibility of acute encephalomyelitis associated with herpes virus reactivation during abatacept therapy for rheumatoid arthritis.

BACKGROUND

Abatacept is a selective costimulation modulator that inhibits T-cell activation by binding to CD80/86 and modulating its interaction with CD28; this costimulatory signal is necessary for complete activation of T cells.^{1–3} Currently, abatacept is used for the treatment of rheumatoid arthritis in cases of an inadequate response to tumour necrosis factor- α (TNF- α) antagonist therapy.⁴ Only a small number of opportunistic infections have been observed in association with abatacept, including mycobacterial tuberculosis, aspergillosis, blastomycosis and systemic candidiasis.⁴ In addition, there have been no previous reports showing neurological complications. Herein, we report a serious case of acute encephalomyelitis associated with the reactivation of varicella zoster virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV) following abatacept treatment.

CASE PRESENTATION

A 61-year-old woman developed a disturbance in her consciousness and was referred to our hospital 2 weeks after the onset of gait disturbance. Her medical history included rheumatoid arthritis, which had been treated with methotrexate and prednisolone, as well as TNF- α antagonist for 6 years. Four months prior to admission, she was switched from the TNF- α antagonist to abatacept (500 mg every 30 days intravenously). At the time of admission to

our hospital, she was in a somnolent mental state and showed paraplegia with bilateral pyramidal signs. She had no skin rash. Laboratory tests revealed lymphopenia: the white blood cell count was 7900/ μ l and the lymphocyte cell count was 474/ μ l (below the normal range of 1500–4000/ μ l). Her serum C reactive protein level was 5.7 mg/dl (a normal level is <0.20 mg/dl). She had an elevated titre of antinuclear antibodies (1:80). However, the other serum antibodies such as anti-CCP, anti-SSA, anti-SSB, anti-dsDNA, anti-Sm and anti-RNP were negative. A cerebrospinal fluid (CSF) study showed pleocytosis (73/ μ l, all mononuclear cells), elevated protein level (382 mg/dl), normal glucose level (102 mg/dl), elevated myelin basic protein level (588 pg/dl) and no oligoclonal IgG bands. A culture of a CSF sample was negative for bacteria, tuberculosis and fungi. PCR analysis showed no herpes simplex virus (HSV). MRI performed at admission indicated multifocal parenchymal lesions in the brainstem, supratentorial areas and cervical spinal cord (figure 1A–E). Based on these findings, we diagnosed her with acute disseminated encephalomyelitis (ADEM), and methylprednisolone (1000 mg/day for 3 days) was administered for 3 days following intravenous dexamethasone (12 mg/day). During follow-up, her mental status normalised, and brain MRI on the 13th day demonstrated marked improvement (figure 1F–I). On the 17th day, she showed acute loss of vision in the left eye, and CMV retinitis was revealed. Although ganciclovir and immunoglobulins were administered, CMV retinitis did not improve. She showed newly developed pneumonia and CMV antigenemia was revealed by a C7-HRP test and elevated serum (1,3)- β -D-glucan. Although a follow-up brain MRI on the 20th day revealed no recurring exacerbation, the patient died of sepsis aggravated by a fungal coinfection on the 34th day. Retrospectively, PCR analysis to test for HSV-1, HSV-2, VZV, CMV, EBV, human herpes virus 6 (HHV-6) and HHV-7 was performed. High copy numbers of VZV, EBV and CMV were detected from serum collected on admission and the 28th day (Day 1: VZV 68 900 copies/ml, EBV 65 400 copies/ml, CMV 650 copies/ml, Day 28: VZV 78 450 copies/ml, EBV 52 950 copies/ml, CMV 2350 copies/ml), and VZV and EBV were detected from CSF samples (Day 2: VZV 4750 copies/ml, EBV 9200 copies/ml, Day 18: VZV 3650 copies/ml, EBV 5300 copies/ml).

DISCUSSION

The present case was of acute encephalomyelitis associated with systemic reactivation of VZV, EBV and CMV during abatacept therapy for rheumatoid

To cite: Nakajima H, Takayama A, Ito T, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009731

Figure 1 Brain and cervical spinal cord MR images on admission (A–E) and the 13th day (F–I). The T2-weighted image shows multiple hyperintensities in the cervical spinal cord (A), and FLAIR images of the brain shows multiple high-signal intensity lesions disseminated in the brainstem and supratentorial areas (B–E). On the 13th day, lesions were markedly diminished (F–I).

arthritis. Although this patient showed CMV retinitis, CSF analysis did not reveal the reactivation of CMV. Therefore, the reactivation of VZV and/or EBV may have contributed to this condition. In this case, it is possible that the encephalomyelitis was directly caused by the invasion of VZV and/or EBV. However, the clinical symptoms and MRI findings of encephalomyelitis significantly improved after steroid therapy. The virus DNA copy number did not increase, and no exacerbation in the CSF and the brain MRI findings occurred after the steroid therapy. These findings indicate that the patient may have an autoimmune inflammatory disease associated with the reactivation of these viruses.

Abatacept employs the high-binding avidity of cytotoxic T lymphocyte-associated molecule-4 (CTLA-4) for CD80/CD86 on antigen presenting cells (APCs), which prevents the CD28-mediated costimulatory pathway critical for complete T cell activation, also producing immunological tolerance. The increased risk of serious infections associated with TNF- α antagonists has been well documented.^{5–7} Aseptic meningo-encephalitis,⁸ herpes simplex encephalitis⁹ and EBV encephalitis¹⁰ have been reported in patients receiving TNF- α antagonists. The incidence rate of serious infections or opportunistic infections with abatacept therapy tends to be lower than

that with TNF- α antagonist therapy.⁴ The present case had been receiving methotrexate, prednisolone and TNF- α antagonist for 6 years. Four months after switching from TNF- α antagonist to abatacept, she was admitted to our hospital. As she showed lymphopenia (474/ μ l), these immunosuppressive agents may have caused the reactivation of VZV and EBV. Thus, the two biological agents, TNF- α antagonist and abatacept, may have contributed to the demyelinating event and the adverse outcome. Clinicians must be aware of the possibility of acute encephalomyelitis associated with herpes virus reactivation during abatacept therapy along with other immunosuppressive agents for rheumatoid arthritis.

Contributors Acquisition of data: HN, AT, and TI. Analysis and interpretation of data: HN and TY. Drafting of the manuscript: HN and AT. Administrative, technical, and material support: HN, AT, TI, and TY.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Yamada A, Salama AD, Sayegh MH. The role of novel T cell costimulatory pathways in autoimmunity and transplantation. *J Am Soc Nephrol* 2002;13:559–75.
- Vandenborre K, Van Gool SW, Kasran A, *et al.* Interaction of CTLA-4 (CD152) with CD80 or CD86 inhibits human T-cell activation. *Immunology* 1999;98:413–21.
- McCoy KD, Le Gros G. The role of CTLA-4 in the regulation of T cell immune responses. *Immunol Cell Biol* 1999;77:1–10.
- Schiff M. Abatacept treatment for rheumatoid arthritis. *Rheumatology* 2011;50:437–49.
- Furst DE. Serum immunoglobulins and risk of infection: how low can you go? *Semin Arthritis Rheum* 2009;39:18–29.
- Salliot C, Gossec L, Ruysen-Witrand A, *et al.* Infections during tumor necrosis factor- α blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. *Rheumatology* 2007;46:327–34.
- Bongartz T, Sutton AJ, Sweeting MJ, *et al.* Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;295:2275–85.
- Quispel R, van der Worp HB, Pruissen M, *et al.* Fatal aseptic meningoencephalitis following infliximab treatment for inflammatory bowel disease. *Gut* 2006;55:1056.
- Bradford RD, Pettit AC, Wright PW, *et al.* Herpes simplex encephalitis during treatment with tumor necrosis factor- α inhibitors. *Clin Infect Dis* 2009;49:924–7.
- Nozaki K, Silver RM, Stickler DE, *et al.* Neurological deficits during treatment with tumor necrosis factor- α antagonists. *Am J Med Sci* 2011;342:352–5.

Learning points

- ▶ Acute encephalomyelitis associated with the reactivation of varicella zoster virus, Epstein-Barr virus and cytomegalovirus can occur during abatacept therapy.
- ▶ The incidence of serious infections in abatacept-treatment patients has generally been lower compared with that in other biological agents-treatment patients. Herpes virus reactivation should be susceptible to abatacept, if taken with other immunosuppressive agents.
- ▶ Checking lymphopenia is necessary to prevent serious opportunistic infection associated with herpes virus reactivation.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow