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【 CASE REPORT 】

Successful Treatment of SARS-CoV-2 Vaccination-related Activation of Rheumatoid Arthritis with Positive Findings for Epstein-Barr Virus

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Abstract:
We herein report a 60-year-old woman who experienced severe flare of rheumatoid arthritis (RA) and Epstein-Barr virus (EBV) positivity following administration of the messenger ribonucleic acid (mRNA)-type severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine. Since 40 years old, she had been in long-term remission of anti-citrullinated protein antibody-positive RA. Ten days after SARS-CoV-2 vaccination, she presented with a high fever and polyarthritis, active synovitis on joint ultrasound, a clinical disease activity index of 35, and positivity for anti-early antigen, diffuse type and restricted type (EA DR) IgG and EBV deoxyribonucleic acid (EBV-DNA). Tocilizumab was introduced to treat RA. The RA disease activity disappeared, and anti-EA DR IgG and EBV-DNA became negative.

Key words: COVID-19, vaccine, rheumatoid arthritis, tocilizumab, Epstein-Barr virus

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Introduction

For many patients with rheumatic diseases who are undergoing immunosuppressive treatment (1, 2), vaccination (3-5) against specific microorganisms, such as herpes zoster or *Streptococcus pneumonia*, is important to prevent aggravation of the underlying diseases. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination for patients with rheumatoid arthritis (RA) or other rheumatic diseases is no exception. Indeed, it has been reported (6, 7) that complications of cardiovascular disease, interstitial lung diseases and chronic renal diseases as well as glucocorticoid use in RA patients can greatly aggravate the disease course of coronavirus disease 2019 (COVID-19).

Neither the American College of Rheumatology (ACR) nor the European Alliance of Associations for Rheumatology (EULAR) has discouraged SARS-CoV-2 vaccination in patients with rheumatic diseases. Well-known side effects of the SARS-CoV-2 vaccine itself include a risk of thrombosis and subsequent thrombocytopenia (8, 9) and myocarditis (10) in addition to gastrointestinal symptoms, a fever, musculoskeletal symptoms, and nausea within a few days after the administration. However, whether or not the vaccine causes severe flare of RA - and if so, the mechanism underlying such a flare and its optimal treatment strategy - are not fully known.

We herein report the efficacy of tocilizumab and the involvement of viral infection in a severe flare of RA following SARS-CoV-2 vaccination.

Case Report

Clinical course

A 60-year-old woman who had had RA for 20 years was treated with a low dose of prednisolone (approximately 5 mg) at another medical institution because she was allergic to many disease-modifying anti-rheumatic drugs (DMARDs). Although she had diabetes, her RA disease ac-

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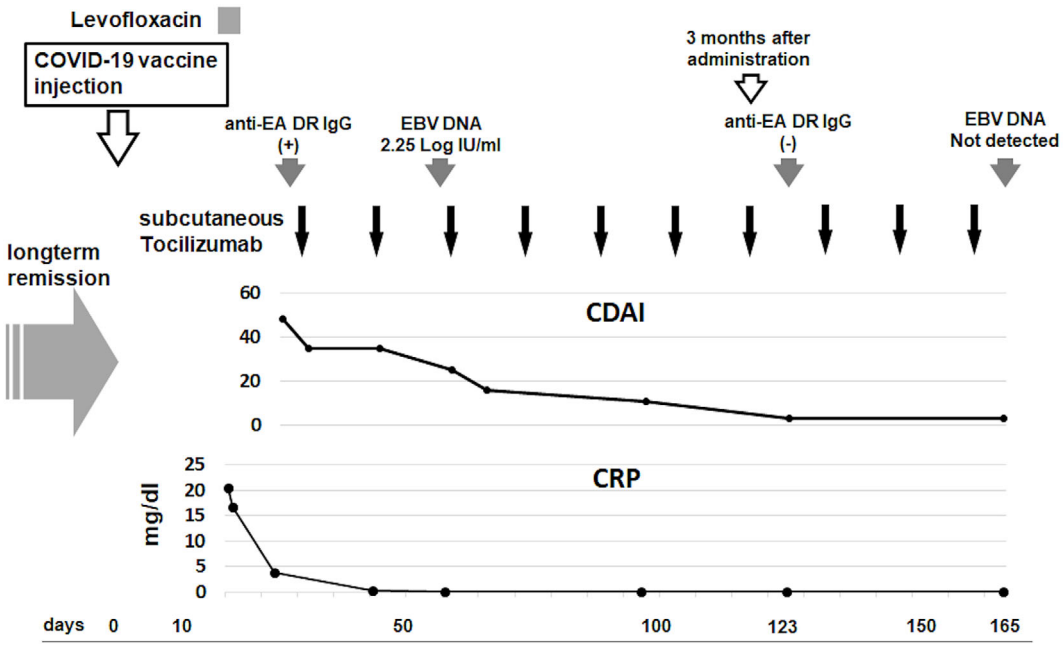

Figure. **Clinical course of rheumatoid arthritis treated with tocilizumab. The horizontal axis of each graph shows the days after the administration of the vaccine, and the vertical axis shows the CDAI and C-reactive protein values. The arrow at the top of the graph represents the administration of tocilizumab. CDAI: clinical disease activity index**

tivity had been controlled over the long term without tender/swollen joints. Ten days after the administration of the first dose of the messenger RNA (mRNA)-type SARS-CoV-2 vaccine [i.e. mRNA-1273 (Moderna)], the patient experienced a fever of 38.6°C and arthralgia, and she visited our hospital because her body temperature increased further to 39.6°C. There was no sore throat, and the physical findings showed no skin rash or tonsillar hypertrophy. Pyelonephritis was suspected based on her C-reactive protein (CRP) level of 20.46 mg/dL and abnormal urine examination findings of urine protein 1+, occult blood 2+, leukocytes 3+, and 20-29 leukocytes/high-power field in the sediment. No hydronephrosis or hepatosplenomegaly was observed on computed tomography (CT), and there was no fluffing of the perirenal tissue suggesting pyelonephritis.

Urine culture was not performed, but urinary tract infection was suspected from the above findings, so levofloxacin and acetaminophen were administered. However, no bacterial infection was noted in two sets of blood cultures or on whole-body CT. Other tests for urine legionella/streptococcus antigens, SARS-CoV-2 antigen quantification and COVID-19-polymerase chain reaction were negative. Although she responded to levofloxacin, she had polyarthritis, CRP 3.97 mg/dL, an erythrocyte sedimentation rate of 59 mm/h, rheumatoid factor (RF) 208.7 IU/mL, and anti-CCP antibody 35.3 U/mL, and she met the 2010 ACR/EULAR classification for RA (11). We therefore introduced her to the Division of Immunology and Rheumatology.

At that time, her body temperature was 37.3°C, her blood pressure was 138/69 mmHg, and her heart rate was 106/min. No liver dysfunction or cytopenia was observed. Her blood work showed aspartate aminotransferase 13 U/L, alanine aminotransferase 14 U/L, white blood cell count 7,800/mL with no atypical lymphocytes, hemoglobin 14.1 g/dL, and platelet count 327,000/mL. Negative results for other autoantibodies and anti-neutrophil cytoplasmic antibody were demonstrated, so severe flare of RA was ultimately suspected. With respect to viral markers, cytomegalovirus IgM was negative, but anti-early antigen, diffuse type and restricted type (EA DR) IgG and anti-Epstein-Barr virus-nuclear antigen (EBNA) IgG were positive at 2.0 and 2.1 by the enzyme immunoassay method, respectively. Since positive findings for virus capsid antigen (VCA)-IgG and negative findings for VCA-IgM were detected, reactivation of EB virus (EBV) was suspected.

Based on the findings of synovial thickening and strongly positive power Doppler signal at the wrists, proximal interphalangeal joints and metacarpophalangeal joints, and despite the absence of bone erosion and joint space narrowing on the wrists and finger joints on X-ray, we diagnosed her with severe flare of RA. However, the EBV-DNA quantification value was positive at 2.25 log IU/mL. We ultimately selected subcutaneous injection of tocilizumab (TCZ) without methotrexate for RA treatment, and her elevated clinical disease activity index of 35 was improved to 3 after administration of TCZ every 2 weeks for 3 months (Figure). Blood sampling at 123 days after SARS-CoV-2 vaccination showed negative anti-EA DR IgG. Negative conversion of EBV-DNA was confirmed at 165 days after vaccination.

Discussion

The pretreatment clinical features of this case were severe flare of RA and EBV positivity 10 days after the administration of the mRNA-type SARS-CoV-2 vaccine. This is the first report to describe the eradication of both EBV and RA activity by TCZ administration.

In a cross-sectional study (12) of the adverse events (AEs) from six different SARS-CoV-2 vaccines, no serious AEs were observed except for common symptoms, including fatigability, headache, and myalgia. With respect to exacerbation of rheumatic diseases after the administration of SARS-CoV-2 vaccine, flare of adult-onset Still's disease has been reported (13). Although subcutaneous TCZ has also been used, it was reported that another SARS-CoV-2 vaccine, BNT162b1, had the potential to activate type 1 helper T cells. With regard to the relationship between RA and SARS-CoV-2 vaccination, it was reported (14) that RA with RF and anti-citrullinated protein antibodies (ACPAs) newly developed in a healthy subject after the administration of the adenovirus-based SPUTNIK-V vaccine. Although our patient had ACPAs before the administration of the SARS-CoV-2 vaccine, the emergence of ACPAs due to vaccination in healthy subjects should have been considered.

The mechanism by which SARS-CoV-2 vaccine causes arthritis is currently unclear. We speculate that some of the nucleic acids of the mRNA vaccine may be recognized by innate immune receptors, such as retinoic acid-inducible gene I (15), resulting in the subsequent activation of acquired immunity. It is also difficult to identify a clear mechanism to account for the association between the SARS-CoV-2 vaccine and the emergence of EBV. However, we suspect that the mechanism may involve the activation of innate immunity mentioned above. Although there is no clear evidence that activation of innate immunity is linked to an increased EBV viral load, Teijaro et al. (16) suggested one possible connection. They showed that the mRNA vaccine itself became an immune substance and was recognized and bound to innate immune system receptors such as toll-like receptor 3/7 in endosomes. As a result, they hypothesized that the T cell immune system would be activated through the production of type I interferon. However, there have been no studies confirming a link between innate immunity activation and increased viral load of EBV.

Although we concluded that this was a case of SARS-CoV-2 vaccine-induced arthritis, it had similarities to long COVID (17) in terms of the possibility of EBV reactivation.

TCZ (18, 19) is an anti-interleukin 6 receptor antibody that strongly inhibits interleukin 6 (IL6)-derived synovial inflammation and activation of osteoclasts. We selected TCZ for our patient because of the high disease activity determined by the clinical disease activity index (CDAI) and concerns about the emergence of lymphoproliferative disorders. Strategies for the first use of methotrexate (MTX) should be considered based on treatment recommendations for RA. However, since EBV-DNA was positive in this case, there was a strong concern about other iatrogenic immunodeficiency-associated lymphoproliferative disorders (20, 21) due to the use of MTX. Another concern was the exacerbation of EBV reactivation associated with TCZ use. Although the impact of TCZ on the virus is not well known, we previously showed (22, 23) that the administration of tumor necrosis factor inhibitors or TCZ to human T-cell leukemia virus cell lines did not affect the *tax* gene or proviral load. If similar studies are conducted on EBV in the future, it may be possible to prove the direct impact of TCZ. At present, there is only one reported case of TCZ reactivation of EBV (24) in a patient with viral hepatitis. TCZ should thus be administered with caution, with consideration for its potential effects on other viruses.

There are some limitations associated with this study with regard to EBV infection. We have no data with respect to anti-EA DR IgG or EBV-DNA quantification before the administration of the SARS-CoV-2 vaccine. If information on EBV infection had been available, it would have helped clarify the involvement of SARS-CoV-2 in EBV-related activation of RA. With respect to the disease activity of RA before the flare, there were no joint symptoms, but the CDAI could not be confirmed because there was no subjective evaluation using a visual analogue scale. In addition, we tested for cytomegalovirus and EBV, but the possibility of unknown viruses that may have been involved in the polyarthritis and fever accompanying vaccination in this case cannot be denied. We may simply have been observing the natural course of the viral infection, particularly since the inflammatory response improved in response to the antibiotics.

We reported the first case of mRNA SARS-CoV-2-related severe flare of RA with positive EBV-DNA. In addition, TCZ resulted in a good outcome for this complicated case of RA. Constant monitoring of the EBV infection status during RA treatment may help elucidate factors associated with RA flare, such as specific cytokine profiles that occur after vaccination.

The patient provided her written informed consent for the publication of her data.

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

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