

Cytomegalovirus-induced Infectious Mononucleosis-like Syndrome in a Rheumatoid Arthritis Patient Treated with Methotrexate and Infliximab

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Abstract

We report a patient with rheumatoid arthritis (RA) who developed cytomegalovirus (CMV)-induced infectious mononucleosis-like syndrome (IMLS) while being treated with methotrexate and infliximab. She suddenly developed intermittent high fever and general fatigue with liver dysfunction, remarkable lymphocytosis and laboratory data suggestive of CMV reactivation. Her clinical symptoms quickly improved after the cessation of methotrexate and infliximab without the use of anti-viral drugs such as ganciclovir. CMV-induced IMLS might be a cause of persistent fever in RA patients, particularly when biologics are used for treatment.

Key words: cytomegalovirus, infectious mononucleosis-like syndrome, infliximab, TNF- α , rheumatoid arthritis

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Introduction

Biological agents targeting inflammatory cytokines or surface molecules of lymphocytes are presently used in the treatment of autoimmune disorders, including rheumatoid arthritis (RA). These drugs often show good therapeutic effects, but infection is the most common and important complication. The chimeric anti-tumor necrosis factor- α (TNF- α) monoclonal antibody, infliximab, is one such biological agent (1-3). Here, we report an RA patient who developed cytomegalovirus (CMV)-induced infectious mononucleosis-like syndrome (IMLS) while being treated with methotrexate and infliximab. The patient showed high fever and general fatigue, but these symptoms quickly improved with no specific treatment for CMV reactivation. This is the first case of RA complicated by CMV-induced IMLS during anti-TNF therapy, although a recent report has demonstrated infectious mononucleosis (IM) due to Epstein-Barr virus (EBV) in a patient receiving similar treatment (4). We focus upon the clinical picture, pathogenetic mechanisms and treatment of

CMV-induced IMLS in this report.

Case Report

A 35-year-old woman visited our hospital 3 years after onset of RA. She was treated with disease-modifying antirheumatic drugs, including methotrexate, but her arthritis persisted mainly in her hands with a slight increase in C-reactive protein (CRP). At age 39 administration of infliximab was started because the disease activity of RA could not be kept at a sufficiently low level with methotrexate alone. Her arthritis quickly improved with no adverse events, and the doses of methotrexate and infliximab were maintained at 8 mg/week and 3 mg/kg/2 months, respectively. The disease activity score including a 28-joint count (DAS28)-CRP calculated according to the approved formula (<http://www.das-score.nl/>) was stable at approximately 1.2.

At age 43 she suddenly developed intermittent high fever persisting for 2 weeks, general fatigue and appetite loss with no obvious precipitating cause approximately 6 weeks after the previous administration of infliximab. Physical examina-

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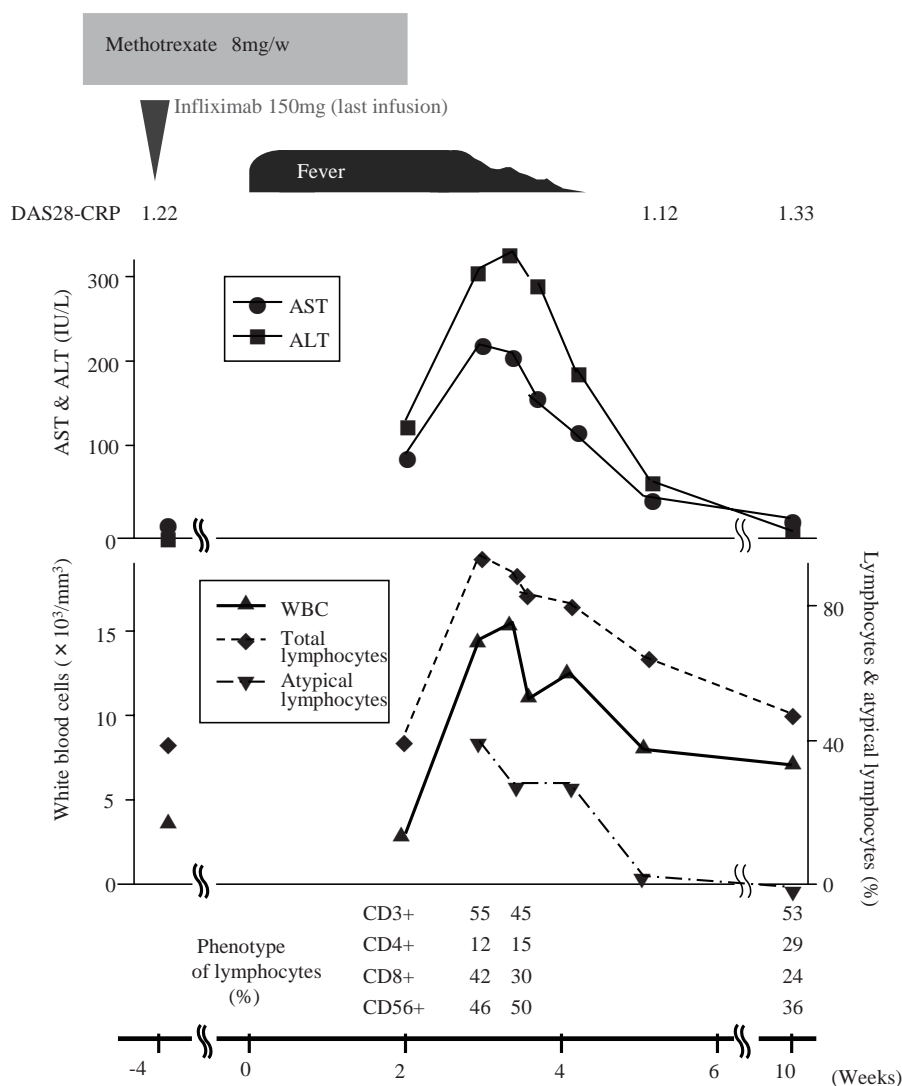


Figure 1. Clinical course of the patient. AST: aspartate aminotransferase, ALT: alanine aminotransferase, CD: cluster differentiation, CRP: C-reactive protein, DAS28: disease activity score including a 28-joint count

tion showed no abnormal findings suggestive of RA exacerbation, such as tenderness and swelling of joints, or lymphadenopathy. There was no apparent splenomegaly. Laboratory data demonstrated a slight increase in CRP (1.53 mg/dL, normal <0.1 mg/dL) and liver dysfunction (aspartate aminotransferase 91 IU/L, normal 28-35 IU/L; alanine aminotransferase 124 IU/L, normal 32-45 IU/L; γ -glutamyl transpeptidase 100 IU/L, normal 0-15 IU/L), although these indices had been normal at the previous administration of infliximab (Fig. 1). Chest X-ray was normal. Even after the cessation of methotrexate her clinical symptoms persisted, and laboratory data showed leukocytosis (14,320/ μL , normal 3,500-9,900) with a remarkable increase in atypical lymphocytes (46%, Fig. 2) in addition to worsening of liver dysfunction 3 weeks after onset of fever (Fig. 1). CMV pp65 antigen-positive cells were 7 per 10^5 leukocytes, and the IgG and IgM antibodies against this virus were 16.0 U/mL (normal <6.0) and negative, respectively. EBV-related antibodies were as follows: the anti-VCA IgG and anti-EBNA antibodies were $\times 160$ and $\times 40$, respectively, but the anti-VCA IgM

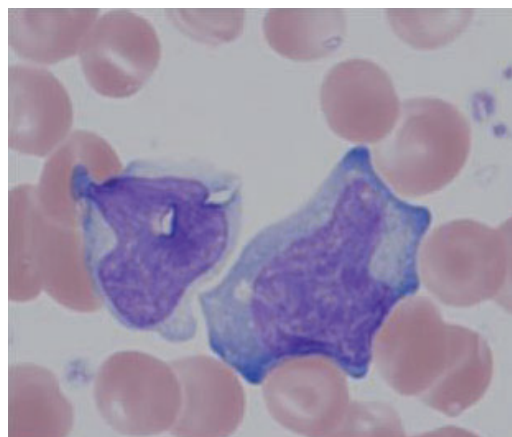


Figure 2. Atypical lymphocytes on a peripheral blood smear sample of the patient.

and anti-EADR antibodies were negative. These results suggested past infection of EBV. DNA of EBV was unquantifiable in leukocytes. There was no significant evidence indi-

cating recent infection with other viruses, such as hepatitis B, hepatitis C or human herpes virus-type 6 (HHV-6).

She was observed in the outpatient clinic with no specific treatment for CMV at her request. Four weeks after onset of fever she spontaneously showed improvement of clinical symptoms in conjunction with decreases in CRP, WBC and hepatic indices. All of these were normalized in approximately 10 weeks after the onset of fever. CMV antigenemia became negative, and the IgM antibody against this virus (0.9 U/mL, normal < 0.9) showed an increase. Flow cytometry demonstrated decreases in CD8⁺ and CD56⁺ cells in peripheral blood (Fig. 1). RA did not worsen throughout the clinical course, and DAS28-CRP was persistently less than 1.4. RA has remained in complete remission without restart of methotrexate and infliximab for the past 5 months.

Discussion

The clinical picture of the present patient was considered to be compatible with that of IM due to EBV infection with regard to the high fever and leukocytosis with the appearance of atypical lymphocytes in peripheral blood. Serological tests, however, provided no evidence suggesting the involvement of EBV, and the patient was finally diagnosed as having CMV-induced IMLS based on positive antigenemia and an increase in the IgM antibody titer. IMLS can be caused by infection or reactivation of various viruses, including CMV and HHV-6. According to several reports CMV is a causative agent for 7 to 27.5% of total IMLS patients (5, 6). CMV-induced IMLS is clinically similar to IM, but lymphadenopathy, skin rash, pharyngitis and splenomegaly are less frequent in the former than in the latter (7, 8). The present patient also did not show these symptoms. Considering that the IgG antibody against CMV was already elevated 2 weeks after the onset of fever, reactivation of this virus may have caused IMLS in this patient. In general, primary infection with CMV usually produces no clinical symptoms, while reactivation of this virus sometimes causes serious systemic events, of which IMLS is a relatively rare manifestation (7, 9-11, 12).

The precise pathogenetic mechanism of IMLS in the present patient is unclear, but there are 2 possible steps worth consideration. The first is CMV reactivation. Methotrexate and infliximab used for RA treatment in the present patient may have played an important role in this step. Methotrexate is an inhibitor of dihydrofolate reductase, and acts as a potent immunomodulator particularly on lymphocytes. Infliximab is a chimeric monoclonal antibody to TNF- α , which strongly suppresses CMV replication (13). Simultaneous use of both drugs may have allowed CMV to become active in the present patient, although clinical remission of RA had been maintained for approximately 4 years

after commencement of infliximab. The second possible step is immunomodulatory effects of CMV. EBV causing IM proliferates in B lymphocytes, while CMV is usually present in polymorphonuclear leukocytes and monocytes (14) and causes an increase in CD8⁺ and natural killer T cells in peripheral blood at reactivation irrespective of the development of IMLS (15). Atypical lymphocytes in CMV-induced IMLS are CD8⁺ T cells (12, 16). Phenotypic analysis of peripheral blood lymphocytes in the present patient also showed an increase in CD8⁺ T cells and decreases in CD4⁺ T cells and the CD4/CD8 ratio at onset of disease, and these parameters reflected well the clinical activity of IMLS. As methotrexate and anti-TNF- α therapy show no significant effects on CD4⁺ and CD8⁺ T cells in peripheral blood (17, 18), follow-up of the CD4/CD8 ratio in the outpatient clinic might be helpful instead of testing for CMV antigenemia in order to early detect reactivation of this virus in patients receiving intensive treatment for RA, such as infliximab.

The treatment strategy for CMV-induced IMLS has not yet been established. Several recent reports have demonstrated that the severity of CMV infection in patients with rheumatic disorders correlates well with the number of pp65 antigen-positive cells in peripheral blood (9, 10). When CMV pp65 antigen-positive cells remain less than 10 per 10⁵ leukocytes with no significant visceral organ involvement, the administration of ganciclovir might be unnecessary (9, 10). In addition, IM or IMLS patients often show drug hypersensitivity. As CMV pp65 antigen-positive cells in the present patient were 7 per 10⁵ leukocytes with mild liver dysfunction, we discontinued methotrexate and infliximab in the outpatient clinic without using anti-viral drugs such as ganciclovir. The patient's high fever and general fatigue improved 4 weeks after the onset of clinical symptoms in parallel with normalization of CRP, WBC and hepatic indices. These results suggest that CMV-induced IMLS may spontaneously ameliorate merely with the cessation of immunosuppressive drugs. RA has remained in complete remission in the present patient even after the cessation of methotrexate and infliximab, but we plan to restart these drugs after confirming negative CMV antigenemia if there are clinical symptoms or laboratory data suggestive of recurrence of RA.

In summary, CMV-induced IMLS may occur as an adverse event during methotrexate and infliximab treatment in RA patients. Cessation of such drugs, which produce negative effects on the immune system, may be the most important approach.

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