INTERNAL MEDICINE

□ CASE REPORT □

Development of Adult T-cell Leukemia in a Patient with Rheumatoid Arthritis Treated with Tocilizumab

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Abstract

Tocilizumab (TCZ) was administered from 2004 to 2008 in a 52-year-old woman with rheumatoid arthritis (RA) refractory to methotrexate (MTX) as a clinical trial. TCZ therapy with MTX was resumed in March 2009 due to exacerbation of RA. The patient was an human T-lymphotropic virus type I (HTLV-I) carrier, and, in April 2011, a peripheral blood smear showed many atypical lymphocytes, thus leading to a diagnosis of adult T-cell leukemia (ATL). Complete remission of ATL was achieved with a standard therapeutic regimen.

Key words: adult T-cell leukemia, rheumatoid arthritis, tocilizumab

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Introduction

The treatment of rheumatoid arthritis (RA) has drastically changed over the past decade with the introduction of biological agents (1). A humanized anti-interleukin 6 receptor monoclonal antibody, tocilizumab (TCZ), has been verified to be effective for treating RA (2). In general, treatment with TCZ is reported to be safe, although the most frequent adverse event observed in TCZ-treated patients is infection (3, 4). In addition, increased incidences of malignancy in patients treated with TCZ compared with that observed in conventional RA patients or the general population has not been reported in clinical trials (3, 4). On the other hand, there may be endemic problems among RA patients treated with biological agents. Nagasaki Prefecture, located in the western part of Kyushu Island in Japan, is an area in which human T-cell leukemia virus type 1 (HTLV-I) is endemic (5). Therefore, one such endemic problem may be the development of adult T-cell leukemia (ATL) in HTLV-I carriers with RA treated with biological agents. Iwanaga et al. demonstrated that both a high baseline proviral load and the presence of HTLV-I infection during treatment of other diseases are independent risk factors for the development of ATL (6), the latter being described in the present case. We herein report the first case of ATL developing during treatment for RA with TCZ.

Case Report

A 52-year-old woman with polyarthritis visited Sasebo Chuo Hospital in September 2000 with a diagnosis of RA. Since methotrexate (MTX) and prednisolone (PSL) were not effective in attaining a low disease activity, the patient was enrolled in a clinical trial (MRA012JP; SAMURAI followed by the long-term MRA214JP trial) of an anti-IL-6 receptor monoclonal antibody in the beginning of January 2004 (Fig. 1). The patient's laboratory findings at the time of enrollment showed a hemoglobin level of 10.6 g/dL, a total leukocyte count of 4,400/mm^3 with no abnormal lymphocytes and a platelet count of 22.3×10^4/mm^3. Rheumatoid factor (22.4 IU/mL: normal range <14) was positive without elevation of anti-double-stranded DNA antibodies or anti-SS-A/Ro antibodies. The patient exhibited a high level of disease activity with a disease activity score (DAS) 28-ESR of 6.47 points. TCZ monotherapy (MRA012JP; SAMURAI

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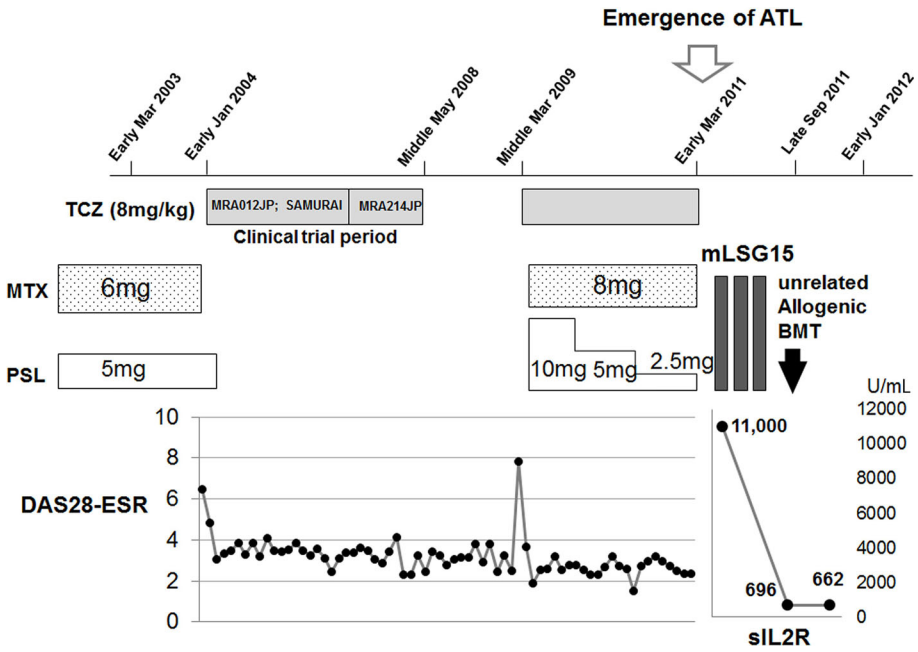

Figure 1. **The patient's clinical course following the clinical trial of tocilizumab (TCZ). When the diagnosis of rheumatoid arthritis (RA) was determined, treatment with 6 mg of methotrexate (MTX) and prednisolone (PSL) was initiated. The patient was then enrolled in a clinical trial of TCZ. Although MTX and PSL were discontinued after a low level of disease activity was attained, 8 mg/kg of TCZ coupled with 8 mg of MTX and PSL was administered again, as of the exacerbation of RA in March 2009. Since adult T-cell leukemia (ATL) appeared in March 2011 after MTX and TCZ were discontinued, the mLSG chemotherapy protocol was introduced, followed by unrelated allogenic bone marrow transplantation. Although a few opportunistic infections were observed following the administration of these regimens, no recurrence of ATL was detected. BMT: bone marrow transplantation**

followed by the long-term MRA214JP trial) at a dose of 8 mg/kg was effective for achieving a low level of disease activity, according to DAS28-ESR, and remained effective until the completion of the above clinical trial in the middle of May 2008 (Fig. 1). In March 2009, 8 mg/kg of TCZ was restarted with the administration of MTX and PSL due to exacerbation of polyarthritis. At that time, the patient was initially screened for anti-HTLV-I antibodies and found to be positive (10.0 C.O.I.). Following the readministration of TCZ for two years, many ATL-like cells with 44% atypical lymphocytes without obvious signs of ATL were detected on a peripheral blood smear performed at the administration of TCZ late in April, 2011. The patient was diagnosed with chronic-type ATL with monoclonal integration of HTLV-I proviral DNA in peripheral blood mononuclear cells verified by a Southern blot analysis (data not shown); however, a tendency toward elevation of lactose dehydrogenase indicated conversion to acute-type disease, regardless of the absence of skin rashes and lymph node enlargement. Because elevation of the total leukocyte count to 14,100/mm^3 with 66% atypical cells was observed (Fig. 2, left panels) with double-positive findings for CD4 and CD25 in the peripheral blood on flow cytometry (Fig. 2, right panel), TCZ and MTX were discontinued. Following the administration of a modified version of the Lymphoma Study Group 15 chemotherapy protocol (7) containing three regimens described in the Japan Clinical Oncology Group (JCOG) 9303 in addition to allogeneic bone marrow transplantation (BMT) from an human leukocyte antigen (HLA)-matched unrelated donor, remission was achieved followed by normalization of the soluble interleukin-2 receptor (sIL-2R) level. No recurrence of ATL has since been observed (Fig. 1). Tacrolimus was administered as an immunosuppressant after transplantation following the discontinuation of glucocorticoids. Subsequently, no exacerbation of the rheumatoid arthritis disease activity or elevation of the C-reactive protein (CRP) level was observed.

Discussion

In the present case, ATL emerged following treatment with MTX for 11 years and TCZ for six years. The use of immunosuppressive agents may be related to the development of ATL. For example, ATL was detected in a systemic lupus erythematosus patient treated with steroids and cytotoxic agents (8). Another case of adult T-cell leukemia/lymphoma (ATLL) was reported under the administration of MTX in a patient with disseminated psoriasis (9). The incidence is low; however, it is known that the reactivation of hepatitis B virus occurs during immunosuppressive therapy

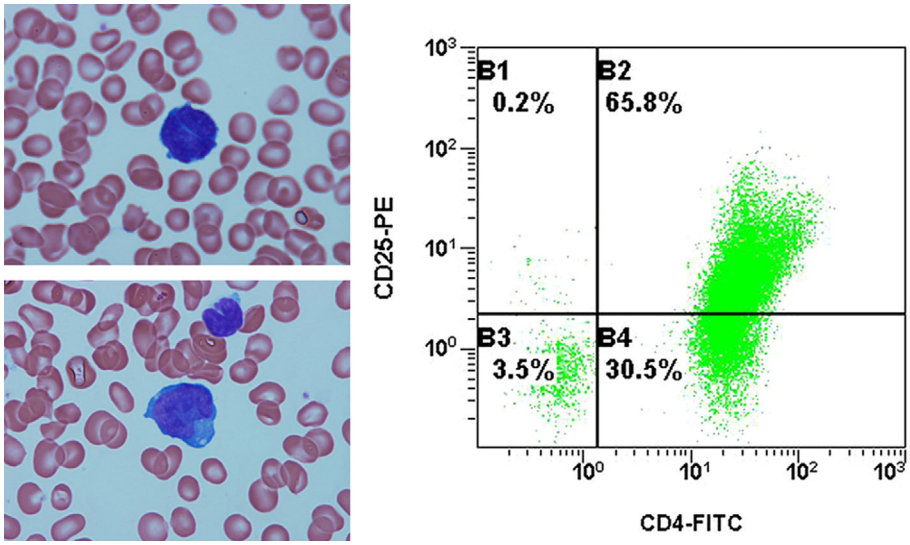

Figure 2. **Presence of abnormal lymphocytes on a peripheral blood smear. When adult T-cell leukemia (ATL) was diagnosed, abnormal lobulated lymphocytes were detected in the peripheral blood. The neoplastic cells co-expressed CD4 and CD25 (Left: high amplification of the peripheral blood smear; right: flow cytometry dot plots in the peripheral blood).**

for rheumatic diseases, including the administration of biological agents to treat RA (10, 11). Therefore, although we are not able to show direct evidence that the proliferation of HTLV-I-infected cells observed in this case was induced during treatment, it can be speculated that the administration of TCZ in conjunction with MTX accelerated the increase in the copy number of HTLV-I, resulting in ATL. Although it has been previously shown that leukemic cells freshly isolated from patients with ATL have the potential to produce high levels of IL-6 (12), there have been no reports of a direct relationship between the inhibition of IL-6 and the administration of TCZ with respect to the emergence of ATL until now. Rather, HTLV-I infection *per se* has been reported to have the potential to cause opportunistic infections, such as strongyloidiasis (13), suggesting that immunological impairment related to HTLV-I infection is accelerated by the administration of biologic agents.

The majority of HTLV-I carriers remain asymptomatic throughout their lives, with an estimated lifetime risk of developing ATL of approximately 2.5% to 5% (14, 15). Therefore, prospective and/or retrospective studies are needed to explore the risk of the development of ATL/ATLL during therapy with biological agents and/or immunosuppressive drugs, including MTX, in patients with RA who are HTLV-I carriers, especially in HTLV-I-endemic areas.

Another important point is the influence of BMT on the disease activity of RA. The efficacy of BMT in a murine model mimicking RA has been previously reported (16), demonstrating the inhibition of joint destruction and bone absorption by BMT. In human RA patients, the efficacy of autologous transplantation has also been reported (17). However, clinicians should allow for the use of premedication, such as high-dose cyclophosphamide, that may modify the RA disease activity. In that report (17), the application of BMT in patients with RA was shown to be limited to cases refractory to ordinary therapies, including biologics. Additionally, the administration of tacrolimus may have exerted an influence on the clinical course of RA in the present case.

This is the first report of the emergence of ATL during treatment with TCZ and MTX in a patient with RA. The medium-term efficacy and safety of TCZ have been reported, and, in general, no increases in the incidence of malignancy, including hematologic malignancy, have been found. However, in some specific situations, such as HTLV-I carriers, the pharmacologic actions of TCZ and MTX may affect the life cycle of HTLV-I, inducing reactivation. Accumulating further ATL/ATLL cases occurring in association with treatment using immunosuppressive agents is therefore necessary.

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

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