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CASE REPORT

Reversible infliximab-related lymphoproliferative disorder associated with Epstein-Barr virus in a patient with rheumatoid arthritis

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Abstract A 63-year-old woman with active rheumatoid arthritis (RA) had been treated with methotrexate and prednisolone. She developed cervical lymph node swelling 30 months after the initiation of infliximab therapy. A computed tomography revealed cervical and mediastinal lymph node swelling and multiple nodules (up to 13 mm in diameter) in the lungs. A lymph node biopsy showed infiltration of numerous Hodgkin-like and Reed-Sternberg-like cells. Immunohistological studies showed that these cells were positive for CD15, CD30, and Epstein-Barr virus (EBV) latent membrane protein. In site hybridization revealed the presence of EBV RNA in the nuclei of these cells. EBV DNA was detected in the biopsy specimen by southern blot analysis. She was diagnosed as having EBV-associated lymphoproliferative disorder (LPD). Immunodeficiency-associated LPD related with infliximab therapy was considered. Cessation of infliximab therapy only led to dramatic regression of LPD. This case illustrates that EBV-associated LPDs can occur as part of infliximab adverse effects in patients with RA.

Keywords Epstein-Barr virus · Infliximab · Lymphoproliferative disorders · Rheumatoid arthritis · Methotrexate

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Introduction

A large cohort study by Ekström et al. [1] demonstrated that patients with rheumatoid arthritis (RA) are at a twofold increased risk for malignant lymphomas in Sweden. A recent case-control study by Baecklund et al. [2] suggested an association between high disease activity and lymphoma risk. There has also been a general concern that medications used in RA, including methotrexate (MTX) and tumor necrosis factor α (TNFα) antagonists, might lead to lymphoproliferative disorders (LPDs) by altering immune function [3].

The recent World Health Organization classification recognizes four broad clinical settings of immunodeficiency associated with an increased incidence of lymphoma and other LPDs [4]. These are: (1) primary immunodeficiency syndromes and other primary immune disorders; (2) infection with the human immunodeficiency virus (HIV); (3) iatrogenic immunosuppression in patients who have received solid organ or bone marrow allografts; (4) iatrogenic immunosuppression associated with MTX treatment, most commonly for RA. MTX-associated LPDs are often Epstein-Barr virus (EBV) related and may regress with cessation of MTX [4]. Morphologically, the reported cases are most commonly diffuse large B-cell lymphoma and Hodgkin lymphoma or Hodgkin lymphoma-like lesions [4]. Although occurrences of lymphomas have been observed in patients with RA treated with TNFα antagonists, etanercept and infliximab [5], a recent study by Wolfe and Michaud [6] did not show evidence for an increase in the incidence of lymphomas in anti-TNFα-treated patients with RA.

We describe EBV-associated LPD in a patient with RA after the initiation of infliximab therapy. Withdrawal of infliximab resulted in complete resolution. This case

suggests a causal relationship between infliximab therapy and the development of LPD.

Case report

A 63-year-old Japanese woman with a 14-year history of RA had been treated with MTX (8 mg/week) and prednisolone (10 mg/day) since 1998. Treatment with infliximab (3 mg/kg) was started from November 2004 because of high inflammatory activity. Thereafter, her RA was well controlled. However, she developed cervical lymph node swelling on May 2007.

Physical and roentgenographic examinations showed lymphadenopathy involving the cervical and mediastinal regions, and multiple nodules in the lungs (Fig. 1a, b).

Leukocyte count was 8,500/μl (76% neutrophils, 2% eosinophils, 1% basophils, 10% monocytes, and 11% lymphocytes), hemoglobin 12.4 g/dl, and platelet count 338,000/μl. Serum lactate dehydrogenase was 270 U/l (normal range, 119–229), C-reactive protein 2.37 mg/dl, IgG 1,730 mg/ml, and soluble interleukin-2 receptor (sIL-2R) 983 U/ml (less than 500). Serological tests for antibody titers for EBV showed previous infection: anti-VCA IgG antibody was 11.3 EU (less than 1.0), anti-VCA IgM antibody 0.0 EU (less than 1.0), anti-EA IgG antibody 3.6 EU (less than 1.0), and anti-EBNA IgG antibody 5.8 EU (less than 1.0). Serological tests for HIV and human T-cell lymphotropic virus type I were negative. A gallium scintigraphy showed no abnormal uptake.

A cervical lymph node biopsy revealed infiltration of numerous Hodgkin-like and Reed-Sternberg-like cells (Fig. 2a). Immunohistochemical staining showed that these cells were positive for CD15, CD30, and EBV latent membrane protein. In site hybridization revealed the presence of EBV RNA in the nuclei of these cells (Fig. 2b). EBV DNA was detected in the biopsy specimen by southern blot analysis.

From these findings, we considered that she developed EBV-associated LPD (Hodgkin-like disease) due to immunodeficiency caused by infliximab administration. Cessation of infliximab therapy only led to dramatic regression of LPD (Fig. 1c, d). The regression has continued for 5 months until the present.

Discussion

It is well-known that patients with RA are at increased risk for malignant lymphoma [1]. Baecklund et al. [7] reviewed medical records and lymphoma subtypes in 35 patients with RA in whom malignant lymphomas were diagnosed during the period 1965–1984, an era when aggressive immunosuppressive therapy in RA was still rare. Their findings suggested an increased incidence of diffuse large B cell lymphoma, as well as a possible association with RA disease activity. A recent case-control study by Baecklund et al. [2] also suggested an association between high RA disease activity and lymphoma risk. An increased risk for malignant lymphomas in patients with RA appears to be

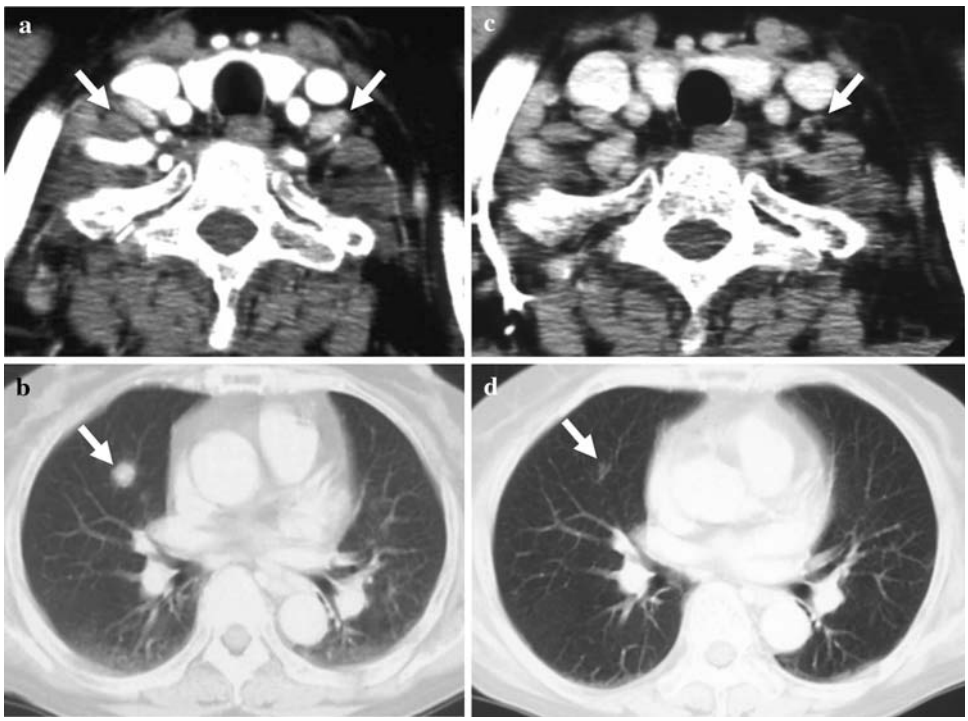

Fig. 1 **a** A cervical CT scan showing bilateral lymph node swelling (*arrows*). **b** A chest CT scan showing lung nodule (*arrow*). **c** A cervical CT scan showing diminution of lymph node swelling (*arrow*) after cessation of infliximab therapy. **d** A chest CT scan showing resolution of lung nodule (*arrow*) after cessation of infliximab therapy

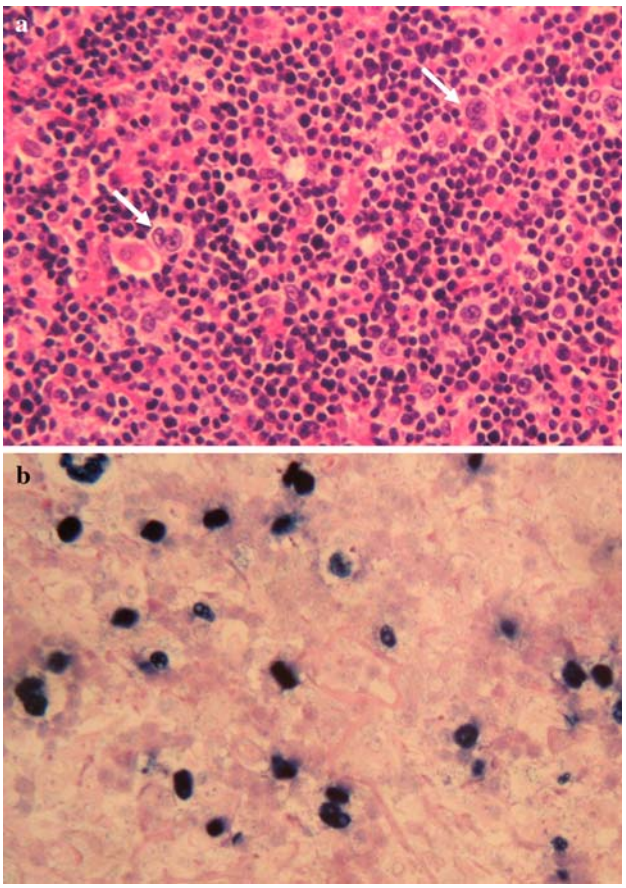

Fig. 2 **a** A lymph node biopsy specimen showing numerous Hodgkin-like and Reed-Sternberg-like cells (H&E, ×400). **b** In site hybridization showing the presence of EBV RNA in the nuclei of these cells

attributed to the dysregulated immune function that is part of the pathophysiology of the disease.

On the other hand, it has been known since 1993 that some LPDs appearing in patients treated with MTX are associated with EBV and may spontaneously resolve after withdrawal of the drug [4, 8]. Whether or not RA patients treated with MTX have an increased risk of malignant lymphomas remains a matter of controversy. Baecklund et al. [2] recently performed a large case-control study. They did not observe any increase in lymphoma risk associated with MTX. They also did not find an increased occurrence of EBV-positive lymphomas, or any EBV-positive lymphoma that regressed spontaneously.

TNFα antagonists represent an important new group of agents shown to significantly improve symptoms and quality of life in patients with RA. Brown et al. [5]. reviewed relevant data in the post-market adverse event surveillance system in the US and identified 26 cases of LPDs following treatment with etanercept (18 cases) or infliximab (8 cases). Wolfe and Michaud [3] prospectively studied 18,572 patients with RA who were enrolled in the National Data Bank for Rheumatic Diseases in the US. Although the standardized incidence ratio for lymphomas was greatest for anti-TNFα therapies, differences between therapies were slight, and confidence intervals for treatment groups overlapped. They suggested that the "increases" may reflect channeling bias whereby patients with the highest risk of lymphomas preferentially receive anti-TNFα therapy. A recent study by Wolfe and Michaud [6] also did not show evidence for an increase in the incidence of lymphomas in anti-TNFα-treated patients with RA.

In Japan, 14 patients developed LPDs among 575,000 RA patients treated with MTX (data from K.K. Wyeth, Tokyo, Japan). On the other hand, there is no data on the incidence of LPDs in anti-TNFα-treated Japanese patients with RA. To our knowledge, there is only one case report suggesting an association of EBV-related LPD and MTX and infliximab therapies [9]. The causal link between infliximab and LPD was uncertain in this case, because LPD regressed with cessation of both agents. In our patients treated with MTX and infliximab, we first discontinued infliximab therapy in consideration of RA disease activity. Thereafter, LPD regressed completely. The disappearance of LPD after the withdrawal of infliximab suggests that the therapy was a major factor in the generation of EBV-associated LPD in our patient. Although there is no evidence that anti-TNFα therapy increases the incidence of LPDs in patients with RA [3, 6], our case illustrates that EBV-associated LPDs can occur as part of infliximab adverse effects in patients with RA. Brown et al. [5] also described that a 70-year-old man with infliximab-associated lymphoma displayed significant reduction of lymphadenopathy after discontinuation of infliximab, in the absent of standard antilymphoma chemotherapy. In this patient, there was no information whether the lymphoma was associated with EBV.

Oyama et al. [10] recently documented 22 cases named as senile EBV-associated B-cell LPDs arising in elderly patients aged over 60 years without predisposing immunodeficiencies, suggesting that this disease has a relationship with an immunologic deterioration derived from the aging process. Our patient was 63 years of age and had a long history of taking MTX and prednisolone. Therefore, her aging process and predisposing immunodeficiencies might be partly associated with the development of EBV-associated LPDs.

In conclusion, EBV-associated LPDs can occur as part of infliximab adverse effects in patients with RA, particularly in elderly patients. Careful physical examination to check for lymphadenopathy development in patients receiving anti-TNFα therapy is important. If the patients develop lymphadenopathy, the measurement of serum sIL-2R is necessary. It is also necessary to evaluate serological

tests for antibody titers for EBV, EBV-DNA levels in serum or peripheral blood mononuclear cells, and the presence of EBV-DNA in the lymph node biopsy specimen. When serological tests for antibody titers for EBV are positive, but the titers do not increase so much in these RA patients similar to our patient, we should perform lymph node biopsy and study the presence of EBV-DNA in the lymph node biopsy specimen. For the treatment of TNFα antagonist-associated LPDs, the withdrawal of TNFα antagonist should be the first choice after careful histological examination.

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