Spontaneous regression of Epstein-Barr virus-associated lymphoproliferative disorder in a juvenile idiopathic arthritis patient after the discontinuation of methotrexate and etanercept

Ariane Klein, Harald Reinhard, Annette M Mueller, Gerd Horneff

Abstract

A case of a 16-year-old female with polyarticular juvenile idiopathic arthritis (JIA) since the age of 4 years is reported here. This patient also suffered from multiple congenital anomalies. On long-term treatment with oral methotrexate (MTX) and etanercept, multiple subcutaneous nodules were detected, which were accompanied by increased lactate dehydrogenase and uric acid levels. A biopsy of the largest nodule revealed Epstein-Barr (EB) virus-positive diffuse large B-cell lymphoma (DLBCL). The patient was classified as clinical stage IIIA due to a mediastinal lesion. Immunosuppressive treatment was discontinued immediately, which led to regression of the remaining nodules and normalization of the lactate dehydrogenase levels. The patient was considered to have an iatrogenic lymphoproliferative disorder classified as "other iatrogenic immunodeficiency-associated lymphoproliferative disorders" by the World health organization (WHO). To our knowledge, this is the first case report of a JIA patient with EBV-positive DLBCL following the administration of etanercept and methotrexate and spontaneous regression of lymphoproliferation after the discontinuation of antirheumatic treatment.

Keywords: Juvenile idiopathic arthritis, methotrexate, TNF-α inhibitor, lymphoma, EBV, lymphoproliferative disorder
were noted. Laboratory analysis revealed normal blood counts and normal C-reactive protein (CRP) but elevated lactate dehydrogenase (LDH) and uric acid levels. Ultrasound tests showed several round lesions with a maximum diameter of 1.7 cm with an enhanced signal of capsules and hypoechoic centers in some of the lesions (Figure 1).

The largest tumor was removed for histopathological examination and showed a blast-rich clonal EBV-associated B-cell lymphoproliferative disorder, areas with CD30-positive diffuse large B cells, and areas consistent with lymphomatoid lymphohgranulomatosis grade III (Figure 2a). EBV-RNA (EBER in situ hybridization) could be detected in the nuclei of the blasts (Figure 2b). Immunoglobulin (Ig)G antibodies to EBV VCA and Epstein Barr nuclear antigen (EBNA) were positive, while EBV Virus capsid antigen (VCA) IgM was negative, and in the patient’s peripheral blood, EBV deoxyribonucleic acid polymerase chain reaction was negative. Staging revealed a suspect posterior mediastinal lymph node in the computed tomography scan.

Immunosuppressive treatment with MTX and etanercept was discontinued, and the patient was followed-up closely. Over the next months, the remaining lesions, including the mediastinal lymph node, decreased in size or vanished completely (Figure 3) and LDH levels normalized. JIA has not relapsed to date.

**Discussion**

Our JIA patient suffered from a complex congenital heart malformation. The case history gave no susceptibility for infections, hypothyroidism, or hypoparathyroidism. Since patients with microdeletion 22q are prone to develop JIA and there are reports about patients with DiGeorge syndrome and EBV-associated lymphoma, microdeletion of the chromosome 22q was excluded by the microarray technique (2). T-cell function tests were not available in our patient. The clinical course with no history of susceptibility for infections and spontaneous regression of the tumor after the discontinuation of iatrogenic immunosuppression makes immunodeficiency in this patient unlikely. MTHFR-mutation may have increased MTX toxicity in this patient, although she received a reduced dosage of MTX and folate acid was given. There are no studies showing an association of MTHFR-mutation and an increased risk for LPD under MTX treatment.

Rheumatic disease in this patient was successfully treated with MTX and etanercept combination therapy, leading to acceptable disease activity. Lymphoma was suspected due to the combination of subcutaneous nodules and elevated LDH. Histological analysis revealed the above-described LPD.

Reviewing the clinical course with spontaneous regression of the lymphoproliferative lesions and the normalization of LDH after the discontinuation of MTX and etanercept led to the assessment of the neoplasm as LPD associated with iatrogenic immunosuppression rather than manifest lymphoma.

Lymphoproliferative disorder and even lymphoma have been described in patients treated with immunosuppressants, especially post-transplant lymphoproliferative disorders (PTLD) in patients after organ transplants or bone marrow transplantation. In a survey of data from the Swedish Hospital discharge register and the Swedish cancer register, a higher incidence of diffuse large B-cell lymphoma (DLBCL) was found in rheumatoid arthritis (RA) patients (22 of 35 reviewed lymphomas). Only 6 patients with DLBCL had received disease modifying antirheumatic drugs (DMARD) therapy for a minimum of 1 year (3). In patients with RA and long-term MTX treatment, several cases have been described where the discontinuation of MTX led to the spontaneous regression or remission of LPD (4). In a Japanese analysis of 76 cases of LPD in RA patients with or without MTX therapy were compared with patients with sporadic LPD. Interestingly, the rate of EBV-positive LPD was significantly higher than in the control group, whether the patients had MTX or not. Also the frequency of DLBCL was significantly higher in the RA group. In this cohort, 11 patients showed spontaneous regression of their LPD after MTX discontinuation. Of those, 5 patients remain in remission, 1 patient died of intercurrent disease and 5 patients had a recurrence of LPD and received chemotherapy (5).

In a retrospective review of 37 cases of LPD in RA patients receiving MTX, 16 patients were initially observed after MTX withdrawal without additional antitumor therapy. Here, 6 achieved spontaneous complete remission, 3 had a partial response, 1 had a minimal response, and 6 had no response to MTX withdrawal. In 8 of the 10 responding patients, EBV was detected (6).
Enhance the malignancy rate while the occurrence of EBV or an increase of EBV-load could not be detected during treatment with Tumor necrosis factor (TNF) α-antagonists (7). To the best of our knowledge, immunodeficiency-associated LPDs have not been described during etanercept monotherapy. This leads to the assumption of an association of the herein described lymphoproliferation to MTX treatment. In the case of relapsing JIA in this patient, etanercept may be reconsidered. Tocilizumab and Rituximab are further options. Rituximab has also been used successfully in PTLD as well as in the treatment of B-cell Non-Hodgkin lymphoma, but is not approved for the treatment of JIA.

Whether monitoring for latent or recent EBV-infection before the start of MTX treatment is feasible remains to be discussed.

Further, some cases of lymphoma are reported in JIA patients treated with MTX and other immunosuppressants, some of them EBV-associated (8). Three cases have been reported where JIA patients developed lymphoma after combination therapy of MTX and etanercept and with other immunosuppressants in two of the cases (9). Thus far, all patients had specific oncologic treatment after the diagnosis of malignancy. To the best of our knowledge, this is the first report in a pediatric patient with spontaneous resolution of an EBV-associated LPD after the discontinuation of antirheumatic treatment.

The risk for malignancies, particularly lymphomas, seems higher for JIA patients (1). Thus far, treatment with TNF inhibitors, particularly with etanercept, has not been described to further enhance the malignancy rate while the occurrence of such cases has been described (10). To our knowledge, this is the first case of a JIA patient suffering from EBV-associated LPD on immunosuppressive treatment with etanercept and MTX with spontaneous regression of the lesions upon the discontinuation of immunosuppressive treatment. Patients on such combination therapies should be monitored closely.

Conflicts of Interest: The authors declared that this study has received no financial support.

Acknowledgements: The authors acknowledge the contributions of the Department of Radiology, Asklepios Klinik Sant Augustin.

Financial Disclosure: The authors declared that this study has received no financial support.

References
7. Couderc M, Payet S, Henquell C, Dubost JJ, Soubrier M. TNFα antagonist therapy does not increase the Epstein-Barr virus burden in patients with rheumatoid arthritis or ankylosing spondylitis. Joint Bone Spine 2010; 77: 414-7. [CrossRef]