

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

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## 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- $\alpha$  inhibitor, lymphoma, EBV, lymphoproliferative disorder

## Introduction

Lymphoproliferative disorders (LPDs) occur at an increased rate in immunosuppressed patients. Patients with juvenile idiopathic arthritis (JIA) also seem to be at an increased risk for malignancies, particularly lymphomas (1). It is still debated whether antirheumatic treatment enhances this risk. To our knowledge, this is the first case of a JIA patient suffering from EBV-associated LPD on combination with etanercept and methotrexate (MTX), showing spontaneous regression of the disorder after the discontinuation of immunosuppressive treatment.

## Case Presentation

A 16-year-old female was diagnosed with rheumatoid factor-negative polyarticular JIA at the age of 4 years. The patient also had a complex congenital cardiac anomaly, a left multicystic kidney, tracheomalacia and obstruction of the trachea at the bifurcation of the pulmonary artery, anomalies of the ribs and vertebrae, mental retardation, sensorineural hearing loss, growth retardation, and delayed puberty. Diagnostic tests for thrombophilia revealed elevated lipoprotein a levels and elevated homocysteine levels due to a methyltetrahydrofolate reductase (MTHFR) mutation. Microdeletion 22q was ruled out, and a microarray assay in search of an underlying genetic disorder showed normal results.

After the diagnosis of JIA, MTX treatment was started, but discontinued due to elevated liver enzyme levels 10 months later. Consecutive treatment consisted of repeated intra-articular steroid applications. At the age of 13 years, JIA relapsed with multiple joint involvement, and treatment with MTX in reduced dosage with folate acid and etanercept was initiated, leading to an acceptable clinical condition but with functional impairment due to restricted joint movements.

At the age of 16 years, the patient reported multiple subcutaneous nodules on the legs. On palpation, the nodules were 0.5 to 2.0 cm in size; the largest of these nodules was slightly tender. No skin changes



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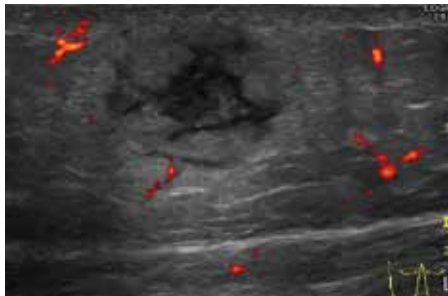
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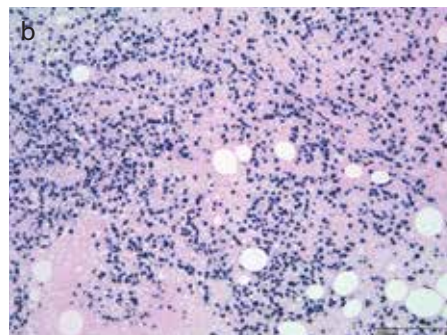
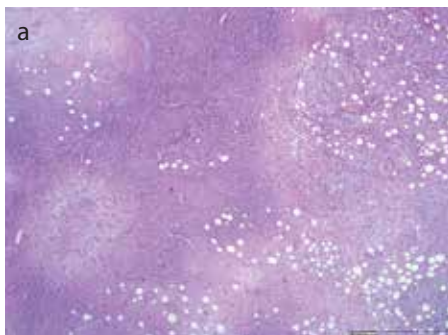
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were noted. Laboratory analysis revealed normal blood counts and normal C-reactive protein (CRP) but elevated lactate dehydrogenase (LDH) and uric acid levels. Ultrasound tests showed several round lesions with a maximum diameter of 1.7 cm with an enhanced signal of capsules and hypoechoic centers in some of the lesions (Figure 1).

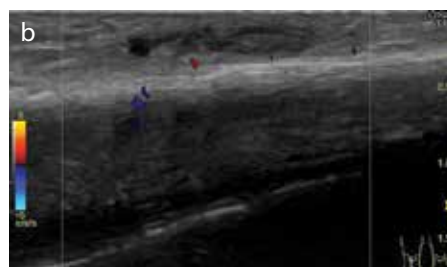
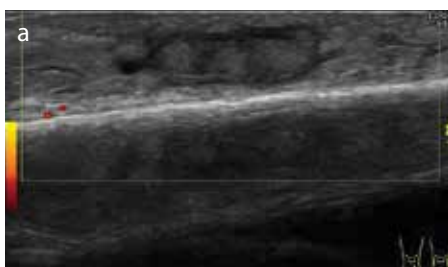
The largest tumor was removed for histopathological examination and showed a blast-rich clonal EBV-associated B-cell lymphoproliferative disorder, areas with CD30-positive diffuse large B cells, and areas consistent with lymphomatoid lymphogranulomatosis grade III (Figure 2a). EBV-RNA (EBER in situ hybridization) 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



**Figure 1.** Ultrasound image of the largest lesion on the right upper thigh: hypoechoic center and surrounding hyperperfusion



**Figure 2. a, b.** Histopathology of the subcutaneous tumor removed from the right upper thigh: subcutaneous tissue with lymphomatoid granulomatosis grade III (a), merging into an EBV-positive diffuse large B-cell lymphoma (b) EBER ISH



**Figure 3. a, b.** Ultrasound images of the lesion in the left lower leg: (a) at the time of diagnosis, and (b) 3 months after the discontinuation of immunosuppressive treatment

(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 LDP 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 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).

Patients with RA are described as having a defect in EBV-directed suppressor T-cell function. Whether weekly low-dose MTX augments this defect has not been established. The reactivation of EBV or an increase of EBV-load could not be detected during treatment with Tumor necrosis factor (TNF)  $\alpha$ -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 remission 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.

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**Informed Consent:** Written informed consent was obtained from patient who participated in this study.

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**Conflict of Interest:** Klein, H. Reinhard and A. M. Muller state no conflicts of interests. G. Horneff has been a member of the advisory boards for Wyeth Biopharma, Muenster, Germany; Abbott Pharma, Wiesbaden, Germany; Novartis Pharma, Nuremberg, Germany; Roche Pharma, Grenzach-Wyhlen, Germany and Essex Pharma, Munich, Germany. G. Horneff is conducting clinical studies sponsored by Wyeth Biopharma, Muenster, Germany, and Abbott Pharma, Wiesbaden, Germany.

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