Reversible Epstein-Barr Virus–Negative Lymphadenopathy and Bone Marrow Involved by Hodgkin’s Lymphoma in a Rheumatoid Arthritis Patient Undergoing Long-term Treatment with Low-Dose Methotrexate: A Case Report and Review of the Literature

Annika M. Svensson,a,b Erica R. Jacobson,a,b David Ospina,c Barbara H. Tindle,a,b

aDepartment of Pathology, University of Vermont College of Medicine, Burlington, Vermont; bDepartment of Pathology and Laboratory Medicine, Fletcher Allen Health Care, Burlington, Vermont; cCentral Vermont Medical Center, Berlin, Vermont, USA

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Abstract

We report a case of spontaneous regression of Epstein-Barr virus (EBV)-negative methotrexate-associated lymphadenopathy occurring with Hodgkin’s lymphoma in the bone marrow of a 48-year-old woman with rheumatoid arthritis. Following 10 years of treatment with low-dose methotrexate, the patient developed pancytopenia, hypercalcemia, and elevated levels of liver enzymes over the course of 2 months. A computed tomography scan of the abdomen revealed splenomegaly and enlarged abdominal lymph nodes. A bone marrow biopsy demonstrated cellular marrow with 2 paratrabeular granuloma-like lesions composed of histiocytes, fibroblasts, small lymphocytes, a few plasma cells, and scattered CD30+CD15+ Hodgkin’s cells, including a classic Reed-Sternberg cell. The results of EBV studies of the bone marrow were negative. Within a month from withdrawal of methotrexate treatment, the patient’s symptoms and the abnormalities in the laboratory results had regressed completely. A positron emission tomography scan failed to detect lymphadenopathy. Twelve months later, the patient remains free of symptoms.


Key words: Hodgkin’s lymphoma; Methotrexate; Rheumatoid arthritis; Epstein-Barr virus

1. Introduction

The development of lymphoproliferative disorders in patients with rheumatoid arthritis (RA) undergoing long-term treatment with methotrexate is a rare but recognized entity, with approximately 100 cases having been reported [1]. Among methotrexate-associated lymphoproliferative disorders, Hodgkin’s lymphoma (HL) is the second most frequently reported at 25% of cases [1].

We report the case of a 48-year-old woman with RA who had received methotrexate treatment for 10 years without complications but who developed severe weight loss, vomiting, and fatigue over the course of 2 months without any changes in medication. The workup demonstrated extensive enlargement of abdominal lymph nodes in computed tomography imaging studies and granuloma-like changes in the bone marrow that were interpreted as HL. The results of an in situ study of the bone marrow for the presence of Epstein-Barr virus (EBV) RNA were negative. Upon discontinuation of methotrexate therapy, the lymphadenopathy as well as the symptoms regressed without further treatment. Rare cases of spontaneous partial or complete regression of methotrexate-induced HL have previously been reported, mainly in EBV-positive cases [2-12]. To our knowledge, only 4 patients with EBV-negative methotrexate-induced HL with spontaneous regression have been described in the literature [2,3,10,13].

2. Case Report

A 48-year-old woman who had been treated for RA with low-dose pulsed methotrexate over the previous 10 years presented for a routine visit. In addition to methotrexate treatment (10 mg weekly), her medication list included pred-
nisone, piroxicam, folic acid, calcium, and multivitamins. She was found to have a mild normocytic anemia and mild leukopenia (hemoglobin, 11.1 g/dL; mean corpuscular volume, 91.9 fl; white blood cell [WBC] count, 3100 cells/µL, with 44% neutrophils [absolute neutrophil count, 1364 cells/µL] and 8% band forms [absolute band count, 248 cells/µL]). The platelet count was normal (273,000/µL). The patient was hypercalcemic (calcium, 13.2 mg/dL; normal range, 8.5-10.6 mg/dL), and her liver enzyme levels were elevated (aspartate aminotransferase, 84 U/L [normal range, 10-37 U/L]; alanine aminotransferase, 84 U/L [normal range, 30-65 U/L]; and alkaline phosphatase, 222 U/L [normal range, 42-121 U/L]). She complained of mild abdominal discomfort and nausea. The results of an ultrasound examination of the pelvis were unremarkable.

Over the course of 2 months, the patient’s symptoms progressed and included loss of appetite, vomiting, fatigue, dyspnea on exertion, and severe weakness. During this time she experienced a 40-pound weight loss. The symptoms did not include fevers or sweats. Additional studies carried out at a follow-up visit 2 months after the initial evaluation of her symptoms revealed a more pronounced anemia (hemoglobin, 7.3 g/dL; hematocrit, 22.3%; red cell distribution width, 18.4%) and leukopenia (WBC count, 1400 cells/µL with 81% neutrophils [absolute neutrophil count, 1134 cells/µL]). The platelet count was initially normal (153,000/µL) but decreased over the course of the following 4 days to 77,000/µL. A peripheral blood smear revealed only rare spherocytes and no schistocytes and did not suggest hemolysis. The patient was also found to have hypercalcemia (calcium, 13.2 mg/dL; normal range, 8.5-10.6 mg/dL); blood urea nitrogen, 41 mg/dL [normal range, 7-18 mg/dL]) with hypercalcemia (calcium, 13.9 mg/dL; normal range, 8.5-10.6 mg/dL). A physical examination revealed signs of anemia, such as a heart rate of 110 beats/min and a systolic murmur (grade II/IV) along the left sternal border. The liver edge was felt below the ribs. The spleen tip was felt at approximately 3 fingerbreadths below the rib margin. There were no palpable cervical, supraclavicular, or axillary lymph nodes. Methotrexate treatment was discontinued, and the patient was hospitalized.

A computed tomography scan of the abdomen without intravenous contrast revealed enlargement of the spleen with a questionable small hypodense lesion within the parenchyma. Retroperitoneal lymphadenopathy was seen within the abdomen and in the upper aspect of the pelvis. Lymphadenopathy was also noted in the perigastric and porta hepatitis areas. The liver and gallbladder appeared unremarkable. The clinical differential diagnosis at this point included possible aleukemic leukemia, plasma cell dyscrasia, lymphoma, aplastic anemia, and hypersplenism. To evaluate for these disorders, a bone marrow biopsy was performed.

One month after withdrawal of methotrexate treatment, the patient was seen at a follow-up visit. She reported complete regression of all symptoms. Furthermore, the hemoglobin level was 11.5 g/dL, the WBC count was 9800 cells/µL, and the platelet count was 273,000/µL. A positron emission tomography (PET) scan, performed to detect nodes suitable for biopsy, was essentially normal.

The morphologic examination of the bone marrow biopsy showed a cellular marrow with a fat-cell ratio of 60:40. The myeloid-erythroid ratio was 3:1 to 4:1. The number of megakaryocytes averaged 4 per high-power field with a few 2-cell clusters and a spectrum of forms. Moderate plasmacytosis was seen. A granulopoiesis evaluation showed mild cytologic changes with rare large neutrophils. The erythropoiesis features included mild cytologic changes with rare, large late-stage forms. Less than 1% blasts were seen. The most prominent feature of the biopsy was the presence of 2 paratrabecular noncaseating granuloma-like lesions (Figure 1). These lesions were fairly discrete, but their margins seemed to intermingle with the surrounding hematopoietic tissue. They were composed of histiocytes, fibroblasts, small lymphocytes, a few plasma cells, and a few scattered large pleomorphic cells somewhat resembling transformed lymphocytes. The large cells included mononuclear forms, some appeared to be polyploid, and a few appeared to have segmented nuclei. Some of the cells had single or multiple large nucleoli. Rare classic bilobed Reed-Sternberg cells were identified in sections routinely stained with hematoxylin and eosin as well as in the immunohistochemical preparations (Figure 2).

Staining with a B-cell antibody (clone L26 against CD20; DakoCytomation, Carpenteeria, CA, USA) and a T-cell antibody (clone F7.2.38 against CD3; DakoCytomation) demonstrated scattered small B-lymphocytes and small T-lymphocytes. Most of the lymphocytes in the granuloma-like lesions were small T-cells with a few small B-lymphocytes scattered throughout the lesions. Staining with antibodies to CD15/Leu-M1 (clone MMA; BD Medical Systems, San Jose, CA, USA) and CD30/Ki-1 (clone Ber-H2; DakoCytomation)