Methotrexate-Induced Pulmonary Lymphoma*

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Methotrexate has proven to be effective in treating rheumatoid arthritis (RA), and is believed to be nononcogenic in the low weekly dose typically employed in the patients with RA. We report, however, a patient with RA in whom a rapidly enlarging diffuse large B-cell lymphoma developed in the left upper lung after weekly treatment with methotrexate for 5 years. The patient had a positive serum IgG for Epstein-Barr virus but a negative in situ hybridization of the resected specimen. Methotrexate therapy was discontinued, and the patient elected for clinical observation instead of chemotherapy or radiation therapy. There has been no clinically detectable recurrence of the lymphoproliferative disorder for 2 years. We believe that methotrexate has an oncogenic potential even in low weekly dosing in a subset of patients with RA and latent Epstein-Barr virus infection. The strongest causal link is demonstrated by the persistent tumor remission after stopping treatment with methotrexate.

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Abbreviation: RA = rheumatoid arthritis

The current trend in treating rheumatoid arthritis (RA) is to initiate disease-modifying antirheumatic drugs early in the course of the illness. Methotrexate is emerging as the initial choice among other immunomodulatory and immunosuppressive agents because it has a fast onset of action, modifies several different clinical variables, improves functional status, and decreases the erythrocyte sedimentation rate.1,2

Methotrexate, however, has an inherent toxicity. As many as 60 to 90% of patients treated with methotrexate eventually have at least one adverse reaction, usually involving the skin, GI tract, or CNS.3 Major and life-threatening toxicities may affect the pulmonary, hepatic, and hematologic systems.4 Pulmonary toxicity was first reported in 1969 among children undergoing treatment for leukemia.5 Hypersensitivity pneumonitis is the most common adverse pulmonary event associated with the use of methotrexate.6 An increasing incidence of lymphoma in patients with RA treated with methotrexate has been reported7; however, there is no large prospective cohort study to confirm this association. We report an additional case of a pulmonary lymphoma that was associated with methotrexate use.

Case Report

A 54-year-old man received a diagnosis of RA 12 years earlier, and had been treated with methotrexate for the past 5 years. The initial dosage was 7.5 mg every week and was later increased to 20 mg. He also received nabumetone, 1 g bid for 1 year, and prednisone, 5 mg/d for the past 12 years. His other significant medical history included hypothyroidism and 30 pack-years of cigarette smoking. He quit smoking 3 years ago and has remained a nonsmoker since then. The patient did not use any non-prescription medications, including herbal products.

On examination, he was afebrile and in no distress. His vital signs were within normal limits. His physical examination was remarkable for mild ulnar deviation of the wrists with decreased range of motion. The remainder of his examination failed to identify lymphadenopathy or hepatosplenomegaly. The cardio-pulmonary examination was normal. He did not have active joint swelling, edema, or clubbing. His neurologic examination was also within normal limits.

Results of a CBC count, serum electrolytes, liver function tests, and urinalysis were unremarkable. A 1-cm nodule was identified in his left upper lobe on routine chest radiography. This was found to be pleural based by chest CT. He subsequently underwent percutaneous fine-needle aspiration of the nodule, but the biopsy sample was nondiagnostic.

The patient remained free of productive cough, hemoptysis, febrile, night sweats, weight loss, or chest pains. A repeat CT scan of the chest was performed 3 months later. The size of the nodule had increased from 1 cm to 3.3 × 3.2 cm (Fig 1). A left upper lobectomy with mediastinal lymph node biopsies was performed. The histopathology of the lung mass was a diffuse large B-cell lymphoma. The diagnosis was confirmed by immunoperoxidase studies that were strongly positive for the leukocyte common antigen and CD-20 (L26) in the large pleomorphic tumor cells. The patient had a positive serum IgG for Epstein-Barr virus. The lymphoma cells, however, were negative for Epstein-Barr virus RNA detection using in situ hybridization. All of the mediastinal lymph nodes were negative for malignancy.

The patient’s surgical recovery was uneventful; however, he decided to forego any chemotherapy or radiotherapy. His methotrexate therapy was discontinued, and he has remained off methotrexate. He continued his other medications (prednisone and nabumetone) as previously prescribed. The patient did not use any herbal products or other medication from alternative medicine. Follow-up was performed with chest CT scan at 3 months, then every 6 months until 2 years after the surgery. During the follow-up, the patient did not receive any additional corticosteroids except his maintenance dose of prednisone, 5 mg/d. There has been no recurrence of his lymphoma.

Discussion

Methotrexate is a structural analog of folic acid that inhibits the enzyme dihydrofolate reductase, thereby blocking the conversion of dihydrofolate to tetrahydrofolate.8 Cellular proliferation is reduced. The effects are...
most prominent in tissues with high mitotic rates, as occurs in malignant tumors, bone marrow, testes, GI tract, and the bladder mucosa. It also has anti-inflammatory and immunomodulating properties; however, the exact mechanism by which it improves the signs and symptoms of RA is still unknown.

The use of this drug has mirrored the conceptual revolution regarding RA, a disease now appreciated to be aggressive, rapidly erosive, and life shortening. Because of this better understanding of the disease, many rheumatologists use methotrexate early in the course of the illness. In addition to its effectiveness and fast onset of action, it is believed that low-dose methotrexate is nononcogenic. Evidence supporting its lack of oncogenicity was demonstrated by the absence of secondary tumors seen in 450 choriocarcinoma and psoriasis patients undergoing long-term treatment with the drug. Nevertheless, the number of lymphomas reported in patients with RA who were treated with this drug is increasing. Although there is no absolute established correlation between methotrexate and lymphoma, there are possible oncogenic mechanisms and risk factors that might predispose patients with RA to acquire lymphoma while receiving methotrexate. These include intense immunosuppression, genetic predisposition, and an increased frequency of latent infection with pro-oncogenic viruses such as Epstein-Barr virus. The strongest causal link between methotrexate and lymphoma in patients with RA is demonstrated by spontaneous tumor remission after stopping the drug. This may be due to a regeneration of the immune system that coincides with the recovery of oncogenic surveillance and the subsequent elimination of a malignant clone.

Previous studies have demonstrated independent abnormalities of T-cell surveillance and function in patients with RA, commonly associated with deficiencies of Epstein-Barr virus-specific immunity. The poor handling of Epstein-Barr virus infection may lead to latent infection, immunodeficiency, and malignant transformation. The Epstein-Barr virus may induce some of its effects through a decrease in B-lymphocyte apoptosis; however, Epstein-Barr virus is found in only 41% of lymphoma patients treated with methotrexate for RA. Therefore, there must be a subset of patients with RA who are predisposed to acquiring this disease. The immunosuppressive effects of methotrexate may intensify the immune abnormalities already present in patients with RA.

Methotrexate may also act as a co-carcinogen. When administered to mice for a prolonged period of time, methotrexate acts as a co-carcinogen for the development of skin cancer. RA itself has also been reported to have an inherent risk of lymphoma developing. A review of several cohort studies by Kinlen showed that patients with RA have 2.5-fold-increased frequency of non-Hodgkin’s lymphoma in the absence of immunosuppressive therapy and a 10-fold-increased frequency when receiving such therapy. However, other investigators failed to show any significant increase in incidence of hematologic malignancy in RA. A retrospective study done at Mayo Clinic studying 16,263 patients with RA showed that hematologic malignancies are uncommon in those patients treated with disease-modifying antirheumatic drugs, including methotrexate. Another study with 862 patients conducted over a mean period of 17.4 years identified only three cases of non-Hodgkin lymphoma.
giving a standardized incidence ratio of 0.5 (95% confidence interval, 0.11 to 1.60).²⁷

The pathogenesis of lymphoma in patients with RA treated with methotrexate may be similar to patients receiving cyclosporine after organ transplantation. In the latter situation, emergence of a lymphoproliferative disorder is associated with an Epstein-Barr virus infection and completely regresses when immunosuppressive therapy is reduced or stopped.²⁸ Most lymphomas have a B-cell phenotype with either serologic evidence of active Epstein-Barr virus infection or detection of Epstein-Barr virus-specific nucleic acid sequences in biopsy specimens.²⁹ This process has led to the hypothesis that Epstein-Barr virus induces B lymphoproliferation with an initial reversible polyclonal stage. Although there is no consensus, this observation would suggest that the increased risk of acquiring a lymphoproliferative disorder is linked to the interplay between Epstein-Barr virus infection, immunosuppression, and an autoimmune disease, such as RA. Kamei et al.³⁰ showed that Epstein-Barr virus-associated lymphoproliferative disorder represents only a small fraction of all non-Hodgkin lymphoma in the general RA patient population. Based on this study, there was no significant difference identified between non-Hodgkin lymphoma in the RA case group and the control group without RA with respect to any variables. The test for Epstein-Barr virus was positive in only 2% of cases and 2% of control groups.³⁰ Nevertheless, it should be noted that only 3 of the 42 patients in the case group received methotrexate. Thus, the role of methotrexate in developing lymphoproliferative disorder in patients with RA and with Epstein-Barr virus infection cannot be totally disregarded. A large case-control study to prove the association between lymphoma, methotrexate, RA, and Epstein-Barr virus infection is still needed to answer this question.

The management of Epstein-Barr virus-associated lymphoproliferative disorder in patients with rheumatologic disease can be based on the study conducted by Saloum et al.,³¹ who reviewed 37 patients who acquired lymphoproliferative disorder while receiving methotrexate.³¹ Sixteen of the 37 patients were observed after discontinuation of methotrexate without additional therapy. Six of these 16 patients (38%) achieved a complete remission. Four patients (24%) showed a partial response, and the remaining six patients (36%) showed no response. Based on this data, they recommend that withdrawal of methotrexate and observation for a short period (4 to 8 weeks) should be considered as the initial treatment of immunodeficiency-related lymphoproliferative disorder in patients with RA.³¹

**CONCLUSION**

In the absence of a large controlled study confirming the association of methotrexate therapy in RA and diffuse B-cell lymphoma, we hope our report will stimulate other clinicians to be vigilant in monitoring the emergence of lymphoproliferative disorder as more patients with RA are treated with methotrexate. We suspect that methotrexate has an oncogenic potential even in low weekly dosing in a subset of patients with RA and latent Epstein-Barr virus infection. The strongest causal link was demonstrated by persistent tumor remission after stopping this drug, which was the case in our patient. We recommend reporting similar cases to help further assess the inherent oncogenic potential of low-dose methotrexate in the treatment of patients with RA.

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