Methotrexate sodium use in the management of various immunologic disorders has increased—as have the number of reported adverse effects associated with this therapy. While methotrexate has helped combat various autoimmune and cancerous disorders, the paradoxical risk of causing an often fatal malignancy may still occur as a result of the drug’s effect on suppressing immune function. We present a case of methotrexate-induced Hodgkin disease in a 48-year-old man with a history of systemic lupus erythematosus (SLE). Discontinuation of methotrexate facilitated Hodgkin disease reversal. In addition, we review other lymphoproliferative hematologic malignancies caused by methotrexate.

Two studies published in 2004 noted a shared gene autoimmunity in systemic lupus erythematosus (SLE), suggesting a more significant genetic role in the disease process than previously expected. Although different environmental and drug-related factors contribute to disease pathology, autoimmune dysfunction against nuclear antigens is observed in almost every case. Presenting symptomology for SLE varies depending on the genes involved and may even differ in monozygotic twins, leading to various outcomes.

The relative risk of hematologic malignancy is estimated to be 60% higher in patients with SLE than in the general population. Of all hematologic cases reported in patients with SLE, the most common is non-Hodgkin lymphoma followed by Hodgkin disease, leukemia, and multiple myeloma.

The initial presenting features of SLE and Hodgkin disease are similar, with fever, weight loss, and peripheral lymphadenopathy seen in most cases. Persistent large lymph nodes not responding to conventional therapy in SLE should be biopsied for alternative diagnosis (ie, lymphoma).

Several conditions and links have been identified that could potentially predispose patients with SLE to cancer. In addition, the mechanisms of hematologic malignancies are thought to be related to the following:

- Failure or dysregulation of apoptosis as a result of mutated genes in SLE (fas ligand)
- Accumulation of and mutations in B and T lymphocytes in the lymph nodes
- T-cell immunodeficiency, allowing Epstein-Barr virus–infected B-cell proliferation
- Exposure to immunosuppressive medications (possible increased risk of EBV infection in patients with SLE)

Methotrexate sodium is one such immunosuppressive agent. It is an antimetabolite, antifolate drug that inhibits dihydrofolate reductase in tetrahydrofolate synthesis, which is further used in the synthesis phase of DNA replication. Furthermore, it is used to manage disorders such as acute lymphoblastic leukemia and autoimmune disorders such as rheumatoid arthritis, Crohn disease, and psoriasis.

In recent years, methotrexate has been increasingly used in the management of various immunologic disorders. However, this increased use has resulted in an increased number of reported adverse effects. While methotrexate has been implicated as a source of iatrogenic malignancy, the present report is, to our knowledge, the first case exhibiting the drug’s contributory effects in the development of reversible Hodgkin disease in a patient with SLE.

Report of Case

In December 2004, a 48-year-old white man presented to the Regional Cancer Center in Erie, Pa, with complaint of dyspnea, chest pressure, chest “fullness,” and some acute discomfort. Blood pressure, body temperature, heart rate, and respiratory rate were all normal on examination. The patient’s medical history included smoking 40 packs of cigarettes per year with a concomitant presentation of chronic obstructive pulmonary disease and an associated...
chronic smoker’s cough. In addition, he was diagnosed as having SLE characterized by cutaneous lupus erythematosus and pulmonary lupus in 2001. He was initially treated with prednisone and hydroxychloroquine sulfate. However, these medications were stopped after a generalized rash occurred, and the patient began dapsone therapy.

After 1 year of dapsone therapy, methotrexate was added to his drug regimen. Methotrexate therapy was slowly titrated from 10 mg per week to 20 mg per week over 6 months. He had been taking a standard dose of methotrexate for no longer than 2 years before his initial presentation. Other medications the patient was taking at the time of presentation included cetirizine hydrochloride, clonazepam, doxepin hydrochloride, and sertraline hydrochloride.

After physical examination, a computed tomography (CT) scan of the chest was ordered. Results revealed a mediastinal mass (140 U/L), normal hemoglobin level, and limited lymph node involvement (four). Thoracic surgery and medianoscopy with biopsy of tissue approximately 2 months after the initial presentation revealed a classic nodular sclerosing Hodgkin disease. Additional staging workup included an abdominal pelvic CT scan and bone marrow aspiration and biopsy. Results of these tests were normal, and the patient was seronegative for EBV. He was diagnosed as having Ann Arbor Stage II Hodgkin disease.

According to the Follicular Lymphoma International Prognostic Index, he was classified as having low-risk lymphoma based on age (48 years), normal serum lactate dehydrogenase (140 U/L), normal hemoglobin level, and limited lymph node involvement (four).

A second CT scan 3.5 months after the patient’s initial CT scan revealed a clinically significant improvement in mediastinal mass (Figure 2). In March 2005, the patient received one cycle of chemotherapy using a protocol based on EVA (etoposide, vinblastine, doxorubicin). A single 3-day cycle of the regimen comprised intravenous administration of the following:

- 100 mg/m² of etoposide on days 1, 2, and 3
- 6 mg/m² of vinblastine on day 1
- 50 mg/m² of doxorubicin on day 1

As recommended in the medical literature, chemotherapy was stopped and the patient was observed for the next 6 months. Eight months later, a repeated CT scan of the chest revealed a 3.5 cm right hilar mass. In December 2005, the patient began EVA therapy, receiving six cycles of therapy—one cycle every 28 days—with complete radiographic resolution of his recurrence. Growth factor therapy was used as a supportive treatment after chemotherapy, while granulocyte colony-stimulating factor was used for prevention of neutropenia. The patient tolerated all therapy well, with the exception of responsive leucopenia to growth factor therapy. Findings from a confirmatory PET scan were negative.

In light of these radiologic findings and the absence of constitutional symptoms, the patient demonstrated a successful remission of Hodgkin disease.

Discussion

According to one study, 55 cases of methotrexate-induced lymphoproliferative disorder have been reported in the United States. Only 5 of those 55 patients had Hodgkin disease, all of whom were seropositive for rheumatoid arthritis. After careful review of the literature, we found that cessation of methotrexate therapy is recommended to improve or potentially resolve Hodgkin disease, as in the present case.

There are many reported cases of non-Hodgkin lymphoma associated with methotrexate therapy. These cases typically resolve with discontinuation of the drug, as in the present case. The patient’s history of lupus and treatment with methotrexate may have contributed to the development of his Hodgkin disease.

In conclusion, the patient’s case highlights the potential for methotrexate to induce lymphoproliferative disorder, even in patients with a history of lupus. Further study is needed to determine the risk factors for methotrexate-induced lymphoma and the optimal management of this complication.
but it may be useful in patients who do not respond to low-dose corticosteroids or antimalarials.\textsuperscript{14} Most benefit has been reported in uncontrolled studies of patients with skin or joint disease.\textsuperscript{14} Although reversible Hodgkin disease is well described in the literature of rheumatoid arthritis,\textsuperscript{10,15} it is lacking in patients with SLE.

Epstein-Barr virus is prevalent among individuals with SLE. Although between 19\% to 48\% of all reported cases of Hodgkin disease are thought to be related to EBV in the general population,\textsuperscript{10} almost all patients with SLE are seropositive for EBV. By comparison, only 70\% of individuals in the general population are seropositive for EBV.\textsuperscript{10} One review\textsuperscript{16} proposed that “correctly” timed exposure to EBV may cause SLE to develop in genetically predisposed individuals.

In patients who are EBV seropositive, T cells are unable to control virally infected B cells, whereas, in vitro, EBV-infected cells are seen to activate and proliferate independently of T-cell help. In healthy individuals, B cells are eliminated by EBV specific CD8\(^+\) T cells. The B cells in SLE may be deficient in major histocompatibility complex class I molecules, making them less susceptible to T-cell control. These B cells may produce autoreactive antibodies as well as activate locally circulating autoreactive T cells accounting for the symptoms seen in SLE. Increased survival of EBV-infected B cells and immunosuppression used to manage SLE symptoms provide an opportunity for the development of premalignant clones and ultimately lymphoproliferative disorder.\textsuperscript{15} However, unlike the majority of patients with lymphoma, the patient described in the present report was seronegative for EBV exposure.

In the current report, Hodgkin disease regressed after withdrawal of an immunosuppressive agent (methotrexate). Compared with the outcomes of Hodgkin disease and other lymphoproliferative disorders in patients with rheumatoid arthritis, results have not been consistent.

In 1996, Salloum et al\textsuperscript{11} published the largest report thus far on the withdrawal of immunosuppressive agents. The authors\textsuperscript{11} combined data from 37 patients with rheumatic disease and found that the withdrawal of immunosuppressive agents in 16 patients who did not receive immediate anti-tumor therapy resulted in 6 complete remissions, 3 partial responses, and 1 minimal response to methotrexate withdrawal. Of the 6 patients who had complete responses to withdrawal of methotrexate, 1 patient remained in complete remission for 4 years after withdrawal, 4 had complete remission for 16 months to 3 years, and 1 was not reported. Only 5 patients had Hodgkin disease, of whom 3 were treated with methotrexate, 2 had no evidence of disease, and 1 was alive with disease at the time of publication.\textsuperscript{11}

After extensive study and research, the authors\textsuperscript{16} concluded that methotrexate withdrawal and closely monitored observation of 4 to 8 weeks should be attempted before the start of radiation therapy or chemotherapy.
Conclusion
Physicians should be aware that methotrexate-induced Hodgkin disease may be reversible. As described in the present report and previously published studies, withdrawal of immunosuppressive agents in patients with lymphoproliferative disorders—including SLE—may cause the regression or, possibly, complete resolution of lymphomas. Radiation therapy and chemotherapy may be necessary adjuvants to agent withdrawal.

References