

Hodgkin's lymphoma in a patient of psoriasis treated with long-term, low-dose methotrexate therapy

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ABSTRACT

Methotrexate (MTX) is used in the treatment of a variety of diseases such as rheumatoid arthritis, dermatomyositis, juvenile rheumatoid arthritis and chronic plaque psoriasis. It has been well documented that there is a risk of development of lymphomas in these patients although none have been reported in patients of psoriasis treated with methotrexate. A 58-year-old male patient, a known case of psoriasis since 1994, had been receiving treatment with a low dose of MTX, 5 mg weekly for ten years intermittently (7-8 months/year). The cumulative dose of MTX taken was 1.5 gm. He developed high-grade fever with cervical lymphadenopathy that was nonresponsive to routine line of management. Lymph node biopsy revealed the presence of mixed cellularity type of Hodgkin's lymphoma. CT scan showed cervical, mediastinal and abdominal lymphadenopathy. The patient responded well to withdrawal of MTX and chemotherapy. This is the first case of lymphoma occurring in a patient of psoriasis treated with low-dose MTX.

Key Words: Chronic treatment, Hodgkin's lymphoma, Low-dose methotrexate, Psoriasis

INTRODUCTION

Low dose methotrexate (MTX) (7.5-15 mg weekly) has emerged as the first choice of therapy for patients with resistant and widespread, chronic plaque psoriasis.^[1] Many studies have suggested an increased risk of lymphoma in patients with rheumatoid arthritis treated with low doses of MTX.^[2-4] Although a variety of lymphoproliferative disorders have been described in the setting of methotrexate therapy for rheumatoid arthritis, cases of Hodgkin's disease (HD) have rarely been reported. Recognition of these lymphoproliferative disorders is clinically important because a subset of these neoplasms may completely resolve with discontinuation of methotrexate, thereby obviating the need for chemotherapy or radiation therapy.^[5] An increased risk of lymphoma is described in patients treated with immunosuppressants such as azathioprine, cyclophosphamide, cyclosporine, and steroids.^[6-7] We report here a case of Hodgkin's lymphoma

that developed after ten years of intermittent methotrexate therapy for widespread psoriasis.

CASE REPORT

A 58-year-old diabetic male who was a diagnosed case of Hodgkin's lymphoma, was referred to us in July 2005 for the management of psoriasis [Figure 1]. On enquiry, he gave us a history of being diagnosed with psoriasis vulgaris in early 1994, and had been treated by a local dermatologist with 5 mg MTX per week. In addition, he had been treated with intermittent topical steroids (mometasone furoate 0.1%, betamethasone dipropionate 0.05%, clobetasol propionate 0.05%) and white soft paraffin. He had responded well to this therapy. Being an Ayurvedic physician himself, he used to consult his dermatologist intermittently on the phone and continued to take the same dose for ten years intermittently (for an average of 7-8 months per year). In addition, he had monitored his blood counts and liver function every two

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Figure 1: Psoriatic plaques on trunk

months during this period. Since his psoriasis had improved, he had stopped MTX treatment in late 2003 and 2004. In January 2005, he restarted the same dose of MTX himself to treat the recurrence of the disease. The cumulative dose of MTX taken by him was approximately 1.5 g (7-8 months per year for ten years).

Hematological investigations done at all times as well as in January 2005 were normal. In April 2005, he developed high-grade fever (40-41°C) of one month's duration, which was not responding to the routine treatment. He also developed multiple swellings in the neck at the same time. Examination revealed multiple, discrete, nontender, firm, posterior cervical lymph nodes varying from 0.5-3 cm in diameter. Per abdominal palpation revealed mild hepatomegaly. He was investigated for the fever and lymphadenopathy. Right cervical lymph node biopsy showed total architectural loss due to a polymorphous infiltrate of epithelioid histiocytes, lymphocytes, plasma cells, a few eosinophils, and Reed Sternberg giant cells. Focal areas of necrosis were also seen. Based on these observations, he was diagnosed to have Hodgkin's lymphoma of mixed cellularity type.

Results of further investigations were as follows: hemoglobin: 8.5 mg%; total leukocyte count: 3650/mm³; differential count: polymorphs: 76%, lymphocytes: 20%, monocytes: 04%; erythrocyte sedimentation rate (ESR) 100 mm at the end of one hour; blood urea: 9.8mg%; serum creatinine: 1.1mg%; serum alkaline phosphatase: 107 U/L; alanine transaminase: 28 IU; aspartate transaminase: 19 IU; serum gamma glutamyl transferase: 35 IU; total proteins: 7g%; serum albumin: 3.2g%; Mantoux test-negative; serum ELISA test for HIV and serum hepatitis B surface antigen (HBsAg)-negative.

Bone marrow biopsy showed evidence of metastatic Hodgkin's disease in the bone marrow. Ultrasonography of the abdomen showed multiple, hepatic, hypoechoic lesions that resembled lymphoma. A computerized tomography (CT) scan of the neck and abdomen showed multiple, enlarged lymph nodes [Figures 2 and 3]. High-resolution CT (HRCT) of the chest revealed mediastinal lymphadenopathy. A positron emission tomography (PET) scan detected multiple areas of abnormal uptake in the right cervical, submandibular, and mediastinal group of lymph nodes, in the spleen and the bones.

MTX was discontinued and a chemotherapy regimen consisting of adriamycin 42 mg, bleomycin 17U, vinblastine 10 mg and dexamethasone 8 mg was given intravenously once a month by an oncologist. There was complete clinical remission as evident on X-rays after twelve cycles of chemotherapy.

DISCUSSION

Several cases of Hodgkin's lymphoma have been reported

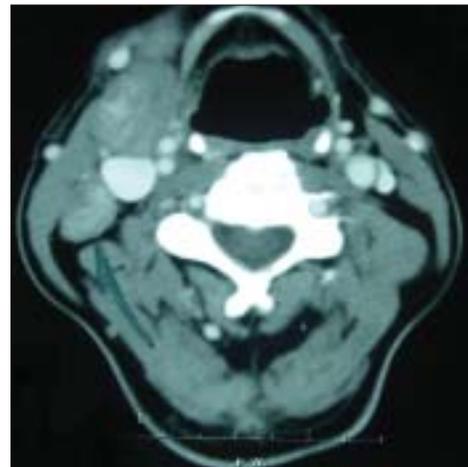


Figure 2: CT scan of cervical region showing lymphadenopathy

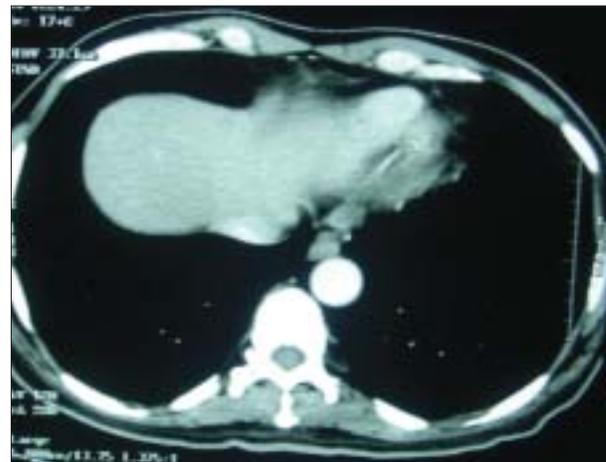


Figure 3: CT scan of abdomen showing lymphadenopathy

following low-dose MTX therapy for various autoimmune conditions that include rheumatoid arthritis (RA), dermatomyositis, and inflammatory bowel disease.^[8-11] However, no case of Hodgkin's lymphoma following low-dose MTX therapy for psoriasis has been reported to date. This is important because, the compromised immune status due to the disease process itself is believed to play some role in the development of Hodgkin's disease in patients of RA treated with MTX.^[12] Such general compromise of immunity is not known in patients with psoriasis. The widely accepted hypothesis for the development of these tumors is that there is a lack of immune surveillance in these patients who are on immunosuppressive agents. This allows proliferation of *Epstein Barr virus* (EBV)-transformed B lymphocytes. However, virological studies were not done in our case.^[9]

There are various reports of lymphomas developing after low-dose MTX administered for different diseases [Table 1]. The mean age at the onset of lymphoma in a three-year prospective study conducted by Mariette *et al*, in 2002 in France was 63 years.^[5] The cumulative dose of MTX was 2.2 g in this study whereas in our case, it was about 1.5 g. In this study, a high incidence of HD was observed in RA treated with MTX, whereas no significant increased risk was found of non-Hodgkin's lymphoma (NHL). Hodgkin's disease, most often in association with EBV infection, is frequent in immunosuppressed patients.^[5] Kamel *et al*, reported Hodgkin's disease (four cases) and lymphoproliferations resembling Hodgkin's disease (four cases) that developed after receiving methotrexate for various disorders.^[9] All three patients with lymphoproliferations resembling HD on whom follow-up was available, experienced tumor regression with methotrexate withdrawal, with or without

steroids. All three patients with HD on whom follow-up was available, were free of disease following chemotherapy or radiation therapy.

In view of the above reports, it is surprising that no cases of lymphoma have been reported in psoriasis patients treated with long-term, low-dose methotrexate. In fact, a retrospective-prospective analysis conducted by Balin *et al*, in 2005 psoriasis patients treated with MTX found no increased incidence of internal malignancies in these patients.^[13] In a large study on 248 patients, Nyfors *et al*, observed the frequency of malignant neoplasms in psoriatics (mean follow up period = 7 years) treated with long-term MTX.^[14] Ten malignant neoplasms were seen during the period of follow-up in those 248 patients. These included seven females with ovarian (3), breast (2), and pancreatic (1) cancers and lymphoma (1) and three males with esophageal (1) and scrotal (1) cancers and lymphoma (1). The types of lymphomas encountered were not specified. However, they were concluded that methotrexate therapy used in the treatment of psoriasis does not seem to contribute to the development of malignant neoplasms.^[14] A similar conclusion was drawn by Stern *et al*, who evaluated the risk of noncutaneous and cutaneous malignancy associated with exposure to methotrexate.^[15] Although 26 cases of noncutaneous cancer were encountered in this study, the 104 matched controls observed also showed a similar incidence of malignancy. Hence, they concluded that there was no association between the development of noncutaneous malignancy and exposure to methotrexate. It has been hypothesized that psoriasis itself is associated with lymphomas.^[16-19] However, most studies have shown that the risk of lymphoma in psoriasis patients is not greater than that in the general population.^[16] The latest study conducted by Gelfand *et al*,

Table 1: Studies of lymphoma associated with low-dose methotrexate therapy for various diseases

Author	Year	No. of cases	Duration of MTX	Cumulative dose of MTX	Condition treated	Type of lymphoma	Course
Mariette ^[5]	2002	25	5.2 years	2.2 g	RA	18: NHL 7: HL	-
Jardine ^[11]	2002	1	4 years	1.6 g	RA	Lymphocyte depleted HL	Expired two weeks > diagnosis
Moseley ^[10]	2000	1	5 years	5-15 mg/week	RA	NSHD	Complete regression > three months of withdrawal of MTX, recurred ten months later
Munro ^[12]	1998	1	-	-	JRA	NSHD	-
Padeh ^[8]	1997	1	16 months	-	JRA	-	Regressed 18 months after chemotherapy, relapsed later.
Kamel ^[9]	1993	8	-	-	RA, dermatomyositis	4: HD, 4: LPD	Three patients of HD - remitted with chemo/ radiotherapy, 3 pts of LPD remitted

RA, rheumatoid arthritis; JRA, juvenile rheumatoid arthritis; HL, Hodgkin's lymphoma; NHL, non- Hodgkin's lymphoma; NSHD, nodulosclerotic Hodgkin's disease; LPD, lymphoproliferative disease.

to estimate the risk of lymphoma in patients with psoriasis suggested that the absolute risk of lymphoma attributable to psoriasis is low.^[20] However, the present case indicates that the last has not been said on this issue and more long-term studies, including those from India, are needed. Our case is the first reported instance from India of methotrexate-associated lymphoma. The rapid response of the tumor to chemotherapy and the withdrawal of MTX in our case, suggests that MTX therapy was a factor in the generation of the tumor.

Many dermatologists use MTX as the first line of therapy in recalcitrant plaque type psoriasis. The rapid response to such therapy coupled with its simplicity and low cost has made it popular in India and has increased chances of self-medication. Such extended therapy may make psoriatic patients prone to lymphoproliferative diseases. Hence, in spite of the ease of therapy, MTX should be used with caution in psoriasis. Regular follow-up in such cases should not only include evaluations for liver and bone marrow toxicity, but also for early detection of lymphoma, particularly after the initial anxieties about tolerance are alleviated. Thus, a detailed clinical examination for lymph node enlargement is considered absolutely necessary at long term follow-up visits. Aggressive investigation of any unexplained lymphadenopathy by fine needle aspiration cytology, and if required, lymph node biopsy, is also necessary. This would go a long way in detecting a rare though serious and frequently reversible side effect of MTX therapy.

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