Lymphoma in a patient with rheumatoid arthritis receiving methotrexate treatment: successful treatment with rituximab

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Abstract
A 55 year old man with chronic lymphocytic leukaemia (CLL) and rheumatoid arthritis (RA), treated for four years with methotrexate (MTX), who developed a B cell non-Hodgkin’s lymphoma (B-NHL), is described. The tumour was localised to the shoulder and axillary lymph nodes, and positive for Epstein-Barr viral antigens. After failure of radiation and chemotherapy, a complete remission was achieved with a combination of antibody treatment (rituximab) and EPOCH. The development of a second malignancy in a patient with RA receiving MTX has not been described before. The summation of T cell deficiencies induced by MTX, CLL, and RA may all have contributed to the development of the B-NHL.

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It is unclear whether the development of lymphoproliferative disorders in patients with rheumatoid arthritis (RA) treated with methotrexate (MTX) occurs by chance alone, is due to the underlying RA, or is facilitated by MTX. The potential link between RA and lymphoproliferative disorders is supported by studies that show a reduced ability of T cells in a patient with rheumatoid arthritis to control Epstein-Barr virus (EBV) infection. An increased number of circulating EBV infected B lymphocytes have been described in patients with RA treated with MTX.

We describe here a man with severe RA and a 10 year history of chronic lymphocytic leukaemia (CLL), who developed a B cell non-Hodgkin’s lymphoma (B-NHL) after four years of MTX treatment.

Case report
A 55 year old man developed polyarthritis in 1981, affecting hands, wrists, elbows, feet, and ankles. Four years earlier, he had been found to have unexplained splenomegaly. In 1988 he developed CLL, confirmed by flow cytometry, with 19×10⁹ white blood cells/l, predominantly small mature lymphocytes, that by 1993 gradually increased to 50×10⁹/l, with 98% small lymphocytes. The lymphadenopathy remained stable and he received no treatment for his CLL. During this interval, he had numerous arthritic flares with progressive joint deformities affecting hands, wrists, elbows, ankles, and shoulders fulfilling criteria for definite RA. Treatment included non-steroidal anti-inflammatory drugs, hydroxychloroquine, oral and parenteral gold, and penicillamine, all with poor response.

In January 1993 treatment was started with oral MTX 7.5 mg/week. The dose was slowly increased to 12.5 mg/week by 1996. His arthritis responded partially, and his white cell count levelled at 60–70×10⁹/l. He was never given concomitant folic acid.

In 1993, at age 50, because of persistent pain and progressive loss of motion, he underwent right total shoulder replacement, with excellent results. By June 1997 his left shoulder had worsened to the point of consideration of a similar procedure. In October 1997 an erythematous swelling was noted anterior to the left shoulder. A magnetic resonance imaging scan showed destructive arthritis, and a total left shoulder replacement was performed. Tissue obtained at that time showed B-NHL of large cells with pleomorphic nuclei. The large cells were strongly positive for CD45, L26 (CD20), for the latent membrane protein antigen of EBV (LMP-1), and were CD23 negative. A computed tomographic (CT) scan of the chest, abdomen, and pelvis showed interval enlargement of the left axillary lymph node to 4 cm, while other adenopathy was stable. A bone marrow biopsy showed infiltration of small mature CD5 positive, CD23 positive B cells, consistent with CLL. No large lymphoid cells or EBV positive cells were detected in the bone marrow. A diagnosis of an EBV associated large cell B-NHL, stage IIE, was made.

The postoperative course was complicated by infection in the left shoulder prosthesis, which required its removal followed by prolonged antibiotic treatment. The shoulder mass increased in size despite stopping MTX and treatment with oral acyclovir. Radiation produced a temporary response, followed by rapid regrowth of the shoulder mass. The patient received three cycles of CHOP chemotherapy with no response. Treatment was then started with a combination of the EPOCH regimen with rituximab, a humanised anti-CD20 antibody. The left shoulder mass and all peripheral lymphadenopathy resolved completely after the fourth cycle.

The lymphocytosis resolved and the arthritis became quiescent. The patient is asymptomatic, with normal blood counts, and no evidence of recurrence of his B-NHL by CT, two years after completion of chemotherapy.
Lymphoma in a patient with RA

Discussion

We describe here a patient who developed a second malignancy presenting as an aggressive, EBV positive, B-NHL, superimposed on CLL and RA treated with MTX. When this neutropenic, immunocompromised patient presented with a mass anterior to the left shoulder, he was initially thought to have an infection, resulting in delayed recognition of the lymphoma. The lymphoma did not regress when MTX was discontinued and required aggressive chemotherapy for control. To our knowledge, the development of a second malignancy in a patient with RA treated with MTX, has not been described before.

Several studies have suggested that there is an increased risk of lymphoproliferative malignancies in patients with RA alone. Some studies suggest that MTX increases this risk, whereas others do not.1,2,13

Those that implicate MTX suggest that adding the immunosuppression of MTX to the immunocompromised state of RA allows the proliferation of EBV transformed B lymphocytes. Patients with RA have been shown to have an abnormally high prevalence of EBV infected B lymphocytes. The tumours seen in these cases show the features of lymphomas associated with immunosuppression. They are typically large cell or polymorphous B-NHL located extranodally, and often regress when MTX is discontinued.1,8,9,10

The postulated mechanisms by which MTX can be oncogenic are multiple. MTX facilitates growth of EBV transformed B cells by further decreasing the already impaired function of cytotoxic T cells and natural killer cells found in patients with RA. MTX accentuates T cell dysfunction through direct apoptosis and inhibition of polyamines that are essential for cell growth and replication.14 It has been shown that EBV clones can undergo lymphomatosus transformation not only in lymph nodes but also in synovium,15 which may have been the case in our patient.

Our patient had CLL, a B cell neoplasm accompanied by abnormalities of T cell phenotype and function. A high incidence of second malignancies has been described in CLL.16 Richter’s syndrome, an aggressive B-NHL, develops in about 3% of these patients, but there are several reasons to suggest that this was not Richter’s syndrome.17 The histology of the B-NHL and the prolonged remission after treatment were not consistent with Richter’s syndrome. The LMP-1 antigen positivity in the large neoplastic cells and lack of staining with C23 favour an EBV induced lymphoproliferative disorder rather than Richter’s syndrome. In this patient, the summation of immunodeficiencies induced by MTX, CLL, and RA may have led to malignant transformation.

The sustained remission of our patient’s RA for more than two years after the use of rituximab was surprising but has now been described in five other patients.18 The mechanism is unknown but may be due to the profound B lymphocyte depletion that occurs.