CASE REPORT

Polyarticular juvenile idiopathic arthritis treated with methotrexate complicated by the development of non-Hodgkin's lymphoma

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A 10 year old boy with juvenile idiopathic arthritis is described. He was treated with methotrexate (MTX) for 2 years 8 months, and presented at routine review with hepatosplenomegaly and suspicious bilateral cervical lymphadenopathy, two months after discontinuing therapy. Magnetic resonance scan revealed significant lymphadenopathy around the upper abdominal aorta and coeliac axis. Lymph node biopsy was consistent with non-Hodgkin's lymphoma, similar to that reported in several adults with rheumatic diseases taking low dose MTX therapy. He was successfully treated with a standard cytotoxic chemotherapy regime, but unfortunately his polyarthritis has subsequently flared some months after completion of his treatment.

CASE REPORT

Clinical findings

A 10 year old boy with a four year history of juvenile idiopathic arthritis (JIA) presented at routine review with bilateral non-tender but firm and suspicious cervical lymphadenopathy. He had hepatosplenomegaly. He had been treated with methotrexate (MTX) 7.5 mg per week, for 2 years 8 months; cumulative dose was 1042.5 mg. The MTX had been given by subcutaneous injection for four months prior to its discontinuation because of nausea associated with oral preparations. MTX had been discontinued two months prior to his presentation with lymphadenopathy as his arthritis had been quiescent for one year. He had also intermittently been treated with daily or alternate daily prednisolone throughout the period of his JIA, and with several intra-articular corticosteroid injections. There were no other co-morbid conditions.

He was admitted for urgent investigation. Full blood count, urea and electrolytes, and lactate dehydrogenase were normal. Serology indicated recent Epstein–Barr virus (EBV) infection, with IgG to EBV detected. Cytomegalovirus (CMV) IgG was not detected. Bone marrow aspirate and trephine revealed no evidence of malignant disease, and there were no malignant cells in his cerebrospinal fluid. Abdominal ultrasound confirmed hepatosplenomegaly and the presence of para-aortic nodes. Magnetic resonance scan revealed a diffusely enlarged spleen, 14 cm in length, with normal texture of liver, pancreas, and both kidneys. There was significant lymphadenopathy around the upper abdominal aorta and coeliac axis, with individual nodes measuring 2 cm in diameter. Computed tomography of the chest revealed evidence of bilateral cervical lymphadenopathy, extending to the sternoclavicular joints. There was no evidence of significant mediastinal or axillary lymphadenopathy, and no evidence of parenchymal lung disease.

Pathological findings

A tissue diagnosis of non-Hodgkin's lymphoma was obtained. Histopathology of a lymph node biopsy revealed T cell rich B cell lymphoma. Most of the larger cells were positive for CD79A, CD20Y, and CD45RA (B cell markers), but negative for CD10, CD15, CD30, EBV, and T cell markers (including CD3, CD4, CD5, CD8, CD43, CD43RO), and dendritic reticulum cells (CD21).

Treatment

The patient was treated according to a standard treatment protocol (LMB89), which consists of six months of cytotoxic chemotherapy. This comprised vincristine, cyclophosphamide, prednisolone, MTX, doxorubicin, cytarabine, and intrathecal MTX. During this treatment programme his arthritis went into remission. At follow up six months after completion of chemotherapy his lymphoma is in remission, but unfortunately his arthritis has recurred, requiring careful consideration of treatment options.

DISCUSSION

The literature relating to lymphoma occurring in patients with rheumatoid arthritis treated with weekly low dose MTX has recently been reviewed; at least 50 cases have been reported.[1] To the best of our knowledge, four children with JIA treated with MTX have developed Hodgkin's lymphoma.[2–5] Two of these children had evidence of EBV infection associated with their lymphoproliferative disease.[3 4] Table 1 summarises the characteristics of the cases.

The incidence of non-Hodgkin's lymphoma in the age group 5–9 years for the period 1968–95 was 6.5 per million per year.[6] At present approximately 100 children at our institution with JIA are treated with MTX. Several other paediatric rheumatology units were contacted (Great Ormond Street, Birmingham, Nottingham, Leeds, and Newcastle). Any other cases of lymphoproliferative disease (LPD) occurring during treatment with MTX were sought, as it was acknowledged that since case reports were not the favoured format for most journals, other cases may exist. In fact only one other case was noted; this was in a child who also had Blackfan–Diamond syndrome and therefore was at increased risk of haematological malignancy (Professor Woo, personal communication).

Post-transplant lymphoproliferative disorder (PTLD) in an immunocompromised host following paediatric renal transplantation has been reported. Srivastava *et al* reported PTLD in six of 84 renal transplant recipients in one centre.[7] In all of these patients PTLD was associated with EBV infection (primary in five, reactivation in one). All patients received therapeutic immunosuppression post-transplantation, with prednisolone and various combinations of mycophenalate

Abbreviations: Abbreviations: CMV, cytomegalovirus; EBV, Epstein–Barr virus; JIA, juvenile idiopathic arthritis; LPD; lymphoproliferative disease; MTX, methotrexate; PTLD; post-transplant lymphoproliferative disorder

Table 1 Characteristics of patients with juvenile arthritis developing lymphoma while treated with MTX

Ref.	Diagnosis	Duration of MTX therapy	Other therapy during treatment with MTX	Cell type	Spontaneous remission on stopping MTX	Outcome
2	Systemic JIA Mixed cellularity Hodgkin's lymphoma	16 months	Prednisolone	CD30 CD15 EBV neg	Yes	Late LPD relapse Autologous stem cell transplantation
3	Systemic JIA Nodular sclerosing Hodgkin's lymphoma	33 months*	Not known	CD30 EBV pos	Not attempted	Remission of LPD and JIA
4	Polyarthritis (RF positive) Nodular sclerosing Hodgkin's lymphoma	30 months†	Prednisolone Cyclosporin A	CD30 CD15 CD20 LMP1 EBV pos	Not applicable	Death (respiratory failure secondary to legionella pneumonia)
5	Polyarthritis (RF negative) Nodular sclerosing Hodgkin's disease	21 months‡	Sulphasalazine	EBV negative	Partial response	Remission of LPD and JIA after 12 months follow up
Our case	Polyarthritis Non-Hodgkin's lymphoma	32 months	Prednisolone Intra-articular steroids	CD79A CD20Y CD45RA	No	Remission of LPD Relapse of polyarthritis

*MTX discontinued for eight weeks during proven EBV infection 21 months prior to presentation with nodular sclerosing Hodgkin's lymphoma.
†MTX discontinued for two months during episode of intercurrent pneumonia.
‡MTX discontinued after 20 months due to disease remission, and recommenced after one year due to relapse.

mofetil, azathioprine, and cyclosporin. Five of the six patients responded completely to a decrease in immunosuppression and antiviral treatment alone. The sixth patient was unusual in that he developed T cell rich Hodgkin's disease and was EBV positive at the time of transplant. He responded to a combination of chemotherapy and CMV hyperimmune globulin.

No cases of LPD have occurred during MTX therapy for JIA in children registered with the United Kingdom Children's Cancer Study Group (D Walker, personal communication). In contrast, 42 cases of transplantation related LPD have been registered. It is important that all cases of malignant disease occurring in patients with JIA treated with immunosuppressants are registered.

The predominant type of lymphoma reported in adult patients with rheumatic disease treated with MTX and steroids is the same as that occurring in the immunosuppressed (for example, post-transplant and AIDS patients), namely large B cell non-Hodgkin's lymphoma with extranodal involvement.[8] Our patient also developed such a disorder, and as such is the first case reported of non-Hodgkin's lymphoma occurring in a patient with juvenile idiopathic arthritis treated with MTX.

The hypothesis that MTX has a role in the aetiology of LPD is supported, at least in part, by the observation of spontaneous remission of lymphoma on cessation of MTX therapy.[9] This has been reported in at least eight adult patients.[1] Resolution of peripheral adenopathy, but not of thoracic or abdominal lymph node and spleen involvement, was noted in one child with JIA on withdrawal of MTX.[5] She subsequently received one of a projected three cycles of combination chemotherapy (MOPP-ABVD) with radiographically documented complete resolution. The role of EBV virus infection in the pathogenesis of LPD in patients treated with MTX is unclear. EBV positive staining was shown in the lymph node biopsy specimens from two of four previously reported patients with JIA who developed lymphoma; similar findings in adult patients have been reported.[10] It may be speculated that MTX interferes with the handling of EBV by T cells, and allows the subsequent proliferation of EBV infected lymphocytes.

MTX is an established and effective treatment for polyarthritis in children.[11] It is not clear how physicians caring for children with polyarthritis should interpret these isolated case reports, as there is no epidemiological or proven causal association between therapeutic immunosuppression and the development of LPD. Another dilemma that has been raised by the subsequent clinical course in our patient has been the relapse of his polyarthritis some months after completing chemotherapy for his non-Hodgkin's lymphoma. His family are understandably very concerned about the potential impact of further immunosuppressant therapy.

Children with polyarthritis are being treated earlier, with larger doses and for longer durations with MTX. Only with data collected prospectively and collaboratively will it be possible to clearly define the risk of LPD in this group. Vigilant clinical observation for the development of lymphoproliferative disorder is recommended as a routine part of the clinical follow up of all children with JIA treated with weekly low dose MTX, especially as routine haematological monitoring is unlikely to alert physicians to the diagnosis.

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