Lymphadenopathy in a patient with systemic onset juvenile chronic arthritis

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Case history

A boy aged 12 years presented to the local general hospital with a four week history of fever, rash, and arthralgia in September 1982. The rash was migratory and appeared urticarial, the most commonly affected sites were his trunk and thighs. The arthropathy was asymmetrical and mainly affected medium and large joints. At presentation he complained of discomfort in his ankles, left knee, and right wrist.

Clinical examination confirmed the presence of the rash and active synovitis of his right wrist. There was no evidence of lymphadenopathy, organomegaly or cardial murmurs. Initial investigations included a raised erythrocyte sedimentation rate (ESR) at 34 mm 1st h and a moderate leucocytosis. Radiology of the affected joints was unremarkable and his electrocardiogram was normal. His rheumatoid factor and anti-nuclear antibodies were negative. An infection screen included negative blood cultures, negative serology for toxoplasmosis and brucella but an increased anti-streptolysin (ASO) titre of 500 Todd units.

The initial diagnosis was considered to be rheumatic fever. However, despite treatment for two to three weeks with salicylates and benzyl penicillin his symptoms including fever continued unabated. A diagnosis of systemic onset juvenile chronic arthritis (SOJCA) was made and he was given prednisolone 60 mg/day (approximately 1 mg/kg). This led to a rapid improvement in his joint symptoms and resolution of his rash.

His systemic features remained problematic over the next few months reappearing with attempted reductions in his corticosteroid dose. However, they eventually settled by July 1983 and he was maintained with non-steroidal agents alone. His care at this stage was transferred to the local paediatric rheumatologist. His joint disease however deteriorated over the next six months and corticosteroids had to be given again with prednisolone 60 mg/day (approximately 1 mg/kg). This led to a rapid improvement in his joint symptoms and resolution of his rash.

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of $2.2 \times 10^9/l$ (39% lymphocytes, 7% monocytes) and thrombocytopenia of $102 \times 10^9/l$. There was a mild hypertransaminasaemia with aspartate aminotransferase (AST) 66 u/l (normal range 12–48). Throat, urine, and blood cultures were sterile, and a chest radiograph was normal. Assays of vitamin B12 and folic acid were normal. A monospot test was positive and active Epstein-Barr virus (EBV) infection was confirmed by the presence of anti-EBV IgM in the serum. Methotrexate treatment was withdrawn partly because of his haematological abnormalities and partly because of abnormal liver function tests. Over the next 10 days a steady clinical improvement was noted although the abnormalities of his liver function tests initially deteriorated, peak AST 380 u/l, alanine aminotransferase 270 u/l (normal range 3–55), and alkaline phosphotase 870 u/l (normal range 80–280) before they returned to normal. The platelet count reached a nadir after four days of $50 \times 10^9/l$ before normalising over the next five days. Over the same time period his anti-EBV IgM became negative and anti-EBV IgG appeared in his serum.

In June 1990, eight weeks after his EBV infection his liver function tests and haematology had returned to normal and methotrexate was restarted at 7.5 mg/week. His arthritis remained well controlled but a right total shoulder joint was required in January 1991.

In March 1992 he returned to outpatients complaining of a short history of anorexia, malaise and approximately 5 kg weight loss. On examination he was afebrile but there was a mass of matted lymph nodes in his right axilla. The spleen was palpable two fingerbreadths below the costal margin. The full blood count was normal (Hb 12.8 g/dl, WCC 9.2 x $10^9/l$, and platelets $355 \times 10^9/l$). The differential white cell count showed a mild lymphopenia (13%, absolute count $1.2 \times 10^9/l$). Liver function tests (including alkaline phosphotase), albumin, lactate dehydrogenase, serum calcium, and immunoglobulins were all within the normal range. His renal function was well preserved (urea $6.7$ mmol/l and creatinine $80$ µmol/l). Fine needle aspiration was performed and the histology was suggestive of Hodgkin’s lymphoma. An excision biopsy specimen was undertaken and histological examination showed the presence of nodular sclerosing Hodgkin’s lymphoma (fig 2) with typical staining for the cell marker CD 30 (BerH2, Dako).

In addition a number of the cells stained positive for EBV latent membrane protein (M897, Dako). Staging computed tomography showed evidence of axillary (fig 3), mediastinal and para-aortic lymphadenopathy but bone marrow biopsy showed no involvement. The disease was classified as stage IIIb Hodgkin’s lymphoma on the basis of disease on both sides of the diaphragm and the presence of weight loss—“B” symptom.

Methotrexate was withdrawn and he was treated with a modified MOPP/EVAPP chemotherapy regimen, which used a combination of mustine, vincristine, adriamycin, VP16, vinblastine, prednisolone, and procarbazine. Treatment was given over the next eight months. Serial computed tomography showed improvement and ultimately resolution of his lymphadenopathy and serial bone marrow biopsy specimens showed no evidence of involvement. Chemotherapy was complicated by three episodes of septicaemia associated with drug induced neutropenia, each responded to intravenous antibiotics.

In November 1992 his disease was judged to be in complete remission and chemotherapy was stopped. His bone marrow was harvested and stored, lest his disease should relapse, necessitating autologous bone marrow transplantation. In August 1997 his lymphoma had been in remission for 56 months. His joints have remained quiescent after chemotherapy, corticosteroids were withdrawn in February 1995.

**Discussion**

**INITIAL PRESENTATION**

The initial presentation of a child with a persistent fever and arthralgia has a wide differential diagnosis, some of the diagnoses to consider are shown in table 1.

In this case the additional features of a rash and positive ASO titre led to the initial diagnosis of rheumatic fever. Subsequently the possibility of SOJCA was considered in view of the poor response to appropriate antibiotics and salicylates. In retrospect the initial presentation was fairly classic for systemic onset JCA and apart from exact details on the periodicity of the pyrexia fulfils the criteria proposed by the International League Against Rheumatism (ILAR) for systemic onset JCA (table 2).

The presence of a positive ASO titre can be misleading early in the presentation of SOJCA as happened in this case. It should be borne in
Lymphadenopathy and systemic onset juvenile chronic arthritis

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chemotherapy. This has recently been de-

mind that the ASO titre can be increased in

approximately one third of children who are

subsequently diagnosed as JCA.1

TREATMENT FOR SYSTEMIC ONSET JCA

There have been significant developments in the treatment for systemic JCA since the initial presentation of this case. Non-steroidals con-
tinue as the first line treatment for both the

arthropathy and systemic features. If these

agents fail to control the symptoms or there is
evidence of an erosive arthropathy then meth-

trexate would be the disease modifying agent

of choice. Methotrexate not only controls the

arthropathy1 but may also ameliorate some of

the systemic features2 and thus reduces the

requirement for other treatment such as corti-

costeroids.

Gold and sulphasalazine are no longer recom-

mended if there are any systemic fea-
tures. Gold has been associated with severe

hepatotoxicity, encephalopathy, and dissemi-
nated intra-vascular coagulation.67 Similar

toxicities exist over the use of sulphasalazine.8 Azathioprine has been super-
seded by methotrexate and is little used in paed-
iatric practice.

Corticosteroids still have a place in the treat-

ment of systemic onset JCA particularly when

systemic features predominate. Initial doses of

0.5–1 mg/kg on alternate days may be required.

An alternate day dose regimen reduces the risk

of growth retardation. As the symptoms

improve the corticosteroid dose can be gradu-

ally reduced and eventually withdrawn.

A point of interest in the case discussed is the

prolonged remission that has occurred after

chemistry. This has recently been de-

scribed in another case where chemotherapy

was used to treat a child with SOJCA and

Hodgkin’s disease.9

LYMPHADENOPATHY IN SYSTEMIC ONSET JCA

The reticuloendothelial system is commonly

involved in systemic JCA. Up to 70% of

children will develop lymphadenopathy, splenomegaly or hepatomegaly.10 The lymph

nodes are generally firm, non-tender, and not

matted. Histologically the lymphadenopathy is

caused by follicular hyperplasia. Features that

should cause concern are new lymphadenopa-

thy without any other features of systemic JCA,

weight loss, anorexia, and pruritis. Lymph

nodes that are rubbery, craggy or matted

require further investigation.

Moderate splenomegaly was the only feature of

reticuloendothelial involvement in the case

presented and this was only detectable by

ultrasound initially in 1988. The development

of lymphadenopathy and palpable spleno-

megaly on both occasions was new and associ-

ated with other systemic features not typical of

JCA. This is what should cause concern. Dur-

ing the presentation with glandular fever he

had a new pyrexia, pharyngitis, hepatitis, and

blood film abnormalities, none apart from the

pyrexia had been features of his initial rheuma-
tological presentation. The pharyngitis in par-
nicular raised the possibility of an infective aeti-

ology to his new symptoms and this was con-

firmed on screening by the discovery of

positive IgM EBV serology.

The presentation of his lymphoma again was

accompanied by new systemic features—in this

case weight loss and general malaise. The

lymphadenopathy was also not typical of that seen in systemic onset JCA in that it was rubbery

and matted. The initial investigation per-

formed was a fine needle aspiration of a node.

The discovery of atypical cells in the case

discussed led to an open biopsy that gave the

definitive diagnosis of nodular sclerosing

Hodgkin’s lymphoma.

LYMPHOMA AND EBV

The role of EBV in the development of

lymphoreticular malignancies is unclear. EBV

infection has been implicated in the aetiology of

Burkitt’s lymphoma, X-linked recessive lympho-
proliferative syndrome, and some non-

Hodgkin’s lymphomas developing after

transplantation.11–13 Many post-transplantation

lymphoproliferative disorders appear to be

driven by clonal expansion of B lymphocytes

containing EBV DNA.14 Post-transplantation

EBV related lymphoma is thought to occur

because of immunosuppression caused by

agents such as cyclosporin and azathioprine

allowing proliferation of B cells previously

infected with EBV.

There is evidence to link EBV with lym-

phoma in the general population. Previous

glandular fever is associated with up to a four-

fold increase in risk in developing lymphoma.15

Additionally EBV material is frequently found

in lymphoma tissue. Staal et al16 in a study of

unselected malignant and non-malignant lym-

phoid specimens, detected EBV DNA in 29%
of patients with Hodgkin’s disease compared with only 4% of patients with non-Hodgkin’s lymphoma and none of the patients with non-malignant conditions or chronic lymphocytic leukaemia. The type of Hodgkin’s disease also seems important with EBV DNA found in only 10% of lymphocyte predominant cases, 32% of nodular sclerosis cases and most (96%) of mixed cellularity cases.17

There are theoretical reasons to suggest that rheumatoid arthritis (RA) patients may be at an increased risk of developing EBV related disorders because of abnormal handling of EBV by T cells.18 Although similar abnormalities can be found in polyarticular JCA19 they do not appear to be present in SOJCA.20 In our report it is interesting to speculate that the use of methotrexate may have led to impaired viral clearing initially and later allowed clonal proliferation of previously infected B cells similar to that seen after transplantation.

**LYMPHOMA, METHOTREXATE, AND SYSTEMIC ONSET JCA**

The place of methotrexate in the development of lymphoreticular malignancies is less clear. There is no evidence of an increased risk of malignancies in psoriasis patients treated with methotrexate.21 In rheumatological practice the use of methotrexate in RA has been the most extensively studied. Two large studies of 16 263 and 5803 RA patients respectively found no evidence of a significant increase in risk of malignancies in those treated with methotrexate.22 23 The confidence intervals in the second study for the risk of developing any malignancy were wide (0.3 to 10) and it is possible neither study had significant power to truly answer the question despite their large sample sizes.

There is growing anecdotal evidence in the form of case reports (approximately 50) implicating methotrexate in the development of lymphoma in patients with rheumatological disease (mainly RA).24 At present there has only been one report of Hodgkin’s disease in a 6 year old girl with systemic onset JCA.25 She had received 18 months treatment with methotrexate before developing a mixed cellularity Hodgkin’s lymphoma with no evidence of EBV involvement. The existence of only one other case report for systemic onset JCA is possibly partly because of the relatively small number of children being treated with methotrexate compared with the estimated 100 000 to 200 000 RA patients currently being treated with methotrexate.24

Potentially the strongest evidence to implicate methotrexate is spontaneous regression of the lymphoproliferative disorder in a number of cases on cessation of methotrexate without the requirement for chemotherapy.26–27 Our case received chemotherapy as, at the time he was treated, the phenomenon of regression with withdrawal of methotrexate alone had not been fully reported. It is possible to speculate that formal chemotherapy may not have been required and that a period of observation without methotrexate should have been considered. This was attempted in the other case report in systemic onset JCA with initial success, however, chemotherapy was eventually required.28

**Conclusion**

This case raises some important questions regarding the use of methotrexate in SOJCA particularly in the face of an EBV infection. At present this is only the second case report of Hodgkin’s disease in SOJCA and therefore the association may be coincidental, however vigilance and diligent reporting is required to ensure this is not a true association.

**KEY MESSAGES**

- Lymphoreticular involvement is common in SOJCA.
- Changes in lymphoreticular involvement warrants further investigation, particularly when associated with features that may be associated with a lymphoproliferative disorder.
- A trial of withholding any concurrent immunosuppressant treatment may be warranted in EBV positive lymphoproliferative disorders appearing in the setting of a rheumatic disease.

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