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 cardiac 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 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 (0.7 mg/kg) on alternate days. In August 1985 when he was 15 years old azathioprine 100 mg daily (1.5 mg/kg) was added to his regimen on the basis of a recent report of its usefulness in the treatment of juvenile chronic arthritis. His corticosteroid requirements generally ranged from 5–20 mg/day.

Radiological examinations showed progression of his joint disease with erosions appearing at his wrists and elbows and significant narrowing of the joint space at his hips. In November 1986 it was felt that azathioprine was no longer effective and he was given intramuscular gold 30 mg/week. Unfortunately this was complicated by the development of significant proteinuria (3.6 g/24 h) after five months. A renal biopsy was performed to exclude amyloidosis, this showed evidence of gold induced glomerulonephritis and a degree of interstitial nephritis. His proteinuria settled over the next 18 months with withdrawal of gold. At age 18 years his joint disease again became more active and sulphasalazine 2.5 g/day was given along with prednisolone 5–10 mg/day and a non-steroidal agent. The arthritis in his hips had continued to progress (fig 1) to the extent that he underwent bilateral hip replacements.

In June 1989, aged 19 years his joint disease became more active and he developed an intermittent rash on his upper arms. Sulphasalazine was stopped and he was given oral methotrexate 7.5 mg/week and folic acid 5 mg weekly, his dose of prednisolone was increased back to 10 mg daily. He responded to the change in medication and his renal function, liver function, and haematology remained normal over the next 10 months.

After 10 months of methotrexate treatment he presented with a five day history of fever, anorexia, vomiting, and a sore throat. On examination he was febrile at 40.5°C. The fauces were inflamed and a left sub-mental lymph node was enlarged. The splenic tip was also just palpable, however splenomegaly of 13.2 cm had been noted in 1988 on an ultrasound performed to investigate his proteinuria. Full blood count showed a leucopenia

Figure 1 Radiograph of hips showing an advanced erosive arthropathy.
of 2.2×10^9/l (39% lymphocytes, 7% monocytes) and thrombocytopenia of 102×10^9/l. There was a mild hypertransaminasemia 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 folate 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 phosphatase 870 u/l (normal range 80–280) before they returned to normal. The platelet count reached a nadir after four days of 50×10^9/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 9.2×10^9/l and platelets 355×10^9/l). The differential white cell count showed a mild lymphopenia (13%, absolute count 1.2×10^9/l). Liver function tests (including alkaline phosphatase), 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—a “B” symptom.

Methotrexate was withdrawn and he was treated with a modified MOPP/EVAPP chemotherapy regimen, which uses a combination of mustine, vincristine, adriamycin, VP16, vinblastine, prednisolone, and procarbazine. Treatment was given over the next eight serials. 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 responding 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
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sulphasalazine. Azathioprine has been superseded by methotrexate, but may also ameliorate some of the symptoms of arthritis (in the absence of specific exclusion criteria). Methotrexate not only controls the arthritis but may also ameliorate some of the systemic features of juvenile chronic arthritis. There have been significant developments in the treatment for systemic JCA since the initial presentation of this case. Non-steroidal agents fail to control the symptoms or there is evidence of an erosive arthropathy then methotrexate should be the drug of choice. Methotrexate not only controls the arthropathy but may also ameliorate some of the systemic features and thus reduces the requirement for other treatment such as corticosteroids.

Gold and sulphasalazine are no longer recommended if there are any systemic features. Gold has been associated with severe hepatotoxicity, encephalopathy, and disseminated intravascular coagulation. Similar toxicity concerns exist over the use of sulphasalazine. Azathioprine has been superseded by methotrexate and is little used in paediatric practice.

Corticosteroids still have a place in the treatment 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 gradually reduced and eventually withdrawn.

A point of interest in the case discussed is the prolonged remission that has occurred after chemotherapy. This has recently been described in another case where chemotherapy was used to treat a child with SOJCA and Hodgkin’s disease.

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. 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 lymphadenopathy 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 splenomegaly on both occasions was new and associated with other systemic features not typical of JCA. This is what should cause concern. During 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 rheumatological presentation. The pharyngitis in particular raised the possibility of an infective aetiology to his new symptoms and this was confirmed 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 performed 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 lymphoproliferative syndrome, and some non-Hodgkin’s lymphomas developing after transplantation. Many post-transplantation lymphoproliferative disorders appear to be caused by clonal expansion of B lymphocytes containing EBV DNA. 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 lymphoma in the general population. Previous glandular fever is associated with up to a fourfold increase in risk in developing lymphoma. Additionally EBV material is frequently found in lymphoma tissue. Staal et al in a study of unselected malignant and non-malignant lymphoid 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 polyclinical RA,19 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 malignancy 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.25–27 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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