Arthritis as a presenting feature of non-Hodgkin's lymphoma

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Abstract

Leukaemia can present with joint swelling in the absence of abnormal haematological findings. Arthritis as a presenting sign of lymphoma, however, is extremely rare. Three children with non-Hodgkin's lymphoma who had joint swelling at the onset of their disease are reported. Two cases showed histological features of anaplastic large cell lymphoma (Ki-l/CD30 positive), and one of angioimmunoblastic T cell lymphoma. In all patients the unusual presentation delayed correct diagnosis.

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Several non-rheumatological diseases in children can present with musculoskeletal involvement, mimicking juvenile chronic arthritis (JCA), in particular, infection and malignancy. Both need to be excluded early in the course of the disease to avoid errors in diagnosis, inappropriate treatment, and possible serious complications. Childhood leukaemia is the most common malignancy mimicking JCA, possibly presenting with only joint pain or swelling, even in the presence of normal haematological findings.[1] There are a variety of pathogenetic mechanisms for bone or joint pain, including malignant cell invasion of bone and bone marrow. Osteoarticular pain due to bone involvement is rarely present in non-Hodgkin's lymphoma (NHL); we know of only one case report of paediatric NHL presenting with true arthritis.[2]

We report three cases of paediatric NHL that presented with joint swelling. The preliminary diagnosis in two of the cases was JCA, while the third patient had a presumptive diagnosis of septic arthritis. In all three cases the final diagnosis was delayed because of the unusual presentation.

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Case reports

CASE 1

A 5 year old white boy was admitted to hospital in September 1992 because of high spiking fevers (up to 39.5°C in the evening), recurrent episodes of severe abdominal pain, and myalgia and arthralgia of both upper and lower extremities.

On admission the child was in no acute distress; his height and weight were at the 50th centile and vital signs were stable. Physical examination showed bilateral axillary and inguinal painful lymphadenopathy. The rest of his examination was unremarkable; in particular there was no other palpable lymph node nor significant hepatosplenomegaly (with liver and spleen at the costal margin).

Laboratory values showed an erythrocyte sedimentation rate (ESR) of 119 mm/hour, C reactive protein 10 mg/l, white cell count 27.8 $\times 10^9$/l, haemoglobin 113 g/l, and platelet count 359 $\times 10^9$/l. All other blood investigations performed were within normal limits, including transaminases, total proteins, creatine kinase, lactate dehydrogenase, complement levels, antinuclear antibodies, and a peripheral blood smear.

Serological tests and blood cultures excluded common viral and bacterial infections. Chest radiography, abdominal ultrasound, electrocardiography, and two dimensional echocardiography were normal. Bone marrow did not contain malignant or abnormal cells. A cervical lymph node biopsy specimen documented the presence of non-specific inflammatory changes.

After four weeks of high spiking fever unresponsive to antibiotics and paracetamol, a diagnosis of systemic JCA was presumed. A course of aspirin (80 mg/kg/day) was started and there was improvement in fever and musculoskeletal pain and a slight reduction in acute phase reactant concentrations. One month after discharge he was readmitted with high continuous fever and painful swelling of both elbows. Plain radiographs of the upper extremities were negative. Corticosteroids (prednisone 2 mg/kg/day) were added to aspirin. The only benefit observed was a reduction of elbow swelling. The patient worsened again, and was readmitted in poor general condition. He had lost weight, was pale, tachypnoeic, and complained of severe diffuse articular pain, without joint swelling. Physical examination revealed significant enlargement of cervical, axillary, and inguinal lymph nodes. Hepatosplenomegaly was noted with liver and spleen palpable 3 cm below the costal margin. Cardiac and pulmonary examination was normal. Laboratory investigations revealed an ESR of 46 mm/hour, white cell count 20.2 $\times 10^9$/l (neutrophils 66%, lymphocytes 31%, no blasts), haemoglobin 82 g/l, platelet count 101 $\times 10^9$/l, C reactive protein 8.2 mg/l. A second chest radiograph (two months after the first) revealed enlargement of the mediastinum. An abdominal ultrasound confirmed the presence of hepatosplenomegaly and generalised lymphadenopathy, most evident at the hepatic hilum. Chest and abdominal computed tomography showed enlarged lymph nodes at the aortic arch and peribronchial area.

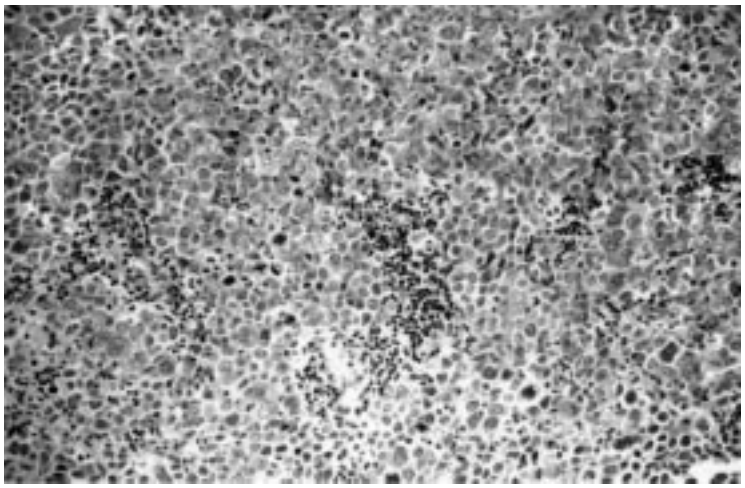

Figure 1 Anaplastic large cell lymphoma involving lymph node. The nodal architecture is destroyed. There is an intense proliferation of large cells with clear cytoplasm, and nuclei with prominent nucleoli. Among the large neoplastic cells there are scattered residual normal lymphocytes (haematoxylin and eosin stain).

A second bone marrow examination showed only myeloid hyperplasia. A second lymph node biopsy (supraclavicular) was then performed. Histological and immunohistochemical analysis was diagnostic of T cell anaplastic large cell lymphoma (Ki-1/CD30 positive) (fig 1).

The boy underwent chemotherapy and has been in remission since 1994.

CASE 2

A 10 year old white boy with an unremarkable medical history was admitted to the hospital because of a five month history of right knee swelling, a maculopapular and vesicular rash over the trunk, and generalised micropolyadenopathy. During the weeks before admission he also had a low grade fever. He had been admitted previously to two different hospitals, where presumptive diagnoses of Lyme arthritis and JCA were made. Two biopsies had been performed. A skin biopsy specimen revealed chronic lichenoid pityriasis, and a preauricular lymph node specimen showed non-specific chronic inflammation. The acute phase reactants had always been elevated. A radiograph of the right knee had shown an area of bone resorption in the lower extremity of the right femur.

Physical examination on admission to our hospital showed an enlarged left inguinal lymph node and a swollen right knee, which was tender, painful, and with restricted motion. On the medial aspect of the knee, a few erythematous infiltrated lesions were present. Scars were evident over the lower trunk from a previous papulovesicular rash. The rest of the examination was unremarkable; in particular liver and spleen were not palpable. Laboratory investigations revealed a haemoglobin of 100 g/l, white cell count 7.9×10^9/l (65% neutrophils), an ESR of 94 mm/hour, and C reactive protein 50 mg/l. Arthrocentesis yielded 50 ml of turbid yellow synovial fluid with a white cell count 49.0×10^9/l, and culture negative. A bone marrow examination was normal. Antibiotic treatment was started (first teicoplanin, then amikacin, then ceftriaxone) but because of persistence of fever and knee swelling, his knee joint was incised and drained. An oval osteolytic lesion 1×2 cm in diameter covered by greyish material was identified in the distal femur. The lesion was excised; it was culture negative for bacteria and mycobacteria. Histological examination was not performed. The patient was discharged on antibiotics with a diagnosis of septic arthritis and osteomyelitis.

During subsequent follow up visits no significant clinical or investigative abnormalities were found, except for persistent submandibular adenopathy.

Eighteen months after the first admission the patient presented with a left inguinal node 3×4 cm in diameter and an erythematous lesion (1.5×1 cm) on the overlying skin. High spiking fever (up to 40°C) was also present. All laboratory tests, including ESR and blood count, were normal. A lymph node biopsy specimen showed (fig 2) a T cell anaplastic large cell lymphoma. Immunohistochemistry was positive for Ki-1 antigen. The patient underwent chemotherapy for two years, and has been in total remission since 1992.

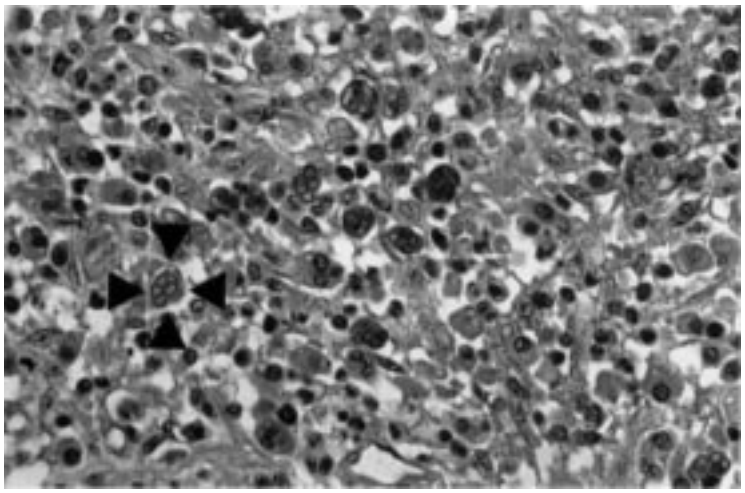

Figure 2 Lymph node biopsy: T cell anaplastic large cell lymphoma. Pronounced cell polymorphism, with a component of reactive erythrophagocytic histiocytes (see arrowheads) (haematoxylin and eosin stain).

CASE 3

A 6 year old white boy presented with an erythematous macular rash on his face and limbs, which was transient and pruritic. He complained of diffuse joint pains and had arthritis of the right ankle. After admission he developed persistent high fever (up to 40–41 °C) with concomitant rash and skin desquamation of his hands and feet. Investigations included an ESR of 90 mm/hour, white cell count 20.6×10^9/l, and a platelet count of 515×10^9/l. Autoantibodies were negative. A presumptive diagnosis of Kawasaki disease was made and he was treated with intravenous immune globulins and aspirin. Because of the persistence of his symptoms, together with the appearance of inguinal adenopathy and mild hepatosplenomegaly, a diagnosis of systemic JCA was made and corticosteroid treatment was started. After initial improvement, the disease relapsed during an attempt to withdraw

corticosteroids. Prednisone was resumed at high dose (2 mg/kg/day) and non-steroidal anti-inflammatory drugs were added. On referral we found normal cardiac and abdominal ultrasound and laboratory screen for autoimmune diseases. The cutaneous rash and ankle arthritis wer still present. Antinuclear antibodies were slightly positive (1:40) and inflammatory reactants were high (ESR 75 mm/hour, C reactive protein 51 mg/l). The patient followed a waxing and waning course on steroid treatment, but after six months (almost one year from onset of symptoms) he deteriorated with fever, axillary, inguinal, and cervical adenopathy (2 × 2 cm inguinal), hepatosplenomegaly, and polyarthritis (right ankle, left knee, right wrist, left elbow, cervical spine). Plain films, chest radiographs, and a bone scan were all within normal limits. Laboratory investigations showed severe anaemia (haemoglobin 60 g/l) and raised acute phase reactants (ESR 131 mm/hour, C reactive protein 141 mg/l, white cell count 12.9×10^9/l). Lactate dehydrogenase levels were raised (1675 U/l). Bone marrow biopsy was normal. A lymph node biopsy specimen (right supraclavicular and axillary) showed polymorph lymphoid proliferation mainly of T cell type and epithelioid venular component. Final diagnosis was angioimmunoblastic T cell lymphoma. The patient was started on chemotherapy, but despite aggressive treatment the disease process continues to worsen.

Discussion

Leukaemia, and more rarely other tumours such as lymphoma, may present with musculoskeletal manifestations[3–6]; however, true articular signs such as joint swelling are less frequent, and have been reported only rarely at the onset of NHL.[7–10] Our report describes two children with Ki-l positive large cell anaplastic lymphoma and one with angioimmunoblastic T cell lymphoma who presented with a major complaint of either joint pain or swelling.

Ki-1, a member of the nerve growth factor receptor superfamily, is a monoclonal antibody (produced by Schwab *et al* in 1982) which reacts against Hodgkin and Sternberg-Reed cells.[11] Ki-l (CD30) positive anaplastic large cell lymphoma (ALCL) is a recently described nosological entity[12–19] that accounts for about 10% of paediatric NHL and principally involves lymph nodes (80% of cases). Malignant cells have the propensity to invade lymphoid sinuses and biopsy specimens frequently show a histiocytic proliferation. Clinical information on Ki-1 ALCL is limited but the disease occurs in children and young adults. Adenopathy is the main clinical feature and extranodal disease is mainly confined to the skin. Bone involvement has been reported in 20% of cases, but rarely if ever with concurrent joint swelling. Immunophenotype is mainly T cell (60–70%); a high number of reactive macrophages with a lymphohistiocytic appearance and erythrophagocytosis is sometimes seen. The prognosis appears quite favourable, especially in children; the disease is very sensitive to chemotherapy with our two patients in remission two and four years after completion of treatment.

The final diagnosis was delayed, in one case as long as two years. The unusual manifestations account for this delay, but even in more typical cases a delay can occur because of the indolent course of the disease. However, some features were not consistent with the first presumptive diagnoses. In particular, spiking fever without rash, and arthritis in joints such as elbows, make a diagnosis of systemic JCA unlikely. On the other hand, prominent lymphadenopathy is a common feature of systemic JCA, even with a histological appearance that can mimic malignancy.

Angioimmunoblastic T cell lymphoma is a lymphoproliferative disorder with clinical features that include generalised lymphadenopathy, hepatosplenomegaly, skin rash, and constitutional symptoms such as fever and weight loss. Histology usually shows effaced lymph node architecture and peripheral sinuses are typically open and even dilated. There is a characteristic proliferation or arborisation of venules. This entity, previously thought to be an abnormal immune reaction (angioimmunoblastic lymphadenopathy with dysproteinaemia), is now generally accepted as a T cell lymphoma[20] ; most cases show clonal rearrangements of T cell receptor genes. Despite treatment the prognosis is usually poor. Articular involvement in angioimmunoblastic T cell lymphoma is rare, with polyarthritis described only in a few adult patients.[21 22]

We emphasise that malignancies should always be ruled out in patients with unexplained arthritis, especially if the joint pattern is not characteristic of the presumptive diagnosis, if pain is out of proportion to the objective findings, or if there are other associated unusual manifestations. Ostrov *et al* reported that there are few early clinical signs or symptoms to differentiate systemic JCA from leukaemia.[23] Articular examination findings provided the most helpful clues to diagnosis, while haematological abnormalities were often absent for a prolonged period. Other authors[1] have also reported that arthritis can precede haematological abnormalities by several months. If possible, corticosteroids should not be administered before a definite diagnosis is made, as they may induce temporary improvement in symptoms but negatively affect the prognosis of malignancy.

The presence of joint swelling in leukaemia is more frequent in children than in adults, and in acute rather than in chronic forms. Proposed pathogenetic mechanisms[3] include: infiltration of leukaemic cells into bone or synovial tissue, haemorrhage into the joints secondary to thrombocytopenia, joint infection, gouty arthritis, synovial reaction to periosteal or capsular infiltration, and immune complex induced synovitis. Arthritis as a presenting feature of lymphoproliferative disorders can be due to direct synovial involvement or to a reaction to an adjacent process (as probably occurred in case 2).

Synovial immunocytology was not performed in our patients; however the few studies on synovial fluids in leukaemia/lymphoma and arthritis have shown variable leucocyte counts and cytologic characteristics, with questionable results in terms of specificity and sensitivity.[24] In conclusion, malignancy (leukaemia but also lymphoma) must be suspected in every child with arthritis and unusual characteristics before assuming a diagnosis of JCA. Studying subsequent cases with modern immunocytology techniques will be helpful to clarify and elucidate the exact pathogenetic mechanisms of joint swelling.

1 Jonsson OG, Sartain P, Ducore JM, Buchanan GR. Bone pain as an initial symptom of childhood lymphoblastic leukaemia: association with nearly normal hematologic indexes. *J Pediatr* 1990;**117**:233–7.
2 Emkey RD, Ragsdale BD, Ropes MW, Miller W. A case of lymphoproliferative disease presenting as juvenile rheumatoid arthritis. Diagnosis by synovial fluid examination. *Am J Med* 1973;**54**:825–8.
3 Evans Tl, Nercessian BM, Sanders KM. Leukemic arthritis. *Semin Arthritis Rheum* 1994;**24**:48–56.
4 Costello PB, Brecher ML, Starr Jl, Freman Al, Green FA. A prospective analysis of the frequency, course, and possible prognostic significance of the joint manifestations of childhood leukemia. *J Rheumatol* 1983;**10**:753–7.
5 Schaller J. Arthritis as a presenting manifestation of malignancy in children. *J Pediatr* 1972;**81**:793–7.
6 Fink CW, Windmiller J, Sartain P. Arthritis as the presenting feature of childhood leukemia. *Arthritis Rheum* 1972;**15**: 347–9.
7 Ueno Y, Manabe T, Shimizu S. Non-Hodgkin's lymphoma and polyarthritis. *Br J Rheumatol* 1995;**34**:293–7.
8 McDonagh JE, Clarke F, Smith SR, Kesteven P, Walker DJ. Non-Hodgkin's lymphoma presenting as polyarthritis. *Br J Rheumatol* 1994;**33**:79–84.
9 Menon N, Madhok R. Symmetrical polyarthritis is not always rheumatoid. *Ann Rheum Dis* 1994;**53**:631–2.
10 Seleznick MJ, Aguilar JL, Rayhack J, Fenske N, Espinoza LR. Polyarthritis associated with cutaneous T cell lymphoma. *J Rheumatol* 1989;**16**:1379–82.
11 Schwab U, Stein H, Gerdes J, *et al*. Production of a monoclonal antibody specific for Hodgkin and Sternberg-Reed cells of Hodgkin's disease and a subset of normal lymphoid cells. *Nature* 1982;**299**:65–7.
12 Schmidt D. Monocyte/macrophage system and malignancies. *Med Pediatr Oncol* 1994;**23**:444–51.
13 Pileri S, Bocchia M, Baroni CD, *et al*. Anaplastic large cell lymphoma (CD30+/Ki-1+): results of a prospective clinico-pathological study of 69 cases. *Br J Haematol* 1994; **86**:513–23.
14 Greer JP, Kinney MC, Collins RD, *et al*. Clinical features of 31 patients with Ki-1 anaplastic large-cell lymphoma. *J Clin Oncol* 1991;**9**:539–47.
15 Kadin ME. Primary Ki-l-positive anaplastic large-cell lymphoma: a distinct clinicopathologic entity. *Ann Oncol* 1994;**5**(suppl 1):25–30.
16 Kadin ME. Ki-1-positive anaplastic large-cell lymphoma: a clinicopathologic entity? *J Clin Oncol* 1991;**9**:533–6.
17 Kadin ME. Ki-l/CD30+ (anaplastic) large-cell lymphoma: maturation of a clinicopathologic entity with prospects of effective therapy. *J Clin Oncol* 1994;**12**:884–7.
18 Reiter A, Schrappe M, Tiemann M, *et al*. Successful treatment strategy or K-1 anaplastic large-cell lymphoma of childhood: a prospective analysis of 62 patients enrolled in three consecutive Berlin-Frankfurt-Munster group studies. *J Clin Oncol* 1994;**12**:899–908.
19 Sandlund JT, Pui CH, Santana VM, *et al*. Clinical features and treatment outcome for children with CD30+ large-cell non-Hodgkin's lymphoma. *J Clin Oncol* 1994;**12**:895–8.
20 Harris NL, Jaffe ES, Stein H, *et al*. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994;**84**1361–92.
21 Boumpas DT, Wheby MS, Jaffe ES, Steinberg AD, Klippel JH, Balow JE. Synovitis in angioimmunoblastic lymphadenopathy with dysproteinemia simulating rheumatoid arthritis. *Arthritis Rheum* 1990;**33**:578–82.
22 Minguez C, Olmedo J, Perez EV, Simon E. A new case of polyarthritis as a presenting sign of non-Hodgkin's lymphoma [letter]. *Br J Rheumatol* 1995;**34**:794–5.
23 Ostrov BE, Goldsmith DP, Athreya BH. Differentiation of systemic juvenile rheumatoid arthritis from acute leukemia near the onset of disease. *J Pediatr* 1993;**122**:595–8.
24 Fam AG, Voorneveld C, Robinson JB, Sheridan BL. Synovial fluid immunocytology in the diagnosis of leukemic synovitis. *J Rheumatol* 1991;**18**:292–6.