Childhood acute lymphoblastic leukaemia masquerading as primary skeletal problem

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Abstract

Acute lymphoblastic leukaemia (ALL) usually presents with signs of bone marrow failure. Occasionally ALL in children may present with non-specific or misleading clinical features. In a retrospect analysis of 25 consecutive cases of childhood ALL, we identified three children who were initially managed and discharged as acute osteomyelitis, juvenile chronic arthritis and post-infectious arthralgia respectively. They had mild normochromic, normocytic anaemia and two had transient leucopenia. Their platelet counts were normal and none had circulating blasts. The severity of their skeletal symptoms was out of proportion to the clinical and radiological finding. They failed to respond to the initial management and diagnosis was delayed for an average of 42 days and eventually confirmed on the marrow aspirate. Complete remission was attained in all cases with standard chemotherapy and had been maintained for an average of 29 months. ALL should be considered as a differential diagnosis in children complaining of multiple or persistent joint pains, especially in the presence of atypical clinical features or poor response to treatment.

Keywords: Acute lymphoblastic leukaemia; Children; Skeletal complication

Introduction

Acute lymphoblastic leukaemia (ALL) is the commonest childhood malignancy both in Hong Kong[1] and elsewhere.[2] It represents 30% of all children undergoing cancer treatment in the Department of Paediatrics, Queen Mary Hospital, between 1986 and 1992. The typical child presents with signs and symptoms of pancytopenia such as bleeding, anaemia and infectious manifestations.[3] Atypical presentation, such as orthopaedic or rheumatoid features, is not uncommon and could be mistaken as the primary diagnosis.[4] The presence of a normal or near-normal blood count, with or without anti-nuclear factor (ANF), could further complicate the diagnosis.[5] A retrospective analysis is undertaken to assess the local prevalence of this presentation and identify factors which could prompt to the correct diagnosis.

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Materials and methods

All children under the age of 12 years presented to the Children Haematology and Oncology Service (CHAOS), Department of Paediatrics, Queen Mary Hospital, with a diagnosis of ALL between January 1989 and December 1992 were included for study. Patients were noted for their first diagnosis upon discharge, as well as their demographic data, haematological and biochemical findings, leukaemic cytoimmunohistochemical analysis, and treatment outcomes.

Patients first discharged with a diagnosis other than ALL after complete physical examination and a minimal investigations of complete blood counts with differentials, blood biochemistry and relevant radiological investigations, were studied in detail (the study cases). Follow-up and survival are calculated from

the date of diagnosis to 31 December 1993 or to the date of death where appropriate. Relapse-free survival is calculated from the date of first complete remission to the date of relapse, date of death or 31 December 1993, whichever is earlier. Study cases are compared with other cases diagnosed in the same period of study in terms of age at diagnosis, follow-up and haematological indices at the time of diagnosis. The two sample Student's t test using the Instat™ (GraphPad™, San Diego, U.S.A.) is applied where appropriate.

Results

A total of 26 cases of ALL were diagnosed during the study period. These include 25 Chinese children and one Caucasian boy. One child with Burkitt's leukaemia was excluded from further analysis as the disease is clinically distinct and requires different management. The mean age of the remaining 25 patients was 4.9 years (range 0.4 to 11.7) and the male:female ratio was 2.6 (18 boys:7 girls). Children were treated with a modified protocol from the American Children Cancer Study Group[6] before 1991, while others diagnosed in and after 1991 were treated with the United Kingdom Acute Lymphoblastic Leukaemia protocol.[7] Two patients were further excluded for analysis of survival because of transferral and repatriation to other centres for treatment. Twenty (87%) were surviving of which 18 (78%) remained in the first complete remission for a mean duration of 30 months (range 16 to 57 months). Five patients relapsed and three died at 14, 16, and 36 months respectively after diagnosis, including one patient with infantile ALL and one with Philadelphia-chromosome positive ALL.

Twenty-two cases had a straight forward diagnosis of ALL with manifestations of pancytopenia and organomegaly soon after admission. Three patients (12.0%), however, were initially managed differently upon the first discharge. They were treated as acute osteomyelitis, juvenile chronic arthritis and post-infectious arthralgia respectively. Despite the absence of circulating blasts, the diagnosis of ALL was made with bone marrow aspirations. With appropriate chemotherapy, they all remained in the first complete remission for 20, 24 and 42 months respectively. Compared with other children, they were similar in terms of age and duration of follow-up. A significantly higher presenting haemoglobin level and platelet count was evident, and a tendency towards a low and normal leucocyte count was also seen (Table 1). The case histories of these three patients are as follows and their relevant laboratory findings were listed in Table 2.

Case 1

A five-year-old boy complained of backache and left hip pain and refused to walk. There was no history of trauma. He had a fever of 39.4°C but no obvious focus of infection. There was no lymphadenopathy or hepatosplenomegaly. The left hip was held in abduction and external rotation while adduction and internal rotation was limited by pain. Examination of the back was normal. Initial investigations showed a mild normochromic, normocytic anaemia (haemoglobin 10.2 g/dl) and a white cell count of 2.2×10^9/l. The erythrocyte sedimentation rate (ESR) was 60 mm in the first hour. Blood biochemistries were normal and repeated blood cultures were negative. On plain radiograph, the spine and the pelvic bones were normal. There was a small lucency seen in the proximal metaphysis of the left femur. ^{99}Tc-bone scan, however, showed an increased uptake over the left hip joint but not the metaphysis. Bone marrow aspiration from the posterior iliac crest revealed normal haemopoiesis without malignant infiltration.

The child was therefore managed as a case of acute osteomyelitis with a combination of ampicillin, cloxacillin and fusidic acid for a duration of six weeks. The temperature subsided but the child still complained of intermittent left hip pain. A repeat bone scan after completion of antibiotic treatment showed normal uptake in the left hip region. There was, however, an increased uptake in the left 11th rib. Repeat blood

Table 1. A comparison of the haematological indices between the study and other cases

	Study cases (n=3) Mean ± SD	Other cases (n=22) Mean ± SD	p value
Age (years)	4.0 ± 0.7	5.0 ± 3.2	NS
Follow-up (months)	30 ± 9	31 ± 14*	NS
Haemoglobin (g/dl)	10.0 ± 0.5	7.4 ± 1.6	0.01
White cell count ($x10^9$/l)	4.6 ± 1.2	48.9 ± 66.2	NS
Platelet count ($x10^9$/l)	243 ± 61	75 ± 69	0.0006

* Excluding 2 children who have been transferred to other centres.
NS = Non significant

Table 2. The clinical and laboratory features of the three study cases

	Case 1		Case 2		Case 3	
Sex/Age	M/5		F/3		M/4	
Clinical joint involvemen	Left hip Lumbar spine		Right shoulder Cervical spine Elbows, knees		Left knee	
Initial diagnosis	Osteomyelitis		Juvenile chronic arthritis		Post-infection arthralgia	
Day of investigation*	−50	0	−45	0	−14	0
Hgb (g/dl)	10.2	10.3	10.2	10.6	9.0	9.6
WCC (x 10^9/l)	2.2	4.0	6.8	6.0	3.6	4.05
— neutrophils	0.72	1.08	2.79	2.22	1.91	2.38
— lymphocytese	1.41	2.80	3.88	3.00	1.58	1.38
Platelets (x 10^9/l)	413	295	446	198	285	365
ESR (mm/hour)	60	135	ND	127	66	95
Calcium (mmol/l)		2.45		2.52		2.44
PO_4 (mmol/l)		1.50		1.76		1.73
ALP (u/l)		164		172		140
ALT (u/l)		42		46		7
Bilirubin (μmol/l)		16		7		4
LDH (u/l)		472		702		473
Antinuclear factor	−	ND	−	−	+	ND
RF	−	ND	−	−	−	ND

* Day 0 denotes the day of diagnostic bone marrow examination.

Abbreviations: ALT = alanine transferase; ALP = alkaline phosphatase; ESR = erythrocyte sedimentation rate; Hgb = haemoglobin; LDH = lactate dehydrogenase; ND = not done; PO_4 = phosphate; RF = rheumatoid factor; WCC = white cell count; + = positive; − = negative.

counts and biochemistries showed essentially the same findings as before. Bone marrow aspiration was repeated nine weeks after initial presentation, which confirmed the diagnosis of common ALL.

Case 2

A three-year-old girl complained of fever and right shoulder and neck pain limiting movements for one week. A viral respiratory illness was diagnosed by her family doctor and symptomatic treatment resulted in subsidence of temperature but not the joint pains. Clinical examination and plain radiographs of the cervical spine and right shoulder joint, however, were normal. Investigations showed only a mild normochromic, normocytic anaemia (haemoglobin 10.2 g/dl) while other haematological and biochemical tests were normal. Her symptoms waxed and waned for another five weeks and the elbows and knees became involved before she was re-admitted with a fever of 38.5°C. Examination then found a miserable child with an enlarged liver of 3 cm below the costal margin. Repeat serological markers, blood counts and biochemistries, and X-rays were normal. The ESR was 127 mm/hour. She was put on aspirin with a provisional diagnosis of juvenile chronic arthritis (JCA), but no response was seen after the first week of treatment. A bone marrow aspiration performed six weeks after initial presentation confirmed the diagnosis of common ALL.

Case 3

A four-year-old boy complained of on and off fever-associated left knee pain for a duration of one month. A mild pharyngitis was found and the rest of the clinical examination including joints were normal. Initial investigation showed only a mild normochromic, normocytic anaemia of haemoglobin 9.0 g/dl. The ESR was 66 mm/hour and the ANF was positive at 1:40. The anti-DNA antibody and rheumatoid factor were negative. The fever and joint symptoms responded to oral penicillin therapy and the child was discharged with a diagnosis of post-infectious arthralgia. However, he was re-admitted ten days later with resurgence of symptoms and fever. Blood

counts and biochemistries remained essentially the same. X-ray of the left knee remained normal but a skeletal survey showed a suspicious osteolytic lesion over the right femoral head. A bone marrow aspiration was performed which revealed a diagnosis of common ALL two weeks after the initial presentation.

Discussion

Acute lymphoblastic leukaemia in children is now a curable disease, with a long term remission rate approaching 70%.[3] Although the majority of childhood ALL present with signs and symptoms of pancytopenia, an occasional child may complain of atypical features. Skeletal complaints are common at diagnosis, but could be the sole or predominant clinical feature occasionally.[8] Where patients present with a normal or near-normal blood count without detectable circulating blasts, the diagnosis could be mistaken as a primary skeletal problem.[9] Positive serological test to ANF, as in Case 3, could add further confusion.[5] Several clinical and laboratory features may lend clues to the underlying diagnosis.

ALL and juvenile chronic arthritis share a number of common clinical features, such as fever, joint pains, and signs of organomegaly.[10] The pattern of joint involvement tends to be pauci-articular and affects the lower limbs more often in ALL.[11,12] Children with ALL often have symptoms that are out of proportion to the clinical findings.[9] In this series, we also noted that the radiological features did not correspond to the clinical features, such as the finding of a normal X-ray (Cases 2 and 3), or the presence of a lesion distant to the clinically involved site (Cases 1 and 3). Raised ESR could be found in leukaemia, JCA and skeletal infections. The presence of a high ESR, however, should alert the possibility of leukaemia when the skeletal X-rays are normal.[13]

Haematological findings could be deceptive as illustrated by our three cases. Normochromic, normocytic anaemia is fairly non-specific and could be present in any children with chronic illness or infections. It has been noted that children with JCA rarely become leukopenic or thrombocytopenic.[9] A vigorous search for circulating blast should be attempted in each case, but it is absent in up to one-third of such cases.[5] Bone marrow aspiration may have to be repeated before the diagnosis becomes apparent[12] as in Case 1.

Children with multiple or persistent bone or joint pains should be followed up for at least five months.[9] The emergence of atypical features or failure of responding to standard treatment should prompt the search for an underlying malignancy. It is important for clinician dealing with such children not to institute steroid treatment empirically. Steroid therapy not only blurs the distinction between ALL and rheumatoid disorders, but also makes subsequent laboratory investigations difficult. Children with ALL often respond partially to steroid treatment alone, but subsequent relapse is inevitable with a much worse prognosis.[14]

Finally, it is interesting to see that, provided these children are managed with the appropriate anti-leukaemic treatment, their prognosis is comparable to other leukaemic children despite the initial delay in diagnosis as illustrated in our cases. Common ALL appears to be the phenotype associated with such presentation but the available literature does not contain enough studied cases to confirm the association.

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References

1 Hospital Authority. Hong Kong Cancer Registry: 1989 annual statistical report. Hong Kong: Government Printer, 1993: 25–8.
2. Riehm H, Feickert HJ, Lampert F. Acute lymphoblastic leukaemia. In: Voute PA, Barrett A, Bloom HJG, Lemerle J, Neidhardt MK, eds. Cancer in children. Berlin: Springer-Verlag, 1986: 101–8.
3. Poplack DG. Acute lymphoblastic leukemia. In: Pizzo PA, Poplack DG, eds. Principles and practice of pediatric oncology. Philadelphia: Lippincott, 1989: 323–66.
4. Spilberg I, Meyer GJ. The arthritis of leukemia. Arthritis Rheum 1972; 15: 630–5.
5. Jonsson OG, Sartain P, Ducore JM, Buchanan GR. Bone pain as an initial symptom of childhood acute lymphoblastic leukemia: association with nearly normal hematologic indexes. J Pediatr 1990; 117: 233–7.
6. Gaynon PS, Bleyer WA, Steinherz PG, et al. Modified BFM therapy for children with previously untreated acute lymphoblastic leukemia and unfavorable prognostic features. Report of Children's Cancer Study Group Study CCG-193P. Am J Pediatr Hematol Oncol 1988; 10: 42–50.
7. Medical Research Council Working Party on Leukaemia in Children. Acute lymphoblastic leukaemia trial UKALL XI children. United Kingdom: Medical Research Council, 1990.
8. Gallagher D, Heinrich SD, Craver R, Ward K, Warrier R. Skeletal manifestations of acute lymphoblastic leukemia in childhood. Orthopedics 1991; 14: 485–92.

9. Ostrov BE, Goldsmith DP, Athreya BH. Differentiation of systemic juvenile rheumatoid arthritis from acute lymphoblastic leukemia near the onset of disease. J Pediatr 1993; 122: 595–8.
10. Musiej-Nowakowska, Rostroposicz-Denisiewicz K. Differential diagnosis of neoplastic and rheumatic diseases in children. Scand J Rheumatol 1986; 15: 124–8.
11. Costello PB, Brecher ML, Starr JI, Freeman AI, 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.
12. Silverstein MN, Kelly PJ. Leukemia with osteoarticular symptoms and signs. Ann Intern Med 1963; 59: 637–45.
13. Schaller J. Arthritis as a presenting manifestation of malignancy in children. J Pediatr 1972; 81: 793–7.
14. Revesz T, Kardos G, Kajtar P, Schuller D. The adverse effect of prolonged prednisolone pretreatment in children with acute lymphoblastic leukemia. Cancer 1985; 55: 1637–40.