Musculoskeletal manifestations in children with acute lymphoblastic leukaemia

H. Mulder, N. Herregods, V. Mondelaers, Y. Benoit, B. De Moerloose

Acute lymphoblastic leukaemia (ALL) is the most common kind of childhood malignancy. Although the vast majority of patients are presented with medullary signs and symptoms such as an abnormal blood count, about one third will initially be presented with musculoskeletal complaints (with or without radiological abnormalities) as the only apparent abnormality. These skeletal manifestations in ALL are not pathognomonic and may mimic several orthopaedic conditions, such as juvenile rheumatoid arthritis, osteomyelitis, septic arthritis and transient synovitis. This may therefore contribute to a delay in diagnosis, resulting in higher morbidity and mortality rates. However, musculoskeletal manifestations in leukaemia are usually associated with a precursor-B-ALL and have a good prognosis.

The purpose of this review is to highlight the diagnostic pitfalls in this type of ALL. ALL should always be considered as a differential diagnosis in any child with unexplained or persistent bone pain and a bone marrow examination is highly recommended when steroid therapy is being considered.

(Belg J Hematol 2012;3:3-11)

Introduction

Leukaemia is the most common childhood malignancy accounting for 30-40% of all malignancies. Acute lymphoblastic leukaemia (ALL) is the most common subtype with a frequency up to 85% and a peak incidence at age 2-6 years.[1] Leukaemias are heterogeneous in clinical presentation and course. Due to excessive clonal proliferation of leukaemic blasts and their impaired differentiation, normal haematopoiesis is disrupted and results in bone marrow failure. Hence, patients characteristically are presented with signs and symptoms such as pallor, fever, anorexia, lethargy, lymphadenopathy, organomegaly and variable haematological abnormalities (anaemia, thrombocytopenia, leukopaenia/leukocytosis and circulating blasts). Moreover, a third of paediatric patients with ALL initially are presented with complaints associated with the musculoskeletal system.[2,3] Sometimes these manifestations are the only symptoms at presentation and therefore may mask ALL when peripheral blood changes are subtle or even absent. In the literature, several reports can be found in which musculoskeletal manifestations (MSM) and near normal haematological variables are associated with immunophenotypes consistent with precursor-B-ALL.[2,4-11]

Localised or diffuse bone pain, limping, arthritis, myalgia and failing to use an extremity are the most

Authors: H. Mulder[1], N. Herregods[2], V. Mondelaers1, Y. Benoit[1] and B. De Moerloose.[1] [1]Department of Paediatric Haematology-Oncology and Stem Cell Transplantation, Ghent University Hospital, Ghent, [2]Department of Radiology, Ghent University Hospital, Ghent

Please send all correspondence to: B. De Moerloose, Department of Paediatric Haematology-Oncology and Stem Cell Transplantation, Ghent University Hospital, 3K12D, De Pintelaan 185, 9000 Ghent, Belgium; tel: 0032 933 26417, email: barbara.demoerloose@uzgent.be.

Conflict of interest: The authors have nothing to disclose and indicate no potential conflicts of interest.

Key words: acute lymphoblastic leukaemia, musculoskeletal manifestation, bone pain.

Table 1. Haematological parameters at first presentation.

	Hemoglobin (g/dL)	WBC (10^9/L)	Differential WBC	Platelets (10^9/L)	LDH (U/L)	ESR (mm/u)
Case 1	10,8	6,42	nF: 61% Ly: 33% Mo: 5% Eo: 1%	371	ND	60
Case 2	9,8	4,13	ND	221	325	80

WBC: white blood cell count; LDH: lactate dehydrogenase; ERS: erythrocyte sedimentation rate; nF: neutrophils; Ly: lymphocytes; Mo: monocytes: Eo: eosinophils; ND: not determined.

Table 2. Haematological parameters at ALL diagnosis.

	Hemoglobin (g/dL)	WBC (10^9/L)	Differential WBC	Platelets (10^9/L)	LDH (U/L)	ESR (mm/u)
Case 1	8,5	6,22	nF: 53% Ly: 42% Mo: 4% IG: 1%	245	539	116
Case 2	2,7	1,31	nF: 6% Ly: 89% Mo: 5%	25	344	ND

WBC: white blood cell count; LDH: lactate dehydrogenase; ERS: erythrocyte sedimentation rate; nF: neutrophils; Ly: lymphocytes; Mo: monocytes; IG: immature granulocytes; ND: not determined.

common MSM.[9] Based solely on MSM, diagnosing ALL can be difficult since the bone and joint complications often mimic orthopaedic conditions such as osteomyelitis, transient synovitis, septic arthritis and juvenile rheumatoid arthritis (JRA). Consequently, correct diagnosis and proper management are often delayed. Radiographic abnormalities are usually, but not always, found in children with MSM. These radiographic abnormalities can also be present without any musculoskeletal complaint. Moreover, the degree of skeletal pain does not always correlate with the degree of radiological anomaly.[3,12]

Two ALL patients presenting with musculoskeletal complaints, subtle changes in initial blood counts and who both had a substantial delay in diagnosis will be described. We will review MSM and possible radiological abnormalities in children with ALL to highlight the diagnostic pitfalls.

Case 1

Over a period of three months, a 6-year old girl regularly complained of lower back pain with increasing intensity. She developed a fever and pyelonephritis was diagnosed. Intravenous antibiotics were started. The lower back pain subsided for a few days but reappeared as excruciating nocturnal pain, refractory to acetaminophen and non-steroidal anti-inflammatory drugs (NSAID). A physical examination revealed no abnormalities except for tenderness in the back. Blood count tests revealed mild anaemia (*Table 1*), signs of inflammation with a C-reactive protein level of 6,8 mg/dL (N <0,5 mg/dL) and an erythrocyte sedimentation rate of 60 mm after one hour. Plain X-rays were normal, but multifocal lumbar laesions were detected on bone scintigraphy. A tentative diagnosis of osteomyelitis was made. Although multiple doses of intravenous antibiotics and opioid analgesics were administered, the lower back pain persisted. Magnetic resonance imaging (MRI) of the spine revealed extensive multifocal laesions in the thoracolumbar region and in the sacroiliac joint (*Figure 1*). These radiographic findings and the intensity of the pain, which was unresponsive to antibiotic therapy and analgesics, prompted a bone marrow examination, which revealed 34% lymphoblasts on microscopic evaluation with a precursor-B immunophenotype and the TEL/AML1 fusion transcript on molecular analysis. Induction chemotherapy according to the contemporary European Organization for Research and Treatment of Cancer – Children Leukaemia Group (EORTC-CLG) protocol was initiated and the pain resolved instantaneously. The patient is presently in complete remission.

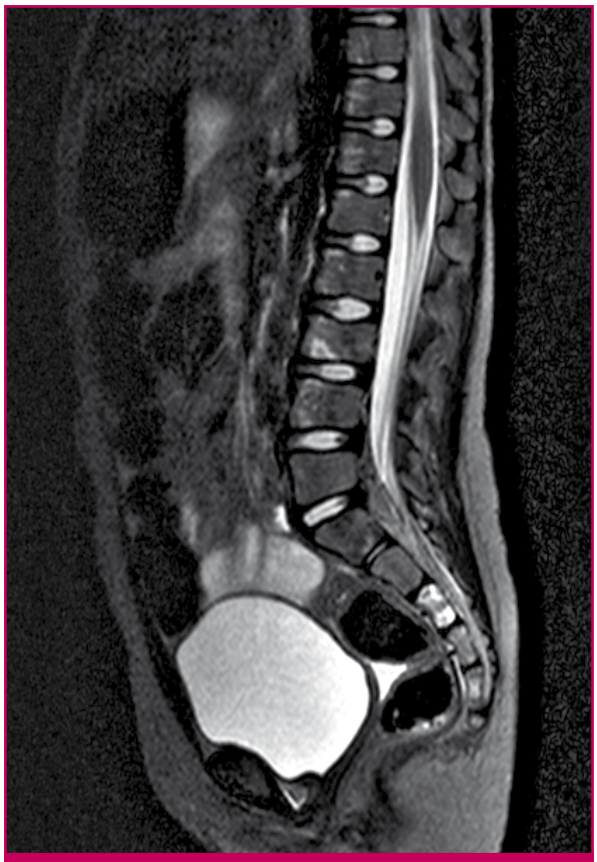

Figure 1. MRI of the spine showing multiple laesions involving vertebrae Th9, Th12, L1, L3, S2 and S3, without cortical destruction or involvement of the spinal canal.

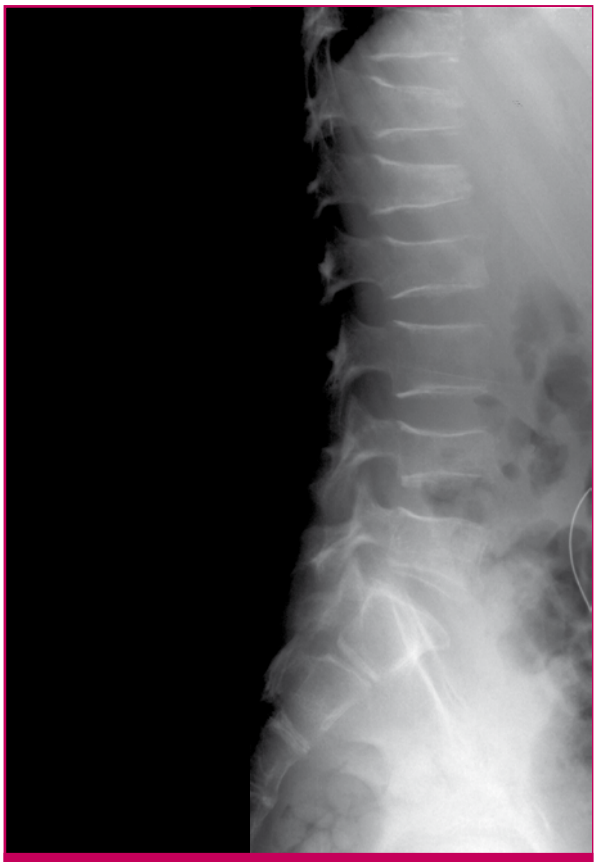

Figure 2. X-ray of the spine showing diffuse osteopaenia and several compression fractures (appearing as wedge deformities) of the vertebral bodies D10, L1-4.

Case 2

A 10-year old girl was presented initially with abdominal pain. Physical and ultrasound examination of the abdomen were normal. Psychological assistance was initiated because of familial problems. Three months later, the patient also began to complain of muscle weakness and pain in the back and extremities. In the ensuing two months this led to the patient refusing to walk. Physical examination showed a thin girl, who was bent forwards and refused, or was unable, to stand upright but without any other apparent physical abnormality. Blood count tests revealed a mild anaemia (*Table 1*) and subtle inflammatory signs: an erythrocyte sedimentation rate of 80 mm after 1 hour and an elevated C-reactive protein of 2,0 mg/dL (N <0,5 mg /dL). Anti-nuclear antibodies were slightly positive (+) and an MRI of the lower extremities showed an inflammatory focus of the periosteum of the right fibula. A tentative diagnosis of juvenile rheumatoid disease was made and treatment was commenced with an NSAID.

The pain subsided somewhat, but the patient had several febrile episodes. Almost two months after the initial blood examination, she was admitted to the hospital with a high-grade fever, anorexia, weight loss (6 kg in 5 months), extreme pallor and lethargy. There were no palpable peripheral lymph nodes or hepatosplenomegaly. Blood examination showed extreme anaemia, leukopaenia and thrombocytopaenia. (*Table 2*) A bone marrow examination revealed ALL with 95% lymphoblasts on microscopic evaluation with a precursor-B immunophenotype.

X-ray examination revealed diffuse, extensive osteopaenia and compression fractures involving several thoracolumbar vertebral bodies (*Figure 2*). Induction chemotherapy according to the contemporary EORTC-CLG protocol was initiated, resulting in complete remission. The patient remained bedridden for several weeks and needed a corset, intensive

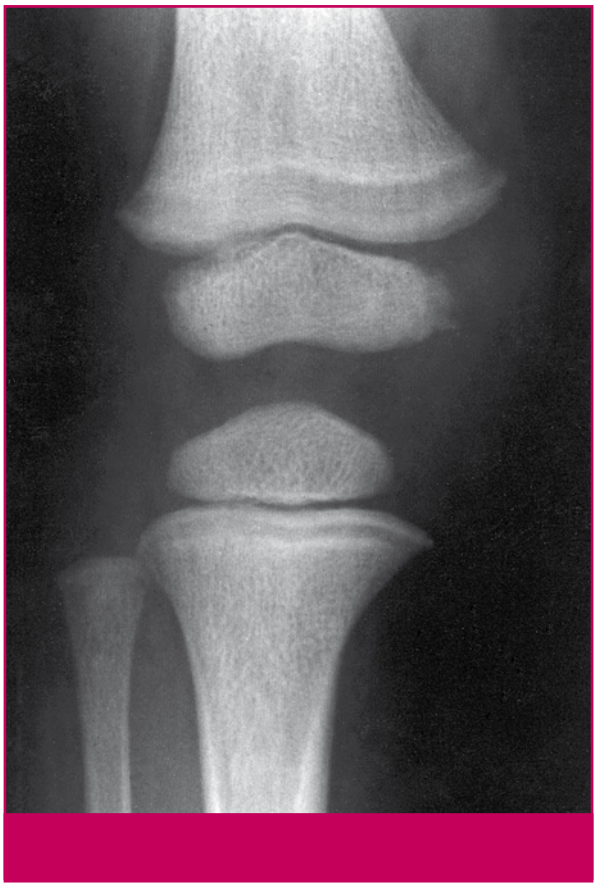

Figure 3. X-ray of the knee of a 20 month old child with ALL showing metaphyseal radiolucent bands (leukaemic lines), a sclerotic metaphyseal band at the distal metaphysic and cortical erosion.

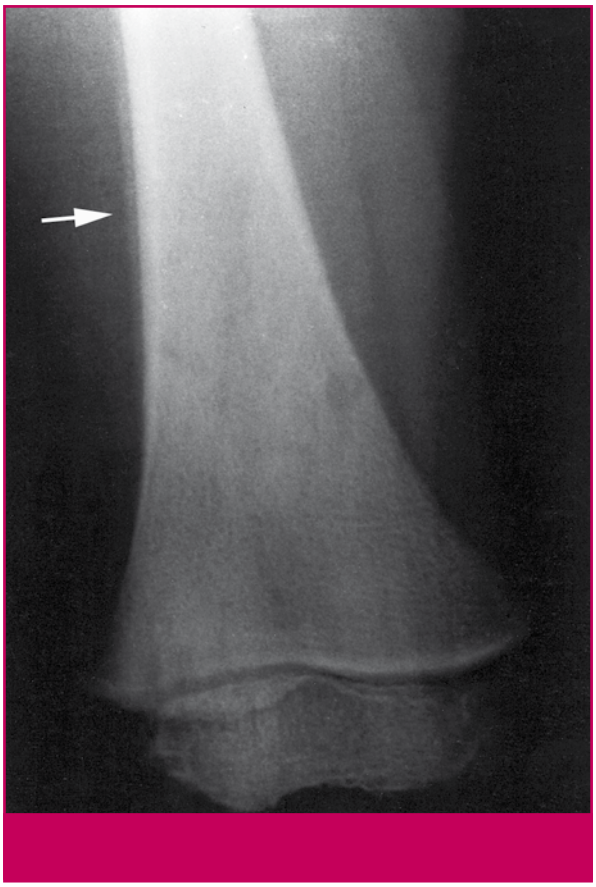

Figure 4. X-ray of the knee of a 4 year old child with ALL showing periosteal new bone formation in the femur, a single diaphyseal lytic bone laesion and osteoporosis.

revalidation and opioid analgaesics for a prolonged period of time. The patient is still in complete remission 4 years later. Calcium and Vitamin D supplements were started during the ALL treatment because of the severe osteopaenia. Treatment with biphosphonates was initiated after completion of the ALL treatment because of persistent reduced bone-mineral density.

Muskuloskeletal signs and symptoms

Muskuloskeletal complaints with or without haematological abnormalities in the presentation of ALL are common. The symptoms may be related to bone involvement, affected joints or the muskuloskeletal system in general.

Aside from muskuloskeletal pain, children affected by ALL are at risk of several major secondary skeletal problems during and after treatment, such as osteonecrosis, reduced bone mineral density (BMD), osteoporosis and transient or permanent impairment of their growth.

Bone pain is a frequent (15-30%) complaint in children with ALL, often present in various localisations.[13] Musculoskeletal pain is caused by expansion of the medullary cavities due to a massive proliferation of haematopoietic cells or direct infiltration of the periosteum and bone by the leukaemic cells, with or without periosteal haemorrhage.

More commonly, the pain occurs in the lower extremities, especially in the long bones. The vertebral bodies may also be involved and this may result in considerable back pain due to osteoporosis and, infrequently, compression fractures as described in our second patient.[3,12,14]

Joint pain is usually referred pain, secondary to synovial effusion with swelling of the adjacent metaphysis rather than direct synovial infiltration. In some cases, as a result of severe swelling of the metaphysis, the joint may appear swollen and mimic JRA. The presence of subtle changes in the blood count along with nocturnal pain is reported to pro-

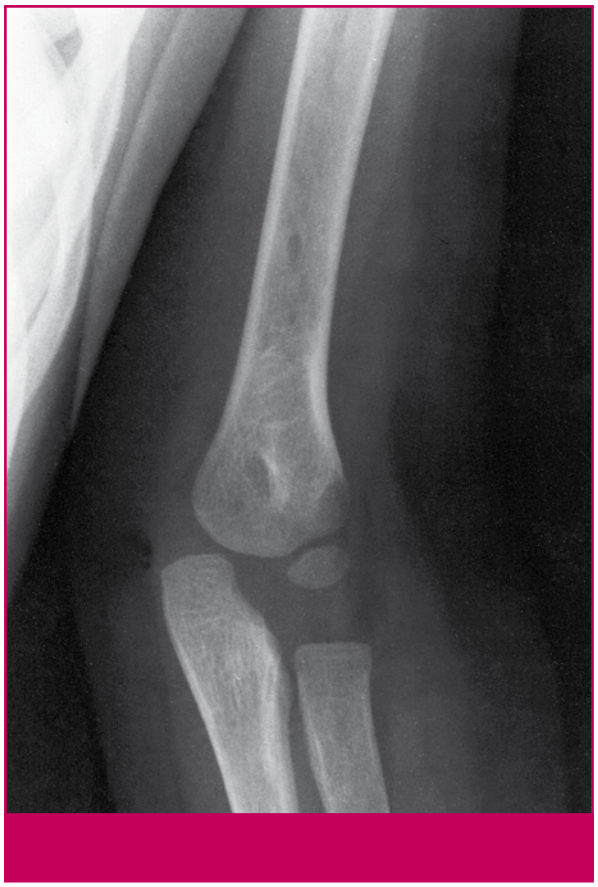

Figure 5. X-ray of the elbow of a 3 year old ALL patient showing multiple osteolytic laesions and a generalised osteoporosis.

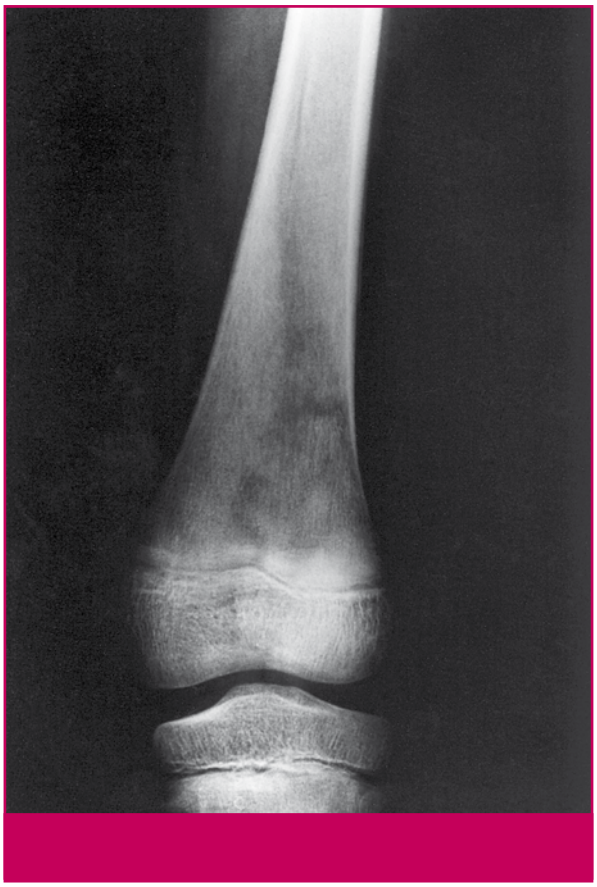

Figure 6. X-ray of the knee of a 8,5 year old ALL patient showing a generalised osteoporosis.

vide the highest predictive value for distinguishing ALL from JRA.[2,3,12,13,15,16]

Pain in the hip may be related to leukaemic infiltration or to avascular necrosis of the femoral head, the latter being a late complication of ALL treatment rather than a MSM.

The pain is usually non-specific in nature and 20-90% of patients describe it as intermittent, localised, stabbing, severe and sudden in onset.[3,15] Excruciating nocturnal pain, non-articular pain, pain disproportionate to arthritis or pain non-responsive to major analgaesics are highly suggestive for malignancy.[5,13,16] Regression of the severe bone pain should occur rapidly after starting ALL treatment. In the event of a relapse, the location and severity of the bone pain is often identical to the initial presentation.[3,13,14,17]

Radiological manifestations

Acute leukaemia is known to be associated with several radiographic osseous abnormalities, such as metaphyseal bands (leukaemic lines), lytic laesions, osteopaenia and less frequently sclerotic laesions, periosteal new bone formation or a combination of the aforementioned laesions. None of these pathological changes are pathognomonic, but depending on the patient's age and location of the laesions, some are highly suggestive of underlying leukaemia. According to recent publications up to 6% of these radiographic osseous abnormalities are reported at presentation. With the inclusion of osteopaenia, 90% of patients will develop these changes during the course of treatment for ALL.[3,9,15]

Both bone size and bone mineral density increase gradually throughout the childhood years with critical periods of growth and bone accumulation during puberty. Because of the smaller bone marrow reserves in children which can be more quickly replaced by the leukaemic cells, bone changes due to leukaemia are more common in children than in adults.[3,18] The pathological bone laesions are caused by leukaemic infiltration as a primary MSM as well as by chemotherapy and steroid treatment (secondary MSM) which alter normal bone metabolism and

mineral homeostasis.[19,20] They can be radiographically detected throughout the skeleton and can affect both cortical and trabecular bones.[3] More commonly, the metaphyseal regions of the lower extremities are affected, especially the knees.

As a result of bone infiltration, pathological changes can also be demonstrated by scintigraphy. In 75% of patients with ALL at presentation, symmetrical changes and diffuse reactivity in cortical bone are detected. However these sites of abnormal bone metabolism demonstrated by scintigraphy do not always correlate with X-ray changes, nor do they correlate with the clinical localisation of pain.[19,21] A bone scan is more helpful in distinguishing leukaemic MSM from other orthopaedic conditions or tumours. It results in a prompt evaluation of the entire skeleton and helps to identify bone or bone marrow infiltration. In addition, MRI can accurately demonstrate the local tumour size and intraosseous and extraosseous extent.[22]

Although bone pain and radiographic abnormalities are similarly located, in only 13% of the patients with leukaemic MSM a clinical-radiological correlation has been described.[15] In JRA however, soft tissue swelling in the joints is frequently present on plain X-ray.[23]

Metaphyseal radiolucent bands (leukaemic lines)

Radiolucent metaphyseal bands are a common radiographic finding, reported in up to 90% of patients with ALL (*Figure 3*).[3,12,24] These so-called leukaemic lines are the result of a generalised metabolic dysfunction that interferes with a proper osteogenesis at the site of the epiphyseal growth plate rather than an accumulation of leukaemic cells in the marrow. They are therefore usually located at sites of rapid growth, such as the proximal and the distal femur, proximal tibia, humerus and distal radius. Although considered non-specific and associated with other chronic diseases and various malnutritional states in children under two years of age, they are more specific for leukaemia than for other diseases in children over two years of age.[15,23]

The zones of diminished intensity are typically uniform and regular across the width of the metaphysis, usually 2-15 mm wide. Adjacent to the metaphyseal translucencies, a sclerotic band representing the line of growth arrest may be observed. After starting treatment, these leukaemic lines resolve quickly.[3,15,25]

Periosteal new bone formation

The frequency of periosteal reaction in literature varies from 2-50% (*Figure 4*).[12,24,26] These laesions, uncommon as an early manifestation, can be solitary, but are usually associated with osteolytic laesions. The new bone is formed beneath the periosteum, after leukaemic infiltration in the medullary cavity reaches and lifts the periosteum from the cortex. The newly formed bone has an identical structure to the original bone. The laesions are commonly observed in the diaphysis of the tibia and fibula and can involve a segment or the whole bone circumference. During treatment, the new periosteal bone resolves completely.[3,15,23]

Lytic bone laesions

Lytic bone laesions are reported in 10-50% of patients with ALL and are the result of a combination of leukaemic infiltration of the bone marrow, local haemorrhage and osteonecrosis of the adjacent bone (*Figure 4, Figure 5*).[3,6,12,17] Aseptic osteonecrosis is usually a late and secondary effect of leukaemia due to steroid treatment as well as to chemotherapy. It is a severe complication, which may cause limb or joint destruction eventually necessitating replacement of the affected limb or joint.[27]

On plain X-ray focal infiltration of cortical bone in leukaemia can cause photopaenic areas as a result of vascular compromise with avascular necrosis or osteonecrosis.[19] The lytic bone laesions are well-demarcated, radiolucent areas of bone destruction, which can be multiple and have an ovoid shape. They involve tubular and flat bones, mostly the metaphysis of long bones.[3,15,25] However, solitary laesions may be difficult to differentiate from foci of osteomyelitis. The laesions are associated with cortical thinning with or without periosteal reaction. Solitary cortical erosions are an early but uncommon feature of childhood leukaemia (*Figure 3*). They usually occur on the medial side of the proximal end of the humeral and tibial shafts and are bilateral. After starting treatment the laesions persist for a while before they resolve.[3]

Sclerotic bone laesions

Osteosclerosis is a less common but well-recognised primary manifestation (3-7%), although it can also develop during the course of the treatment

Key messages for clinical practice

1. ALL with musculoskeletal manifestations at presentation may mimic juvenile rheumatoid arthritis, osteomyelitis, septic arthritis and transient synovitis
2. Patients with musculoskeletal pain may be presented with or without radiographical abnormalities
3. The skeletal manifestations in ALL are not pathognomonic and may be seen in association with other diseases.
4. Haematological abnormalities can be subtle or even absent.
5. Musculoskeletal manifestations in leukaemia are often associated with a precursor-B ALL and have a good prognosis.
6. In any child with unexplained (persistent) bone pain and/or before treatment with steroids is started, bone marrow examination is highly recommended.

(*Figure 3*).[3,12,15] It is derived from reactive new bone formation secondary to leukaemic infiltration and osseous infarction. Laesions commonly affect the metaphysis of long bones. They resolve slowly but completely after ALL treatment has been started. A simultaneous presence of sclerosis and lysis in the same bone is rare and unlikely (2.5%), since this would imply an increased osteoblastic and osteoclastic activity in different sites of the same bone at the same time.[15,17]

Osteoporosis

Osteoporosis is a commonly reported (9-41%), though non-specific finding in leukaemia patients at the onset of the disease (*Figure 5, Figure 6*).[15,23] The degree and severity of osteoporosis increases after introduction of steroids and chemotherapy and is reported in up to 83% of children with ALL. Osteopaenia is caused by alteration in the patient's protein and mineral metabolism and diffuse infiltration of leukaemic cells in bone and bone marrow. Although most commonly located in the spine, vertebral collapse and pathological fractures are not frequently found (1-6%). After treatment, osteopaenia is reported to persist for six months to two years.[3,6,15,28]

Discussion

ALL is the most common childhood malignancy. Although the vast majority of these patients presents with medullary signs and symptoms with an abnormal blood count, approximately one third will initially present only with musculoskeletal complaints, with or without radiological abnormalities. Identifying ALL in this group of children can be difficult because it may mimic several orthopaedic conditions such as osteomyelitis, JRA, septic arthritis or transient synovitis. Distinctive radiographic abnormalities, such as metaphyseal bands, periosteal new bone formation, lytic or sclerotic bone laesions and osteoporosis have been described as being suggestive for leukaemia, especially in children over two years of age and should therefore alert physicians to this possibility. Although abnormalities are not pathognomonic and often delayed, X-ray examination should be performed in any child complaining of persistent musculoskeletal pain. Additional bone scintigraphy or MRI might be useful when X-ray examination reveals atypical laesions or when the patient's pain is disproportional.

The association between musculoskeletal complaints and nearly normal haematological findings at ALL diagnosis has frequently been reported.[2,4-11] However, the prognostic implications still remain

unclear. Some suggest that patients with MSM may belong to a subgroup of ALL with a good prognosis, because of a tendency towards low leukocyte counts with a few blast cells in the peripheral blood at presentation, together with mild anaemia and a normal or nearly normal platelet count.[5-7,24]. This less aggressive type of leukaemia would have a slower progression with a tendency to affect primarily the intramedullary space and structures, consistent with an immunophenotype of precursor-B ALL. Precursor-B ALL is a disease, starting in the bone marrow itself and therefore interferes with bone metabolism at an early stage.[9-11] Others found either a strong association between radiologically documented severe bone involvement and poor prognosis or no relation at all.[8-29] Chemokines would play a role in leukaemia cell traffic, causing actively proliferating lymphoblasts to skip peripheral blood and directly disseminate into extramedullary space or organs.[4] Although the severity of musculoskeletal complaints and the presence of single or multiple bone laesions, with or without radiographic abnormalities are not considered prognostic factors, the literature does indicate a difference between precursor-B and T-cell leukaemia with a higher event-free survival due to a slower growth of leukaemic cells in precursor-B ALL.[6,9,11,30,31]

There is no specific guideline for early detection, but a combination of clinical, laboratory and aforementioned radiographic findings may be helpful in distinguishing between a variety of orthopaedic conditions and this type of ALL. Given the large impact on treatment and prognosis bone marrow examination should not be postponed in any child with atypical MSM, even if blood counts are (near) normal.

Conclusion

ALL should always be considered in children with unexplained musculoskeletal pain with or without radiographic abnormalities, even in the presence of (near) normal blood counts. Pronounced bone pain is a common symptom preceding the diagnosis of ALL. It can mimic other orthopaedic conditions, which may contribute to a delay in diagnosis, resulting in a higher morbidity or even mortality. Early bone marrow examination should be performed, especially when steroid treatment is being considered.

References

1. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. N Eng J Med 2006;354:166-78.

2. Jones OY, Spencer CH, Bowyer SL et al. A multi-centre case-control study on predictive factors distinguishing childhood leukemia from juvenile rheumatoid arthritis. Pediatrics 2006;117:e840-4.

3. Abbas AAH, Baker DL, Felimban SK et al. Musculoskeletal and radiological manifestations of childhood acute leukemia: a clinical review. Haema 2004;7:448-55.

4. Chen CC, Weng HH, Hwang CE et al. Acute leukemia presenting with extramedullary diseases and completely normal hemogram: An extremely unusual manifestation unique to pre-B ALL. Am J Hematol 2010;85:729-31.

5. Jonsson OG, Sartain P, Ducore JM et al. Bone pain as an initial symptom of childhood acute lymphoblastic leukemia: association with nearly normal hematologic indexes. J Pediatr 1990;117:233-7.

6. Kai T, Ishi E, Matsuzaki A et al. Clinical and prognostic implications of bone lesions in childhood leukemia at diagnosis. Leukemia and Lymphoma 1996;23:119-23.

7. Muller HL, Horwitz AE, Kuhl J. Acute lymphoblastic leukemia with severe skeletal involvement: a subset of childhood leukemia with a good prognosis. Pediatr Hematol Oncol 1998;15:121-33.

8. Masera G, Carnelli V, Ferrari M, et al. Prognostic significance of radiological bone involvement in childhood acute lymphoblastic leukemia. Arch Dis Child 1977;52:530-3.

9. Maman E, Steinberg DM, Stark B, et al. Acute lymphoblastic leukemia in children: correlation of musculoskeletal manifestations and immunophenotypes. J Child Orthop 2007;1:63-8.

10. Benoit Y, Delbeke MJ, Eggesbø S. Skeletafwijkingen bij kinderen met acute lymfoblastenleukemie. T Kindergeneesk 1981;49:153-9.

11. Sweet EM, Willoughby MLN. Radiological bone changes in T-cell and 'common'ALL of childhood. Br Med J 1980;280:367-8.

12. Rogalsky RJ, Black GB, Reed MH. Orthopedic manifestations of leukemia in children. J Bone Joint Surg Am 1986;68:494-501.

13. Marwaha RK, Kulkarni KP, Bansal D, et al. Acute lymphoblastic leukemia masquerading as juvenile rheumatoid arthritis: diagnostic pitfall and association with survival. Ann Hematol 2010;89:249-54.

14. Chell J, Fernandes JA, Bell MJ. The orthopedic presentation of acute leukemia in childhood. Ann R coll Surg Engl 2001;83:186-9.

15. Sinigaglia R, Gigante C, Bisinella G, et al. Muskuloskeletal manifestations in pediatric acute leukemia. J Pediatr Orthop 2008;28:20-8.

16. Cabral DA, Tucker LB. Malignancies in children who initially present with rheumatic complaints. J Pediatr 1999;134:53-7.

17. Gallagher DJ, Philips DJ, Heinrich SD. Orthopedic manifestations of acute pediatric leukemia. Orthop Clin North Am 1996;27:635-44.

18. Gordon CL, Halton JM, Atkinson SA, et al. The contributions of growth and puberty to peak bone mass. Growth Dev Aging 1991;55:257.

19. Bernard EJ, Nicholls WD, Howman-Giles RB, et al. Patterns of abnormality on bone scans in acute childhood leukemia. J Nucl Med 1998;39:1983-6.

20. Halton J, Atkinson SA, Fraher L, et al. Mineral homeostasis and bone

mass at diagnosis in children with acute lymphoblastic leukemia. J Pediatr 1995;126:557-64.

21. Clausen N, Gotze H, Pedersen A, et al. Skeletal scintigraphy and radiography at onset of acute lymphoblastic leukemia in children. Med Pediatr Oncol 1983;11:291-6.

22. Yaw KM. Pediatric bone tumors. Semin Surg Oncol 1999;16:173-83.

23. Tafaghodi F, Aghighi Y, Yazdi HR, et al. Predictive plain X-ray findings in distinguishing early stage acute lymphoblastic leukemia from juvenile idiopathic arthritis. Clin Rheumatol 2009;28:1253-8.

24. Heinrich SD, Gallagher DJ, Warrior R, et al. The prognostic significance of the skeletal manifestations of acute lymphoblastic leukemia of childhood. J Pediatr Orthop 1994;14:105-11.

25. Dugan LO, Meyer SJ, Chua GT. General case of the day. Radiographics 1993;13:221-3.

26. D'Astous J, Corrigan M, Wiley J. The musculoskeletal manifestations of acute lymphatic leukemia in childhood. Orthop Trans 1984;8:460.

27. Korholz D, Engelbrecht V, Ruther W, et al. Aseptic osteonecrosis in children with acute lymphoblastic leukemia. Pediatr Hematol Oncol1998;15:307-15.

28. Vassilopolou-Sellin R, Ramirez I. Severe osteopenia and vertebral compression fractures after complete remission in an adolescent with acute leukemia. Am J Hematol 1992;39:142-3.

29. Hann IM, Gupta S, Palmer MK, et al. The prognostic significance of radiological and symptomatic bone involvement in childhood acute lymphoblastic leukemia. Med Pediatr Oncol 1979;6:51-5.

30. Pullen J, Shuster JJ, Link M, et al. Significance of commonly used prognostic factors differs for children with T cell acute lymphocytic leukemia (ALL) as compared to those with B-precursor ALL: a pediatric oncology group (POG) study. Leukemia 1999;13:1696-1707.

31. Rajantie J, Jaaskelainen J, Perkkio M, et al. Prognostic significance of primary bone changes in children with acute lymphoblastic leukemia. Pediatr Radiol 1985;15:242-4.