Pediatric leukemia revealed by a limping episode: A report of four cases

Y. Lefèvre\textsuperscript{a,}\textsuperscript{*}, D. Ceroni\textsuperscript{b}, A. Läedermann\textsuperscript{b}, V. de Rosa\textsuperscript{b}, G. de Coulon\textsuperscript{b}, H.O. Ayse\textsuperscript{b}, A. Kaelin\textsuperscript{b}

\textsuperscript{a} Pediatric Orthopedics and Traumatology Department, Robert-Debré Hospital, 48, boulevard Serurier, 75935 cedex 19 Paris, France
\textsuperscript{b} Pediatric Orthopedics Department, The Children Hospital, Academic Hospitals, Geneva, Switzerland

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Summary
Acute limping in children is a common reason for consultation in pediatric emergency units. Acute leukemia is a rarely encountered disease in the orthopedic surgeon’s activity. In addition, its clinical presentation is not typical and therefore is a source of possible diagnostic delay. For such reasons, there is a definite risk of undiagnosing the actual etiology of the limping episode. We report our experience with four cases of children initially seen in the pediatric emergency department for limping, as their revealing presentation of acute leukemia. The limb pain was highly variable. The radiographic work-up was always normal. Peripheral blood abnormalities were initially absent in one case and blastic cells were absent in two cases. The physician in charge should remember that paraclinical work-up normal results do not exclude a diagnosis of acute leukemia, that any drop in hematopoietic cell counts should call for a myelogram and that paraclinical exams, including the hemogram, should be repeated until a diagnosis and improvement or confirmed cure is achieved over time.

Level of evidence: level IV. Diagnostic study.

Introduction
Limping is a frequent reason for consultation in pediatric emergency units \cite{1,2,3}. Most often, this acute limping is related to lower limb, pelvis or even lower spine pain. Clinically, limping caused by a painful disorder presents as a protective limp \cite{4}. In young children, the list of etiologies responsible for protective limp is long; moreover, the protective limp often corresponds to nonverbalized or poorly verbalized pain. Certain causes are classic and frequently encountered by specialists such as acute transitory synovitis of the hip, bacterial osteoarthritis and Legg-Calvé-Perthes disease \cite{3,4}. Other etiologies such as tumors are rarer and more or less easily brought out depending on the practitioner’s training and experience \cite{5}. In this sense,
acute leukemia (AL) can be responsible for lower-limb pain and limping, sometimes manifesting as the disease’s initial symptoms. This diagnosis remains rare in these circumstances and is not usually a domain familiar to the orthopedic surgeon, particularly since its presentation is not always typical. For this reason, we believe it is useful to present our experience with four cases so as to review the various clinical and paraclinical presentations of AL diagnosed following pediatric emergency consultations for limping in children under the age of 6 years and to discuss the pitfalls and other considerations in reaching a diagnosis.

Case presentation

Merging the Geneva Children’s Hospital registries of patients hospitalized in pediatric hematology with the registries of patients managed by practitioners in pediatric orthopedics identified four patients hospitalized between 1997 and 2007 for AL diagnosed during a consultation for limping in the pediatric emergency unit. These four patients were all seen initially by the pediatric emergency unit’s surgical team.

Case no. 1

A 2-year-old boy was seen in the pediatric emergency department for protective limping on the right side, consecutive to lower limb pain that had appeared the morning before. This protective limping had come on in the context of fatigue and weight loss (1 kg), initially attributed to active gastroenteritis over the preceding 72 hours. The pain had spontaneously improved at the end of the day before and normal walking was resumed. The next morning, the pain had returned, more intense and with a slight fever (38 °C) responding to antipyretics. The child was brought to the emergency department that evening because the child continued to limp and complain of pain. The gait study confirmed clear protective limping on the right. Since the child was irritable and insufficiently compliant, it was difficult to locate the seat of the pain, with nevertheless doubts concerning the right foot and knee. In addition, examination of the spinal cord revealed pain when the lumbar spine was mobilized. X-rays of the right foot, right knee and lumbar sacral spine were interpreted to be normal. However, the hemogram revealed normochromic, normocytic anemia at 95 g/l (normal, 115—135 g/l), with 13% circulating blast cells. The myelogram done the next day confirmed the diagnosis of pre-B acute lymphoblastic leukemia (ALL). The time from the first symptoms to diagnosis was 48 hours.

Case no. 2

A 5-year-old boy was referred to the emergency department by his pediatrician for limping with fever, following pain in the right thigh that had appeared 2 weeks before. This pain, vague and intermittent at first, had become more intense and more constant over the last week, resulting in preventive limping, then the child refusing to walk the last 2 days. The child had also presented several fever peaks over the past 2 weeks. Initially seen by his pediatrician, the child was immediately referred to the pediatric emergency services. At his arrival, the child had no fever. He refused to walk more than a few steps, which were nonetheless sufficient to observe clear protective limping in the lower right limb. The child located the pain specifically in the distal half of the right thigh, with sensitivity found on palpation, with no tumefaction and no sign of inflammation. There was no pain in the ipsilateral hip and knee, which showed normal functional range of movement. There was a slight 5 mm amyotrophia in the right thigh. Palpation also revealed slight pain in both arms. The rest of the clinical examination brought out no other particularities. The x-rays of the painful limbs were normal. The hemogram showed thrombocytopenia with a value just below the norm and 26.5% circulating blast cells. A myelogram was done on the same day, revealing pre-B type ALL. The time between the beginning of symptoms and diagnosis of AL was 2 weeks. A whole-body bone scintigraphy with technetium-99 injection later revealed several areas of hyperfixation.

Case no. 3

A 4-year-old boy was seen the first time in the emergency unit for pain in the right knee that was difficult to pinpoint. The child’s parents attributed this pain to a fall 2 days before. X-rays centered on the knee were taken and interpreted as normal. With no other worrying symptoms than the pain and protective limping, the child was sent home with a diagnosis of simple contusion and symptomatic treatment. Over the next 2 weeks, the symptoms remained constant despite antalgics, motivating a second consultation. The pain was more precisely localized in the right medial tibial plateau with an impression of softening. The child’s general condition was the same, with no fever or clinical signs other than pain. The hemogram and CRP were normal, as were the new x-rays (Fig. 1A). An ultrasound of the knee demonstrated a small collection at the posterior side of the lateral tibial plateau and a thin section of effusion within the adjacent soft tissues, which appeared abnormally hypoechogenic. The child was hospitalized and MRI revealed a slight hypersignal in the periphery, suggesting a subperiosteal collection of the upper right tibial cortex (Fig. 1B) and a very slight hyperintense signal of the upper third of the tibia’s bone marrow compared to the left tibia, which was only visible on T2-weighted spin-echo sequences. An infectious process as well as a neoplastic process were suspected, motivating bacteriological sampling and a bone biopsy for pathological examination. Intravenous antibiotic treatment was initiated after surgery and then interrupted because the bacteriological cultures turned out to be sterile. The pathological examination demonstrated no acute inflammation or tumoral lesion. A whole-body technetium-99 bone scintigraphy revealed an expected hyperfixation at the tibial plateau and overall asymmetry of the activity in the whole lower right limb compared to the left (Fig. 1C). From a biological point of view, the child presented moderate thrombocytopenia (136 g/l for a normal level above 168 g/l) 2 weeks after being hospitalized. This rapidly worsened (114 g/l) on a follow-up at 72 hours with appearance of neutropenia and anemia, with no circulating blast cells visible. Based on these peripheral blood anomalies, a myelogram was done, which allowed us to conclude on pre-B type ALL.
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The time between the first symptoms and ALL diagnosis was 5 weeks.

Case no. 4

A 2.5-year-old child was brought to the emergency department for the first time for protective limping with pain in the lower right limb, attributed by his parents to a fall from a height the day before. The pain seemed to involve either the right foot or leg, with precise localization difficult. X-rays of the foot and leg taken in the emergency department were initially considered normal. Nevertheless, reading the x-rays the next day by several colleagues brought out a possible impaction fracture at the base of the first metatarsal. The foot was then immobilized in a walking boot for 3 weeks. After removing the cast, a new x-ray confirmed the fracture, showing a fine periosteal apposition opposite the area of the suspected fracture. From that time on, the child presented no pain on palpation or walking. One week later, the child was brought back to the emergency department by his mother for protective limping on the right, which was difficult for the examiners to demonstrate. New x-rays of the lower right limb showed no anomalies. A biological work-up done on the same day revealed isolated, normochromic, normocytic anemia at 88 g/l. Given the recurring pain that was difficult to demonstrate, a bone scintigraphy was planned but was not done because of the father’s refusal, who deemed it unnecessary because the symptoms were regressing. The clinical examination was indeed strictly normal. The scintigraphy was postponed to a later follow-up visit. Three weeks later, the child returned and the parents reported new complaints centered on the right lower limb, limping and the child’s refusal to walk. A new biological work-up was done, showing the known normochromic, normocytic anemia but now associated with moderate thrombocytopenia as well as moderate neutropenia; in addition, circulating erythroblastic cells were found. A myelogram was done, establishing the diagnosis of pre-B type ALL. The time between the beginning of the symptoms and AL diagnosis was 7 weeks.

Discussion

Limping is a frequent reason for consultation in pediatric emergency units [1,2,3], with initial management by an emergency unit physician or a general practitioner, a pediatrician, or a pediatric or orthopedic surgeon specializing in pediatric orthopedics or other domains. Surgeons are often less familiar with childhood medical pathologies and the diagnosis of malignant diseases, particularly hematological diseases, remain rare in the orthopedist’s activity, which can account for possible delays in reaching this diagnosis.

Protective limping or painful limping in children is a frequent symptom with a number of etiologies. Initially distinguishing traumatic and nontraumatic limping is a commonly accepted practice. Although this distinction is most often obvious, it can be difficult to make, particularly in a small child who has just learned to walk and who falls several times a day [6,7]. Parents therefore often explain limping by a fall or a hypothetical fall. Limping was thus first erroneously blamed on an injury in two of the cases described. Questioning in relation to the patient’s history should therefore be refined and the traumatic origin of limping should be challenged if it does not evolve as expected.

When a traumatic origin for limping has been ruled out, the etiologies are discussed in relation to the child’s age [2,7]. The cases of leukemia diagnosed from limping most often affect young children between the ages of 2 and 10 years. In a young child belonging to this age group, the different nontraumatic etiologies to search for are infections (arthritis, osteoarthritis, osteomyelitis, Lyme...
disease, borreliosis); osteochondritis, in particular Legg-Perthes-Calvé disease, which is more often found after 5 to 6 years of age; inflammatory or rheumatisms monoarthritis or polyarthritids; and more rarely malignant and tumor etiologies, including benign bone tumors, malignant bone tumors, non-bone tumors and their metastases, as well as leukemias. Finally, one of the most frequent causes of limping in children is transient acute synovitis, which remains a diagnosis of elimination (from bacterial infectious etiologies and Legg-Perthes-Calvé disease, at least), with the only positive feature, in a case of hip pain, being the presence of anechogenic intra-articular effusion [8].

Anamnesis, the clinical exam, and an adapted para-clinical work-up primarily based on imaging (plain x-rays, ultrasound or even MRI) and biological tests with the total blood count and inflammation markers (CRP at the minimum, sedimentation rate, orosomucoid, etc.) most often orient the diagnosis toward one of these etiologies [2,7]. Bone scintigraphy can be useful when the above-mentioned tests are insufficient [3]. It should be noted that although its sensitivity is high for most limping etiologies in the young child, its specificity is less so, particularly when there is hyperfixation [9]. For two of the cases presented, scintographies were done, but finally they contributed little to the final diagnosis of AL.

Tumoral and neoplastic etiologies remain relatively rare, as confirmed by the study conducted by Fischer and Beattie on 243 patients who had consulted for limping, with only one presenting with limping related to AL (0.4%) [1]. We found four cases of AL diagnosed from limping that was managed in the pediatric emergency department (0.4 cases per year), whereas this symptom accounts for 90 consultations per year in the emergency department of the Geneva University Hospitals (averaged over the last 4 years), accounting for 0.4% of the causes for limping.

AL accounts for an average of ten new cases per year in our institution. The incidence is estimated at 3.93 for both sexes for 100,000 inhabitants aged from 0 to 14 years in Western Europe [10]. The malignant tumor is the most frequent etiology in 1- to 4-year-old children (41% of the malignant tumors in this age group) [11,12]. Among the different forms of AL, ALL predominates with a peak of frequency between 2 and 6 years of age [10], followed by myeloblastic acute leukemia (MAL). The myeloblastic forms can also be responsible for limping, as reported by Tuten et al. [13] on a series of nine cases of AL diagnosed following a consultation for limping, with seven cases of ALL and two of MAL.

Clinical manifestations of leukemia affecting the bones and joints are frequent (20.6–33% of cases) at the first consultation [14]. Limb pain is the most frequent symptom. It is most often located in a single limb, readily leading to protective limping when it is in the lower limbs. Tuten et al. [13] report that 11.6% of patients with AL admitted to their institution presented limping among the symptoms present at diagnosis, but it was most often relegated behind other nonskeletal symptoms. This “bone” pain may be related to a rapidly appearing mass effect inside the bone’s medullary canal, related to malignant proliferation of hematopoietic cell counts. It is difficult to classify this pain as either inflammatory or mechanical pain. It can be nocturnal and disrupt sleep, even if it remains for the most part diurnal. It often fluctuates over time and has no triggering factor. This variability is a major difficulty in the diagnostic process because at the time of the tests the pain may have regressed or disappeared between two examinations, as in case no. 4. Moreover, hematologic tumor disease may favor the onset of osteomyelitis, septic or aseptic arthritis, and pathologic fractures. In these precise situations, the cause of pain is correlated to the pathology induced.

The case of a young child presenting protective limping caused by pain in a lower limb without injury remains a relatively frequent occurrence with little specificity. One must therefore remain attentive to the other clinical features that should lead to suspecting leukemia. The clinical features reported by Tuten et al. [13], and found in some of our patients, are episodes of fever, present in half the cases, diffuse adenopathies in one-third of patients and more rarely splenomegaly or even hepatomegaly. Recent episodes of infection such as otitis media, strep throat or even pneumonia are also suggestive. It should be remembered, however, that these clinical findings never rule out the diagnosis.

In addition to these clinical features, the radiological signs classically considered to be suggestive of leukemia are osteopenia, more or less localized, clear metaphyseal bands, lytic lesions, sclerosing lesions and periosteal apposition. It should be remembered that these signs can be entirely absent, as in the four cases reported herein. Tuten et al. [13] describe only a single case of anomaly on the plain x-rays — localized osteopenia on the proximal femur — among the six patients who had a radiological work-up. In a series of 107 patients with AL with and without skeletal symptoms, Rogalsky et al. [14] reported 56.1% normal x-rays. Bone scintigraphy, classically recommended in this context of protective limping with no obvious cause [3], can be contributive even if the results are uncertain. Scintigraphy is normal in 20–25% of cases [15,16]. In the 75–80% of cases where anomalies are present, they are most frequently in one or several zones of hyperfixation, but the correlation with the topography of pain and the possible radiological anomalies could not be established with certainty [15,16]. Cases of hypofixation have also been described [17]. Bone scintigraphy can therefore assist the diagnosis, but it must be kept in mind that a normal result does not rule out the diagnosis. CT and MRI can also be proposed with most often results that are not highly specific — locally increased contrast uptake or hyperintense signal — as for case no. 3.

Finally, the third aspect of the classical work-up for acute nontraumatic limping is the biological work-up, particularly if certain clinical features suggest a possible infectious cause. The essential test is the hemogram (grouping full blood count and platelet count as well as blastic cell count). The presence of blastic cells, especially if their percentage is high, is the strongest element suggesting leukemia and is followed directly by a myelogram. We found them only in two of the four cases reported during the first biological tests. Tuten et al. found them in seven out of nine patients [13]. The absence of circulating blastic cells does not rule out the diagnosis of leukemia. They may appear secondarily and therefore it is important to repeat the biological tests when the symptoms persist and a precise etiology has not been found. All of the hematopoietic cell counts can be disturbed, with, in descending order of frequency,
thrombocytopenia, normochromic normocytotic anemia and neutropenia [13]. Morphological anomalies of the white blood cells can also be encountered. The finding of one or several of these anomalies on the blood work-up is capital and testing should be extended immediately, in collaboration with hematologists. Nevertheless, a normal hemogram during the first tests does not rule out leukemia, as shown by our case no. 3, for whom all the cell counts were initially normal, even if this remains a rare case. Inflammation markers are most often modified, but again, without this being mandatory and with no particular specificity.

Conclusion

In conclusion, in AL, the practitioner should not remain only within the cliché of the child in poor general health presenting clear metaphyseal bands on skeletal x-rays and circulating blastic cells on the hemogram. Even if the orthopedist only rarely encounters this diagnosis, it is important to bear in mind that AL in a small child can initially be expressed as acute nontraumatic limping related to pain limited to one segment of the lower limb, whether or not it is associated with clinical findings. The clinical expression, including pain, can fluctuate over time and is a potential source of diagnostic digression. Radiological signs are absent in half the cases and bone scintigraphy is negative in nearly one-fourth. The hemogram is certainly the most sensitive test and any drop in hematopoietic cell counts should be explored immediately in a specialized unit. If the results are normal and a precise diagnosis or cure is not confirmed over time, the blood tests should be repeated.

References