Osteoarticular Manifestations as Initial Presentation of Acute Leukemias in Children and Adolescents in Bahia, Brazil

Teresa Cristina Martins Vicente Robazzi, MD, MS, José H. S. Barreto, MD, MS,† Luciana R. Silva, MD, PhD,‡ Mittermayer B. Santiago, MD, PhD,§ and Núbia Mendonça, MD†‖*

Objective: This study was to determine the prevalence and characteristics of the osteoarticular manifestations on initial clinical presentation of acute leukemias (ALs) on childhood in the state of Bahia, Brazil.

Materials and Methods: This retrospective study assessed the medical records of 406 patients with AL from January 1995 to December 2004.

Results: Acute lymphocytic leukemia (ALL) was diagnosed in 313 (77.1%) patients and acute myeloid leukemia (AML), in 93 (22.9%) patients, including 241 males (59.4%) and 165 females (40.6%). Age ranged from 9 months to 15 years (average: 6.18 y). The most common presenting features were fever (18.5%), musculoskeletal diffuse tenderness (15.0%), pallor (11.4%), and leg tenderness (5.7%). Prior referral to our center, the most frequent initial diagnosis was anemia (15.8%), leukemia (15.0%), amygdalitis (3.7%), and rheumatic fever (2.7%). Osteoarticular manifestations were found on 54.7% of the patients with AL, with a higher frequency among patients between 1 and 9 years of age (58.7%, $P = 0.0007$). The presence of joint tenderness (16.2% in ALL × 5.4% in AML), arthritis (26.6% in ALL × 9.7 in AML), bone tenderness (26.1% in ALL × 16.1% in AML), limb tenderness (49.5% in ALL × 25.8% in AML), and antalgic gait (32.8% in ALL × 9.7% in AML) had higher prevalence on ALL. The large joints, chiefly the knees (10.6%), ankles (9.4%), elbows (4.4%), and shoulders (3.6%) were more often affected.

Conclusions: AL should be considered on the differential diagnosis of osteoarticular symptoms of unknown etiology in children.

Key Words: acute leukemias, osteoarticular manifestations, children and adolescent

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Acute leukemia (AL) is the most common cancer occurring in children, representing 25% of cancer diagnoses among children younger than 15 years and occurring at an annual rate of approximately 30 to 40 per million.[1,2] Acute lymphocytic leukemia (ALL) is the most common type of leukemia occurring during childhood, representing 75% of all AL diagnoses among this specific age. The initial clinical manifestations of ALs are highly variable and nonspecific.

In children, AL can mimic several rheumatologic pathologies and this variable presentation creates difficulties in achieving the correct diagnosis.[3] Bone pain and musculoskeletal complaints may be present in 10% to 50% of all cases of childhood AL, and it is more frequent in ALL than acute myeloid leukemia (AML).[1–4] Bone pain, a limp, or refusal to walk are the most common presenting features. Despite its rarity as the first symptoms of leukemia, these complaints precede the classic manifestation of disease in months and illustrate that delay in diagnosis occurs frequently, with the classic features of the disease being uniformly absent. This article reports the prevalence and the characteristics of the osteoarticular manifestations on initial clinical presentation of childhood AL in a Pediatric Cancer Center in Salvador, Bahia, Brazil.

PATIENTS, MATERIALS, AND METHODS

Between January 1995 and December 2004, 414 children and adolescents with previous diagnosed AL were seen at ONCO, Bahia Oncology Society Ltda. Of the 414 patients, 8 patients with ALL were excluded from the study because they did not have sufficient data related to the initial presentation of disease. The variables used in

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From the *Pediatric Rheumatology Unit at Hospital São Rafael, Fundação Monte Tabor and Hospital Geral Roberto Santos; †Pediatric Oncology Unit Dr Jorge Bahia de Carvalho, ONCO, Bahia Oncology Society Ltda, Salvador; ‡Pediatric Gastroenterology and Hepatology Service of Federal University of Bahia; §Bahian Medical and Public Health School (Rheumathology Unit of St Izabel Hospital) Salvador, Bahia, Brazil; and ‖Member of Brazilian Pediatric Academy.
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Reprints: Teresa Cristina Martins Vicente Robazzi, MD, MS, R. Leonor Calmon, 44, 1203/1204. Cidade Jardim, Salvador-Bahia, Brasil-CEP: 40280-633 (e-mail: trobazzi@gmail.com).

the study were patient's age and sex, ALL; AML, initial diagnosis, first symptom, constitutional symptoms in the early course of the disease, osteoarticular complaints, laboratory tests, time between the initial rheumatic complaint and the diagnosis, health professionals consulted before the pediatric oncologists, and osteoarticular complaints after chemotherapy.

The term arthralgia was used for joint pain without evidence of inflammation (swelling, pain, and limitation). The presence of inflammatory complaints in the joint was referred to as arthritis. To describe limb and bone pain we adopted the information reported by the child or his family: bone pain was used for localized pain and limb pain was used for diffuse limb complaint.

Statistical Analysis

Statistical analysis was performed, using Fisher exact test or the χ^2 as appropriate, to test for association between categorical factors. The Mann-Whitney test or student *t* test were used to compare continuous variables, which were described by their average, SD and median, and categorical variables were described by their relative frequencies. To evaluate normal distribution among continuous variables, the Kolmogorov-Smirnov test was used. All *P* values reflected 2-sided tests. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS, Inc, Chicago, IL) version 12.

RESULTS

The diagnosis of AL was based on morphologic findings of the bone marrow content.[4] An institutional Research Ethics Committee approved this study project.

Medical records of 414 patients were systematically reviewed. ALL was diagnosed in 313 (77.1%) patients and AML, in 93 (22.9%). Two hundred forty-one patients (59.4%) were males and 165 were females (40.6%). Age varied between 0.75 and 15 years (average: 6.18 y). Evaluating the time between the onset of symptoms and the final diagnosis of leukemia indicated there were no differences between ALL and AML ($m = 50.2 \pm 66.7$ d and 64.7 ± 85.3 d; $P = 0.083$).

The most common complaints were fever (18.5%), musculoskeletal diffuse tenderness (15.0%), pallor (11.4%), and leg tenderness (5.7%). Refusal to walk, as a presenting symptom, was observed in 0.6% of the patients. Constitutional symptoms in the early course of the disease, such as weight loss, dizziness, weakness, lethargy, paleness, anorexia, and fatigue, were present and more frequent in ALL than in AML (Table 1). The most frequent initial diagnoses were anemia (15.76%), leukemia (15.0%), amygdalitis (3.7%), and rheumatic fever (RF) (2.7%). The health professionals more often consulted before the pediatric oncologists were pediatricians (61.3%) and general physicians (48.3%). Osteoarticular manifestations were found in 54.7% of the patients with AL, with a higher frequency among patients between 1 and 9 years of age (58.7%, $P = 0.0007$). No association was seen between osteoarticular manifestations and sex ($P = 0.3$). The association between leukemia subtype and osteoarticular manifestation is discussed below. The presence of joint tenderness, arthritis, bone tenderness, limb tenderness, and claudicating were also evaluated with a higher prevalence on ALL than in AML (Table 2). The large joints, chiefly the knees (10.6%), ankles (9.4%), elbows (4.4%), and shoulders (3.5%), were more often affected than the other joints (10.8%). The involvement of the small articulations on the feet and hands was more common in ALL (85.7%) than in AML (14.3%). The incidence of single joint involvement was greater (88.5%) than that of multiple joints (13.5%). Initial white blood cell (WBC) count showed absence of blasts in 48.0% of the cases (ALL = 53.5% and AML = 30.1%; $P < 0.001$); WBC counts were within the normal range in 52.2%; platelets were below 150,000/mm^3 in 84.0% and were normal in 15%. No association was found to exist between limb tenderness and WBC count inferior to 50,000/mm^3. Most of our patients had increased erythrocyte sedimentation rate (ESR) (Westergreen method; normal range, 0 to 20 mm/h) (ALL = 72.4 ± 37.9 mm/h and AML = $64.9\% \pm 2.8$ mm/h; $P = 0.34$). Fifteen patients (3.7%) received steroids before diagnosis of leukemia for an average time of 55 ± 66 weeks for treatment of rheumatologic disease or other pediatric disorders. No difference was observed in time of onset of symptoms and diagnosis of leukemia between patients who received steroids and those who did not (55.0 ± 66.1 wk $\times 52.3 \pm 73.6$ wk; $P = 0.1$). Osteoarticular complaints subsided with chemotherapy in 97.7% of the cases.

TABLE 1. Association Between Leukemia Subtype and Constitutional Symptoms in the Early Course of the Disease: Children and Adolescents With AL, 1995 to 2004

Complaints	ALL, n (%)	AML, n (%)	PR	CI 95%
Weight loss	109 (42.1)	43 (46.2)	0.9	0.7–1.2
Fever	231 (79.7)	73 (78.5)	1.0	0.9–1.2
Dizziness	10 (4.4)	01 (1.1)	4.1	0.7–24.5
Weakness	55 (22.4)	14 (15.1)	1.5	0.9–2.6
Lethargy	55 (22.4)	14 (15.1)	1.5	0.9–2.6
Paleness	220 (79.4)	74 (79.6)	0.1	0.9–1.1
Anorexia	93 (36.6)	29 (31.2)	1.2	0.8–1.7
Fatigue	68 (27.3)	18 (19.4)	1.4	0.9–2.3

ALL was considered for calculus of PR.
CI indicates confidence interval; PR, prevalence ratio.

TABLE 2. Association Between Leukemia Subtype and Osteoarticular Manifestation: Children and Adolescents With AL, 1995 to 2004

Complaints	ALL, n (%)	AML, n (%)	PR	CI 95%
Arthralgia	49 (16.2)	5 (5.4)	3.0	1.3–7.2
Arthritis	80 (26.4)	9 (9.7)	2.7	1.5–5.2
Bone pain	79 (26.1)	15 (16.1)	1.6	1.0–2.7
Limb pain	149 (49.5)	24 (25.8)	1.9	1.4–2.8
Antalgic gait	86 (32.8)	9 (9.7)	3.4	1.8–6.5

ALL was considered for calculus of PR.
CI indicates confidence interval; PR, prevalence ratio.

DISCUSSION

AL is the commonest childhood malignancy, which can produce a host of complaints that mimic other more common pediatric diseases.[5–8]

Musculoskeletal symptoms are very well documented as initial manifestation of leukemia in children. Initial presentation may involve the musculoskeletal system in up to two-thirds of cases,[3] and arthritis may be the only presenting feature of leukemia.

The initial presentation of childhood AL consists of diverse signs and symptoms, and they should be considered in the differential diagnosis of osteoarticular symptoms (OASs) of unknown etiology, even if initial laboratory tests, including arthritis, arthralgia, and limb pain are normal.[9]

Children with undiagnosed AL may have complaints that mimic any number of more common childhood illnesses and are frequently referred to the pediatric rheumatologist initially with a supposition of many diseases. All patients presenting with arthritis or other OASs should have a thorough clinical examination. Patients with leukemia may have constitutional symptoms as their major manifestations and, therefore, may also present the possible diagnosis of child abuse, rheumatic disorders [vasculitis, RF, juvenile idiopathic arthritis (JIA), systemic lupus erythematosus, dermatomyositis, reactive arthritis], infectious conditions (osteomyelitis, septic arthritis, infectious mononucleosis, acute infectious lymphocytosis, pertussis and parapertussis, or certain viral illnesses), other malignant processes (metastatic neuroblastoma, metastatic rhabdomyosarcoma, metastatic retinoblastoma, non-Hodgkin lymphoma, Langerhans cell histiocytosis, Ewing sarcoma, and osteosarcoma), and other bone disease as osteoid osteoma.[10–12]

We evaluated 406 patients diagnosed with AL who have been treated at the ONCO, Bahia Oncology Society Ltda between January 1995 and December 2005. Most children had ALL (77.1%) and 22.9% had AML.

This distribution is in accordance with those described by other authors.[7,13,14]

The median time elapsed between the initial rheumatic complaint and the diagnosis of leukemia was 50.2 ± 67.7 days for ALL and 64.7 ± 85.3 days for AML. Rheumatic diseases, in particular RF and JIA, are important differential diagnoses for leukemia, and 19 of the 406 patients had these initial diagnoses before the diagnosis of leukemia delaying the introduction of the appropriate therapy. The most common referring misdiagnosis in the literature is JIA, especially the systemic onset subtype.[15–18]

RF was the most frequent rheumatologic diagnostic described in this series of patients, in disagreement with other authors who refer to JIA as the most important rheumatologic differential diagnostic.[19–22] The incidence of RF in the developing countries may be 100 to 206/100,000 children, with a prevalence of 2.1/1000 poor families.[23] Despite the high rate of incidence of RF in our country, the authors do not believe that this was the only reason to justify this finding. The failure of medical personnel to diagnose osteoarticular complaints in children in our state may also be a contributory factor that overestimate the diagnosis of RF.

The incidence of OASs or findings as presentation of neoplasms is highly variable and its importance as a "marker" for cancer has not yet been sufficiently evaluated.[9,19,20,24,25] These manifestations have been described in lymphoproliferative diseases by many authors.[21,22,26,27] In our study, the frequency of OAS was 54.7% and it was similar to those found in other studies in the literature. In our series, 44.3% of patients had limb pain as initial complaint followed by antalgic gait (24.6%), bone pain (23.6%), arthralgia (22.4%), and arthritis (13.8%). Refusal to walk was present in only 0.6% of the patients in this series. However, the refusal to walk by a child, with no evidence of trauma, requires the physician to include leukemia in the differential diagnosis, with transient synovitis, joint sepsis, and osteomyelitis.[27]

In this series, the knee was the most frequently affected joint at presentation of leukemia, followed by the ankle and elbow. In the same way, the knee is also the most common involved joint in pauciarticular JIA. In contrast, elbow, hip, shoulder, cervical, or lumbar spine involvement is unusual in the onset of JIA, especially when they are an isolated complaint, and should alert the physician to an alternative diagnosis.[27] Low back pain as the presentation of ALL is rare.[11]

The oligoarticular form of arthritis was predominant in this study in concordance with other observations.[27–30]

Osteoarticular manifestations associated with underlying leukemia include diffuse bone pain or joint involvement with systemic manifestations such as fever, weight loss, malaise, and hepatosplenomegaly.[27] Often, very difficult to differentiate JIA from a malignant disease, particularly at presentation when systemic features and hematologic abnormalities are often mild or absent.[29]

Fever, elevated ESR, anemia, and leukocytosis are frequently seen in both leukemia and JIA. Thrombocytopenia, neutropenia with lymphocytosis, blast cells on peripheral smear, and acute phase response, disproportionate to severity of arthritis, help establish the diagnosis of leukemia.[18,31]

Arthritis accompanying fever and signs of cardiac involvement with elevated ESR may suggest RF in leukemic children and adolescents. The decrease of peripheral WBC, severe anemia, and sometimes thrombocytopenia, which appeared during the treatment with anti-inflammatory agents, led to the correct diagnosis of leukemia.[32]

Leukopenia and thrombocytopenia can suggest the diagnosis of systemic lupus erythematosus, but other associated symptoms and laboratory tests may lead to the diagnosis of leukemia.[32]

Many pathways to explain the involvement of joint in a leukemic child have been described. Musculoskeletal pain, joint pain, and joint effusion may be due to

leukemic infiltration of the synovial tissue. Intra-articular bleeding secondary to thrombocytopenia and synovial reaction due to capsular or periosteal infiltration are also mechanisms of joint pain. Arthritis secondary to deposition of monosodium urate crystal and a synovitis related to immune complex are referred to by some authors in the physiopathology of joint involvement in leukemia.[27,32] Bone marrow expansion induced by colony-stimulating factors and lumbar puncture are cause of back pain in leukemic patients.[32,33]

Laboratory tests may mislead the diagnosis of leukemia.[27] Most of our patients had increased ESR levels at onset of the disease. Some patients presented at diagnosis normal WBC count and no evidence of blasts (48.0%). Dissociation of the inflammatory indices, with a normal or low platelets count or low WBC count, should alert the physician to the possibility of hidden leukemia.[20,21,27] Moreover, the blood cell count may sometimes be normal for weeks or months even after the onset of symptoms. Peripheral blast cells may be absent at onset of the disease,[21,27] which may further delay diagnosis and influence the outcome poorly.[21,25]

CONCLUSIONS

Our study underlines the importance of a complete clinical examination and of a careful analysis of the pattern of joint involvement and confirms that children and adolescents with AL may present osteoarticular symptoms. When osteoarticular complaints dominate the early course of the disease, the differential diagnosis should include various rheumatic disorders.[27] As far as we know, this is the largest study about this theme described in Brazil.[9,13,30]

The diagnosis of malignancy must not be excluded in children with osteoarticular symptoms, especially when the clinical pattern is not characteristic of a specific rheumatic disease.

The presence of intensive pain, atypical pattern of arthritis, high lactate dehydrogenase levels, anemia, leukopenia, and increased ESR, especially in the presence of systemic manifestations, are important features that suggest the diagnosis of underlying malignancy and should lead to additional investigations.

Treatment for childhood leukemia has improved significantly over the past 50 years, and this has changed the prognosis from a uniformly fatal disease to one with an overall cure rate greater than 75% (ALL).[11] The early recognition of the disease, the correct classification of AL, the adequate treatment, and the absence of the use of steroid therapy before the diagnosis of AL have been profoundly influenced by the success of the therapy and the outcome.

The correct diagnosis of leukemia and its prompt treatment are crucial. If the clinical and laboratory tests suggest leukemia, then it is very important to perform bone marrow aspiration before starting steroids or cytotoxic therapy. Long delay in the diagnosis may be observed in cases of children with initial diagnosis of rheumatologic disease, owing to the lack of clinical and laboratory manifestations that suggested neoplasia, and to the use of steroid therapy for a short period of time.

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