CLINICAL SCIENCE

# Discrimination of acute lymphoblastic leukemia from systemic-onset juvenile idiopathic arthritis at disease onset

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**OBJECTIVE:** To assess clinical and laboratory features that differentiate acute lymphoblastic leukemia from systemic juvenile idiopathic arthritis at disease onset.

**METHODS:** Fifty-seven leukemia patients with musculoskeletal involvement, without blasts on peripheral blood and without glucocorticoid therapy at disease onset and 102 systemic juvenile idiopathic arthritis patients (International League of Associations for Rheumatology criteria) were retrospectively evaluated. The following features were examined: fever, rheumatoid rash, arthritis, limb pain, hepatomegaly, splenomegaly, pericarditis, myocarditis, pleuritis, weight loss, bleeding, anemia, leukopenia, neutropenia, thrombocytopenia, erythrocyte sedimentation rate, and lactic dehydrogenase levels.

**RESULTS:** The median age at disease onset was significantly higher in leukemia patients than in those with systemic-onset juvenile idiopathic arthritis (5.8 vs. 3.8 years). In addition, the frequencies of limb pain, hepatomegaly, weight loss and hemorrhagic manifestations were significantly higher in leukemia patients than in systemic-onset juvenile idiopathic arthritis patients (70% vs. 1%, 54% vs. 32%, 30% vs. 8%, and 9% vs. 0%, respectively). Likewise, the frequencies of anemia, leukopenia, neutropenia, thrombocytopenia and high lactic dehydrogenase levels were statistically higher in leukemia patients than in patients with systemic-onset juvenile idiopathic arthritis (88% vs. 57%, 39% vs. 1%, 60% vs. 1%, 77% vs. 1%, and 56% vs. 14%, respectively). Remarkably, multivariate analysis revealed that limb pain (OR = 553; 95% CI = 46.48-6580.42) and thrombocytopenia (OR = 754.13; 95% CI = 64.57-8806.72) were significant independent variables that differentiated leukemia from systemic-onset juvenile idiopathic arthritis. The R2 of the Nagelkerke test was 0.91, and the Kaplan-Meier survival curves were similar for acute lymphoblastic leukemia patients with and without limb pain.

**CONCLUSION:** Our study emphasizes the importance of investigating leukemia in patients presenting with musculoskeletal manifestations and, in particular, limb pain associated with thrombocytopenia.

**KEYWORDS:** Acute lymphoblastic leukemia; Juvenile idiopathic arthritis; Children; Limb pain; Thrombocytopenia.

## INTRODUCTION

Acute lymphoblastic leukemia is the most prevalent cancer in children and adolescents[1,2] and is the most frequent malignant neoplasm associated with musculoskeletal complaints at disease onset.[3-9] The main clinical osteoarticular manifestations in early leukemia include limb pain, nighttime pain, arthralgia, and arthritis.[4-9] Moreover,

pediatric leukemia may develop clinical features and laboratory alterations that mimic rheumatic diseases, in particular systemic-onset juvenile idiopathic arthritis (also known as juvenile rheumatoid arthritis).[7,10,11]

Approximately 4-41% of children and adolescents with juvenile idiopathic arthritis (JIA) have systemic-onset JIA (SoJIA).[12,13] This disease subtype is defined as the presence of arthritis in one or more joints associated with a daily fever above 39°C for a minimum period of 15 days and with the presence of at least one of the following manifestations: rheumatoid rash, generalized adenomegaly, pericarditis, pleuritis, hepatomegaly, and/or splenomegaly.[14]

To our knowledge, there are few studies that have evaluated the differences between acute leukemia and

SoJIA at disease onset.[10,11] Ostrov et al[10] showed that musculoskeletal pain causing nighttime wakening was more prevalent in eight leukemia and two acute nonlymphocytic leukemia patients vs. 10 patients with a systemic subtype. Jones et al[11] compared leukemia vs. JIA patients and demonstrated a high sensitivity and specificity of the combination of hematological abnormalities and nighttime pain for a leukemia diagnosis. In their study, however, the three most important JIA subtypes (oligoarthritis, polyarthritis, and systemic) were included, and only 20% of the patients had SoJIA. Furthermore, these two studies did not describe any other relevant alterations at disease onset, for example, hemorrhagic manifestations, macrophage activation syndrome (MAS), pericarditis, myocarditis, or neutropenia. Finally, a multivariate analysis was not performed in either study.

Therefore, we aimed to assess the initial clinical and laboratory features that differentiate leukemia from SoJIA. Kaplan-Meier survival curves in leukemia patients with and without limb pain were also evaluated.

## METHODS AND MATERIALS

The study period took place from August 1996 to October 2010. During this period, 57 consecutive children and adolescents suffering from leukemia with musculoskeletal manifestations but without blasts on peripheral blood smear or glucocorticoid therapy were selected from a population of 190 patients who had complete medical records (the total population of leukemia patients was 285). In addition, 102 consecutive SoJIA patients who did not receive initial glucocorticoid therapy and who had complete medical records were selected from a total population of 136 SoJIA patients. Leukemia and SoJIA patients were retrospectively studied according to their initial clinical and laboratory features. All of the patients were evaluated by a pediatric oncologist and/or a pediatric rheumatologist at our university hospital.

The definitive diagnosis of leukemia was established according to the presence of at least 25% blasts on a bone marrow smear, and all of the slides were reviewed by an expert cytologist. Arthritis was diagnosed according to the International League of Associations for Rheumatology (ILAR) criteria.[14] The Local Ethics Committee of our hospital approved this study.

The initial clinical manifestations and laboratory alterations were evaluated for leukemia and SoJIA patients. The presence of the following initial clinical manifestations were systematically analyzed: fever (axillary temperature ≥37.8°C), rheumatoid rash (erythematous, macular, non-pruritic, and evanescent salmon-colored lesions most commonly over the trunk and proximal limbs), generalized lymph node enlargement, hepatomegaly (liver edge >2 cm above the right costal margin), splenomegaly (palpable spleen), pericarditis and myocarditis (confirmed by Doppler echocardiography), pleuritis (confirmed by thorax radiography and/or thorax ultrasound), weight loss (>2 kg in one month) and bleeding (gingival bleeding, petechiae, ecchymosis, and/or epistaxis).[13]

Musculoskeletal manifestations were defined as the presence of arthralgia (joint pain or tenderness without evidence of inflammation), arthritis (swelling within a joint or a limitation in the range of joint movement with joint pain or tenderness),[14] subjective complaints of limb pain (bone pain, tenderness or other discomfort in one or more limbs without evidence of inflammation), and nighttime pain (musculoskeletal pain causing nocturnal wakening).

The following peripheral blood alterations were systematically evaluated: anemia (<10 g/dl), leukopenia (<4,000/mm$^3$), leukocytosis (>12,000/mm$^3$), neutropenia (<1,000/mm$^3$), thrombocytopenia (<150,000/mm$^3$) and thrombocytosis (>400,000/mm$^3$). The erythrocyte sedimentation rate (ESR) was performed according to the Westergreen method, and high levels were defined as >20 mm/1$^{st}$ hour. High lactic dehydrogenase (LDH) and high uric acid levels were evaluated according to the reference ranges based on the patient's age.

The leukemia patients were classified into two major immunophenotypes, B- or T-lineage leukemia. During the study period, all leukemia patients were treated according to the same institutional protocol. The long-term results of this protocol were reviewed every five years.

**Statistical analysis.** The results are presented as the median (range) or mean ± standard deviation for continuous variables and as a number (%) for categorical variables. The data were compared using the Mann-Whitney test for continuous variables to evaluate differences between leukemia and SoJIA patients. For categorical variables, the differences were assessed using Fisher's exact test. A logistic regression analysis (Backward Stepwise) was performed to identify the initial clinical and laboratory features that distinguish leukemia from SoJIA patients. The overall survival was analyzed by the Kaplan-Meier method, and survival curves were compared by the log-rank test in leukemia patients with and without limb pain as well as in the overall group of 190 leukemia patients vs. leukemia patients with limb pain (n = 40). For all statistical tests, the level of significance for independent variables was set at 5% ($p < 0.05$).

## RESULTS

### Demographic data

The median ages at disease onset and at diagnosis were significantly higher in leukemia patients compared to SoJIA patients [5.8 (0.5-14.2) vs. 3.8 (0.5-13.3) years, $p = 0.0006$ and 6.1 (0.8-14.3) vs. 5 (0.9-15) years, $p = 0.0272$; respectively]. In contrast, the period between disease onset and diagnosis was significantly shorter in the first group [30 days (3-240) vs. 150 days (42-3210), $p < 0.0001$]. No statistical differences were observed for the female gender in both groups (38% vs. 53%, $p = 0.0987$). The median follow-up period for leukemia patients was eight years (1-13), and the median of follow-up period for SoJIA patients was 6.9 years (1-14).

### Clinical features

The occurrence of clinical manifestations in leukemia patients compared to SoJIA patients is shown in Table 1. The frequencies of limb pain, hepatomegaly, weight loss and hemorrhagic manifestations were significantly higher in leukemia patients than in SoJIA patients (70% vs. 1%, $p < 0.0001$; 54% vs. 32%, $p = 0.0075$; 30% vs. 8%, $p = 0.0005$ and 9% vs. 0%, $p = 0.0053$; respectively).

The frequencies of arthritis, fever, adenomegaly, rheumatoid rash and pericarditis were significantly lower in leukemia patients than in SoJIA patients (25% vs. 100%, $p < 0.0001$; 68% vs. 100%, $p < 0.0001$; 21% vs. 46%, $p = 0.002$ and 0% vs. 69%, $p < 0.0001$; 0% vs. 16%, $p = 0.0006$; respectively). No differences were observed in the frequencies of arthralgia,

**Table 1 -** Initial clinical manifestations in acute lymphoblastic leukemia patients vs. systemic-onset juvenile idiopathic arthritis patients.

| Variables | LEUKEMIA (n = 57) | SoJIA (n = 102) | p-value |
|---|---|---|---|
| Arthralgia | 40 (70) | 75 (73) | 0.7128 |
| Arthritis | 14 (25) | 102 (100) | <0.0001 |
| Limb pain | 40 (70) | 1 (1) | <0.0001 |
| Nighttime pain | 2 (3) | 2 (2) | 0.6183 |
| Fever | 39 (68) | 102 (100) | <0.0001 |
| Hepatomegaly | 31 (54) | 33 (32) | 0.0075 |
| Splenomegaly | 26 (46) | 31 (30) | 0.0602 |
| Adenomegaly | 12 (21) | 47 (46) | 0.002 |
| Weight loss | 17 (30) | 8 (8) | 0.0005 |
| Hemorrhagic manifestations | 5 (9) | 0 (0) | 0.0053 |
| Rheumatoid rash | 0 (0) | 70 (69) | <0.0001 |
| Pericarditis | 0 (0) | 16 (16) | 0.0006 |
| Myocarditis | 0 (0) | 8 (8) | 0.0513 |

Values expressed in n (%).

nighttime pain, splenomegaly, or myocarditis in either group (Table 1).

## Laboratory alterations

The median hemoglobin, white blood cell count, neutrophil count, and platelet counts were significantly lower in leukemia patients than in SoJIA patients (7 g/dl vs. 9.7 g/dl, $p<0.0001$; $4.6\times10^3/mm^3$ vs. $12.3\times10^3/mm^3$, $p<0.0001$; $0.8\times10^3/mm^3$ vs. $7.3\times10^3/mm^3$, $p<0.0001$ and $56.5\times10^3/mm^3$ vs. $490\times10^3/mm^3$, $p<0.0001$). Conversely, the median LDH level was significantly higher in leukemia patients than in SoJIA patients (822.5 mg/dl vs. 305 mg/dl, $p<0.0001$). No differences were observed in the median uric acid levels for the two groups (Table 2).

The percentages of anemia, leukopenia, neutropenia, thrombocytopenia, and high LDH levels were statistically higher in leukemia patients than in SoJIA patients (88% vs. 57%, $p<0.0001$; 39% vs. 1%, $p<0.0001$; 60% vs. 1%, $p<0.0001$; 77% vs. 1%, $p<0.0001$ and 56% vs. 14%, $p<0.0001$; respectively). In contrast, the frequencies of leukocytosis and thrombocytosis were significantly lower in leukemia patients than in SoJIA patients (17% vs. 54%, $p<0.0001$ and 2% vs. 68%, $p<0.0001$; respectively), whereas the levels of uric acid were similarly high in both groups (Table 3).

## Leukemia patients

The distributions of immunophenotypes (B- and T-lineages) were similar in leukemia patients with limb pain compared to those without limb pain (98% vs. 88%, $p=0.2$ and 2% vs. 12%, $p=0.2$; respectively). These immunophenotypes

were also similar in the overall group of patients (n = 190) compared to leukemia patients with limb pain (92% vs. 98%, $p=0.3189$ and 8% vs. 2%, $p=0.3189$; respectively).

The percentage of high-risk patients was similar in leukemia patients with limb pain compared to those without limb pain (28% vs. 29%, $p=1.0$). In addition, the percentage of high-risk patients was also similar in the overall group of patients compared to leukemia patients with limb pain (41% vs. 28%, $p=0.1527$).

## Multivariate analysis

Logistic regression analysis was performed by including the following 10 independent variables that presented a level of statistical significance of $\leq20\%$ in the univariate analyses: limb pain, hepatomegaly, splenomegaly, weight loss, hemorrhagic manifestations, anemia, leukopenia, neutropenia, thrombocytopenia and high LDH levels. The choice of the variables included in this model was performed according to the clinical plausibility for a leukemia diagnosis. Only limb pain (OR = 553; 95% CI = 46.48-6580.42; $p<0.0001$) and thrombocytopenia (OR = 754.13; 95% CI = 64.57-8806.72; $p<0.0001$) remained independent risk factors that distinguished leukemia from SoJIA patients. The R2 of the Nagelkerke test was 0.91 (Table 4).

## Kaplan-Meier survival curves

The Kaplan-Meier overall survival curves were similar in leukemia patients with and without limb pain ($p=0.8322$; Figure 1). The survival percentage of leukemia patients with limb pain six years after disease onset was 77%. The survival percentage of leukemia patients without limb pain five years after disease onset was 76%.

The overall Kaplan-Meier survival curves were also similar in the overall group of 190 leukemia patients and leukemia patients with limb pain ($p=0.4875$; Figure 2). The survival percentage of the overall group of leukemia patients six years after disease onset was 83%, and the survival percentage of leukemia patients with limb pain six years after the disease onset was 77%.

## DISCUSSION

To our knowledge, this is the first study to evaluate the largest series of children and adolescents with leukemia and remarkable musculoskeletal manifestations and compare these patients to those with SoJIA followed in a tertiary pediatric university hospital. The results clearly showed that limb pain and thrombocytopenia discriminate leukemia from SoJIA patients at disease onset.

One of the most significant advantages of the present study was a systematic evaluation by the same team of

**Table 2 -** Initial laboratory alterations in acute lymphoblastic leukemia patients vs. systemic-onset juvenile idiopathic arthritis patients.

| Variables | LEUKEMIA (n = 57) | SoJIA (n = 102) | p-value |
|---|---|---|---|
| Hemoglobin (g/dl) | 7 (3.1–11.3) | 9.7 (5.4–15.5) | <0.0001 |
| WBC (x10$^3$/mm$^3$) | 4.6 (0.5–80) | 12.3 (3.1–71.8) | <0.0001 |
| Neutrophils count (x10$^3$/mm$^3$) | 0.8 (0–15.6) | 7.3 (0.7–69.7) | <0.0001 |
| Platelets count (x10$^3$/mm$^3$) | 56.5 (12.8–499) | 490 (70–1200) | <0.0001 |
| LDH (mg/dl) | 822.5 (167–7900) | 305 (13–4486) | <0.0001 |
| Uric acid (mg/dl) | 4.1 (1.3–14.4) | 3.7 (0–6.1) | 0.2209 |

Values expressed in median (range), WBC - white blood cell count, LDH - lactic dehydrogenase.

**Table 3 -** Initial laboratory alterations in acute lymphoblastic leukemia patients vs. systemic-onset juvenile idiopathic arthritis patients.

| Variables | LEUKEMIA (n = 57) N/n (%) | SoJIA (n = 102) N/n (%) | p-value |
|---|---|---|---|
| Anemia (<10 g/dl) | 50/57 (88) | 58/102 (57) | <0.0001 |
| Leukopenia (<4.000/mm³) | 22/57 (39) | 1/102 (1) | <0.0001 |
| Leukocytosis (>12.000/mm³) | 10/57 (17) | 55/102 (54) | <0.0001 |
| Neutropenia (<1.000/mm³) | 34/57 (60) | 1/102 (1) | <0.0001 |
| Thrombocytopenia (<150.000/mm³) | 44/57 (77) | 1/102 (1) | <0.0001 |
| Thrombocytosis (>400.000/mm³) | 1/57 (2) | 69/102 (68) | <0.0001 |
| High LDH (mg/dl) * | 32/57 (56) | 6/43 (14) | <0.0001 |
| High Uric acid (mg/dl) * | 19/57 (33) | 3/11 (27) | 0.73 |

LDH - lactic dehydrogenase,
*reference range based on age.

pediatric rheumatologists and oncologists, with the exclusion of patients treated with glucocorticosteroids. In fact, this treatment may delay a malignancy diagnosis and reduce the subsequent response to chemotherapy.[15] Moreover, not all leukemia patients had blasts in their peripheral blood when they were assessed.

Conversely, our study was retrospective in nature and included evaluations of peripheral blood smear abnormalities, acute phase reaction, LDH and uric acid levels. In particular, the last two examinations were not collected in all patients; however, missing values have also been an issue in others studies.[9,11]

Leukemia is the most common pediatric cancer in the United States[1] and Brazil.[16] The disease can present with musculoskeletal findings mimicking rheumatic diseases, including JIA,[17-23] rheumatic fever,[5] juvenile systemic lupus erythematosus, and pediatric vasculitis,[6,9] as reported by our pediatric rheumatology and oncology services.[7] The initial presentation of pediatric leukemia consists of various osteoarticular signals and symptoms, including arthralgia, arthritis and limb pain, which may cause nighttime wakening.[6-11,17-20]

In addition, JIA includes seven different subtypes, arthritis persisting for more than six weeks and a disease onset before the age of 16.[14] SoJIA is a particular and infrequent subtype of JIA and is very similar to adult-onset Still's disease[24] with a specific clinical diagnosis and cytokine profile, as previously described by our group.[25,26] Children and adolescents with

**Table 4 -** Logistic regression analysis to evaluate risk factors distinguishing acute lymphoblastic leukemia from systemic-onset juvenile idiopathic arthritis patients.

| Independent variable | OR | 95% CI | R2 | p-value |
|---|---|---|---|---|
| Limb pain | 553 | 46.48-6580.42 | 0.91 | <0.0001 |
| Thrombocytopenia | 754.13 | 64.57-8806.72 | | <0.0001 |

OR - odds ratio, CI – confidence interval, R2 - R2 of Nagelkerke test.
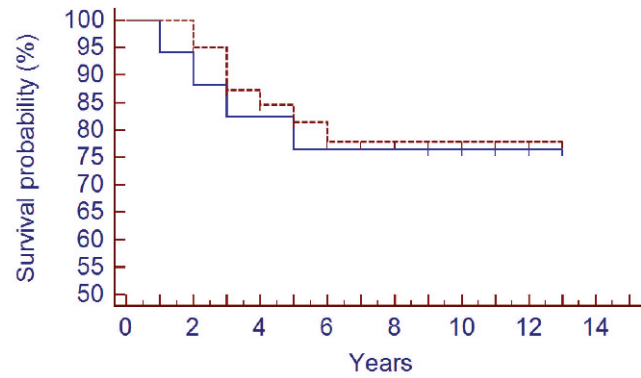


**Figure 1 -** The Kaplan-Meier overall survival curves between leukemia patients without (n = 17) and with limb pain (n = 40) (p = 0.8322).

SoJIA have prominent extra-articular manifestations and a significant elevation in acute phase reactants.[13]

The differential diagnosis of suspected SoJIA may be very difficult, particularly at disease onset, when the patient may have only systemic manifestations without arthritis. Therefore, the possibility of leukemia should be always considered, as patients with SoJIA could have a longer period between disease onset and diagnosis, as observed here. Moreover, these two diseases have an impact on morbidity and health-related quality of life.[27]

In the univariate analysis, limb pain, hepatomegaly, weight loss, and hemorrhagic manifestations were predominantly observed in our leukemia patients compared to SoJIA patients, consistent with previous observations.[7-9] We also found higher levels of anemia, leukopenia, neutropenia, thrombocytopenia, and LDH in our acute lymphoblastic leukemia patients, similar to the findings in other studies.[5-7,10] Interestingly, Wallendal et al[20] showed
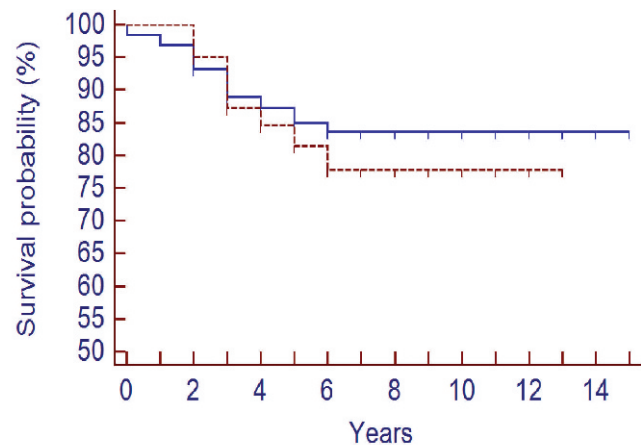


**Figure 2 -** The Kaplan-Meier overall survival curves between the whole group of leukemia patients (n = 190) and leukemia patients with limb pain (n = 40) (p = 0.4875).

that serum LDH levels were significantly higher in cancer patients, including eight patients with leukemia.

Remarkably, we found that limb pain and thrombocytopenia differentiated leukemia from SoJIA patients. The logistic regression revealed a wide confidence interval; however, the minimum values of these confidence intervals for both of the independent variables were high enough to be considered. Importantly, the elevated $R2$ value of the Nagelkerke test showed that the mathematical model of this multivariate analysis was well adjusted to explain this occurrence, indicating that these two independent variables were associated with leukemia in 91% of our patients.

Of note, Jones et al[11] showed that the three most important predictive factors for a pediatric leukemia diagnosis were leukopenia, thrombocytopenia, and a history of nighttime pain. In this multicenter study, the authors included the three most frequent JIA subtypes (pauciarticular, polyarticular, and systemic).

In the present study, arthritis and other extra-articular manifestations such as fever, adenomegaly, rheumatoid rash, and pericarditis were predominantly observed in SoJIA patients. Likewise, leukocytosis and thrombocytosis were frequently seen in the patients with this pediatric rheumatic disease and could distinguish them from leukemia patients. The presence of bicytopenia or pancytopenia should also exclude MAS, which is a potential life-threatening complication of SoJIA[13,24,26,28] and can rarely be one of the first manifestations of this disease. None of SoJIA patients had MAS at disease onset, and none died during the evaluation.

In conclusion, the present study emphasizes the importance of investigating leukemia in children and adolescents that present with musculoskeletal manifestations, and in particular, those with limb pain and thrombocytopenia. These symptoms may mimic SoJIA, even in the absence of blasts on the peripheral blood smear.

## ACKNOWLEDGMENTS

## REFERENCES

1. Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992–2004). Cancer. 2008;112:416-32, doi: 10.1002/cncr.23169.
2. CDC. Trends in childhood cancer mortality–United States, 1990–2004. MMWR Morb Mortal Wkly Rep. 2007;56:1257-61.
3. Musiej-Nowakowska E, Rostropowicz-Denisiewicz K. Differential diagnosis of neoplastic and rheumatic diseases in children. Scand J Rheumatology. 1986;15:124-8, doi: 10.3109/03009748609102077.
4. Cabral DV, Tucker LB. Malignancies in children who initially present with rheumatic complaints. J Pediatr. 1999;134:53-7, doi: 10.1016/S0022-3476(99)70372-0.
5. Menon S, Isenberg DA. Rheumatological manifestations of haematological diseases. Ann Rheum Dis. 1995;54:787-95, doi: 10.1136/ard.54.10.787.
6. Barbosa CM, Nakamura C, Terreri MT, Lee ML, Petrilli AS, Hilario. Musculoskeletal manifestations as the onset of acute leukemias in childhood. J Pediatr (Rio J). 2002;78:481-4, doi: 10.1590/S0021-75572002000600007.
7. Campos LM, Goldstein S, Santiago RA, Jesus AA, Cristofani LM, Odone Filho V, et al. Musculoskeletal involvement as a first manifestation of neoplasm disease. Rev Assoc Med Bras. 2008;54:132-8, doi: 10.1590/S0104-42302008000200015.
8. 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, doi: 10.1016/S0022-3476(05)80535-9.
9. Robazzi TC, Barreto JH, Silva LR, Santiago MB, Mendonça N. Osteoarticular manifestations as initial presentation of acute leukemias in children and adolescents in Bahia, Brazil. J Pediatr Hematol Oncol. 2007;29:622-6, doi: 10.1097/MPH.0b013e3181468c55.
10. 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, doi: 10.1016/S0022-3476(05)83543-7.
11. Jones OY, Spencer CH, Bowyer SL, Dent PB, Gottlieb BS, Rabinovich CE. A multicenter case-control study on predictive factors distinguishing childhood leukemia from juvenile rheumatoid arthritis. Pediatrics. 2006;117:840-4, doi: 10.1542/peds.2005-1515.
12. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet. 2007;369:767-78, doi: 10.1016/S0140-6736(07)60363-8.
13. Silva CA, Silva CH, Robazzi TC, Lotito AP, Mendroni Junior A, Jacob CM, et al. Macrophage activation syndrome associated with systemic juvenile idiopathic arthritis. J Pediatr (Rio J). 2004;80:517-22.
14. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31:390-2.
15. Révész T, Kardos G, Kajtár P, Schuler D. The adverse effect of prolonged prednisolone pretreatment in children with acute lymphoblastic leukemia. Cancer. 1985;55:1637-40, doi: 10.1002/1097-0142(19850415)55:8<1637::AID-CNCR2820550804>3.0.CO;2-H.
16. de Camargo B, de Oliveira Santos M, Rebelo MS, de Souza Reis R, Ferman S, Noronha CP, et al. Cancer incidence among children and adolescents in Brazil: first report of 14 population-based cancer registries. Int J Cancer. 2010;126:715-20, doi: 10.1002/ijc.24799.
17. Schaller J. Arthritis as a presenting manifestation of malignancy in children. J Pediatr. 1972;81:793-7, doi: 10.1016/S0022-3476(72)80108-2.
18. Saulsbury FT, Sabio H. Acute leukemia presenting as arthritis in children. Clin Pediatr. 1985;24:625-8, doi: 10.1177/000992288502401103.
19. Gonçalves M, Terreri MT, Barbosa CM, Len CA, Lee L, Hilário MO. Diagnosis of malignancies in children with musculoskeletal complaints. Sao Paulo Med J. 2005;123:21-3, doi: 10.1590/S1516-31802005000700016.
20. Wallendal M, Stork L, Hollister R. The discriminating value of serum lactate dehydrogenase levels in children with malignant neoplasms presenting as joint pain. Arch Pediatr Adolesc Med. 1996;150:70-3.
21. Murray MJ, Tang T, Ryder C, Mabin D, Nicholson JC, et al. Childhood leukaemia masquerading as juvenile idiopathic arthritis. BMJ. 2004;329:959-61, doi: 10.1136/bmj.329.7472.959.
22. Tafaghodi F, Aghighi Y, Rokni Yazdi H, Shakiba M, Adibi A. Predictive plain X-ray findings in distinguishing early stage acute lymphoblastic leukemia from juvenile idiopathic arthritis. Clin Rheumatol. 2009;28:1253-8, doi: 10.1007/s10067-009-1221-0.
23. Marwaha RK, Kulkarni KP, Bansal D, Trehan A. Acute lymphoblastic leukemia masquerading as juvenile rheumatoid arthritis: diagnostic pitfall and association with survival. Ann Hematol. 2010;89:249-54, doi: 10.1007/s00277-009-0826-3.
24. Martini A, Lovell DJ. Juvenile idiopathic arthritis: state of the art and future perspectives. Ann Rheum Dis. 2010;69:1260-3, doi: 10.1136/ard.2010.133033.
25. Lotito AP, Campa A, Silva CA, Kiss MH, Mello SB. Interleukin 18 as a marker of disease activity and severity in patients with juvenile idiopathic arthritis. J Rheumatol. 2007;34:823-30.
26. Nádia EA, Carvalho JF, Bonfá E, Lotito AP, Silva CA. Macrophage activation syndrome associated with etanercept in a child with systemic onset juvenile idiopathic arthritis. Isr Med Assoc J. 2009;11:635-6.
27. Kuczynski E, Silva CA, Cristófani LM, Kiss MH, Odone Filho V, Assumpção FB Jr. Quality of life evaluation in children and adolescents with chronic and/or incapacitating diseases: a Brazilian study. An Pediatr (Barc). 2003;58:550-5, doi: 10.1157/13048092.
28. Ravelli A, Magni-Manzoni S, Pistorio A, Besana C, Foti T, Ruperto N, et al. Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. J Pediatr. 2005;146:598-604, doi: 10.1016/j.jpeds.2004.12.016.