RESEARCH ARTICLE

Bone involvement at diagnosis as a predictive factor in children with acute lymphoblastic leukemia

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Abstract

Background: Bone involvement represents a common symptom at diagnosis in children with acute lymphoblastic leukemia, and its prognostic value is not entirely clarified. The aim of this study was to evaluate bone involvement at diagnosis in children with acute lymphoblastic leukemia as a predictive factor and to correlate its presence with other demographic, clinical, and laboratory findings.

Methods: We retrospectively reviewed the medical records of 97 children with acute lymphoblastic leukemia diagnosed from January 2005 to December 2014. The mean age of patients was 5.7 years, and 83 (85.6 %) of them were diagnosed with B-acute lymphoblastic leukemia.

Results: Among the 97 children, 46 (47.4 %) reported bone involvement at the time of diagnosis. Among children with B-acute lymphoblastic leukemia 43/83 (51.8 %) reported bone involvement, while among children with T-acute lymphoblastic leukemia only 3/14 (21.4 %) (p =0.04). Bone involvement was registered more frequently among males (30/59; 50.8 %) in comparison to females (16/38; 42.2 %) (p =0.414). The mean white blood cell count at diagnosis was lower among children with bone involvement (109,800/mm^3 vs. 184,700/mm^3) (p =0.092). The mean age of patients with bone involvement was four years, which differs significantly from those without bone involvement (p =0.029). Moreover, children with bone involvement at diagnosis were prednisone "good responders" (79.5 %) when compared with those without bone involvement (58.8 %) (p =0.046). Additionally, mean serum phosphate values were higher at diagnosis among children with bone involvement (5.3 mg/dl vs. 4.8 mg/dl, p =0.035).

Conclusions: The presence of bone involvement at diagnosis is related with immunophenotype of B-acute lymphoblastic leukemia, lower mean age, lower mean white blood cell count and good prednisone response. According to presented data, we conclude that the presence of bone involvement at diagnosis represents a positive predictive factor for outcome/survival. Hippokratia 2016, 20(3): 227-230

Key words: Acute lymphoblastic leukemia, bone pain, prognosis, childhood

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy and accounts for 85 % of leukemias in childhood. Bone involvement (bone pain, limping, arthritis) is reported by 21-59 % of children at diagnosis of ALL and is due to pressure applied to the periosteum by leukemic-cell infiltration, while joint pain is caused by lesions of the periosteum[1]. According to literature, bone involvement is usually manifested in the morning, mainly in the lower extremities, and is the main cause of limping[2-7]. Joint pain affects mainly the lower extremities, most commonly involving the knee joint[2-7]. The predictive value of bone involvement at diagnosis in children with ALL has not yet been fully clarified. However, most studies confirm that bone involvement occurs more often in younger children with lower white blood cell count (WBC) at diagnosis, while in some studies it is associated with normal WBC accompanied by the absence of lymphoblasts in peripheral blood[8-10]. Aim of this retrospective, observational study was to evaluate bone involvement at diagnosis in children with ALL admitted in our Department during the last ten years as a predictive factor and to correlate them with other demographic, clinical, and laboratory findings.

Materials and Methods

The study was a single-center, retrospective, observational study covering the period from January 2005 to December 2014. We included in the study all children with a diagnosis of B- or T-cell ALL hospitalized in the 2nd Pediatric Department of AHEPA Hospital, in Thessaloniki. Treatment of the patients was based on the

protocols ALL-BFM 95 and ALLIC BFM 2009. The following variables were collected retrospectively from the patients' medical records: sex, age (years), presence or absence of bone involvement (bone pain, limping, arthritis) at diagnosis, immunophenotyping (B- or T-cell ALL), presence of CD10 (CALLA+) receptor in immunophenotyping (diagnosis), karyotype (hyperploidy, hypoploidy, normal karyotype), as well as the laboratory findings at diagnosis [WBC, hemoglobin count, platelet count, serum calcium and phosphate, lactate dehydrogenase (LDH)]. Moreover, data regarding the response to chemotherapy ("good" and "poor" prednisone responders on day 8 of chemotherapy according to the presence of blasts in the peripheral blood) and, finally, the outcome [5-year overall survival: (OS)] of patients were collected. Data were initially collected in a database, and subsequently, statistical analysis was conducted with the Statistical Package for the Social Science (SPSS) for Windows, version 15.0 (SPSS Inc., Chicago, IL). Ethics committee approval was deemed unnecessary because this is a retrospective study and patients were treated as per institutional protocols.

Data analysis was initially performed with descriptive statistics; the quantitative variables were described by measures of central tendency (mean, median) and dispersion [standard deviation (SD), range], whereas for qualitative variables the frequencies were calculated and were expressed in absolute number and percentage. The Kolmogorov-Smirnov test was used to test the normality of quantitative variables' distribution, as the number of the observations was more than 50. The quantitative variables that followed a normal distribution are described by the mean and SD, whereas those who did not, are described by the median and range. We compared two different populations of quantitative variables using Student's t-test for the variables that were distributed normally and the non-parametric Mann-Whitney test, for the variables that did not fulfill the normality. In order to study the relationship between the categorical variables, the chi-square test of independence was conducted. A significance level of $p < 0.05$ was determined while taking into account the confidence intervals.

Results

We included in the study 97 pediatric patients who were admitted in the Pediatric department with a diagnosis of ALL over the 10-year-period (2005-2014). The mean age of the patients was 5.7 years (SD: 3.78 years). Out of the 97 patients, 59 (60.8 %) were male. According to immunophenotyping of bone marrow aspirate performed at diagnosis, 83 children (85.6 %) had an immunophenotype compatible with B-lineage ALL and 14.4 % with T-lineage ALL. As regards the bone marrow karyotype at diagnosis, available for 62 patients, hyperdiploidy was revealed in 12 (19.4 %), hypodiploidy in four (6.5 %) and a normal number of chromosomes in the remainder 46 (74.2 %) children. Prednisone response was evaluated based on the peripheral blood blast count at day 8 as follows: 67 subjects (69 %) were prednisone "good responders" (peripheral blood blast count <1,000/mm^3), whereas 30 subjects (31 %) were prednisone "poor responders" (peripheral blood blast count >1,000/mm^3). Finally, regarding the outcome (5-year OS) we found that 72 subjects (74.2 %) survived. These results are shown in Table 1.

At diagnosis 46 subjects presented with bone involvement (47.4 %). The mean value of WBC, hemoglobin count, platelet count, LDH, calcium, and phosphate in the serum at the diagnosis was: 139,420/mm^3 (SD: 80,900), 7.97 mg/dl (SD: 2.5), 80,251/mm^3 (SD: 88,900), 2,356.6 IU/L (SD: 3,785), 9.26 mg/dl (SD: 0.96), and 5.08 mg/dl (SD 0.83), respectively.

The mean age of subjects was 6.07 years for males and 5.2 years for females, which was not significantly different. Respectively, the mean WBC at diagnosis for males was 196,100/mm^3 and for females 56,900/mm^3 ($p < 0.05$) whereas the mean hemoglobin count was 8.01 mg/dl for males and 7.9 mg/dl for females ($p > 0.05$). Concerning the presence or absence of bone involvement at diagnosis, we found that 43 out of 83 children with B-cell ALL (51.8 %) presented with bone involvement in comparison to 3 out of 14 children with T-cell ALL (21.4%) ($p = 0.04$) (Table 1). Regarding bone involvement and sex, we did not find a statistically significant difference between males and females; however, bone involvement was documented mostly in males (30 out of 59, 50.8 %) than in females (16 out of 38, 42.2 %), ($p = 0.414$). The mean value of WBC at diagnosis was lower in children with bone involvement (109,800/mm^3 versus 184,700/mm^3), but this difference was not statistically significant ($p = 0.092$). Finally, the median age of subjects with bone involvement at diagnosis was four years [interquartile range (IQR): 4], whereas the median age of subjects without bone pain was six years (IQR: 5.5) ($p = 0.029$) (Table 1).

The median value of hemoglobin for children with bone involvement was 8.0 mg/dl, while for those without bone involvement was 7.9 mg/dl ($p = 0.6$). The mean value of platelet count was lower in children with bone involvement at diagnosis in comparison to those without (68,400/mm^3 versus 91,200/mm^3, $p = 0.37$). Finally, the mean value of LDH was higher in children with bone involvement, although it did not differ significantly (1,700 IU/L versus 2,558 IU/L, $p = 0.68$).

A significant difference was reported between the two patients' groups regarding the response to corticosteroid treatment at day 8. Specifically, 35 out of 44 subjects with bone involvement at diagnosis were prednisone "good responders" (79.5 %) in comparison to 30 out of 51 subjects without bone pain at diagnosis (58.8 %) ($p = 0.046$). Moreover, the mean value of serum calcium among patients with or without bone involvement did not differ significantly (9.29 mg/dl versus 9.24 mg/dl respectively, $p = 0.558$). Contrary to this, a significant difference in the mean value of serum phosphate between the two groups was recorded, namely serum phosphate was higher in children with bone involvement at diagnosis (5.3

Table 1: Descriptive data of the 97 children included in this retrospective, observational study, as well as laboratory findings, response to prednisone and overall survival for the whole sample and for two subgroups (with or without bone involvement).

	Total sample **n =97**	Presence of bone involvement **n =46**	Absence of bone involvement **n =51**	p
Sex:				
- males	59 (60.8 %)	30/59	30/59	p >0.05
- females	38 (39.2 %)	16/38	22/38	
Age (years)	5.7 (SD: 3.78)	4 (IQR: 4)	6 (IQR: 5.5)	**p =0.029**
Immunophenotype:				
- B-ALL	83 (85.6 %)	43/83	40/83	
- T-ALL	14 (14.4 %)	3/14	11/14	**p =0.04**
Laboratory findings at diagnosis:				
- Calcium (mg/dl)	9.26	9.29	9.24	p =0.558
- Phosphate (mg/dl)	5.08	5.3	4.8	p =0.035
- LDH (IU/L)	2356.6	2.558	1.700	p =0.68
- White blood cell count (/mm3)	139,420	109,800	184,700	p =0.092
- Hemoglobin (mg/dl)	7.97	8	7.9	p =0.6
- Platelets (/mm3)	80,251	91,200	68,400	p =0.37
Karyotype:				
- hyperploidism	12 (19.4 %)	8	4	
- hypoploidism	4 (6.5 %)	0	4	p =0.172
- normal	46 (74.2 %)	18	28	
Response to prednisone:				
- good responders	67 (69 %)	37/ 67	30/67	**p =0.046**
- bad responders	30 (31 %)	9/30	21/30	
Outcome: OS	72 (74.2 %)	38	34	p =0.108

n: number, ALL: acute lymphoblastic leukemia, LDH: lactate dehydrogenase, OS: overall survival, SD: standard deviation, IQR: interquartile range.

mg/dl versus 4.8 mg/dl, p =0.035). Finally, a relationship between bone involvement and karyotype was not found (p =0.172) as well as between bone involvement and patients' 5-year OS (p =0.108) (Table 1).

Discussion

Presented data demonstrate that the presence of bone involvement at diagnosis is more related with B-acute lymphoblastic leukemia immunophenotype, lower mean age, lower mean white blood cell count, and prednisone "good response". According to literature, the frequency of malignancy in children with musculoskeletal pain or any other involvement of the musculoskeletal system (arthralgia, limping, pathologic fracture) ranges from one in 10,000 to 1 %, with ALL being the most common diagnosis[11-13]. Regarding its pathogenesis, the disease itself is responsible for the direct or indirect activation of osteoclasts through the production of mediators by lymphoblasts[14,15]. It is also known that fractures can occur at diagnosis, during or after the end of therapy, and even a long time after the end of therapy[16]. The pediatrician's role in investigating bone involvement in children is important as he should cooperate with other specialists and coordinate the laboratory and imaging studies, especially in children with acute onset of symptoms, without a history of recent trauma and with concomitant signs and symptoms.

The predictive value of bone involvement at diagnosis in children with acute lymphoblastic leukemia has not yet been clarified in the literature. However, it emerges that bone involvement occurs more often in younger children with lower WBC at diagnosis, while in some studies it is associated with normal WBC accompanied by a lack of blasts in peripheral blood[8-10]. According to Robazzi et al, the median time from initial symptoms to definitive diagnosis rises to 50 days, while there are studies that report cases of children with musculoskeletal symptoms being treated initially for rheumatoid arthritis delaying the diagnosis of malignancy[13,17,18]. According to these studies, the delay in diagnosis is due to the lack of other symptoms as well as of laboratory findings indicative of leukemia.

As we already mentioned the presence of bone involvement at diagnosis in children with ALL is reported in 21-59 % of the cases, while in our study this rose to 47.4 %. Presumably, this range is due to different ways of recording data or estimating other symptoms that accompany bone pain, as limping and arthralgia. Maman et al, reported that out of the 765 children with leukemia evaluated, 240 reported musculoskeletal symptoms, such as bone pain, arthralgia, low back pain, limping, arthritis, and refusal to walk (31.4 %)[9]. Moreover, it was found that patients with musculoskeletal symptoms at diagnosis had a lower WBC and blast count in peripheral blood as well as higher hemoglobin value and platelet count at diagnosis. Concerning the WBC our findings are in ac-

cordance with those of Maman et al and other studies in literature[9,16,19]. On the contrary, in our study, we did not find a significant difference in hemoglobin values among children with and without bone involvement, while the platelet count in children with bone involvement was higher but did not differ significantly.

Regarding the immunophenotype of our patients we found that children with B-cell ALL presented more frequently with bone involvement and this difference was statistically significant. Our findings are in accordance with other international and national studies. According to the findings of Maman et al bone pain is reported in 36.3 % of children with B-cell ALL over 14.2 % of children with T-cell ALL[9]. The correlation between bone pain involvement at diagnosis and B-cell ALL has been described in the literature, and it is possibly related to more favorable laboratory findings, primarily with low WBC[9,20,21]. This could be attributed to the fact that B-cell ALL is of medullary origin, whereas T-cell ALL originates from thymus and then expands and involves the bone marrow[22,23]. As a result, 79.5 % of our patients with bone involvement were prednisone "good responders" versus 58.8 % of those without bone involvement. This fact is probably due to the more favorable B-cell immunophenotype as well as to the lower WBC at diagnosis, as also reported in other studies[9,10].

Finally, our data demonstrated a statistically significant difference between the values of serum phosphate that were higher in children with bone involvement at diagnosis. This finding has not been reported in other studies in the literature. We believe that higher values of serum phosphate in children with bone involvement at diagnosis, observed before a possible tumor lysis syndrome in patients with large tumor burden, are probably explained by the pathophysiology of phosphate metabolism. It is known that phosphate is the second most abundant inorganic element after calcium in the human organism and it is a structural component of bones, in which 80 % of its total quantity is found. Therefore, the activation of osteoclasts by lymphoblasts could be responsible for the release of bone phosphate that results to higher serum phosphate values.

In conclusion, our results show that the presence of bone involvement at diagnosis of childhood ALL is associated with better prognosis according to immunophenotype, WBC, and good response to corticosteroids at day 8 of treatment. Moreover, by the above-mentioned data, we concluded that it is of crucial importance the referral of children with bone involvement to specialized centers to establish the diagnosis based on clinical and laboratory findings.

Conflicts of interest

None to declare.

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