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Original Research Article

Clinical, hematological, and laboratory presentation of acute lymphoblastic leukemia of children in Diyala province/Eastern Iraq

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ABSTRACT

Background: To show the initial presenting features the children of acute lymphoblastic leukemia presented till the diagnosis at oncology Center/ Diyala/ Iraq.
Methods: A retrospective study, carried out during 2016-2017. The data include constitutional, hematological, and infiltrative features with laboratory findings registered at patient's files until the diagnosis. Data were analyzed by Statistical Package of Social Sciences v. 20.
Results: The total patients were 55, distributed into: T- cell (10.9%) and B- cell leukemia (89.1%), FAB classification include L1 (11%), L 2 (89%) and L3 (0%). Most of patients presented at 1- 10 years of age (p value= 0.000); M: F= 1.3:1 (p value= 0.345). Fever and pallor were the most common features, 81.8% (p value=0.000) and 67.3% (p value=0.010), respectively. Other features were bone pain (40%), anorexia (36.4%), fatigability (30.9%), muco-cutaneous bleeding (27.3%), hepatosplenomegaly (56.4%), lymphadenopathy (49.1%), and facial palsy (1.8%). Hemoglobin was < 8 gm/ dl in 70.9 %, white cell count was < 50×109 cells/L in 70.9 %; 12.3% has severe leukocytosis, and platelets' count was between 20- 100 × 109 cells/L in 49%. Mediastinal infiltration (7.2%), pleural effusion (1.8%), pericardial effusion (1.8%), and positive cytospin (5.4%).
Conclusions: L2 subtype was the dominant subtype; this contrary to all other studies and may be related to the prognosis. Most of the initial features were general and may indicate more common illnesses, but their constellation with complete blood picture should rise the possibility of leukemia. A rare complication, pleural effusion, was detected as initial feature.

Keywords: Children, Clinical presentation, Leukemia

INTRODUCTION

Pediatric malignancy is a low-prevalence disease in primary care, emergency departments and general paediatrics settings. A general practitioner, for example, is likely to encounter a child with cancer only once every 20 years and this problem is magnified by the heterogeneity of paediatric malignancies, which differ widely in their pathology and presenting symptoms. For example, typical presenting symptoms will vary for leukemia, brain tumors and bone tumors.[1] Early diagnosis of cancer has a fundamental goal in oncology because it allows an opportunity for timely treatment while disease burden is still in its earliest stages. Consequently, the prognosis may improve, and a cure can be attained with minimal side effects or late effects.[2]

Leukemia is the most common childhood malignancy. It accounts for 30% of all cancers diagnosed in children under 15 years of age in industrialized countries, acute

lymphoblastic leukemia (ALL) is the most frequent form, accounting for approximately 80% of leukemias.[3,4] Thorough history taking supported by a precise physical examination of suspicious patients are valuable tools in the diagnosis of the disease and they prevent delaying of therapy. Familiarity with the most common signs and symptoms along with uncommon features of leukemias is vital for faster diagnosis and better management and this will eventually increase the survival rate of these children. Leukemia usually presents with non-specific signs and symptoms which often mimicking the common, self-limiting illnesses and complicating the diagnostic challenge faced by clinicians.[5,6] This study was designed to show and analyze all the presenting features at, or before, the diagnosis of pediatric acute lymphoblastic leukemia at Oncology center of Diyala province/ Eastern Iraq.

METHODS

This is a retrospective study for acute lymphoblastic leukemia patients up to 13 years of age who were treated at Oncology Center of Al- Batool Teaching Hospital for Maternity and Children/ Diyala province/ Iraq which was established at 2012. The study was carried out within October 2016-February 2017. A self-prepared questionnaire was used to record patients' data from their files, then reviewed and analyzed. The diagnosis of leukemia was based on findings of complete blood count and bone marrow examination; only those patients with bone marrow proven diagnosis of ALL were included. Patients who showed morphological and cytochemical features of both myeloid and lymphoid differentiation and could not be classified were categorized as unclassified acute leukemia and excluded from the study.[7]

Classification of ALL in the center was reviewed, gathered and analyzed, it was based on the immunophenotyped of the leukemia (into B- and T- cell leukemia) and according to French- American- British (FAB) classification (morphological and cytochemical staining pattern, into L1, L2 and L3).[8] The data of the clinical presentations included all symptoms and signs the patient presented till proving the diagnosis, including: constitutional (fever, anorexia, fatigue, headache, weight loss, abdominal pain, and limb pain), hematological (pallor and bleeding), infiltrative features (hepatomegaly, splenomegaly, and lymphadenopathy, and neurological symptoms and signs). Routine laboratory investigations were hemoglobin (Hb) concentration, white blood cell (WBC) and platelet count, chest X-ray, echocardiography, and cerebrospinal fluid (CSF) analysis (Cytospin) for malignant cells. Data were analyzed by using Statistical Package of Social Sciences (SPSS) version 20. Chi square test was applied to display the association between variables; level of significance was set at (0.05).

RESULTS

A total of 57 leukemia patients (<13 years of age) were treated at the center, 2 (3.5%) of them were regarded as acute undifferentiated leukemia (AuL) and excluded from the study and 55 (96.5 %) diagnosed as ALL and enrolled in the study, 6 (10.9%) patients of them had T- cell and 49 (89.1%) B- cell leukemia. Regarding FAB classification, these ALL patients were distributed between L1 (n=6, 11%) and L 2 (n= 49, 89%) patients, whereas L3 class was nil.

Age and sex distribution

The first clinical presentation of most of patients were between 1 and 10 years of age (p value= 0.000); 2 years and 6 months was the peak age, the median age was 5 years and 6 months (66 month±41 month), 2 months was the least affected age and 13 years old was the oldest one, Male gender was more an affected than female (M: F= 1.3:1, p value= 0.345), Table 1.

Table 1: Distribution of the study group to the age at initial presentation and gender.

Age/gender	Male number (%)	Female number (%)	Total number (%)
‹ 1 year	0	2 (3.6)	2 (3.6)
1 year-10 years	25 (45.4)	20 (36.4)	45 (81.8) *
›10 years-13 years	6 (11)	2 (3.6)	8 (14.6)
Total	31 (56.4)	24 (43.6)	55 (100)

p value (0.000).

Clinical and hematological features

Fever and pallor were observed as the most common constitutional and hematological features, 81.8% and 67.3% respectively; these features were found together in 28 (51%) patients. Many other features were highly presented by leukemia patients, but significantly not associated with leukemia, including, by decreasing order: limb pain, anorexia, fatigability, and muco-cutaneous bleeding. Other common features were abdominal pain, weight loss, and headache. Infiltrative signs are present in most patients, including hepatosplenomegaly,

lymphadenopathy, and neurological manifestation (facial palsy, n=1, 1.8%). Both hepatosplenomegaly and lymphadenopathy were present simultaneously in about one third of patients (n=20, 36.4%, p value=.043), while isolated hepatomegaly or splenomegaly were less likely detected in ALL patients, Table 2.

Table 2: Clinical presentation of the study group.

Clinical Feature		Positive number (%)	Negative number (%)
Constitutional signs and symptoms	Fever	45 (81.8)**	10 (18.2)
	Limb/ bone pain[a]	22 (40)	33 (60)
	Anorexia	20 (36.4)	35 (63.6)*
	Fatigability	17 (30.9)	38 (69.1)*
	Abdominal pain	5 (9.1)	50 (99.9)**
	Weight loss	4 (7.3)	51 (92.7)**
	Headache	2 (3.6)	53 (96.4)**
	Abdominal distension	2 (3.6)	53 (96.4)**
	Sore throat	2 (3.6)	53 (96.4)**
	Cough and dyspnea	1 (1.8)	54 (98.2)**
	Ankle joint pain	1 (1.8)	54 (98.2)**
Hematological signs	Pallor	37 (67.3)	18 (32.7)
	Muco-cutaneous bleeding	15 (27.3)	40 (72.3)**
Infiltrative features	Hepatosplenomegaly[a]	31 (56.4)	24 (43.6)
	Lymphadenopathy[a]	27 (49.1)	28 (50.9)
	Hepatomegaly	7 (12.7)	48 (87.3)**
	Splenomegaly	3 (5.5)	52 (94.5)**
	Facial palsy	1 (1.8)	54 (98.2)**

p value: [a] Non- significant differences, * Significant association. ** Highly significant association.

Table 3: Initial laboratory and radiological features of the study group.

Laboratory test	Distribution number (%)
Hemoglobin (gm/dl)	
‹ 8	39 (70.9)**
8-10	12 (21.8)
› 10	4 (7.3)
Total	55
WBC count (× 10^9 cells/L)	
‹ 50	39 (70.9)**
50-100	7 (12.7)
› 100	9 (16.4)
Total	55
Platelet count (× 10^9 cells/L)	
‹ 20	14 (25.5)
20-100	27 (49)*
› 100	14 (25.5)
Total	55
Chest X-ray	
Mediastinal widening	4 (7.2)
Pleural effusion	1 (1.8)
Normal	50 (90)**
Total	55
Echocardiography	
Pericardial effusion	1 (1.8)
Normal	54 (98.2)**
Cerebrospinal fluid cytospin	
Positive	3 (5.4)
Negative	52 (94.6)**
Total	55

p value: * significant association, ** highly significant association.

Laboratory and radiological features

Hb concentration was less than 8 gm/ dl in 70.9 %, white cell count was less than 50×109 cells/L in 39 patients (70.9 %) and 12.3% has severe leukocytosis, and about half of children had platelets' count between 20-100 × 109 cells/L, 5 of them had muco-cutaneous ecchymosis; 14 patients had a count below 20× 109 cells/L, 8 of them developed muco-cutaneous ecchymosis, whereas 2 patients of those who had ecchymosis had a platelets count of more than 100 × 109 cells/L. Normal laboratory value, including normal Hb, WBC and platelets count without lymphoblast was reported in one patient (1.8%), this patient was died due to Graft versus Host disease to blood transfusion, Table 3.

Mediastinal infiltration was detected in 7.4% of the study group. Pleural and pericardial effusion were also reported by routine investigations in one patient for each before starting chemotherapy. Although neurological manifestations were present in one patient, cerebrospinal fluid Cytospin isolation for leukemia cells was positive for leukemia cell in 3 patients, Table 3.

DISCUSSION

Knowledge of signs and symptoms along with uncommon features of childhood leukemia will increase the physicians' awareness and early referral for diagnosis, hence improving the patient's outcome. This is the first study of childhood ALL in Diyala province. It was designed to show features of leukemia patients at or before diagnosis.

In a total of 55 patients, T- cell leukemia account for 10.9% and this was consistent with other studies concerning paediatrics population (10-15%), in other study T cell ALL reach 19%.[9-11] FAB L2 was commonest subtype (89%), followed by L1 (11%), whereas L3 is not detected. Previously, many different studies were found that these subtypes are closely related to prognosis, L1 is associated with the most favorable prognosis, L2 has a relatively poor prognosis, and L3 is considered by some as a hematogenous phase of Burkitt\'s.[7,12] In many childhood series worlds widely, Li is the commonest, followed by L2 and L3, respectively.[12,13] L2 was observed as the dominant subtype in the current study; this disparity might be due to genetic/ biological variation.[14]

The most common age of initial clinical presentation of ALL in the current study was between 1 and 10 years old (81.8%, p value=.000), these data were comparable to other studies.[10,15] Under one-year old and over 10 years old accounted for 2.6% and 14.6%, respectively. Historically, the age of presentation has a clear relationship to outcome of ALL; the age above one year - 10 years, which was the most concerned age group in this study, is the most favorable age group in contrast to other age groups.[16,17]

Studies have shown that females have more favorable survival outcomes compared to males and males had low EFS (event free survival) rates and unfavorable prognosis.[16,18,19] In this study, ALL incidence was observed more in male gender (M: F= 1.3:1) matching the finding of further studies, whereas it reached 1.84:1 in others.[11,15,20-22]

The commonest complaint of the study patients was fever, followed by bone pain, weight loss, and fatigability, these were consistent with findings by other studies.[23,24] Bone pain was presented in 22 patients (40%), it was variably reported by many studies (19-67%), Joint pain was present in one (1.8%) patient only (ankle joint), whereas it was presented more (6-9.3%) by other studies.[24-26] A previous study informed that children having ALL tend to present with joint symptoms (mono or polyarticular) rather than bone pain, the present study usually explain the limb pain due to bone involvement.[27]

Abdominal pain was observed in 9.1% of patients and 3.6% of patients had abdominal distension.[24,28] Robazzi et al, found that abdominal pain developed in 19.5% and distension (18.5%) with many other gastrointestinal manifestations, including diarrhea 3.6% and gastrointestinal bleeding 7.9%, which were not registered in the current study, they concluded that gastrointestinal symptoms are not very well-documented as initial manifestation of leukemia in children and should be considered on the differential diagnosis of gastrointestinal symptoms of unknown etiology in children.[28] In the present study, these complaints were less reported. Chronic or recurrent gastrointestinal manifestations are more significant, however, intestinal histopathological examination of complaining patients is needed to confirm infiltration.

Extramedullary invasion signs, include hepatosplenomegaly and lymphadenopathy, were common clinical features in the study, 56.4% and 49.1%, respectively, a study reported hepatosplenomegaly in (42%) and lymphadenopathy in 33-66%.[10,23,29] We believe that variation of rate of leukemia cell infiltration of these organs is related to the timing of diagnosis, thus more involvement is expectedly associated with delayed diagnosis.

Sore throat with cough and dyspnea were observed in 3.6 % and 1.8%, respectively, these are usually developing due to susceptibility to infections and usually associated with cervical lymph node enlargement.

Severe anemia was reported in most patients at diagnosis of ALL (70.9%), this was reported by other studies.[10,12] Low hemoglobin level is often responsible for fatigue and other associated symptoms that cause a decline in the quality of life of these children. Traditionally, a number of contributing factors such as overcrowding of the marrow, coexisting infections, and nutritional deficits have been used to explain it.[30] Teuffel et al, found a very

low hemoglobin levels at diagnosis are associated with more advanced disease in these subgroups, this may be related to the late diagnosis.[31]

Initial WBC count is one of the important prognostic factors in ALL and the count above 50.0×109cells/L was considered unfavorable criteria and classified as high risk of relapse, more than 70% of enrolled patients had a count below 50×109cells/L and 29% patients were having WBC count >50.0×109cells/L which was also observed by other study.[10,11] Patients with severe leukocytosis at diagnosis may present bulky tumor mass, mediastinal enlargement, hepatosplenomegaly and significant lymphadenopathy, this finding is usually associated with the unfavorable chromosomal translocations t (4;11) and t (9;22), this association was not proved in the current study and this may be due to small sample size.[10]

One fourth of presenting patients in the study was complaining from muco-cutaneous bleeding and one of them had bleeding tendency, while it comprises almost half of patients (47%) by other study.[23] A platelet count<100.0 × 109cells/L was observed in 74.5%, and 25.5% had severe thrombocytopenia (<20.0×109cells/L), these percentages were slightly higher than that found by other studies. Mucocutaneous bleeding is a well-known to be the most common site bleeding of thrombocytopenia including acute leukemia and this it was more frequently observed with decreasing platelet count in the current study, thus 18.5% of those who had a platelet count 20-100×109cells/L developed ecchymosis; 57% of a platelet count <20.0×109cells/L patients developed ecchymosis, while 14% patients whose platelets count of more than 100×109 cells/L had ecchymotic spots.[32] Despite the increased risk of bleeding; no severe bleeding was observed in the sample of the study.

Peripheral blood cell count was normal at initial diagnosis of one patient (1.8%), Sousa et al reported 4% of patients with normal complete blood count with no lymphoblast.[10] Neeti et al inform that blast negative patients have more chances of 2 years event free survival than blast positive group anyhow, the alone concerned patient in the present study was died due to Graft versus Host disease.[33]

Mediastinal involvement was detected in 4 (7.3%) patients, one of them of T-cell leukemia and 3 patients had B- cell leukemia, other studies showed mediastinal infiltration in 8-10% and mostly due to T cell ALL, in the present study, the state was inverted so more mediastinal involvement in B- cell ALL and this might be due to small sample size.[34,35]

Pleural effusion was detected in one patient (1.8%); this is previously unrecognized at initial presentation of ALL, but can develop infrequently later on during disease process and relapse and may indicate pleural infiltration.[36,37] Accordingly, this finding is a unique for this study.

Pericardial effusion was reported in one patient (1.8%), studies showed more pericardial effusion and pericarditis than the current study (6%), mostly in T cell ALL and may indicate a disease progression and cardiac/ pericardial infiltration, less reported cases in the present study may be due to small size of T- cell ALL.[38,39]

CNS involvement was presented clinically in one patient (1.8%) by facial palsy, while it was detected in (5.4%) by routine cerebrospinal fluid analysis and this is consistent with the rate reported by others (6.6-8%).[10,11] It indicate CNS infiltration, it was clinically presented in one and asymptomatic in two patients, Sharon et al indicated that real-time PCR analysis of CSF is a quick and reliable tool to assess CNS involvement in patients with ALL and can be a better predictor of outcome than cytomorphology alone, anyhow, many comparative studies are needed to consider such investigation routinely in work-up of leukemia which may detect early asymptomatic infiltration, such as the patients in this study.[40]

Overall, the clinical and laboratory features observed in this study are compatible with the results reported elsewhere in the literatures. Fever, pallor, hepatosplenomegaly, and lymphadenopathy were the most common presenting features.

CONCLUSION

L2 ALL was the dominant subtype; this contrary to all other studies, it might be due to genetic/ biological variation and it may be related to prognosis. Most of the initial presenting features were general; they may indicate more common illnesses, but constellation of these features together with complete blood picture should rise the possibility of leukemia. A rare initial manifestation, pleural effusion, was also registered in this study.

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