

Original Research Article

Clinico-epidemiological study of extramedullary disease manifestations in childhood acute lymphoblastic leukaemia in a tertiary care centre

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ABSTRACT

Background: Data on extramedullary manifestation of acute lymphoblastic leukemia (ALL) in Indian children are very limited, authors analyzed the clinical, epidemiological and immunophenotype profile of these manifestations in our pediatric patients.

Methods: This was a prospective observational study in which data of 46 children with ALL, aged 0 to 14 years were analysed.

Results: Among the total 46 patients of ALL admitted 86.95% presented with extra medullary features. Definite male preponderance (67.5%) was observed, 80% patients were aged between one to ten years. Common extra medullary features included hepatomegaly (95%), followed by splenomegaly (77%), lymphadenopathy (58%), arthritis (17.5%), and CNS involvement in 5%. Mediastinal mass was seen in 5%. Majority of them (67.5%) had White blood cell (WBC) count less than 20,000/mcL. 92.5% were Pre B ALL, while T ALL was seen in three (7.5%) patients. Out of these three T cell ALL two presented with mediastinal mass and one with CNS leukemia.

Conclusions: The clinicians must be aware of the constellation of different extramedullary features to diagnose ALL. Early diagnosis and prompt treatment may improve the clinical outcome in these patients. Authors suggest larger multi-centric studies to understand the clinical and laboratory profile of extramedullary disease in ALL for better risk stratification to help in risk-adopted therapy.

Keywords: Acute lymphoblastic leukemia, B-ALL, Immunophenotype, T-ALL

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is the most commonly encountered pediatric malignancy. It accounts for one third of all childhood cancer.^{1,2} Incidence of ALL worldwide is approximately 3-4 cases per 100,000 children under the age of 15 years. In India its incidence is 9-10 cases per 100,000.³ In West Bengal, ALL accounts for 39.2% of all childhood cancers.⁴ Treatment of ALL has been revolutionized in the past few decades with 5-year overall survival rate reaching 90% in the developed nations. The scenario in India is a bit different

though; with overall survival in pediatric ALL patients are being variously reported to be between 45% to 81%.⁵

One of the keys to favorable outcome in pediatric ALL would be early diagnosis. Undue delays in specialized health care access may negatively impact the outcome. Long delays in diagnosis may adversely affect prognosis.^{6,7}

It has been suggested in various studies that general pediatricians may not be familiar with unusual manifestations on ALL that may lead to delay in referral.

Data on the extramedullary involvement in pediatric ALL patients are rare, especially from India. Hence this study was undertaken to look at the pattern, both clinical and laboratory, of extramedullary involvement in children with ALL. Authors also looked at the possible correlation of different symptomatology with the laboratory profile.

METHODS

A prospective, observational study conducted in Department of Pediatric Medicine, IPGMER and SSKM Hospital, Kolkata, India. Children (age 0 to 14 years) newly diagnosed with all having extramedullary features at presentation between February 2012 -March 2013 were included in the study.

Inclusion criteria

- Patients with newly diagnosed ALL presenting with extramedullary features

Exclusion criteria

- Patients of ALL presenting with only bone marrow infiltration features

Ethical approval was obtained from the Institutional Ethics Committee. Informed, written consent was obtained from the parents/ guardians of all the patients. Pretested, semi structured proformas were filled which included detailed history, systemic examination, investigations like complete blood count, bone marrow aspirate and biopsy, immunophenotyping.

RESULTS

Total of 46 ALL patients were admitted during the study period. Among them 40 children (86.95%) presented with extramedullary features. Among the 40 children of ALL with extra medullary features majority were male (67.5%).

Most of the patients (80%) were in the standard risk age group of 1 to 10 years. 7.5% belonged to the infant group, while 12.5% were over 10 years of age. The minimum age at presentation found was 7 months. Three (7.5%) patients presented with hyperleucocytosis with more than 50000 cells/mcL. While majority (67.5%) of them had total WBC count below 20000 cells/mcL. Morphological typing i.e. FAB classification of ALL showed that patients with extra medullary features have L-2 as the most common morphological typing i.e., 28(70%), while 12 (30%) patient had L-1 typing. Immunophenotyping revealed that pre B cell was more common (92.5%). Present study population had only 3 (7.5 %) patients with T-cell ALL. Out of these three T cell ALL two presented with mediastinal mass and one with CNS leukemia. Clinical and laboratory findings of the ALL patients with extramedullary features are summarized in Table 1.

Table 1: Clinico laboratory profile of the ALL patients with extramedullary features (n=40).

Clinical laboratory feature	Number	Percent
Sex		
Girls	13	32.5
Boys	27	67.5
Age		
<1 year	3	7.5
1-10 years	32	80
>10 years	5	12.5
WBC count (/mcL)		
<20000	27	67.5
20000-50000	10	25
>50000	03	7.5
FAB classification		
L1	12	30
L2	28	70
Immunophenotype		
B cell	37	92.5
T cell	03	7.5

Among patients presenting with extra medullary features, hepatomegaly was the most common presentation (95%), followed by splenomegaly (77%), lymphadenopathy (58%), arthralgia and arthritis (17.5%), CNS involvement in 5%. Mediastinal mass was seen in 5 % (Figure 1).

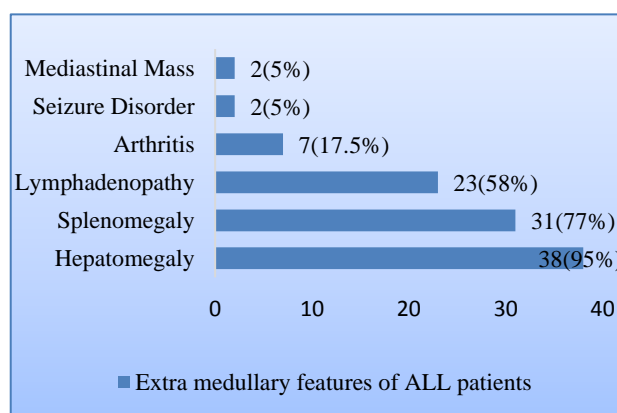


Figure 1: Distribution extra medullary features of ALL among the children (n=40).

Appropriate statistical test (Fisher's exact test) was performed to ascertain the significant association between clinical and laboratory parameters with different extra medullary features. ALL type L2 by FAB classification was found to be significantly associated with splenomegaly ($p = 0.001$). Statistically significant association was not found among other clinical and laboratory parameters and pattern of extramedullary features. Point biserial correlation coefficients (rpb) were calculated to ascertain the relationship between age and TLC with extra medullary features. The results showed that correlation between age and TLC with extra

medullary features are poor and at the same time statistically not significant ($p>0.05$) (Table 2).

Table 2: Correlation between age and total leucocyte count with extra medullary features.

Extra medullary features	Age		Total leucocyte count	
	r pb	P value	r pb	P value
Hepatomegaly	0.13	0.63	0.11	0.56
Splenomegaly	-0.1	0.27	-0.11	0.53
Lymphadenopathy	0.13	0.23	0.01	0.97
Arthritis	0.12	0.24	-0.19	0.23

DISCUSSION

Approximately 1/3 of childhood cancers is leukemia with ALL being the most common entity. There has been insufficient and limited data available on childhood cancers in India. In India annually >10,000 cases have been reported.⁸ Acute leukemia is a malignancy characterized by unrestrained clonal proliferation of hematopoietic precursor cells. Most common presentations are thus those suggestive of bone marrow. Extramedullary involvement is more commonly seen in AML patients, but may also be seen in ALL.

In the present study, authors looked at 40 children that presented with extramedullary features of ALL. The present study population revealed a male preponderance with M:F ratio of around 2:1. It is difficult to comment whether this truly reflects the increased incidence of extramedullary features in males, as the sample size is too small. Also, this may be due to the fact that overall ALL in children is associated with male preponderance.⁹⁻¹³ Present study showed a high incidence of extramedullary features of ALL in 1-10 years age range (80%). This is also due to the fact that ALL was reported to be more common in the age range of 2-10 years.¹⁰

In the present study, only 7.5% of the patients presented with hyperleucocytosis (WBC>50000 cells per cubic millimeter) at diagnosis. Hence extramedullary disease may occur even in apparently standard risk ALL features.

Usually ALL presents with symptoms secondary to bone marrow failure like fever, pallor and bleeding.⁹⁻¹³ Most common among extramedullary manifestations in ALL were lymphadenopathy, hepatomegaly and splenomegaly.^{9,11} Joint involvement, CNS involvement, mediastinal involvement are less common.¹³⁻¹⁵ In present study, hepatomegaly (95%) was the most common extramedullary involvement, followed by splenomegaly (77%) and lymphadenopathy (58%). Other extramedullary features reported in present study include joint manifestation like arthritis and arthralgia (17.5%), central nervous system (CNS) 5% and mediastinal mass in 5% cases. Khalid et al reported equal incidence of

hepatomegaly (54.3%) and lymphadenopathy (54.3%) in their study followed by splenomegaly, CNS manifestation (4.3%) and mediastinal mass in 2% patients.⁹ Biswas et al reported joint pain in around 10% of ALL patients.¹³ Bone pain may be the result of leukemic infiltration of the periosteum, bone infarction, or expansion of marrow cavity by leukemic cell infiltrations.¹⁶

Majority of the patients in present study were precursor B ALL similar to the findings of other study. Khalid et al and Ramyar A et al noted L morphology predominant in their study, whereas authors observed predominance of L2 type of ALL (70%) in present patients, which was in accordance with the study done by Settin et al.^{9,14,15}

As present study population was small authors didn't get any significant association between extramedullary features of ALL and different laboratory parameters like TLC count, FAB typing and Immunophenotyping. But this type of study would help the clinicians to get acquainted with the incidence and distribution of extramedullary features of ALL among leukaemic children and help them in early diagnosis and proper management.

There are few limitations in present study. Authors had small population size and also the study was conducted in a single centre.

CONCLUSION

ALL, if diagnosed early and treated adequately with modern chemotherapy protocols has excellent cure rates. But ALL is a heterogeneous disease with myriad manifestations, many of which mimic other unrelated disease conditions like juvenile idiopathic arthritis (JIA), viral infections, sepsis etc. The clinicians must be aware of the constellation of different extramedullary features to diagnose ALL.

Often, physicians inadvertently prescribed supportive care in the form of steroids or blood transfusions that can delay diagnosis or even upstage the ALL risk group. Sensitizing the private sector practitioners about the possibility of hematological malignancy in symptomatic children may be the most effective step in resource poor settings, for an early referral. Authors suggest larger multi-centric studies in developing countries to understand the clinical and laboratory profile of these extramedullary features and their association with the prognostic factors in ALL.

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