BANGLADESH J CHILD HEALTH 2023; VOL 47 (3) : 136-141

Original Articles

Diagnostic clue of Acute Lymphoblastic Leukemia for Frontline Clinicians from Clinicopathological Features: Study of 223 Cases of in a Tertiary Care Hospital from Bangladesh

MD ANWARUL KARIM[1], NAFISA YESMIN[2], MOMENA BEGUM[3], CHOWDHURY YAKUB JAMAL[1]

Abstract:

Pediatric acute lymphoblastic leukemia (ALL) is the most common type of cancer in children.

It accounts for 25% of all childhood cancers and approximately 80% of all cases of childhood leukemia. Understanding the clinicopathological features of pediatric ALL patients is crucial for early diagnosis, hence effective management. As pediatric leukemia is a low-prevalence disease in primary care, emergency departments, and general pediatric settings and screening strategy for identification of ALL yet to be settled, emphasis is to be given on early recognition of the disease by observing sign and symptoms of the affected children and understanding the interpretation of early CBC report.

A total two hundred and twenty-three (223) children with pediatric ALL patients aged between 1-18 years who were diagnosed in the department of Pediatric Hematology and Oncology department at BSMMU from April 2018 to August 2020 were studied to identify the clinical and hematological clue for early diagnosis for the frontline physicians. The demographic characteristics of the patients, including age, gender distribution, and socioeconomic status, clinical presentation with laboratory parameters including CBC, bone marrow morphology, immunopneotyping findings were analyzed.

Majority of the patients were in the age group of 1-5 years, with a slightly higher male prevalence. Fever, pallor, hepatomegaly, splenomegaly were the presenting feature in more 75% cases could be strongly considered as clinical clue for diagnosis of acute leukemia. More than 50% cases had lymohadenopathy and bony tenderness and more than 35% cases had bleeding symptoms could serve as a potential clinical clue for diagnosis of acute leukemia. Joint symptoms were present in more than 25% cases among which 6.7% cases it was the presenting symptoms accounting diagnostic delay. So it should be taken as a potential case of leukemia as differential diagnosis.

Hematologic evaluation reveal decreased percentage of neutrophils for age was the constant feature present in 93.7% cases, should alert the physician for evaluation of acute leukemia.In cases of leucocytosis, it is coined with anemia, thrombocytopenia and peripheral blast giving the typical blood picture of acute leukemia.In normal leucocyte count, neutropenia was associated with anemia and or thrombocytopenia in different combination as bicytopenia with or without peripheral blast serve as diagnostic clue for acute leukemia.Pancytopenia was present at diagnosis in18.8% of cases could also be considered as clue for diagnosis of acute leukemia.

Keywords: *Childhood malignancy, ALL, Immunophenotyping, diagnostic delay, frontline physician.*

DOI: https://doi.org/10.3329/bjch.v47i3.82705

1. Professor, Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka
2. Assistant Professor, Pediatric Hematology and Oncology, Rangpur Medical College, Rangpur
3. Assistant Professor, Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka

Correspondence: Professor Dr. Md. Anwarul Karim, Professor, Pediatric Hematology and Oncology, Room 312, Block D, Level 2, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka 1000, Mobile: 01711-269052, Email: drkarim1990@gmail.com

Introduction:

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer worldwide. It accounts for 25% of all childhood cancers and approximately 80% of all cases of childhood leukemia[1]. The incidence of ALL is approximately 3-4 per 100,000 children younger than 15 years of age[1]. Pediatric leukemia is a low-prevalence disease in primary care, emergency departments, and general pediatric settings so a

general practitioner is less likely to encounter a child with cancer[2].

The common symptoms of acute lymphoblastic leukemia include fever, anorexia, irritability, and lethargy. Children with ALL usually present with signs of bone marrow failure including anemia, bleeding due to thrombocytopenia, fever due to neutropenia and feature of infiltration as visceromegaly and lymphadenopathy[3].

But the early presentation of pediatric leukemia with non-specific symptoms often mimicking the common, self-limiting illnesses complicates the diagnostic challenge faced by frontline clinicians[4]. So, improving the early diagnosis of cancer is a key priority for many health services.

Though the epidemiology, clinical, and laboratory presentation of ALL in children has been well described in Western countries[5], there is scarcity of published data from Bangladesh on childhood ALL clinicopathological profile at presentation. This is important to know as our population differs markedly from a western population concerning the frequency of illiteracy, poverty, malnutrition, and chronic infectious diseases and healthcare service seeking behavior. Because of lack of structured referral system, vast majority of cancers in children are still diagnosed with delay at tertiary care hospital as direct presentations to emergency departments or non-urgent hospital referrals from primary care via different specialist physician[6]. Inadequate information regarding early prediction of the disease causes this delayed diagnosis, hence upstaging of the disease at presentation[6].

To improve our understanding of the early presentation of pediatric ALL, this study was aimed to systematically identify the presenting signs and symptoms at, or before the point of diagnosis along with its clinicopathological presentation in our setting to identify clue for diagnosing ALL by frontline physician.

Methodology:

This retrospective study conducted from April 2018 to August 2020 in the Department of Pediatric Hematology and Oncology at BSMMU. The study included a total of 223 children aged1 to 18 years of both sexes from both urban and rural areas who were diagnosed at the Pediatric hematology and oncology department. Detailed history covering patient identification, duration, description of symptoms and treatment history were taken. Thorough clinical examination findings were recorded in pretested questionnaire. Diagnostic confirmation was ensured through complete blood count with peripheral blood film for each patient and bone marrow morphology and immunophenotyping.

Complete blood count (CBC) was done by using automated blood counters- Sysmex Xn-550 (Sysmex Corporation, Kobe, Japan) according to the manufacturer's guidelines and checked manually by pediatric hematologists. Bone marrow aspiration was done from posterior-superior iliac crest and tibial tuberocity in case of less than 2 year of age. Smears were prepared directly from aspirated marrow and stained with Leishmann's stain on the same day and seen by pediatric hematologists. Two ml of aspirated marrow was sent to Flow cytometry laboratory of the department for immunophenotyping. Immuno-phenotyping was performed on CYTOMICS FC-500 flowcytometer using CXP software. The cells were analyzed with the most appropriate blast gate using the combination of forward and side scatters. An antigen was considered positive when the expression is at least 20% of the gated cell.

Results:

The present study included 223 of both sexes of 1-18 years of age diagnosed in the department of Pediatric Hematology and Oncology, BSMMU. Table I shows the sex distribution of the patients in this study, 140(62.8%) cases were male and 83(37.2%) were female and male to female ratio was 1.7:1.

Table-I

Sex distribution of study population

Gender	No	Percentage
Male	140	62.8
Female	83	37.2
Total	223	100

Age distribution of studied cases shows majority 102 (45.7%) cases were between 1 to 5 years, 72 (32.3%) were between 6-10 years and 49 (22.0%) cases were more than 10 years of age (table II).

Table II
Age distribution of study population

Age	No	Percentage
1-5 years	102	45.7
5-10 years	72	32.3
>10 years	49	22.0
Total	223	100

Common presentations were pallor in 208 (93.3%), fever in 200 (89.7%) patients, hepatomegaly in 199 (89.2%) cases, splenomegaly in 167 (74.9%) cases and lymphadenopathy 142 (63.7%) cases. Fifty percent cases had bony tenderness, and 35.9% cases had bleeding manifestation at presentation. Joint manifestation was found in 57 (25.6%) cases. CNS manifestation (evident by seizure, cranial nerve palsy) was found in 3(1.3%) cases and testicular enlargement was found in 1 (0.44%) case at presentation. Co-morbid condition like ascites and heart failure were present in 3(1.3%) cases (Table III).

Table-III
Clinical characteristics of the study populations

Finding at diagnosis	No.	Percentage
Pallor	208	93.3
Fever	200	89.7
Hepatomegaly	199	89.2
Splenomegaly	167	74.9
Lymphadenopathy	142	63.7
Bony tenderness	113	50.7
Bleeding manifestation	80	35.9
Joint involvement	57	25.6
Jaundice	04	1.8
Feature of AML	04	1.8
CNS involvement	03	1.3
Ascites	03	1.3
Heart failure	03	1.3
Testicular enlargement	01	0.44%

Table IV shows distribution of cases depending on laboratory parameters.

Table IV
Laboratory findings in studied cases

Finding at diagnosis	No	Percentage
Hemoglobin (gm/dl)		
>90	40.4	
7-9	90	40.4
9-11	28	19.3
>11	15	6.7
Total leucocyte count (per cumm)		
<4000	42	18.8
4000-11000	71	31.8
>11000-<50000	56	24.2
50000-100000	22	9.9
>100000	34	15.2
Blast cell in bone marrow study		
>25-<50%	40	17.9
50-75%	69	30.9
>75%	114	51.1
Immunophenotyping		
B cell linage	175	78.5
T cell linage	33	14.8
Mixed linage	15	6.7

Regarding anemia, more than 80% cases had moderate to severe anemia however, 19.3% cases had mild anemia and 6.7% cases had normal hemoglobin at presentation.

Distribution of total WBC shows 49.4% cases had leucocytosis with relative neutropenia, among which 56 (25.2%) cases had >50,000/cumm and 15.2% cases had hyperleucocytosis (WBC >100,000/ cumm), on the other hand, 50.6% % cases had normal or low WBC count where leucopenia was found in 18.8% cases.

ALL was diagnosed on bone marrow morphological finding as > 25% blast. It was found that 40 (17.9%) cases had <50%, 69 (30.9%) had between 50 to 75% and 114 (51.1%) cases had more than 75% blast in bone marrow.

Distribution of ALL depending on Immuno-phenotyping shows B cell ALL in 175 (78.5 %), T-cell ALL in 33 (14.8%) and Mixed lineage ALL in 15 (6.7%) cases.

Discussion:

ALL is a malignant disorder of hematologic progenitor cells that arises as dysregulatedclonal expansion of immature lymphoid progenitor cells that block and / suppress normal hemopoiesis resulting in marrow failure[7].

Leukemia can be quite varied in its presentation. Most signs and symptoms are due to marrow failure presenting as anemia, fever due to neutropenia, bleeding manifestation due to thrombocytopenia and because of specific tissue infiltration by leukemic cells (lymph node, liver, spleen, brain, bone, skin, and testis) causing lymphadenopathy and organamegaly, bone pain, testicular involvement[3].

A total of 223 children were studied to evaluate the clinicopathological presentation of childhood leukemia to identify the diagnostic clue for frontline clinicians. Among 223 cases, predominant cases were male being 140 cases where female cases were 83 and male-female ratio was 1.6:1; similar male preponderance was observed in locoregional reports as 1.7:1 in Pakistan[8], 1.88 from India[9], 1.9:1 from Brazil by Sousa et al[10], 1.85:1 from China by LiS et al[11], and 1.4:1 in developed countries by Meighan[12].

The age ranged from 1-18 years with a mean age of 5.78±0.33 years and 78% were <10 years of age and the most common age group was between 1 year to 5 years (45.7%). Similar findings were observed by Manjula et al[13], Sousa et al[10] and Siddhiqui et al[14].

In the present study, pallor was the most frequent finding (93.3%), similar finding was observed (86%) by Yasmeen and Ashraf[15], 77.5% by Przapati et al[16], 77.4% by Pandian et al[17], however reported pallor was less in developed countries Clarke RT et al[18]. Anemia is due to suppression of normal hematopoiesis by invading blast resulting decrease in erythropoietin activity as well[19]. The present study showing cases are having more anemic may be due to late presentation at our center[2].

Fever was the next common presentation (89.3%), similar high percentage of patients having fever was reported 87% by Pandian at al[17], 81% by Prazapati et al[16], however Bernbeck et al[20] and Clarke et al[18] showed lower percentage (35-53%) of patients presented with fever.

Hepatomegaly (89%) and splenomegaly (74.9%) were also the leading features in the present series. Pandian at al[17] observed higher percentage of Hepatomegaly (96%) and splenomegaly (90.3%) in their study however others[13,16,18] reported lower percentage of hepatomegaly and splenomegaly in their study compared to the present study though rate was higher than 60%.

The present study shows 63.7% cases presented with lymphadenopathy. Similar observation was made by Ahmad et al[3], Prajapati et al[16] , Pandian at al[17] and Bernbeck et al[20], however reported higher percentage of lymphadenopathy was observed in Yasmin and Ashraf's Study[15].

Bony tenderness was another important finding observed in >50% of the cases in the present study, it was observed variably (19-43%) in other's report as bone pain or tenderness[3,8,20]. Bony tenderness may be caused by bone infarction, periosteal elevation by leukemic cells, or by marrow expansion. The rapid disappearance of bony tenderness following cytoreductive chemotherapy indicates a possible relationship to leukemic deposits.

In the present study shows 35.9% cases presented with bleeding manifestation. Siddaiahgari et al[21] and Clarke et al[18] showed higher percentage of patient with bleeding symptoms on the other and Pandian at al[17] and Prajapati et al[16] reported lower percentage of patient with bleeding symptoms.

In the present series, joint involvement was 25.6% of cases mostly of oligo articular arthritis or arthralgia of larger joints. Talukder et al[22] from Bangladesh showed that oligoarticular arthritis mostly of larger joints who were mistakenly diagnosed as sJIA, similar observation was made by Brix et al[23] (18.5%) from Denmark, however Robazzi et al[24] from Brazil (54.7%) and Kesarapu et al[25] from India (68.15%) showed higher percentage of cases whose initial presentation was associated with osteoarticular manifestation.

In the present study 80.8% were moderate to severely anemic among which 40.4% cases had severe anemia, with 6.7% cases had normal Hb. Prazapati et al[16], Siddaaiahgari et al[21] from India and Yesmin et al[15] from Pakistan reported similar findings in their population however they observed less percentage (1.72%) of normal hemoglobin.

In the present study, 49.4% cases had leucocytosis with relative neutropenia, where 24.2% cases showed leucocyte count >50,000 and 15.2% cases had leucocyte count >100,000 and majority (50.6%) of the cases had normal or low leucocyte count with

neutropenia, where 18.8% cases presented with leucopenia. Prazapati et al[16] showed similar report however, they showed more number of cases with leucocyte count <50,000. Hyperleucocytosis was also reported in Pandian et al[17] and Siddaaiahgari et al[21].

Regarding Immunophenotyping, most (78.8%) of the cases was B cell lineage ALL, (14.8%) cases were T cell lineage ALL and 6.7% cases showed mixed lineage leukemia. These findings are comparable to many reports from East and West[12,13,14,17].

Analyzing clinical features shows fever (89.7%), pallor (93.3%), hepatomegaly (89.2%), splenomegaly (74.9%), lymphadenopathy (63.7%) and bony tenderness (50.7%) were the leading feature of leukemia found in > 50% cases. These findings are consistent with the NICE guideline[26] for early CBC examination for detection of leukemia. Bleeding features are less than 50% cases in the present series, however when present serve as apotential clue for diagnosing leukemia.

Though very early features like fever, pallor and fatigue, may also be the presentation of many common, self-limiting diseases of childhood and are therefore may create confusion in discriminating between those children who do or do not have leukaemia; however these features in combination with features like hepatomegaly, splenomegaly, lymphadenopathy and petechiae would serve specific clue diagnosing leukaemia.

Analyzing complete blood report reveals that reduction of neutrophil percentage for age as the constant features.

In cases with leucocytosis in around 50% cases of the present series, there was relative neutropenia, anemia, thrombocytopenia with peripheral blast which has been described in the text as typical feature of leukemia was evident.

In cases of normal leucocyte count, in 31.8% cases of present series, there was neutropenia, which was associated with anemia, thrombocytopenia in different combination as bicytopenia where peripheral blast was identified in some cases. However in 6.7% cases, presents with normal hemoglobin and normal counts. Worth mentioning, these cases had predominant joint symptoms as presenting feature and were evaluated and treated initially by rheumatologists, who diagnosed them as ALL after bone marrow evaluation.

In 18.8% cases, where pancytopenia was the initial finding, they were diagnosed by bone marrow morphology as leukemia.

Conclusion:

Fever, pallor, hepatomegaly, splenomegaly were the presenting feature in more 75% cases could be strongly considered as clinical clue for diagnosis of acute leukemia.

More than 50% cases had lymohadenopathy and bony tenderness and more than 35% cases had bleeding symptoms could serve as a potential clinical clue for diagnosis of acute leukemia.

Joint symptoms were present in more than 25% cases among which 6.7% cases it was the presenting symptoms accounting diagnostic delay. So it should be taken as a potential case of leukemia as differential diagnosis.

Hematologic evaluation revealed decrease percentage of neutrophils for age was the constant feature present in 93.7% cases, should alert the physician for evaluation of acute leukemia.

In cases of leucocytosis, it is coined with anemia, thrombocytopenia and peripheral blast giving the typical blood picture of acute leukemia.

In normal leucocyte count, neutropenia was associated with anemia and thrombocytopenia in different combination as bicytopenia with or without peripheral blast serve as diagnostic clue for acute leukemia.

Pancytopenia was present at diagnosis should be considered as clue for diagnosis of acute leukemia.

References

1. Carroll WLand Pillai PM. Acute Lymphoblastic leukemia.In: Fish DJ, Lipton JM, Lanzkowasky P(eds), Lanzwasky'sMannual of Pediatric Hematology and Oncology.Elsevier ; Academic press, 7th edition, 2022.pp413-38.
2. Feltbower RG, Lewis IJ, PictonS,Richards M, Glaser AW, Kisney SE, MacKinney PA. Diagnosing childhood cancer in primary care—a realistic expectation? British Journal of Cancer.2004; 90:1882–4.
3. Ahmad I, Ghafoor T, Ullah A, Naz S, Tahir M, Ahmed S, Arshad A Ali, A, Khattack T A, Batool F. Pediatric Acute Lymphoblastic Leukemia: Clinical Characteristics, Treatment Outcomes, and Prognostic Factors: 10 Years' Experience From a Low- and Middle-Income Country . JCO Global Oncol 2023; 9:e2200288.
4. Dang-Tan T, Franco EL. Diagnosis delays in childhood cancer. Cancer. 2007; 110:703–13.

5. Hanson MR, Mulvihill JJ. Epidemiology of child-blood cancer. In: Levine AS (ed) Cancer in the Young. Masson Pub, USA. 1982; pp 3-12.

6. Islam A and Eden T. Brief report on pediatric oncology in Bangladesh. South Asian J Cancer 2013; 2:105-6.

7. Pui CH: Childhood leukemias. N Engl J Med 332: 1618 1630, 1995

8. Fadoo Z, Nisar I, Yousuf F Lakhani L S, Ashraf S, Imam U, Zaheer J, Naqvi A, Belgaumi A.Clinical Features and Induction Outcome of Childhood Acute LymphoblasticLeukemia in a Lower/Middle Income Population: A Multi-Institutional Report FromPakistan.Pediatr Blood Cancer 2015;62:1700–1708

9. Rajalekshmy KR, Abitha AR, Anuratha N and Sagar TG: Time trend in frequency of occurrence of major immunophenotypes in paediatric acute lymphoblastic leukemia cases as expe-rienced by Cancer Institute, Chennai, south India during the period 1989 2009. Indian J Cancer 48: 310 315, 2011.

10. Sousa DW, Ferreira FV, Félix FH, Lopes MV. Acute lymphoblastic leukemia in children and adolescents: prognostic factors and analysis of survival. Revistabrasileira de hematologia e hemoterapia. 2015 ; 37(4):223-9

11. Li S, YeJ, MengF,LiC, YangM.Clinical characteristics of acute lymphoblasic leukemia in male and female patients: a retrospective analysis o 705 patients. Oncology letters2015;10:453-58

12. Meighan SS. Leukemia in children. Incidence, clinical manifestations, and survival in an unselected series. Cancer 1963;16:656–64

13. Manjula AA. Clinicopathological Analysis of Childhood Leukemia - A Study Conducted in a Tertiary Care Centre in South India.JMSCR 2018; 06:03:165-171

14. Siddiqui R P, Wasnik M, Bhaskar V, Patra P K, Hiwale S. Morphologic & Flowcytometric Analysis of Acute Leukemias in a Teaching Hospital in Chhattisgarh. Journal of Evidence based Medicine and Healthcare 2015; 2: 7589-93, DOI: 10.18410/jebmh/2015/1026

15. Yasmeen N and Ashraf S. Childhood acute lymphoblastic leukaemia; epidemiology and clinicopathological features. J Pak Med Assoc. 2009; 59:150-53.

16. Prajapati Z, Kokani MJ, Gonsai RN. Clinicoepidemiological profile of hematological malignancies in pediatric age group in Ahmedabad. Asian J Oncol 2017; 3:54-8.

17. Pandian G, Sankarasubramaian M L. A study on clinical, immunophenotypic pattern in pediatric acute leukemias in a teaching hospital. Int J Contemp Pediatr. 2018;5: 1183-89

18. Clarke RT, Van den Bruel A, Bankhead C, Mitchell CD, Phillips B Thompson M J. Clinical presentation of childhood leukaemia: a systematic review and meta-analysis. Archive of Disease of Childhood. 2016; 101: 894–901

19. Teuffel O, Stanulla M, Cario G, Ludwig WD, Rottgers S, Schafer BW, Zimmermann M, Schrappe M, Niggli FK. Anemia and survival in childhood acute lymphoblastic leukemia. Haematologica 2008; 93:1652-57. doi: 10.3324/haematol.13156

20. Bernbeck B, W ü ller D, Jan ß en G, Wessalowski R, G ö bel U, Schneider D T. Symptoms of Childhood Acute Lymphoblastic Leukemia: Red Flags to Recognize Leukemia in Daily Practice. Klin Padiatr 2009; 221: 369 – 373

21. Siddaiahgari SR, Awaghad MA, Latha MS. Clinical, immunophenotype and cytogenetic profile of acute lymphoblastic leukemia in children at tertiary health care centre in India. Muller J Med Sci Res 2015; 6:112 8.

22. Talukder MK, Laila K, Hossain MA, Islam MS, Islam MZ, Gomes KB, Haque M, Islam MM, and Islam MI. Acute Lymphoblastic Leukemia Presenting as Systemic Juvenile Idiopathic Arthritis: Experience from Bangladesh. Open Journal of Rheumatology and Autoimmune Diseases 2024; 14:1-12

23. Brix N, Rosthøj S, Herlin T, Hasle H. Arthritis as presenting manifestation of acute lymphoblasticleukaemia in children. Arch DisChild 2015;100:821–25

24. Robazzi T C M V, Barreto J H S, Silva L R, Mittermayer B S, Mendonc N. Osteoarticular Manifestations as Initial Presentation of Acute Leukemias in Children and Adolescents in Bahia, Brazil. J PediatrHematolOncol 2007; 29:622–626

25. Kesarapu S, Vangala N, Uppin SG, Uppin MS, Paul TR, Rajasekhar L. Acute leukemia presenting with musculoskeletal manifestations: A case series. Indian J Med PaediatrOncol 2020; 41:29-33.

26. NICE guideline,Published: 23 June 2015, Last updated: 2 October 2023 www.nice.org.uk/guidance/ng12.