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ACUTE LYMPHOBLASTIC LEUKEMIA OF CHILDHOOD: VARIED MANIFESTATIONS FROM A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

Introduction: Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy with a multitude of presentations. With appropriate treatment it has an excellent prognosis. We describe this series of patients with ALL to demonstrate the varied manifestations of ALL that presented to a tertiary level pediatric centre.

Materials and Methods : This descriptive study was conducted in the Pediatric Hematology-Oncology Unit from April 2012 to June 2015. All the patients with ALL were included in the study. Clinical features at presentation, laboratory investigations and outcomes were recorded and analysed.

Results: 113 patients with ALL were recruited. The predominant symptom bringing the child to medical attention were PUO like presentation in 44%, severe anemia in 61%, bleeding manifestations in 26%, hepatosplenomegaly in upto 94% and arthritis and bony pain in 35%. There was no organomegaly or lymphadenopathy in 11%.

Uncommon presentations were CNS manifestations in 1.8%, abdominal distension in 8%. Most common hematologic finding was thrombocytopenia seen in 89%, hyperleucocytosis seen in 17% and normal WBC count in 31%.

Blasts in PS were seen in 55%.

Conclusion: ALL in our study is a male preponderant disease most commonly presenting as a febrile illness and pallor accompanied by lymphadenopathy and/or organomegaly. However atypical manifestations of the illness are common in clinical practice.

KEYWORDS :

INTRODUCTION:

Acute Lymphoblastic Leukemia (ALL) is the most common pediatric malignancy, comprising 25% of cancers occurring before 15 years of age and 19% among those less than 20 years old [1]. Despite steady improvements in outcome, ALL remains the leading cause of childhood cancer death(2)

The clinical presentation varies widely and can range from incidentally detected organomegaly to significant bleeding to isolated cranial nerve involvement. A high index of suspicion is therefore required for prompt diagnosis.

An early diagnosis and tailored therapy lead to excellent outcomes in what was previously considered a fatal disease.. In the 1960s, a child with ALL—the most common childhood cancer—had a less than 10% chance of being cured. A child diagnosed with ALL today has almost a 90% chance of being cured.*(3)*

Thus, it is important to be aware of the various manifestations of this disease and to have a high index of suspicion in order to institute early therapy or referral to an advanced pediatric oncology centre.

The objective of our study was to describe the varied clinical presentation and hematological features of childhood ALL presenting to a tertiary care centre in Southern India

MATERIALS AND METHODS:

Children newly diagnosed with Acute Lymphoblastic Leukemia between April 2012 and June 2015 in the Department of Paediatrics, St. John's Medical College Hospital.Bangalore.

We included all consecutive children aged 1 month to 18 years who were diagnosed to have acute lymphoblastic leukemia by bone marrow examination and flow cytometry. Children whose medical records could not be accessed were excluded from this study.

A retrospective study was performed by chart review after taking IEC clearance. ALL cases were identified from the Oncology register. The demographic data, clinical presentation and laboratory investigations were captured in a pretested proforma

The diagnosis of ALL was established on the basis of morphology and flow cytometry of bone marrow aspiration and trephine. A CSF analysis was done in all children at the time of diagnosis to rule out CNS leukemia.. FISH analysis for BCR-ABL and Karyotyping were also performed.

RESULTS:

A total number of cases of Acute lymphoblastic Leukaemia diagnosed during the study period was 113. Two cases were excluded due to inadequacy of data. Boys constituted 65.7%(73) of the cases with a male to female ratio of 1.9:1. The youngest child in our study was 3 months and the oldest was 15 years. The mean age at presentation was 6.2±4.3 years.

Table 1: Age distribution of cases

AGE(years)	NUMBER OF PATIENTS	PERCENTAGE
0-1	1	0.9%
1-9	87	78.3%
10-14	14	12.6%
>/+15	9	8.1%
Total	111	100%

The patients presented with a wide clinical spectrum of clinical findings. The most common presenting complaint was fever seen in 87.4% of children with 44% having fever for more than 3 weeks duration. The other clinical manifestations are as mentioned in Table 2

Table 2: Clinical Presentation

Clinical feature	Percentage
Fever	87.4
Pallor	75.6
Splenomegaly	66.6
Lymphadenopathy	60.3
Bony pains	35
Hepatomegaly	28.8
Bleeding	26
Abdominal distension	8
Cranial nerve palsy	2
Testicular swelling	1

Some children had uncommon presentations of acute leukemia. Isolated skeletal manifestations were seen in 7 patients of whom 2 presented with paraplegia and had vertebra plana detected on MRI, 2 patients had hypercalcemia with bony sclerotic lesions and 3 had polyarthritis

Table 3: Skeletal manifestations and investigations

No	Sex /Age (yrs)	Manifestation/ Duration (wks)
1	Male/ 8 yrs	Pallor Back ache - 4 wks
2	Male/ 3 yrs	Right foot pain and swelling Inability to walk – 6 wks

3	Male/ 3 yrs	Backache, Paraparesis Inability to walk - 6 wks	
4	Male/ 4 yrs	Fever Polyarthritis - 4wks	
5	Male/ 12 yrs	Backpain, polyarthritis –	12 weeks
6	Male/ 2 yrs	Inability to walk – acute onset	2 weeks

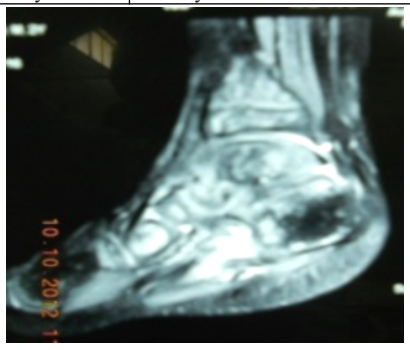


Figure 1: sclerotic lesions of the calcaneum

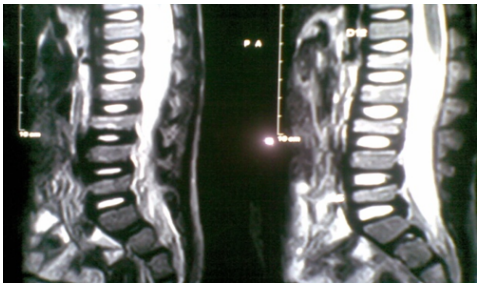


Figure 2: Vertebra plana of lumbar spine

One child presented with acute onset of fever with odynophagia. On examination, she had a white patch on the tonsil with large cervical lymph nodes. Though the blood counts were within normal limits, her peripheral smear revealed atypical cells which led to further revaluation and diagnosis.

Obesity was another unique presenting complaint of a child who also had occasional headache, vomiting, seizures and was being treated for CNS tuberculosis. Due to progressive obesity and recurrence of seizures while on Anti tubercular therapy, he was evaluated further and his CSF revealed blasts suggestive of leukemic meningitis.

Meningoencephalitis like picture with cranial nerve palsy and testicular swelling was seen in one child. Another child presented with isolated facial palsy and had received steroids for a week considering Bells palsy as diagnosis. One month later she presented with fever, pallor and hyperleucocytosis with peripheral smear suggestive of blasts. CSF evaluation showed blasts.

Prolonged fever with pancytopenia was seen in a child whose bone marrow revealed hypocellular picture. Child was kept on supportive treatment. 6 months later, he presented with fever and severe pallor. Repeat marrow revealed acute lymphoblstic leukemia.

Two children who were initially diagnosed as polyarticular JIA presented to us with recurrence of pain and abnormal blood counts. Steroid and methotrexate needed to be withdrawn for a time period before laboratory evaluation revealed ALL.

Syndromic associations with acute lymphoblastic leukemia were found in 2 children, one had neurofibromatosis Type 1 and another was mosaic for Down syndrome.

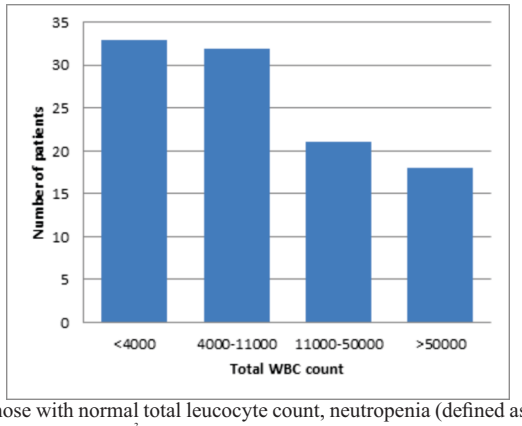
Mean duration of symptoms was 33.2 days ± 31.5 with the shortest history of 2 days and longest being 120 days.

Central Nervous System (CNS) disease as shown by positive CSF cytology was present in two patients (1.8%)

Investigations revealed 82.8% had anaemia of which 60.8% had severe anemia with a Hb of <7g/dl. Mean Hb was 6.7±2.6g/dl at presentation

Table 4: WBC count at admission.

Hemogram	Calcium	Radiologic features
Anemia Hb-8g%	Normal	Vertebra plana
Normal	13.1 mg/dl	Lytic-sclerotic lesion in cuboid
Normal	Normal	Vertebra plana
Anemia Hb-8g%	14.6 mg/dl	Normal
Leucopenia	Normal	Normal
Leucopenia	Normal	Normal



In those with normal total leucocyte count, neutropenia (defined as an ANC<1500cell/mm^3) was seen in all patients. The lowest total count seen was 600cells/mm^3 and highest being 2,87,000cells/mm^3.Median total count was 7000cells/mm^3 (IQR 3292, 28507)

Thrombocytopenia as defined by a platelet count <1,50,000 cells/mm^3 was seen in 89.1% and of these 37% had severe thrombocytopenia (<20, 000cells/mm^3)

Peripheral smear showed blasts in 55%Based on flow cytometry we found that T cell ALL was seen in 1.8% while all the rest were B cell disease. CALLA(CD 10) negativity was found in 6.4% of the patients.

63 patients opted for treatment at our centre. Of these 10 patients have completed treatment and 37 are currently receiving chemotherapy (Intensive phase-12 and maintenance chemotherapy-25)

There were nine deaths; five of these were chemotherapy related deaths; three induction deaths (sepsis with MODS – 2, dengue encephalitis with MODS -1) and two deaths in remission (klebsiella sepsis -1, fungal sepsis -1).

Four children relapsed (very early relapse- 2, early relapse- 2) and died. 2 of these children (very early relapse) were in the high risk ALL group and the other 2 children were standard risk ALL.

Six children were lost to follow-up. They were all in remission after completing induction chemotherapy. One of these children developed refractory candida meningitis and hence discontinued treatment.

The major toxicities during treatment were as follows: Febrile neutropenia requiring PICU care – 12 episodes, invasive fungal infection – 3, pancreatitis – 3, culture proven sepsis in induction – 3, cortical vein thrombosis – 1.

DISCUSSION

ALL is the most common childhood malignancy accounting for one fourth of all childhood cancers and three fourths of all leukemias. Boys are affected more commonly with a sex ratio of 1.3 :1 (4,5,6). However in our study the male to female ratio was significantly different i.e., 1.9:1. This may reflect a sex bias in families coming to tertiary level centre for evaluation. Almost 80% of our patients were between 1-10 years of age while Advani et al(7) and Yasmin et al (8)) found 60-65% and Mushtaq et al (9) found 70% of children in the same age range.

Table 5: Comparison between different studies

	Advani et al(Tata)	Yasmin et al(karachi)	Rao et al(SJMCH)
M:F	1.8:1	1.7:1	1.9:1
Age			
2-9 years	63	66	78
10-15 years	25	28	13

>15 years	8	NA	8
WBC count			
<10000	40	37	65
11000-50000	39	33	21
>50000	20	30	17
CNS involvement	1.3	5	1.8
T Cell Disease	21	NA	1.8

Clinical findings of lymphadenopathy. hepatosplenomegaly and CNS involvement were in concordance with Advani et al (7) however they found a 20% incidence of T cell disease as compared to our study which found only 1.8% patients with T cell disease**.** This may reflect a referral bias to our centre as our centre caters to middle income groups while T cell disease occurs in patients of very low socioeconomic strata. The findings of total counts of <10,000cells/mm3 (half of whom had counts 4000cells/mm3) in our study was 63% while Advani et al(7) found that 40% of patients had similar counts. This is probably due to earlier evaluation in patients with aleukemic leukemia as compared to those with normal total counts.

We had 17% of patients with hyperleucocytosis (Total counts >50,000/mm3) as compared to Advani et al (7) who had 20% and a Karachi study which had 12.5% Our findings of thrombocytopenia (89%) was consistent with Advani et al (7) who had 87% of patients with thrombocytopenia.

Typical features such as lymphadenopathy, hepatosplenomegaly were found in majority of the patients. Atypical manifestations such as obesity, cranial nerve palsies, tonsillar patch , paraplegia and polyarthritis were also seen in a few. The most common cell line to be affected was platelets and peripheral smear picked up blasts in 55% of the cases.

As described in literature those with isolated bone presentations had a relatively normal blood count and smear delaying the evaluation with bone marrow and hence the diagnosis.

CONCLUSIONS

ALL in our study showed a male predominance frequently masquerading as a febrile illness leading to a long interval before a confirmatory study could be established. Pallor accompanied by lymphadenopathy and/or organomegaly in a febrile child are red flags. However atypical manifestations of the illness are common in clinical practice. Hence a high index of suspicion is required to proceed with evaluation ultimately leading to a diagnosis of ALL

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