Scientific Research Publishing

Open Journal of Rheumatology and Autoimmune Diseases, 2024, 14, 1-12
https://www.scirp.org/journal/ojra
ISSN Online: 2164-005X
ISSN Print: 2163-9914

Acute Lymphoblastic Leukemia Presenting as Systemic Juvenile Idiopathic Arthritis: Experience from Bangladesh

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How to cite this paper: Talukder, M.K., Laila, K., Hossain, Md.A., Islam, Md.S., Islam, Md.Z., Gomes, K.B., Haque, M., Islam, Md.M. and Islam, Md.I. (2024) Acute Lymphoblastic Leukemia Presenting as Systemic Juvenile Idiopathic Arthritis: Experience from Bangladesh. *Open Journal of Rheumatology and Autoimmune Diseases*, **14**, 1-12.
https://doi.org/10.4236/ojra.2024.141001

Received: October 30, 2023
Accepted: January 6, 2024
Published: January 9, 2024

Abstract

Background: Acute lymphoblastic leukemia (ALL), the most common paediatric malignancy, is a heterogeneous hematologic disease. ALL patients may present with isolated and persistent osteo-articular complaints, lower incidence of hepatomegaly, splenomegaly or lymphadenopathy without clear laboratory features, and misdiagnosed as systemic juvenile idiopathic arthritis (sJIA). **Methods:** This was a single center cross sectional study over a period of 4 years. Clinic laboratory profiles of 39 ALL children were compared with 39 age and sex-matched sJIA cases. **Result:** Among 39 ALL patients 89.7% were initially misdiagnosed as sJIA upon clinical presentation. Majority (66.7%) of ALL patients had oligo-articular joint involvement. In sJIA, small joints of the hands were most commonly involved. The total WBC count was significantly higher in ALL patients (p-value 0.0065). CRP and LDH values between the two groups showed significant differences (p-value 0.00006 and < 0.00001 respectively). **Conclusion:** The presentation of leukemia with arthralgia or arthritis makes the diagnosis difficult for the physicians. The diagnosis of sJIA must be made with caution keeping the possibility of haematological malignancy in mind.

Keywords

ALL, sJIA, Arthritis, Arthralgia, Musculoskeletal

1. Introduction

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. The age-adjusted incidence rate of ALL in the United States is 1.38 per 100,000 individuals per year [1]. It is also the most common pediatric malignancy, representing 75% - 80% of acute leukemias among children [2].

The development of ALL is believed to involve a transformation event of a single progenitor cell with indefinite clonal expansion. The leukemogenic event may occur in committed lymphoid cells of B- or T-cell lineages or in early precursors, which gives rise to the different subtypes of ALL based on the stage of lymphoid differentiation of the cell in which the event occurred [2].

Children with ALL develop symptoms related to infiltration of blasts in the bone marrow, lymphoid system, and extramedullary sites. Common constitutional symptoms include fever (60%), fatigue (50%), pallor (25%), and weight loss (26%). Infiltration of blast cells in the marrow cavity and periosteum often leads to bone pain (23%) and disruption of normal hematopoiesis. Infiltration of the lymphoid system may cause lymphadenopathy and hepatosplenomegaly. CNS involvement is found in less than 5% of children at presentation. When present, the signs and symptoms include headache, vomiting, papilledema, and sixth-nerve palsy [2] Apart from these, there remains a number of unusual clinical manifestations including musculoskeletal symptoms which have been reported in childhood leukemia at rates varying from 7.1% to 62.3% [3] [4] [5]. In 15% - 30% of cases, ALL patients may present with isolated and persistent osteo-articular complaints and, lower incidence of hepatomegaly, splenomegaly or lymphadenopathy without clear laboratory features. Musculoskeletal symptoms can manifest with arthralgia or overt arthritis and misdiagnosed as systemic juvenile idiopathic arthritis (sJIA) [6] [7].

Systemic juvenile idiopathic arthritis (sJIA) is a distinctive subtype of juvenile idiopathic arthritis (JIA) according to the classification provided by the International League of Associations for Rheumatology (ILAR) [8]. Cytokine dysregulation is seen in sJIA. Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-8, monocyte chemoattractant protein-1, E-selectin, and intracellular adhesion molecules levels are elevated in sJIA [9]. This dysregulation can result in clinical and laboratory findings in sJIA like fever, anorexia, pain hypersensitivity, joint destruction, vasculitis, and thrombosis [9].

The clinical definition of the systemic arthritis subtype in accordance with the ILAR classification includes 2-week duration of fever and arthritis as cardinal features, as well as at least one of the following: hepatosplenomegaly, lymphadenopathy, serositis or typical rash [8]. Diagnosis is based largely on the identification of clinical criteria and the exclusion of other serious conditions that mimic its symptoms, such as infection and malignancy [10].

Steroid plays a major role in the management course of sJIA. However therapy with corticosteroids may lead to disastrous consequences and might delay the diagnosis of leukemia by relieving symptoms and affecting the cytology and bone marrow picture [11]. Hence, it is imperative to consider acute leukemia in the differential diagnosis of sJIA as ALL may initially present with arthritis as part of a prodromal stage lasting for weeks or even months, without typical signs of leukemia. Thus, ALL may be misdiagnosed as systemic juvenile idiopathic arthritis (JIA), leading to a delay in proper treatment [12].

To our knowledge, there is no study to date in our country that has evaluated the differences between acute leukemia and sJIA at disease onset. Few studies outside the country compared leukemia vs JIA patients and demonstrated a high sensitivity and specificity of the combination of hematological abnormalities and nighttime pain for a leukemia diagnosis [13] [14]. The diagnosis of acute lymphoblastic leukemia should be ruled out in patients who present with arthritis and hematological alterations, with joint pain disproportionate to the degree of arthritis, predominantly at night and that does not improve with the use of analgesics, fever, lymph nodes, and hepatosplenomegaly [15]. So, the objectives of this study were to highlight the arthritic presentation in ALL children and to delineate features that could help differentiate it from sJIA. It was also aimed to assess the clinical features and laboratory parameters that point towards leukemia over sJIA in a child with musculoskeletal pain.

2. Materials and Methods

This was a single-center cross-sectional study carried out in the Paediatric Rheumatology and Immunology Division of the Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from January 2019 to December 2022. Thirty-nine children under 16 years of age with arthritis and/or arthralgia for 6 weeks or more, along with other systemic features (fever, lymphadenopathy, hepatic/splenomegaly, serositis), who attended the outpatient service or were admitted into inpatient of Paediatric Rheumatology and Immunology Division of Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University and subsequently diagnosed as ALL were included in the study. ALL was diagnosed on the basis of bone marrow study where the presence of blast cell population more than 20% was considered as ALL.

The demographic, clinical and laboratory profiles of these children were analyzed and compared with the initial presentation of 39 age and sex-matched sJIA cases who came across the services over the same study period by purposive sampling. sJIA was diagnosed according to ILAR criteria [8]. Ethical clearance was taken from the appropriate body. Data were collected by a structured predesigned questionnaire developed in Bangla (Bengali). Prior pre-testing was done to test the reliability and validity. Later on, the questionnaire was translated into English by competent persons. Both the Bangla and English versions were used according to requirements but data entry and calculation were done in English.

A detailed history including age, gender, disease duration, presenting complaints, any musculoskeletal complaints, constitutional symptoms such as fever, rash, pallor, presence of lymphadenopathy, hepato-splenomegaly, etc were noted. Pain distinctly localized to one or more joints without any other feature of inflammation was considered 'arthralgia'. The presence of joint swelling and pain with or without redness and restriction of motion was defined as 'arthritis'. Children with arthralgia and/or arthritis were considered to have joint involvement. Treatment received before the presentation was also noted. Laboratory evaluation, including complete blood count (CBC), inflammatory markers like ESR, and CRP, and markers of increased cell turnover such as serum lactate dehydrogenase (LDH) were recorded.

The SPSS 25 statistical software was used. Data were expressed as percentages, mean, standard deviation and range. Chi-square and Fisher exact test were used for comparison of means between the groups. A p-value < 0.05 were considered as statistically significant.

3. Result

The demographic and clinical characteristics of the study population are described in Table 1. Thirty-nine patients with a diagnosis of ALL and another 39 with a diagnosis of sJIA were included in the study during the study period (January 2019–December 2022). The study groups were age and sex-matched. There was no significant difference in disease duration between the two groups (Table 1). Six patients (15.4%) had received steroids before the diagnosis of ALL. One of the patients also received weekly methotrexate for two months as a treatment for sJIA before he was diagnosed as ALL.

Fever was the common clinical presentation for both of the groups and was present in almost all the patients. However, irritability, pallor, arthralgia and nocturnal pain were more in ALL patients in comparison to sJIA which are statistically significant. Arthritis was more in sJIA group with a significant reduction of pain after using analgesics. Among 39 ALL patients 89.7% were initially misdiagnosed as sJIA upon clinical presentation (Table 2).

The number of joints affected did not distinguish children with ALL clearly from those with sJIA. Majority (66.7%) of ALL patients had oligo-articular joint involvement, where knee and ankle joints were commonly affected. In sJIA, small joints of hands were most commonly involved with a near-equal percentage of oligo and polyarticular patterns (Table 3).

Four out of 39 children with ALL (10.3%) had cytopenia in one or more cell lines at presentation. The total WBC count was significantly higher in ALL patients. There were lymphocytosis and thrombocytopenia (mean value) in ALL and Neutrophilia and thrombocytosis (mean value) in the case of sJIA. CRP and LDH values between the two groups showed significant differences (Table 4).

4. Discussion

Childhood malignancies with joint complaints, especially ALL may be misdiagnosed

Table 1. Demographic characteristics of the ALL and sJIA patients.

Variable	ALL (n = 39)	sJIA (n = 39)	P value
Age (years) Mean ± SD	5.3 ± 2.4 (2.5 - 7.5)	4.6 ± 1.2 (3.1 - 5.7)	0.5874*
Gender			
Male	24	22	0.6452*
Female	15	17	
M:F	1.6:1	1.3:1	-
Disease duration (days)	65 ± 18.7 (29 - 82)	45 ± 8.7 (29 - 62)	0.55602*

*Chi-Square Test.

Table 2. Clinical characteristics of ALL and sJIA patients.

Variable	ALL (n = 39)	sJIA (n = 39)	P Value
Fever	39 (100%)	39 (100%)	1
Irritability	28 (71.7%)	02 (5.1%)	<0.001
Rash	7 (17.9%)	27 (69.2%)	<0.001
Pallor	31 (79.5%)	11 (28.2%)	<0.001
Arthritis	22 (56.4%)	35 (89.7%)	<0.01
Arthralgia	17 (43.5%)	03 (7.7%)	<0.001
Nocturnal pain	14 (35.9%)	01 (2.6%)	<0.001
Pain intensity (VAS 0 - 10)	7.7 ± 2.1 (6 - 10)	6.7 ± 1.1 (6 - 8)	0.27332
Pain relief by analgesics	09 (23.0%)	29 (74.3%)	<0.001
Lymphadenopathy	39 (100%)	28 (71.7%)	0.02703
Organomegaly	36 (92.3%)	37 (94.9%)	0.4815
Serositis	0 (00%)	01 (2.6%)	-
Initial misdiagnosis			
sJIA	35 (89.7%)	-	-
Reactive arthritis	04 (10.3%)	-	-

*Chi-Square Test.

Table 3. Pattern of joint involvement in ALL and sJIA patients presenting with arthritis and/or arthralgia.

Joint involvement	ALL (n = 39)	sJIA (n = 39)	P Value
Joint count			
<5	26 (66.7%)	20 (51.3%)	0.1687**
≥5	13 (33.3%)	19 (48.7%)	
Joint involvement			
Knee	21 (53.8%)	30 (76.9%)	0.01016*
Ankles	17 (43.6%)	32 (82.0%)	0.03995*

Continued

Small joints of hands	16 (41.0%)	33 (84.6%)	0.08691*
Small joints of feet	13 (33.3%)	21 (53.8%)	0.011*
Hip	0 (00%)	1 (2.6%)	-
Shoulder	4 (10.2%)	1 (2.6%)	0.06789*
Elbow	6 (15.4%)	7 (17.9%)	0.22942*
Spine	1 (2.5%)	5 (12.8%)	0.10247*

*Chi-Square Test; **Fisher Exact Test.

Table 4. Laboratory tests results collected at diagnosis in ALL and JIA patients.

Laboratory test	ALL (n = 39)	sJIA (n = 39)	P value
CBC			
Hb (g/dl)	9.1 ± 2.2 (6 - 11)	7.3 ± 1.7 (6 - 9.4)	0.617088*
TLC (cells/cmm)	37 ± 12.1 (16 - 51)	17 ± 3.4 (14 - 21)	0.0065*
N (%)	31 ± 5.1 (36 - 42)	89.1 ± 8.8 (86 - 92.5)	<0.00001*
L (%)	78 ± 14.5 (66 - 91)	19.1 ± 2.6 (11.2 - 31)	<0.00001*
PC (lac/cmm)	1.1 ± 0.8 (0.5 - 3.2)	10.2 ± 2.2 (6.7 - 11.1)	0.43437*
Inflammatory Parameters			
ESR (mm in 1st hour)	78 ± 15.3 (66 - 117)	94 ± 12.2 (86 - 125)	0.22247*
CRP (mg/L)	39.1 ± 17.6 (26 - 101)	9.7 ± 3.2 (7.6 - 11)	0.00006*
LDH (IU/L)	804 ± 102.2 (666 - 1109)	209.1 ± 112.9 (106 - 411)	<0.00001*

*Chi-Square Test.

as systemic juvenile idiopathic arthritis and diagnosis and treatment of malignancy may be delayed. Moreover, steroid treatment initiated with consideration of rheumatologic indications may mask the clinical and laboratory findings and may affect the response to chemotherapy. So, it is very important to distinguish between the clinic-laboratory profile of ALL and sJIA patients.

The cause of the osteoarticular manifestation of acute leukaemia has been attributed to the direct extension of leukemic cells from the marrow or to the hematogenous dissemination of leukemic cells. The proliferating leukemic cells cause bone destruction, increase intramedullary pressure which interferes with nutrition, or induce osteoclastic or blastic responses. The increased frequency and severity of bone symptoms in children have been attributed to more active bone metabolism, more red marrow with little reserve marrow space, and a less firmly attached perioteum [12].

Acute lymphoblastic leukemia is a malignancy that is most common in children, especially those aged 1 - 4 years old [13]. It is more common in males at almost every age, and this fact remains unexplained [14]. The onset of sJIA may occur at any time during childhood, with a broad peak of onset between 1 and 5 years of age. There is an equal sex ratio for sJIA [15]. Here in this study, the

mean age and duration of illness were little higher in ALL patients in comparison to sJIA (Table 1). Delay in diagnosis, initial misdiagnosis and steroid intake in few cases may be the possible explanation.

In Table 2, a comparison between clinical characteristics between ALL and sJIA patients had been shown. Fever was a common presentation in both groups, though specific fever type could not be clearly stated by parents. Most of the leukaemic patients were irritable throughout the day, whereas sJIA patients showed irritability while febrile, and otherwise playful. Feelings of annoyance, impatience, anger or frustration that often arise over even the smallest of things were considered as irritability [16]. Pain from pressure in the bone marrow can cause irritability in leukamia, and febrile state in the case of sJIA.

Near 18% of ALL patients presented with skin rash in the form of petechiae, purpura or bruising representing underlying thrombocytopenia. In sJIA the rash was evanescent, morbilliform, macular, often with central clearing, migratory and widespread. The rash of sJIA was fleeting (vanishes within a few minutes to a few hours), and correlated with the acute febrile episodes. In both groups the rash was non-pruritic. Histologically, analysis of the cutaneous rash in SJIA shows perivascular infiltration with neutrophils and monocytes and epithelial activation with the expression of myeloid-related protein −8 (MRP-8) and MRP-14 [17].

Pallor was more in ALL in comparison to sJIA group. Anemia is a common finding and an important cause of morbidity in patients with acute lymphoblastic leukemia (ALL) at diagnosis or during the management course. A recent study conducted in India showed 80% of the ALL study population had anaemia with the majority having normocytic normochromic anemia (71%) [18]. There might be different types of anaemia in leukemia, but, rapid production of atypical white blood cells that impair the ability of the bone marrow to produce red blood cells is the most common explanation [18]. The most common pathophysiological mechanism leading to anemia in JIA is inflammation. Other mechanisms include iron deficiency, impaired vitamin B12 absorption, autoimmune hemolytic anemia and anaemia of chronic disease [19].

In this study, early parameters to distinguish ALL from sJIA in children with persistent bone or joint pain were described. Considering bones and joint manifestation, arthralgia and nocturnal pain were more in ALL patients. sJIA group presented with arthritis responsive to analgesics. Pain intensity was higher in ALL when measured by the Visual Analogue Scale (VAS, 0 - 10) (Table 2). Arthritis is the second most common presenting symptom in sJIA after fever, and arthralgia can precede arthritis [20]. Musculoskeletal (MSK) involvement has been reported in childhood leukemia at rates varying from 7.1% to 62.3% [3] [5]. In 2016, a systematic review and meta-analysis reported that MSK symptoms were a prominent clinical presenting feature in childhood leukemia, including limb pain (43%), bone pain (26%), joint pain (15%), and limping (11%) [21]. Therefore, childhood leukemia with MSK involvement can mimic rheumatic or orthopedic conditions and lead to delayed diagnosis of leukemia [11].

There was no significant difference in the presence of lymphadenopathy, organomegaly and serositis in between groups.

In this study, sJIA patients presented with a near-equal percentage of polyarticular and oligoarticular involvement (**Table 3**). In Behrens *et al.*'s study, equal distribution between polyarticular and oligoarticular patterns was noted at presentation (41% polyarticular, 40% oligoarticular, and 7% monoarticular presentation) [20]; however, in a European study the ratio differs, and an oligoarticular pattern is found on presentation twice as often as a polyarticular pattern [22]. The wrists, knees, and ankles are primarily the most commonly involved joints on initial presentation in sJIA [11] [23]. Over the course of the disease, chronic progressive arthritis is seen in approximately one-third to one-half of the patients [24], and ultimately polyarticular joint involvement is found in most of these cases [22]. Cervical spine arthritis as well as hip arthritis (often bilateral and destructive) can also be seen [22]. Typically, children with ALL have asymmetric oligoarthritis, particularly in the large joints of the lower limbs [25]. Most of the ALL patients in this cohort had asymmetric large joint involvement (**Table 3**). About 77% of children with ALL with initial musculoskeletal manifestations met the diagnostic criteria for sJIA. Like ours, Cabral and Tucker [26], Tamashiro *et al.* [27] and Gupta *et al.* [28] noted intense metaphyseal bone pain, which occurs with a sudden onset, was a manifestation that pointed towards ALL, whereas sJIA cases presented with more progressive joint pain associated with arthritis and morning stiffness.

Articular manifestations can be explained by infltration of the synovium, periosteum, or bone marrow by malignant cells, deposition of uric acid or immune complexes in the joint, hemarthrosis secondary to thrombocytopenia [29]. As a result of severe inflammation of the metaphysis, the joint appears to be inflamed, simulating juvenile idiopathic arthritis.

As all the ALL cases came across our service as sJIA cases, we have done preliminary workup only like complete blood count (CBC), C Reactive Protein (CRP) and serum Lactate Dehydrogenase (LDH). A bone marrow study was done in all the cases as per the working protocol of the unit. Significant difference was observed in differential counts and LDH between groups (**Table 4**). Tamashiro *et al.*, in 2011, compared 57 patients of ALL with musculoskeletal symptoms with 102 patients of sJIA [27]. Limb pain, hepatomegaly, weight loss, and hemorrhagic manifestations were predominantly present in leukemia patients as compared to sJIA. Kesarapu *et al.* found that most children with musculoskeletal symptoms along with thrombocytopenia, neutropenia and lymphocytosis turned out into leukemia [30]. So, careful analysis of blood count should be done.

The discordance between low or normal neutrophil or platelet counts and elevated inflammatory markers suggests relative bone marrow failure. Jones *et al.* found that a low-normal platelet count (between 150 and 200 × 109/L) was a sensitive and specific factor for the diagnosis of ALL, in the event of chronic osteoarticular complaints (sensitivity: 82% and specificity: 87%) [31] According to

Agodi *et al.* [32], the combination of neutropenia, anemia and elevated LDH demonstrated a 93% sensitivity and a 100% specificity of having ALL. LDH has also been identified as a useful marker for ALL [5]. Wallendal *et al.* [33] investigated twelve children with malignancies (eight with ALL) and joint involvement with normal blood count and compared with 24 children with JIA. They found LDH as the most valuable marker to differentiate. Kirubakaran *et al.* [34] compared 10 children with ALL and arthritis, initially suspected as systemic JIA with 10 age-matched children with systemic JIA. Lymphocytosis and thrombocytopenia (each occurring in 70% with ALL and none of the children with JIA) were found to be the most helpful laboratory tests to distinguish between ALL and JIA like our study.

Therefore, clinicians must examine bone marrow if a child presents with persistent bone or joint pain associated with hepatomegaly, splenomegaly or lymphadenopathy, even if systemic arthritis is considered. Louvigne in 2020 conducted a multicenter study to identify early clinical and laboratory features that help distinguish between JIA and ALL. This article also concluded as if the patient presents with osteoarticular pain for at least 1 month, a bone marrow aspirate should be performed if accompanied by hepatomegaly, splenomegaly, or adenomegaly [35].

Limitations of this study were that it was a cross-sectional study of two separate and independent patient cohorts, with inherent limitations in design and the risk of selection bias. To our knowledge, this study presents the pioneer population of ALL misdiagnosed as JIA compared to sJIA till date. A prospective study with greater sample size is necessary to reinforce our findings.

5. Conclusion

In this study, it has been found that the clinical manifestations and complete blood count of both ALL and sJIA have both similarities and differences. The presentation of leukemia with arthralgia or arthritis makes the diagnosis difficult for the physicians. The diagnosis of sJIA must be made with caution keeping the possibility of haematological malignancy in mind. Correct analysis of the CBC and bone marrow smears is very important. Prospective studies are needed to help validate our results.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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