“Clinical findings and hematological parameters in cases of Acute Lymphoblastic Leukemia with thrombocytosis at initial diagnosis”

Abstract

Introduction

Acute lymphoblastic leukaemia (ALL) is a bone marrow and blood neoplasm involving precursor cells, or lymphoblasts, dedicated to the B/T-cell lineages. Acute lymphoblastic leukemia (ALL) usually presents with bicytopenia/pancytopenia and thrombocytopenia being the most important key parameter. Thrombocytosis has not been a well-described feature of acute lymphoblastic leukaemia (ALL), hence this study was planned to investigate the incidence of thrombocytosis at initial diagnosis and its correlation with clinicohematological parameters, immunophenotyping and cytogenetics study.

Aim and objective:

To investigate the incidence of thrombocytosis in newly diagnosed cases of ALL and its correlation with clinicohematological parameters, immunophenotyping, and cytogenetics.

Material and methods:

Medical records of all patients diagnosed as ALL at the King George's Medical University Lucknow Leukemia-Lymphoma lab over a five-year period were retrieved. The primary focus of this study was on individuals who had thrombocytosis at initial diagnosis. These patients’ records were
retrieved for chief clinical complaints, laboratory data, immunophenotyping, and cytogenetics.

**Results:**

We retrieved a total of 167 immunophenotypically confirmed cases of ALL at the Leukemia-Lymphoma lab of King George's Medical University, Lucknow over a five-year period to see how frequently thrombocytosis is associated with ALL and whether there are other associated clinical, laboratory, and cytogenetics findings. Out of 167 cases, 6 (3.5%) had thrombocytosis at initial diagnosis. No clinical findings among selected patients clearly showed an association with thrombocytosis, including total leucocyte count, hemoglobin, lymphoblast percentage, and immunophenotypic and karyotyping. None of the patients had major induction-related complications.

**Conclusion:**

To summarize, thrombocytosis can be observed in ALL patients at initial diagnosis, particularly men. This group of patients had no risk of significant events during induction therapy, based on a smaller number of cases.

**Keywords:** Acute lymphoblastic leukemia, Thrombocytosis, Pancytopenia, Bicytopenia, Flow cytometry

“Clinical findings and hematological parameters in cases of Acute Lymphoblastic Leukemia with thrombocytosis at initial diagnosis”
**Introduction**

Acute lymphoblastic leukaemia (ALL) is a bone marrow and blood neoplasm involving precursor cells, or lymphoblasts, dedicated to the B/T-cell lineages. There is a proliferation of lymphoblasts, with enlarged nuclei, coarse chromatin, inconspicuous nucleoli, and a sparse amount of cytoplasm [1]. Bone marrow failure is the most common symptom of ALL, which manifests as weakness, recurrent fever, bruising or bleeding, bone and joint pain [2]. In newly diagnosed cases of ALL, anaemia, neutropenia, and thrombocytopenia are prevalent. The degree of bone marrow replacement by leukemic lymphoblasts determines the severity of the disease [3]. Patients with ALL are on average 14 years old, with 60% of those diagnosed being under the age of 20 [4]. Thrombocytopenia is a characteristic of acute lymphoblastic leukemia (ALL). However, in few previous studies, platelet counts of more than 100,000/mm3 were reported in 25% of cases at diagnosis [5,6]. Thrombocytosis has not been a well described feature of acute lymphoblastic leukaemia (ALL), hence this study was planned to investigate the incidence of thrombocytosis at initial diagnosis and its correlation with clinicohematological parameters, immunophenotyping and cytogenetics study.

**Aim and objective:**

To investigate the incidence of thrombocytosis in newly diagnosed cases of ALL and its correlation with clinicohematological parameters, immunophenotyping, and cytogenetics.

**Material and methods:**
Over a five-year period, all patients' records who were diagnosed as ALL at King George's Medical University Lucknow, Leukemia-Lymphoma lab were retrieved from the departmental leukemia-lymphoma registry. The results of the first platelet count reported at the time of diagnosis were filtered from their medical records. Patients who received packed red cell transfusions or intravenous hydration were excluded from the study. The primary focus of this study was on individuals who had thrombocytosis (platelet count > 4,50,000/mm$^3$) at initial diagnosis. These patients' records were analysed further for chief clinical complaints and laboratory data such as age, sex, presence or absence of hepatosplenomegaly, bulk disease, and lymphadenopathy; complete blood count (CBC), bone marrow examination findings, immunophenotyping, and chromosomal analysis. The final study also eliminated cases with evidence of inflammatory illnesses, concurrent infections, or disorders other than ALL that could have caused thrombocytosis. In all patients, the results of the complete blood count, peripheral blood smears, bone marrow aspirate smears, biopsies, and flowcytometry were re-evaluated.

Results:

The present retrospective descriptive study was done at the Leukemia-Lymphoma lab of King George’s Medical University, Lucknow, through our departmental leukemia-lymphoma registry. A total of 167 immunophenotypically confirmed cases of ALL were retrieved, out of which only six cases presented with thrombocytosis at initial diagnosis. The clinical data and laboratory findings of all six patients are summarised in Table 1. Out of six cases, four were male and two were female. All cases of ALL with thrombocytosis at initial diagnosis presented with generalised
weakness and on/off fever. The patients' ages ranged from 7 to 61 years. There was no substantial medical or familial history in the past. No history of bleeding, oedema, rashes, or joint pain was noted in all the six cases. The X-ray of the chest, an electrocardiogram, and routine microscopy for urine were all normal. The card tests for HIV, hepatitis B, and hepatitis C were negative. There had been no previous blood transfusions. Out of six patients, three showed hepatosplenomegaly, out of which two were presented along with lymphadenopathy. No bulk disease was noted in any of the cases. There was bicytopenia seen by a routine hemogram in two patients, which revealed a haemoglobin level of 6.6 g/dL and 10.7 g/dL with a total leukocyte count of 2.0x10^3/uL and 1.9x10^3/uL respectively. Haemoglobin were ranged from 6.6 g/dL to 13.9 g/dl and total leukocyte count were ranged from 1.9x10^3/uL to 380x10^3/uL among cases. The blast cells in the peripheral blood of cases ranged from 6% to 94%. [Figure 1(A)]. The platelet count was increased in all cases and ranged from 460x10^3/ul to 600x10^3/ul. In four of the six cases, the mean platelet volume (MPV) was raised and ranged from 19.3fL to 50.4fL. Rest two cases show normal MPV. Plateletcrit (PCT), platelet distribution width (PDW), and platelet-large cell ratio (P-LCR) were normal in almost all cases except one, which showed an increase in PDW, and one case showed decreased P-LCR. The peripheral blood smears showed a predominately normocytic, normochromic population with mild anisocytosis. The red cell indices, including MCV, were within the normal range in all cases. In all the cases, bone marrow aspirates showed marked suppression of myeloid and erythroid lineage cells by proliferation of blast cells. However, there was expansion of megakaryocytes noted with normal morphology in all the cases. [Figure 1(B)]. A flow cytometry study showed expression of lymphoid markers; five were diagnosed as B-Acute
lymphoblastic leukaemia (B-ALL) and one as T-Acute lymphoblastic leukaemia (T-ALL). One case of B-ALL showed aberrant expression of CD33. The blasts were also verified to be CD41 and CD61 negative by flow cytometry to rule out acute megakaryoblastic leukemia (M7) at the time of diagnosis, which might be present as thrombocytosis. In all the six cases, bone marrow biopsies had been done in all of them, of which four cases showed an increased number of megakaryocytes and in two cases appeared to be present in a normal number. However, other lineage cells were markedly suppressed by proliferating lymphoblast. The megakaryocytes displayed unremarkable morphology, with occasional mononuclear forms in all cases. No significant dysplasia was noted among megakaryocytes. [Figure 1(C)]. Karyotyping was done in all the cases. Only one case showed the presence of the Philadelphia chromosome. The other five cases displayed normal karyogram on G banding. After four weeks of induction therapy, all patients were in remission without any manifestation of thrombosis or bleeding. In all six cases, platelet counts did not drop below 100,000/uL in the period of induction therapy. After remission, platelet counts were within normal limits and no one required a platelet transfusion. After 12 months of initial diagnosis, two of the patients with lymphadenopathy had relapsed (serial no.2 & 3) and the rest were in remission. Platelet counts at the time of relapse in patients' serial no.2 & 3 were 40,000/mm³ and 32,000/mm³ respectively, and no one required platelet transfusion.

Discussion

Patients with ALL frequently have bicytopenia or pancytopenia at the time of diagnosis, although their total leukocyte counts may increase/decrease or in the normal range. At the time of diagnosis and even during the relapse
period, the platelet lineage is the earliest and most consistently reduced in ALL [7]. Symptoms of ALL are usually caused by bone marrow suppression or leukaemia invasion of medullary or extramedullary locations [2]. At the point of diagnosis, platelet counts are usually low in peripheral blood smears (median: 48–52x10⁹/L), and megakaryocytes are commonly lacking or markedly reduced on bone marrow smear examination [2]. Despite the virtual lack of bone marrow megakaryocyte progenitors, a previous study showed that ALL exhibited an enhanced immature platelet fraction, signifying that thrombopoiesis is activated [8]. However, previous research has shown that 25% of children have platelet counts greater than 100,000/mm³ at the time of diagnosis [5,6]. The 66.66% (4/6) of patients in the present case series were male, which was in concordance with previous studies done in ALL with thrombocytosis [9,10]. Thrombocytosis is often seen in solid tumour such as neuroblastoma and hepatoblastoma, along with a few haematological malignancies like chronic myeloid leukaemia (CML) and essential thrombocytosis (ET). Thrombocytosis has not been a well described feature of ALL. Only a few studies were found after an extensive search of the literature [10]. In the present study, platelet volume indices were studied in all six cases of ALL with thrombocytosis. In four of the six cases, the mean platelet volume (MPV) was raised and ranged from 19.3fL to 50.4fL. The remaining two cases show normal MPV as shown in table 1. Plateletcrit (PCT), platelet distribution width (PDW) and platelet-large cell ratio (P-LCR) were normal in five cases. Only one case showed an increase in PDW and one case showed decreased P-LCR. We could not correlate our findings of platelet volume indices as there were no similar studies found even after an extensive search of the literature. In all patients, the red blood cell indices were within normal limits, and there was stainable iron in bone
marrow particles, ruling out iron deficiency as a cause of thrombocytosis. The medical records of all cases were reviewed, and none of them revealed concomitant infection, inflammatory bowel illness, or haemolytic anaemia, indicating that the elevated platelet count was most likely attributable to the leukaemia process. Out of a total of six cases, four presented with peripheral lymphadenopathy and none showed bulk disease. However, in a study done by Blatt Julie et al., out of seven cases, three showed bulk disease [10]. As shown in table 1, only a single case of ALL was Philadelphia positive (Ph+). Rest all five patients showed normal karyotyping results. A flowcytometry study was done in all cases, which displayed that these blasts are positive for lymphoid blast markers and are negative for CD41 and CD61, so that megakaryoblastic leukaemia with thrombocytosis, which mimics ALL, did not go unrecognised. None of the cases showed similarities in clinical findings except that four cases were presented with lymphadenopathy. As a result, it's possible that ALL with thrombocytosis is more common in patients with the leukemia-lymphoma syndrome. The mechanism of thrombocytosis does not appear to be obvious from these findings. In all six cases, bone marrow aspirates and biopsies revealed an increased or normal number of megakaryocytes, raising the likelihood of lymphoblasts producing a thrombopoietic factor. It has already been described in the literature that leukemic lymphoblasts reduce leukocytes by the production of lymphoblasts-derived leucocyte inhibiting factors [11]. In the present case series, all cases were in remission and without any manifestation of thrombosis or bleeding after four weeks of induction therapy. In all six cases, platelet counts did not drop below 100,000/uL in the period of induction therapy. After 12 months of initial diagnosis, two of the patients with lymphadenopathy had relapsed (serial nos. 2 & 3) and the rest were in
remission. Platelet counts at the time of relapse in patients (serial no.2 & 3) were 40,000/mm$^3$ and 32,000/mm$^3$ respectively. No one required a platelet transfusion. A similar study done by Blatt Julie et al. also showed complete remission in all seven cases and no one required platelet transfusion. However, two of them showed uncommon events during induction therapy, that is, central nervous system thrombosis in one and duodenal perforation in the other [10]. Due to the very small number of cases along with the brief time for follow up of these patients, it is very early to say about the role of thrombocytosis in ALL. However, it is of interest that out of six cases, four were male, MPV was increased in four cases, four cases showed lymphadenopathy, and neither of these patients required platelet transfusion during the course of follow-up.

**Conclusion**

In ALL cases with thrombocytosis at the time of the first diagnosis, there is no risk of complications related to induction, based on a very small number of cases. Studies with a larger number of ALL cases with thrombocytosis and longer follow-up may show its relation to predict prognosis along with clinicohematological, immunophenotyping, and cytogenetic findings.

**Patient consent declaration**

The authors certify that they obtained all the appropriate patient permission forms. By completing the form, the patient(s) has/have given his/her/their consent for clinical information to be published in the journal. The patients are informed that their names and initials will not be published, and that every effort will be made to maintain their anonymity.
Financial support and sponsorship

Nil

Interest conflicts

There are no author conflicts of interest.

References:


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<th>Platelet distribution width (PDW) fL</th>
<th>Platelet large cell ratio (P-LCR)</th>
<th>Hemoglobin (g/dL)</th>
<th>Total leucocyte count (/μL)</th>
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Table 1: Clinical findings and lab parameters in cases of Acute Lymphoblastic Leukemia with thrombocytosis at initial diagnosis
Images:

Bone marrow aspirate (Leishman Giemsa, ×1,000). Two hypolobated megakaryocytes seen in a background of many blasts that have a high nucleo-cytoplasmic ratio, scant cytoplasm, irregular nuclear membranes, and conspicuous nucleoli