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A Case Report on Pediatric Relapsed Acute Lymphoblastic Leukemia Patient with a novel t (1;7) (q32; p22) translocation

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ABSTRACT

Background: *Acute lymphoblastic leukemia (ALL) of the B-cell lineage (B-ALL) is a malignant neoplasm characterized by clonal proliferation, decreased apoptosis and accumulation of immature lymphoid progenitor cells in the bone marrow and in peripheral blood. It is often associated with genetic aberrations that may be correlated with disease outcomes. Relapse cases of B-ALL have a poor prognosis and accumulate additional genetic alterations.* ***Case Report:*** *A 9-year old male presented with relapsed B-ALL and succumbed to the disease despite aggressive treatment, 18 days after reporting to the hospital. Conventional cytogenetic analysis revealed a complex karyotype of 45 XY, t(1,7) (q32:p22),+der (2), add (4q33), del (6q21),-12,-12 including a novel translocation t(1;7) (q32;p22) observed in all the 26 metaphases analyzed.* ***Discussion:*** *This is the first report of a translocation between chromosomes 1 and 7 in B-ALL, and may represent an ancestral clone of B-ALL. The region involved in our reported translocation, in this case, seems to have an impact on B-cell development and proliferation, disease initiation and poor prognosis.* ***Conclusion:*** *We report a translocation involving chromosomes 1 and 7; which has not been reported earlier for B-ALL in hematologic malignancy. Its association with poor prognosis needs to be confirmed by examining the matched samples from more such cases.*

Keywords: B-cell ALL, Novel translocation, Relapse, Poor outcome

INTRODUCTION

Acute lymphoblastic leukemia (ALL) represents approximately 80% of leukemia and occurs mostly in children with peak prevalence between the ages of 2 years and 5 years [1]. ALL is a neoplasm of immature lymphoid progenitors, mostly of B-cell lineage resulting in the uncontrolled and excessive production of lymphoid blasts, hindering the normal production of red and white cells, as well as platelets. Gross chromosomal rearrangements, along with aneuploidy, are present in almost two-thirds of B-precursor ALL (B-ALL) cases [1,2]. While recurring chromosomal rearrangements have been recognized as critical events in leukemogenesis, they often require additional genetic perturbations for a complete disease phenotype. A number of new ALL subtypes have been identified based on sub-microscopic alterations recently using genome-wide microarrays and next-generation sequencing [3,4]. The underlying result of all these alterations driving the disease is the disruption of tumor suppressor genes and arresting hematopoietic development, along with activation of proto-oncogenes and de-regulation of signaling pathways to drive proliferation.

Though long-term rates of event-free survival (EFS) for pediatric B-ALL are approximately 90%, specific chromosomal rearrangements have often been associated with disease outcome [5-7]. For example, t(12;21) (p13;q22) encoding ETV6-RUNX1 (TEL-AML1) is associated with excellent prognosis [8], Philadelphia chromosome-positive BCR-ABL1 has poor prognosis [9], while t(17;19) (q22;p13) encoding TCF3-HLF is practically incurable [10]. Relapsed B-ALL has a very poor prognosis [11]. Though, mitoxantrone has been shown to be significantly better than idarubicin with marginal improvement in the therapeutic outcomes [12,13]. Genome-wide profiling of matched samples exhibits

acquisition of new chromosomal alterations along with the loss of chromosomal aberrations at initial diagnosis, highlighting that ALL genomes continue to acquire additional genetic alterations during disease progression [14,15].

We report the case of a relapsed pediatric B-ALL, a 9-year old male patient with a complex karyotype presentation of 45 XY, t(1,7) (q32:p22),+der (2), add (4q33), del (6q21), -12, -12 including a novel translocation involving chromosomes 1 and 7 t(1;7) (q32;p22). The patient died following two episodes of cardiac arrest after 18 days of reporting to the hospital.

CASE REPORT

A 9-year old male patient was diagnosed initially in 2011 in the native country (Afghanistan) as a case of B-ALL based on bone marrow biopsy and was on maintenance chemotherapy of acute lymphoblastic leukemia relapse Berlin Frankfurt Mustar (BFM-REZ). In August 2014 that patient was reported to Indraprastha Apollo Hospital, New Delhi with complaints of severe body pain, itching all over body, hematuria, gum bleeding, epistaxis and fever. The initial diagnosis was on preliminary clinical evaluation; he was diagnosed with generalized lymphadenopathy, severe bony tenderness along with enlargement of the liver and spleen. Further hematological tests and analysis of bone marrow cells and biopsy confirmed the relapse of B-ALL.

During his stay in the hospital, he received 2 cycles of chemotherapy comprising cytocristin, methotrexate, leucovorin, and leunase. During his treatment, he developed *Pseudomonas aeruginosa* and *Escherichia coli* infections in the blood; later he developed coagulase-negative *Staphylococcus* infection. All the infections were adequately treated. He improved clinically and was discharged after 9 days. Within 3 days he again got admitted with complaints of pyuria and high-grade fever. On the 6th day of the second admission, he developed hemoptysis that he aspirated. He had a cardiac arrest from which he could be revived with prompt efforts, and again a second cardiac arrest developed after 1 hour when he was already shifted to the intensive care unit. This time he could not be revived and succumbed to the disease.

Hematologic analysis of peripheral blood revealed significantly reduced hematocrit and elevated ESR, with a significantly lower number of RBCs and platelets and increased WBC count. Importantly, 97% atypical cells (immature lymphoblast) were detected on differential cell count (Table 1).

Table 1 Hematological parameters of the patient at presentation

Parameter	Result	Reference Interval
Hemoglobin (g/dl)	9.6	9.5-13.5
Hematocrit (%)	**27.7***	35-45
WBC Count (10^3/ mm^3)	**45.1#**	5-15
RBC Count (10^6/µl)	**3.26***	4.5-6.5
MCV (fl)	84.9	79-94
MCH (pg)	29.6	25-33
MCHC (g/dl)	34.8	31-37
RDW (%)	**16.5#**	11.5-14.5
Platelet Count (10^3/ mm^3)	**73#**	180-400
ESR (mm/1st hour)	**73#**	0-15
Differential Count		
Lymphocytes (%)	**3***	38-42
Atypical Cells (%)	**97#**	-

Values different from the biological reference intervals are indicated in bold; *Indicate values lower than reference interval; # indicate values higher than reference interval; WBC, white blood cells; RBC, red blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; ESR, erythrocyte sedimentation rate

Further, hypercellular marrow smears of the bone marrow aspirate were found to be almost entirely replaced by small and large blasts having coarse chromatin, inconspicuous nucleoli and scanty cytoplasm; only occasional normal hematopoietic cells were observed. Bone marrow biopsy showed areas of myelonecrosis along with marrow spaces almost entirely replaced by blasts. Peripheral blood cells were 63.6% CD34+, 32% CD45+, and 91.4% HLA-DR+, and contained a very high proportion of pre-B cells, i.e., 76.9% CD10+, 92.8% CD19+, 6.9% CD20+ cells (Table 2). Diagnosis of CD13+ pre-B ALL with myelonecrosis was established taking into account all these observations.

Table 2 Cell surface marker expression in peripheral blood mononuclear cells by flow cytometry

Cell Surface Marker	% of Gated Region
T Cell Markers	
CD3	6.11%
CD7	5.46%
B Cell Markers	
CD10	76.85%
CD19	92.76%
CD20	6.90%
Myeloid Markers	
CD33	8.86%
Myeloperoxidase (Cytoplasmic)	0.36%
Monocytic Markers	
CD14	0.08%
Other Markers	
CD34	63.64%
CD45	32.00%
HLA-DR	91.36%

The conventional cytogenetic analysis was performed on 24 and 48-hour un-stimulated bone marrow cultured cells. Cells were processed by standard methods and chromosomes stained by G-banding. Karyotype analysis was performed and the latest ISCN nomenclature was followed [16]. In pre-ALL patients, we normally get chromosomes with poor morphology. Analysis on 26 metaphases at ISCN400 banding resolution showed a novel translocation involving the long arm of chromosome 1 and short arm of chromosome 7, t(1;7) (q32;p22) along with an additional derivative of chromosome 2; (+der2), addition of material of unknown origin at q33 region of chromosome 4; add (4q33), deletion of chromosome 6 at q21 region; del (6q21), and deletion of both copies of chromosome 12; (-12,-12) (Figure 1).

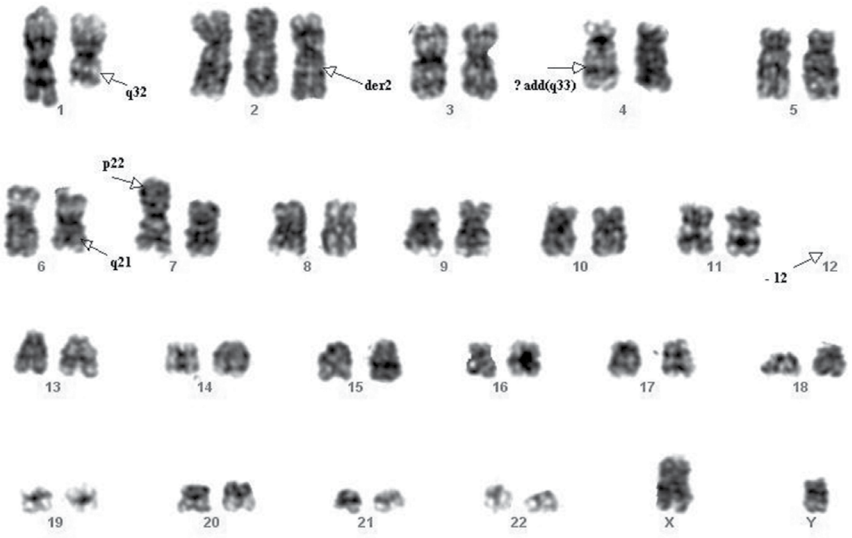

Figure 1 Karyotype analysis of unstimulated bone marrow cells. Analysis of 26 metaphases was performed using standard procedures for G-T-G banding. Structural aberrations including translocation between chromosomes 1 and 7 at regions q32 and p22 respectively, an additional derivative of chromosome 2, addition of a material of unknown origin at 4q33, deletion of 6q21 and both missing copies of chromosome 12 are indicated by arrows

The same karyotype was observed in all the 26 metaphases. Fluorescent *in-situ* hybridization (FISH) was carried out using standard protocol according to the probe manufacturer (Vysis-Abbott, Molecular Abbot Park, Illinois, USA) for detection of BCR-ABL1, TEL/AML, KMT2A (MLL) and TCF3-HLF translocations often detect associated with B-ALL. The sample was found to be negative for all the FISH probes tested. Unfortunately, no karyotype or FISH analysis was performed at the time of initial diagnosis in Afghanistan, probably due to lack of appropriate infrastructure.

Ethical Consent

Written informed consent was obtained from the legal guardian of the patient for publication of this case report and accompanying image.

DISCUSSION

We report the case of a relapsed B-ALL patient who was presented with bacterial infections along with a very high blast count both in peripheral blood and bone marrow. Despite bacterial infections being treated adequately and undergoing two cycles of aggressive chemotherapy, the patient suffered two episodes of cardiac arrest and succumbed to the disease. Since the patient died early during the course of treatment, further follow-up or analysis could not be undertaken.

It is well established that while treatment outcomes for primary B-ALL are favorable [5,6], the prognosis outcomes for relapsed cases is very poor [11,13]. During disease progression, the ALL genomes continue to acquire additional genetic alterations; a majority of relapse samples exhibit loss of chromosomal aberrations present at diagnosis and acquisition of new genetic aberrations, suggesting the existence of a pre-diagnosis clone that acquires additional genetic aberrations during disease progression as the pre-dominant clone at relapse [14,15].

The novel translocation involving chromosomes 1 and 7, t (1;7) (q32;p22) that has not been reported earlier in B-ALL may represent one such "ancestral clone". This is substantiated by the fact that all the translocation was noted in all the 26 metaphases that were analyzed. Other translocations involving chromosome 1 and 7 have been reported in myelodysplastic syndrome [17], acute erythroblastic leukemia, T-cell ALL, and diffuse large B-cell lymphoma [18-21]. The 1q32 region includes harbors interesting genes such as PTPN7 implicated to play roles in B-cell development, and signal transduction, and RASSF5A proposed to function as a Ras-regulated tumor suppressor. Similarly, 7p22 includes ACTB that is proposed to be involved in the transport of chromosomes and FSCN1 that is an independent marker of poor prognosis in a number of solid tumors.

Taken together, the regions involved in the reported translocation seem to influence B-cell development and proliferation, disease initiation and poor prognosis. The t (1;7) (q32;p22) translocation may be an ancestral clone as it was noted in all the 26 metaphases involved. Further, the absence of common translocations linked to poor prognosis (BCR-ABL1, TEL-AML, KMT2A-MLL, and TCF3-HLF) suggests that this novel translocation may be associated with poor prognosis.

CONCLUSION

In summary, we report a translocation involving chromosomes 1 and 7; which has not been reported earlier for B-ALL. Furthermore, the specific t(1;7) (q32;p22) translocation has not been reported earlier for any hematologic malignancy. Since the current case report involves a solitary case, the association of this translocation with a prognosis of relapsed B-ALL needs to be evaluated further using the molecular characterization of matched samples. Also, no prior information is available on the cytogenetic status of the patient, either at initial diagnosis or at any other time during treatment for the next 3 years. It is suggested that this specific translocation is rare and may be considered as a potential poor prognostic factor for pediatric (and possibly adult) B-cell ALL patients.

DECLARATIONS

Conflict of Interest

The authors have disclosed no conflict of interest, financial or otherwise.

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