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Case Report
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The First Case Report of an Infant with Three-Way Philadelphia Chromosome Variant T(9;22;14)(Q34;Q11.2;Q32) Chronic Myeloid Leukemia, King Fahd Specialist Hospital Dammam Experience, Kingdom of Saudi Arabia

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Abstract

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder. It is uncommon disease in childhood, it accounts for only 2-5% of all leukemia and yearly rate of less than 1 case per 100,000 population in the age group younger than 20 years.

Introduction

CML is characterized by the presence of the Philadelphia (Ph) chromosome, formed by reciprocal translocation between the long arms of chromosome 9 and 22, t (9; 22) (q34; q11). The classical Ph chromosome is detected in 90% of CML cases; however, 5-10% of CML cases have variant Ph chromosome translocation in which the Ph chromosome is derived through rearrangements other than the classic t (9; 22).

The present study reports the first CML, presenting in the infantile again accelerated phase and demonstrating the three-way Ph chromosome variant t (9; 22; 14) (q34; q11.2; q32).

Case Report

Our case is a 10 month old boy product of a non-consanguineous marriage with full term, vacuum-assisted vaginal delivery due to delay in progression of delivery, the antenatal period was uneventful and the baby had normal birth weight and Apgar score, he was growing normally till the age of 8 month when noticed to have progressive pallor and reduced activity followed by gradual abdominal distension with intermittent low grade fever, he was evaluated in his scheduled vaccination clinic for the 9 months vaccinations schedule when he was found to have huge splenomegaly and marked leukocytosis with white blood cell (WBC) count of more than 100×109/L.

Family history revealed that the maternal grandfather died of unknown blood malignancy and his maternal uncle was diagnosed with renal malignancy. However, the mother had no history suggestive of inherited cancer syndrome. On physical examination, the child was pale. He had massively enlarged firm spleen, that extended down to his pelvic rim, and generalized minimal lymphadenopathy. He was not dysmorphic and the rest of his physical examination was unremarkable. A written informed consent was taken from the patient's custodian to publish this case report.

Complete Blood Count

Complete blood count (CBC) and differential was performed using an Automatic Hematological Analyzer Sysmex XE-5000(Sysmex America, Mundelein, IL). His CBC and differential showed a hemoglobin (Hb) level of 6.2 g/dL, a platelet count of 615×10^9/L, and a WBC count of 115.28×10^9/L with 19% neutrophils, 11% lymphocytes, 3% monocytes, 19% eosinophils, 23% basophils, 4% metamyelocytes, 4% myelocytes, and 10% blast cells.

Peripheral Blood Smear

Peripheral blood smear showed marked leukocytosis with marked left shift to the level of blast cells, marked eosinophilia and basophilia. Marked anemia and thrombocytosis with

presence of dwarf megakaryocytes were seen throughout the slide.

Bone Marrow Aspirate and Biopsy

Bone marrow aspirate was a particulate and hemo diluted with increased eosinophilic and basophilic precursors. The myeloid precursors showed sequential maturation, decrease in erythroid precursor count with normal maturation. Blast cells were up to 17%. They were large in size with moderate N:C ratio, open chromatin and prominent nucleoli, and basophilic cytoplasm. Marked increase in dwarf megakaryocytes were also seen.

On Biopsy, bone marrow structure was disorganized with significant cellular streaming. The cellularity was similar to the aspirate; however, other areas showed increased megakaryocytes and marked increase in reticulin deposition where megakaryocytes occupied significant part if the marrow and were seen in fibrotic background.

Immuno Pheno Typing

Briefly, immune pheno typing on this patient's EDTA-anti coagulated peripheral blood was performed as follows: 0.5 ml of blood was mixed with 10 mL of red blood cell lysing solution and then centrifuged at 540g for 5 minutes. The supernatant was then discarded and the cell bottom was further washed with in phosphate buffer saline. A 100 µL of cell suspension was added to the tubes containing pre-titrated volumes of monoclonal antibody-cocktails (Becton Dickinson, USA). These monoclonal antibodies were used in conjunction with four fluoro chromes, i.e., FITC, PE, APC, and PerCP in each tube. The samples were run on FACSCanto II instrument and the analysis was done by FACS Diva software (BD Biosciences, San Diego, CA). The flow cytometry data was analyzed, and the lineage blast of the blasts was determined in each case depending upon the expression of lineage specific markers. The blast cells in this sample showed as a population in the CD45 dim (i.e. blast gate) and accounted to 10%. The gate was positive for: CD33, CD 34, CD117, CD38, CD58, HLA-DR and the aberrant marker CD7. It was negative for: MPO, CD13, Tdt and all other T cells and B cells lymphoid markers. The aberrant markers detected were: CD7 expression, and the negative expression of MPO and CD13.

Cytogenetic Analysis

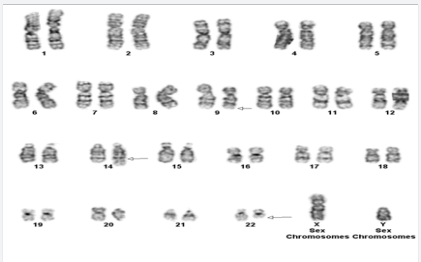

Figure 1: Giemsa-banding karyogram of this patient's bone marrow showing the involvement of chromosomes 9, 14 and 22 (*arrows*) in the translocation process.

Chromosome analysis using GTG banding was done as described previously [1]. Karyotyping was performed in 20 metaphases from this patient's unstimulated bone marrow sample according to the nomenclature of the International System for Human Cytogenetics [2] and 19 showed 46,XY,t(9;14;22) (q34;q32;q11.2) (Figure 1).

Fluorescence In Situ Hybridization

Fluorescence in situ hybridization (FISH) was performed usingBCR-ABL1tri-color dual fusion probes (Yvsis, Abbott Molecular Inc., IL) to detect BCR-ABL1translocation as described previously [3]. It showed "nuc ish(ABL1,BCR)x3 (ABL1 con BCRx1)"seen in all of the 100 analyzed nuclei (Figure 2A).This result was consistent with the three-way variant abnormal pattern seen in the karyogram and indicated the implication of chromosome 14 as the third partner in the t(9;22) translocation (Figure 2A & 2B).

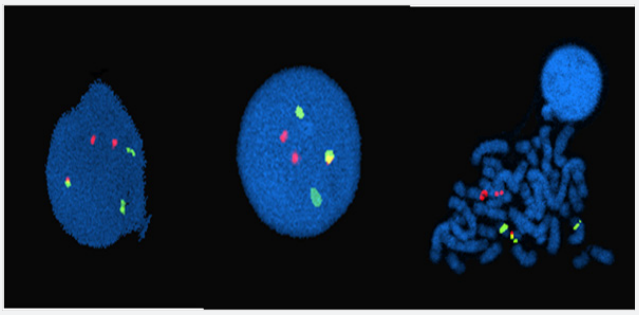

Figure 2A: Fluorescence *in situ* hybridization on interphase nuclei (left and middle) and metaphase (right) showing two ABL1 signals on chromosome 9 (red), two BCR signals (green) one on the normal chromosomes 22, and the other on chromosome 14, and the fusion gene BCR-ABL1 (yellow) on 22q confirming the three-way Philadelphia chromosome translocation.

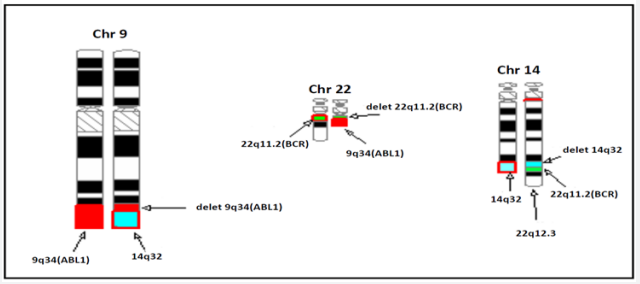

Figure 2B: An ideogram showing the rearrangement occurred in this t (9;22;14) (q34;q11;q32) three-way translocation Philadelphia chromosome seen in this case.

Molecular Analysis

On this patient's EDTA whole blood sample, quantification of BCR-ABL1 P210 transcript by real-time reverse transcriptase polymerase chain reaction (RT-PCR). This was performed by using the GeneXpert® Dx System (Roche Diagnostics GmbH Mannheim) as described before [4,5] and found this chimeric transcript to be present at a level of 36% International Scale (IS) unit (i.e. %BCR-ABL1:ABL1 = 36% (IS)) (Figure 3).

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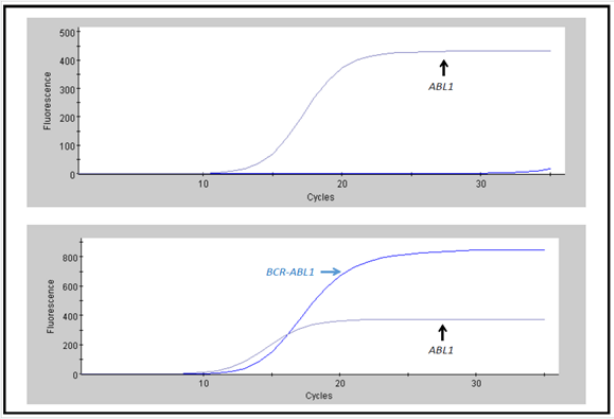

Figure 3: Quantification of BCR-ABL1 P210 transcript by real-time reverse transcriptase polymerase chain reaction showing the fusion transcript curve in this patient's sample (below) and its absence in normal sample.

Discussion

CML is rare among childhood leukemias. Its incidence increases with age, from a rate of 0.09/100000 among those ≤ 15 years old to 7.88/100000 among those ≥ 75 years old [6]. CML is genetically characterized by the presence of the reciprocal translocation t(9;22) with the formation of Ph chromosome. This translocation fuses the ABL1 gene on chromosome 9 with the breakpoint cluster region on chromosome 22. Although indistinguishable by classical cytogenetics, the abnormal fusion leads to the expression of three variant types of BCR-ABL1 mRNAs. The first two, found in up to 98% of CML cases, consist of BCR exons 13 (b2) or 14 (b3) fused with ABL1exon 2(a2). The third variant, found in about 25% of ALL cases, involves BCR exon 1(e1) and ABL1 exon 2(a2) (Figure 4).

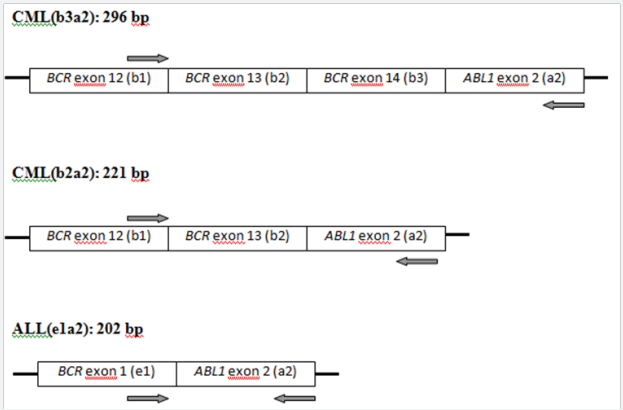

Figure 4: A simplified cartoon showing exon map of *BCR*, *ABL1* and *BCR-ABL1* transcripts. The e14a2 (b3a2) (upper), e13a2 (b2a2) (*middle*), and e1a2 (*lower*) transcripts with their respective length in base pair (bp) and common primer locations are shown (*arrows*).

CML can present in one of three phases-chronic phase, accelerated phase, or blast crisis. Most patients present in the chronic phase and may be asymptomatic. When symptoms and signs are present, they are often mild and are caused by the accumulation of mature and immature granulocytic cells. Generalized malaise, weakness, weight loss, fever, pallor, and organomegaly, particularly splenomegaly, are frequent presenting symptoms. The accelerated phase is characterized by increased marrow or blood blast cell values of 10% to 19%, peripheral basophilia greater than 20%, persistent thrombocytopenia unrelated to therapy or thrombocytosis unresponsive to therapy, and increasing spleen size or WBC count. If marrow or blood blast cell percentages exceed 19% of total leukocytes, this signifies a transition to blast crisis, which may be myeloid, lymphoid, or mixed. Presentation in blast crisis can mimic an acute leukemia of lymphoid or myeloid lineage, and in this case the cells harbor the Philadelphia chromosome [7].

Prior to the availability of Imatinib, the initial treatment with Hydroxy urea, followed by interferon-alpha with or without Cytosine Arabinoside, was the routine clinical management for children with CML before undergoing allogenic-stem cell transplantation, a procedure recommended for all patients with a matched donor. But the management of CMLin children changed dramatically with the introduction of TK inhibitors (TKIs). Unfortunately, outcomes for patients presenting in an advanced stage-accelerated phase or blast crisis CML-continues to be poor, requiring chemotherapy and allogeneic hematopoietic stem cell transplantation to attempt cure. Some CML cases have variant Ph translocation where a chromosome other than 9 and 22 is involved. Several chromosomes have been reported to be involved in variant Ph chromosome formation, some are more frequently involved than others [8]. One of these infrequently reported chromosomes is chromosome 14. The three-way variant Ph t(9;22;14)(q34;q11.2:p11) found in our case has been reported before [9]. However, none of those cases with this particular translocation presented in infancy [10].

Two major mechanisms of this translocation are possible. The first one, t(9;22) occurs as first event and after that, chromosome 14 will be implicated in the process as second event. The second mechanism can involve the three chromosomes, 9, 22, and 14 from the beginning of translocation process [11]. The fact that all studied cells from our patient had t(9;22;14)(q34;q11.2:p11) as the sole cytogenetic abnormality, suggested that in this case, the later mechanism was more likely.

The prognostic impact of the variant translocations is still controversial. Damla Eyüpoğlu et al. [12] found that Among the 180 patients with Ph-positive CML who were treated in Hacettepe University Faculty of Medicine Division of Hematology, variant translocations were detected in Five patients (2.7%) and the rearrangements were in chromosomes 2 (2 cases), 11, 14 and 15. All the patients were treated with imatinib or Dasatinib. All patients reached a stable major molecular response suggesting a prognosis not worse than standard translocation individuals [13]. El-Zimaity et al. [13] investigated the characteristics and

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outcomes of 44 patients with variant translocations among 721 CML patients treated with imatinib. The only significant difference in clinical characteristics was a higher frequency of accelerated phase in those with variant translocations (56% vs. 38%) [14].

It is important to realize that chromosomal abnormalities including variant Ph chromosome appearing as a new cytogenetic abnormality in addition to the classical Ph (clonal evolution) has a bad prognostic value [14,15]. However, our case is different. This patient has the Ph chromosome variant (9;22;14)(q34;q11.2;q32) as the sole chromosomal abnormality (single clone in origin) without previous treatment. Our patient was started on hydroxyl urea (20 mg /kg) and dasatinib (120 mg /m2). His blood count after one month from starting therapy was completely normalized and showed: Hb level of 12.1 g/dL, a platelet count of 225×10^9/L, WBC count of 5.69×10^9/L, with 10% neutrophils, 81% lymphocyte, 0% monocytes, 4%eosinophils, and 4% basophils.

Like the few reported cases with this translocation, our patient seems to be responding well to TKI [16]. However, longer follow up is still needed to confirm that.

Conclusion

The present study reports the first case of an infant CML patient presented with the accelerated phase of the disease, who demonstrated the three-way Ph translocation variant t(9;22,14)(q34;q11;q32). This study also demonstrates that this patient was successfully treated with hydroxyl urea and the TKI, Dasatinib. However, longer follow up is needed to confirm a favorable and prolonged molecular response.

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