

# Isochromosome 6(p) is a rare chromosomal aberration in Acute Lymphoblastic Leukemia: A case report

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## Abstract:

Cytogenetic analysis using G- banding technique was performed on bone marrow cells from a 22-year-old female who was diagnosed with Acute Lymphoblastic Leukemia . The chromosomal analysis showed a complex karyotype which included the Isochromosome 6(p) in 16 metaphases (16%) of 97 total metaphases studied . This finding suggests a strong selective pressure for loss of heterozygosity of genes located on 6q , and is in keeping with the hypothesis that one or more tumor suppressor genes might be located on the long arm of chromosome 6 . Moreover, trisomy (or tetrasomy) for the short arm of chromosome 6, due to the isochromosome formation , indicating also a possible role for amplification of genes located on 6p in tumor progression in this case of acute lymphoblastic leukemia .

**Key words :** Acute Lymphoblastic Leukemia , Isochromosome 6(p) , rare chromosomal aberration .

## Introduction:

Cytogenetic analysis in Acute Lymphoblastic Leukemia (ALL) have revealed a great number of non-random chromosome abnormalities (1) . In many instances , molecular studies of these abnormalities identified specific genes implicated in the process of leukemogenesis (2) .

Non random chromosomal abnormalities have important biologic, diagnostic, and prognostic significance in ALL (3). Chromosomal abnormalities can be numerical or structural in nature, and many karyotypes in ALL contain both types of change (3) . Isochromosomes are uncommon , but a nonrandom structural chromosomal anomaly in ALL (4-6) .

The incidence of i(6)(p) in ALL is very low . Only sixteen cases have been reported in ALL and only one in immunoblastic lymphoma (7-12) . All the patients, except for one adult, were children with a median age of 5 years , sex ratio: 12 Male/5 Female . The isochromosome 6p was associated with pseudo, hyper and hypodiploidies and high ploidies. It occurred more frequently at diagnosis than at relapse . The isochromosome 6(p) was not observed as a sole anomaly .

The majority of cases are part of a complex karyotype and some cases occur with established abnormalities such as der(19)t(1;19) , t(12;21)(p13;q22) and t(14;18)(q32;q21) .

The fact that all of cases had complex karyotypes and the isochromosome 6(p) was not the only abnormality complicated any evaluation of its prognostic significance . Additional cases are needed to delineate the epidemiology of this rare entity.

### Case Report :

A 22-year old female was diagnosed in May (2008) with acute lymphoblastic leukemia in Baghdad Teaching Hospital . At diagnosis Peripheral blood showed a hemoglobin level of 8.6g/dL , white blood cell 38 x10<sup>9</sup> / L , platelets 124 x10<sup>9</sup> / L and 61% blasts . bone marrow was hyper cellular with 93% blasts . After one month of treatment with Adriamycin , Vincristine , and Prednisolone , a Cytogenetic study , using G- banding technique , on bone marrow cells was performed by using direct and short term culture technique (13) in Iraqi center for cancer and medical genetics research . Unstimulated bone marrow cells were cultured for 30 minute (direct culture technique ) and for 24 , 48 hour (short term culture technique ) at 37 °C. cells were exposed to colcemid (0.2 µg/ml) in last 25 minute of culturing time at 37 °C and harvested for chromosome analysis on G-banded metaphases.

Karyotypes were described according to the International System for Human Cytogenetic Nomenclature (ISCN 1995)

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(14) . Cytogenetic analysis showed : 46XX , -8 , +der(5) del(5)(q13-q35)[19] / 46XX , -8 , +mar [15] / 46XX , -6 , +der(4)del(4)(q21-q35)[11] / 46XX , -5 , +mar [10] / 46XX , -5 , -11 , +der(6) i(6p) ,+ mar [ 7 ]/46XX , -16 , +der(6) i(6p) [5] / 46XX , -2 , +der(6) i(6p) [4] / 46 , XX[26] . The number

of cells that were analyzed is given in square brackets after the karyotype . The karyotype revealed a rare aberration , i(6p) , in 16 metaphases (16%) of 97 total metaphases studied (Figure No. 1 ) .

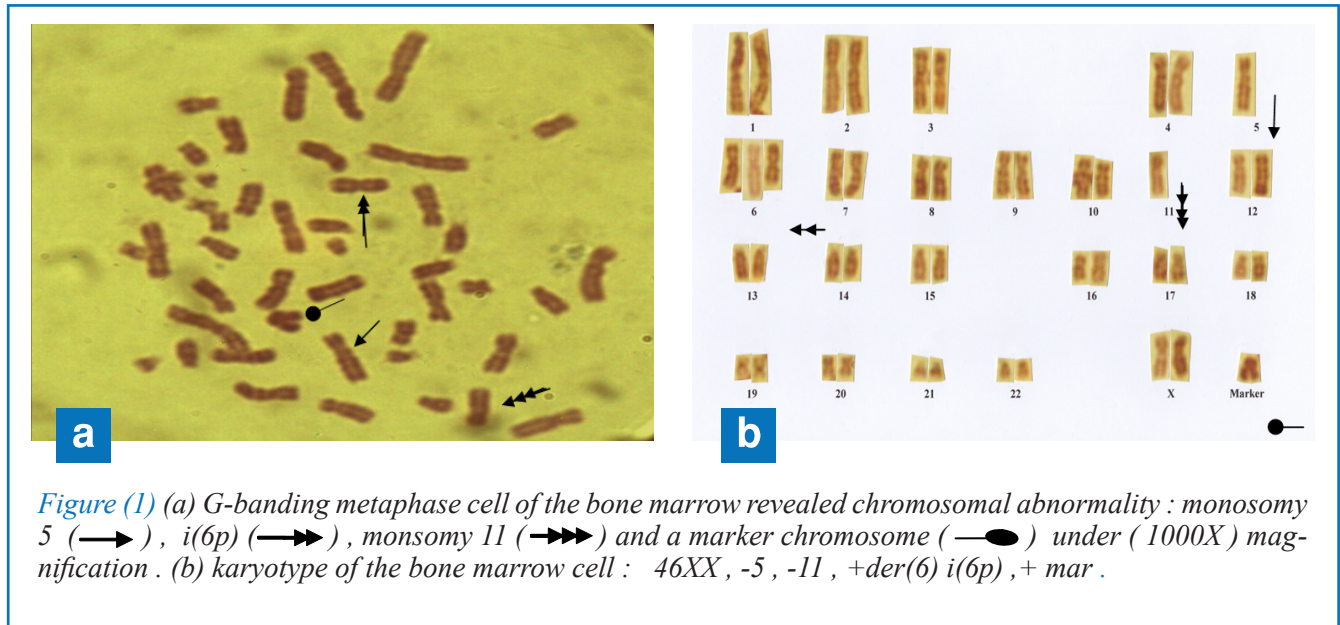


Figure (1) (a) G-banding metaphase cell of the bone marrow revealed chromosomal abnormality : monosomy 5 (→), i(6p) (→→), monosomy 11 (→→→) and a marker chromosome (—●) under ( 1000X) magnification . (b) karyotype of the bone marrow cell : 46XX , -5 , -11 , +der(6) i(6p) ,+ mar .

## Discussion :

In this case of ALL the chromosomal analysis showed a complex karyotype which included the Isochromosome 6(p) in 16 metaphases (16%) of 97 total metaphases studied . Isochromosomes are a nonrandom chromosomal anomaly in ALL (4-6) . The incidence of i(6)(p) in ALL is very low . Only sixteen cases have been reported in ALL and only one in immunoblastic lymphoma . The Isochromosome 6(p) In this case of ALL was not observed as a sole anomaly as the majority of cases reported before (7-12) .

There are several possible ways in which isochromosomes could be formed (15-17) . Misdivision at the centromere across the short axis rather than the long axis of the chromosome appears to be the most plausible explanation (17) . it had been proposed that isochromosomes are mechanical indicators of genetic events central to the etiology of the leukemia (18) .

As a result of the formation of an isochromosome , there is the loss of a normal chromosome , and the structural abnormality results in monosomy for the genes on one arm of the chromosome and trisomy for the genes on the other arm. It is not known whether the overexpression of a proto-oncogene (or other gene) directly involved in tumour progression , or the deletion of a tumor-suppressor gene from the isochromosome contributes to development or proliferation of leukemic blasts in these cases (18, 19).

It has been suggested that a central part of the short arm of chromosome 6p harbours one or more oncogenes directly involved in tumour progression , on the other hand , despite accumulating evidence those deletions of chromosomal bands 6q16-q21 are a critical event in ALL , no suppressor genes have been identified in this region (20, 21) . Recently, it has been described that a minimal deleted interval in 6q21 encompasses the FOXO3A, PRDM1 and HACE1 candidate genes (22).

Both chromosomal abnormalities, Isochromosome 6p and Deletion of 6q, result in loss of genes located on the long arm of chromosome 6, the common region of deletion being 6q21-6qter ( 23-25). This finding suggests a strong selective pressure for loss of heterozygosity of genes located on 6q, and is in keeping with the hypothesis that one or more tumor suppressor genes might be located on the long arm of chromosome 6 (26). Moreover, trisomy (or tetrasomy) for the short arm of chromosome 6, due to the isochromosome formation, indicating also a possible role for amplification of genes located on 6p in tumor progression in this case of acute lymphoblastic leukemia.

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## كروموسوم متناظر الأذرع (p) 6 isochromosome تغير كروموسومي نادر في ابيضاض الدم اللمفاوي الحاد : تقرير حالة

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### الخلاصة :

اجري التحليل الوراثي الخلوي باستخدام تقنية التحزيم بالكمزرا على خلايا نخاع العظم لاثني عمرها 22 عاما شخصت بابيضاض الدم اللمفاوي الحاد , تم علاجها بالعقاقير : Adriamycin , vincristine , prednisolone لمدة شهر واحد بعد تشخيصها . أظهر التحليل الكروموسومي هيئة كروموسومية معقدة تضمنت كروموسوم متناظر الأذرع (p) 6 isochromosome في 16 خلية في الطور الاستوائي ( 16% ) من مجموع 96 خلية تم دراستها . هذه النتيجة تشير الى ضغوط قوية انتقائية لفقدان تغاير الزيجية للجينات الموجودة على (p)6 ويتماشى مع فرضية وجود واحد او اكثر من الجينات الكابحة للسرطان على الذراع الطويل لكروموسوم 6 , فضلا عن تثلت الذراع القصير لكروموسوم 6 نظرا لتكوين كروموسوم متناظر الأذرع , مما يدل ايضا على احتمال دور تضاعف الجينات الموجودة على (p)6 في تطور الورم في هذه الحالة من ابيضاض الدم اللمفاوي الحاد .