Case Report :

A rare B-ALL with acquired unbalanced t(9;12)(q13;p13)

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Abstract :

The chromosomal segment 12p13 harboring ETV6 or TEL gene plays a pivotal role in leukemogenesis of childhood acute lymphoid leukemia (ALL) of B-lineage. The plethora of fusion of ETV6 with RUNX1 in 21q22 has led to understand the disease mechanism and prognosis of the ALL-subgroup. Although 12p13 partners rearrangement with any other chromosomes, their entity is limited in the literature. We present the first Indian case, most likely the second global case, with double monosomy of 9 and 12 in a 9 year old girl along with information available in this relevance.

Key words:

B-ALL, conventional cytogenetics, unbalanced translocation, t(9q13;12p13)

Introduction:

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer constituting ~30% before age 15.[1] Although 80 to 90% of children achieve a durable complete response with treatment, ALL is the leading cause of cancer-related deaths among children. Prognosis and/or treatment outcome largely depends on the pattern of genetic alterations. Cytogenetic abnormalities involving 12(p) have been documented in a broad spectrum of hematopoietic malignancies, including acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia, chronic myelomonocytic leukemia, chronic lymphocytic leukemia, myelodysplastic syndromes and rarely in T-ALL.[2, 3] In particular, balanced or unbalanced translocations, insertions, inversions, and deletions, which most frequently involve band 12p13 have been reported in approximately 10% childhood ALL of B-cell lineage. The hallmarked cryptic rearrangements as t(12;21)(p13;q22) or del(12p) are frequently documented in childhood ALL; however, it is shown to be cytogenetically largely undetectable chromosomal anomaly. Fluorescence in situ hybridization (FISH) analysis, however, showed that some of the deletions in fact represent balanced and unbalanced translocations between 12 and 21 or multiple other partners, which were not captured on routine cytogenetic analysis[1]. Deletion or translocation involving12(p) is found clustered around 12p13. We present an unusual ALL case with an unbalanced translocation of 12(p13) with a 9(q13) partner.

Case report:

A 9 year old girl was presented with generalized weakness and fever for last 1 month with complaints of bilateral submandibular swelling about 1 weak back, which subsided after medication. On examination, she had severe anemia, hepatosplenomegaly, and cervical, axillary and inguinal lymphadenopathy. The enlargement of spleen and liver were 2cm and 3cm respectively. She received 2 units of PRBC over last two months. Her hemogram showed 4.3 g% Hb, 1200/cum WBC, 60% lymphocytes, and 140000/cum as platelet count with anisopoikilocytosis, few tear drop cells and scanty reactive lymphocytes in

peripheral smear. Other differential counts were within normal limits. Expression of CD10 and HLA-DR on cell surface drew a diagnosis of ALL of B-lineage. Cytogenetic examination following unstimulated culture of bone marrow cells for 24h and conventional GTG-banding revealed 45,XX,-9,der(12)t(9;12)(q13;p13) in 85% of the cells examined (Fig.1). There was an unbalanced translocation between 9(q13) and 12(p13) wherein 9pter-q12 and 12p13-pter were lost. Apparently normal karyotype was observed with 46,XX in remaining 15% of 25 cells analyzed.

Discussion:

The involvement of chromosome band 12pl3 in childhood and adult ALL has long been recognized. The gene ETV6/TEL located in this region, originally evidenced in a t(5;12)(q33;p13) causing chronic myelomonocytic leukemia (CMML) with fusions of ETV6 (12p13) with PDGFRB (5q33), was identified responsible for leukemogenesis. The second large plethora of entity was childhood ALL hallmarked by t(12;21)(p13;q22). However, its involvement was subsequently observed in a growing number of

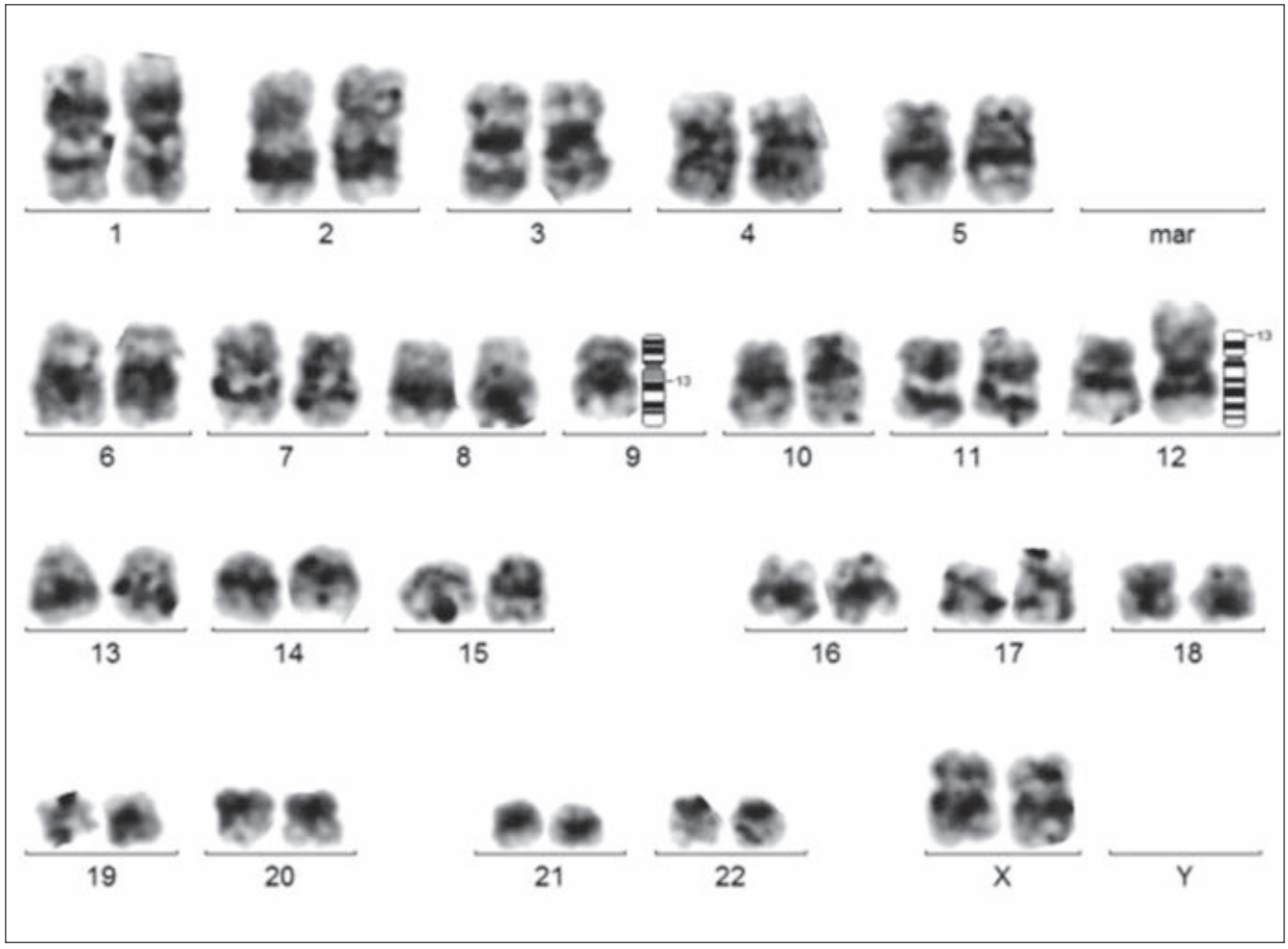

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Fig.1.: Karyogram shows 45,XX,-9,der(12) t(9;12)(q13;p13) pattern

translocations with several other fusion partners such as ABL (9q34), MNI (22q11) and AML1 (21q22) associated with myeloid and lymphoid leukemias.[4] As many as 48 chromosomal bands have been identified to be involved in ETV6 translocations, insertions or inversions and 30 ETV6 partner genes have been molecularly characterized.[5, 6] An internal deletion that includes the CDKN1B (KIP1) locus at 12p13 was reported in YAC 964C10 region[7].

The pivotal role of alteration of ETV6 with the RUNT domain transcription factor RUNX1 (AML1) in ALL-leukemogenesis has been explained[8]. ETV6, a new member of the ETS family, spans 250 kb and consists of eight exons coding for a helix-loop-helix (HLH) and a DNA-binding ETS domain. ETV6 is a strong transcriptional repressor, acting through its HLH and internal domains following five potential mechanisms for leukemogenesis [9] .Analysis of the fusion rearrangement and chimeric proteins indicates involvement of distinct domains of ETV6 in different fusion products, thus ETV6 can provide transcriptional and dimerization properties for partner genes, or also the gene itself can act as an altered transcriptional factor. Apart from forming fusion genes, there are other genetic alterations of ETV6 including deletions, point mutations and possible alterations at the promoter level that could contribute to the malignant phenotype. It is likely that ETV6 is frequently involved in leukemogenesis because of the large number of partners with which it can rearrange and the several pathogenic mechanisms by which it can lead to cell transformation.

In the cases with unbalanced translocation, DNA segments distal to the break-point are lost from the affected homologue and subsequently from the malignant genome. The frequency of deletion involving the 12p13 region, often targets ETV6 and p27KIP1 genes, suggests that these lesions primarily inactivate one allele of a tumor suppressor gene; however, loss of heterozygosity in the 12p possibly indicates additional tumor suppressor genes in this region, although TE_L or p27KIP1 haploinsufficiency could contribute to leukemic transformation.[3,10] The contribution of 12p rearrangement is so significant in leukemia-pathogenesis; the involvement of other partner chromosomes could not draw attention towards prognosis. Also limited case number might have hindered a precise investigation on contribution of the partner chromosomes. In the present case, partial loss of 9q, including loss of ABL gene at 9q34, could perturb chemotherapeutic effect and treatment-outcome. Survival data has been explained in five patients by Sato et al.[7] where all survived less than 6 months that the 12p13 region is genetically unstable and fragile. Also extremely bad prognosis has been reported due to therapy-related genetic instability with multiple chromosomal breaks in patients received chemo- and/or radiotherapy. The present case has just been diagnosed; hence, no comment can be made on her survival. Rearrangements of 9 and 12 have been documented in Mitelman's CGAP database;6 however, only 4 cases of 19 had involvement of 9q at variable breakpoints. Prigogina et al.[11] reported the similar cytogenetic pattern in 1 of 103 ALL patients, whereas Waghray et al.[12] didn't have a single one with t(9q13;12p13) among 25 Indian children. The report describes a rare abnormality in childhood B-ALL with an unbalanced translocation between 9(q13) and 12(p13) and deletion of the remaining counterparts of the two chromosomes resulting in partial monosomy in both the chromosomes. To the best of our knowledge, this chromosomal rearrangement in ALL has been described first in Indian scenario and second in the ALL-literature. However, additional investigations are needed for precise characterization of the rearrangement, identification of gene in 9(q13), its mechanism of action with ETV6 and possible implication on prognosis.

References :

1. Raimondi SC. Current status of cytogenetic research in childhood acute lymphoblasticl-eukemia. Blood 1993; 81:2237-2251.
2. Huret JL. Atlas Genet Cytogenet Oncol Haematol. 2008; 12(6):469-470.
3. Mcgrath IT, Bhatia K, Boffetta P, Dearden C, Diehl V, Gascoyne RD, et al. TheLymphoid Neoplasms, 3rd edn, Hodder Arnold, CRC Press, FL 33487-2742, 2010, pp:445.
4. Wlodarska I1, Mecucci C, Baens M, Marynen P, van den Berghe H. ETV6 generear-rangements in hematopoietic malignant disorders. Leuk Lymphoma. 1996 Oct;23(3-4):287-295.
5. De Braekeleer E, Douet-Guilbert N, Morel F, Le Bris MJ, Basinko A, De Braekeleer M. ETV6 fusion genes in hematological malignancies: a review. Leuk Res. 2012; 36(8):945-61.doi: 10.1016/j.leukres .2012.04.010.
6. Chromosome Aberration Case List Mitelman.html.http://cgap.nci.nih.gov/Chro mosomes/CytList?soleabnorm=0&abnorm_o p=a&abnormality=der(12)t(9;12)(q11;p13)& break_op=a&breakpoint=&morph=1602&no clones=&nochrom.
7. Sato Y, Kobayashi H, Suto Y, Olney HJ, Davis EM, Super HG, Espinosa R 3rd, Le Beau MM, Rowley JD. Chromosomal instability in chromosome band 12p13: multiple breaks leading to complex rearrangements including cytogenetically undetectable sub-clones. Leukemia. 2001;15(8):1193-1202.
8. Bohlander SK. ETV6: a versatile player in leukemogenesis. Semin Cancer Biol. 2005;15(3):162-74.
9. Braekeleer E De, N Douet-Guilbert, Braekeleer M De. t(9;12)(q34;p13) ETV6/ABL1.Atlas Genet Cytogenet Oncol Haematol. 2014; 18(11):859-861.
10. Stegmaier K, Takeuchi S; Golub TR; et al. Mutational analysis of the candidate tumor suppressor gene TEL and KIP1 in childhood acute lymphoblastic leukemia. Cancer Res. 1996, 56: 1413-17.
11. Prigogina EL, Puchkova GP, Mayakova SA. Nonrandom chromosomal abnormalities in acute lymphoblastic leukemia of childhood. Cancer Genet Cytogenet1988; 32:183-203.
12. Waghray M, Rowley JD, Reddy PP, Reddy SV. A cytogenetic study of children in India with acute lymphocytic leukemia: correlation with clinical data. Cancer Genet

    Cytogenet. 1986; 23(3):225-237.