Trisomy 5; a rare isolated finding in pediatric B-lymphoblastic leukemia

Abstract

Background and objectives:

In acute leukemia, all diagnostic criteria and treatment protocols are based on cytogenetic and molecular genetic findings. Despite recent advances in molecular biology, cytogenetic studies still play a pivotal role in the sub-classification of B-lymphoblastic leukemia (B-ALL). B-ALL is characterized by clonal cytogenetic abnormalities with numerical chromosomal aberrations being more common. An extra copy of chromosome 5 is common to see in cases with hyper diploidy. However, a gain of chromosome 5 as a sole anomaly is exceptionally rare in B-ALL. To date, trisomy 5 as a sole abnormality is reported in few cases only. We aimed to report the clinicopathologic profile of this rare finding to increase knowledge and highlight the disease course of these patients.

Methods: We report a case of a 14-year boy presented with fever, lethargy and episodes of nasal bleeding for two weeks. He was admitted to the pediatric oncology unit at Indus hospital and health network, Karachi. Flowcytometry performed on peripheral blood using 8-color flowcytometry. Conventional karyotyping was performed by GTG banding. FISH panel was comprised of dual color dual fusion probes for *BCR::ABL1* and *ETV6::RUNX1* whereas break apart probe for *KMT2A* (Metasystem, Germany). Digital image analysis for karyotyping and FISH was done on Leica Biosystems, Cytovision MB8.

Results: Flowcytometry results were consistent with B-ALL. Cytogenetic analysis on his bone marrow aspirate revealed trisomy 5 as a sole abnormality with no evidence of any other clonal cytogenetic abnormality. FISH studies for *BCR::ABL1*, *ETV6::RUNX1* and *KMT2A* showed no evidence of gene rearrangements.

Conclusion: Trisomy 5 is a very rare cytogenetic aberration. Only few cases reported in children. Inferior outcome is reported in both children and adults. The increasing number of reported cases raises the possibility of a distinct cytogenetic entity. Its prognostic and therapeutic implications are yet to be explored.

Keywords: Cytogenetics, trisomy 5, B-lymphoblastic leukemia, pediatric

Introduction

Acute lymphoblastic leukemia (ALL) is the most commonly occurring cancer in children. [1] It has an impact on immune system, mainly B-cells and T-cells. ALL usually affects B cells in children. High doses of X-rays and other types of radiation exposure as well as chemotherapy for cancer treatment are among the factors that increase the risk of developing this condition. Children having Down syndrome or other genetic disorders are also more prone to develop ALL. B-ALL is the most frequent subtype of acute leukemia in children. With recent advances, all major diagnostic criteria, risk stratification and treatment protocols are based on cytogenetics and molecular genetics. [2]

The diagnosis of hematological malignancies is greatly influenced by cytogenetic analysis. [3] A huge number of chromosomal defects that are not random are connected to particular forms of leukemia. The conclusive diagnosis is frequently provided by the cytogenetic findings. With the use of traditional cytogenetic analysis and current advancements in molecular cytogenetic technologies, the accuracy of the findings has increased and new chromosomal abnormalities in leukemia have been discovered. [4]

We present here a case of B-ALL in which trisomy 5, a rarely occurring chromosomal abnormality was identified. In order to shed light on the clinical characteristics and prognosis of this clonal aberration, we compared it to cases already reported in the literature. The case is being reported to increase awareness of

cytogenetic findings and to document the disease course of patients with these unusual chromosomal aberrations.

Case Presentation

A 14-year-old boy presented with a history of fever, lethargy and episodes of nasal bleeding for last two weeks. On physical examination, there was no hepatosplenomegaly; however sub cervical lymph nodes were palpable approximately 2-3cm in size. X-ray chest was normal. Initial CBC results showed a high WBC count of $75.48x10^9$/L, platelet $9X10^9$/L and hemoglobin of 5.1gm/dl. Peripheral blood film revealed small to medium-sized blasts characterized by a high nuclear to cytoplasmic ratio, fine nuclear chromatin, indistinct nucleoli, and scant to moderate pale basophilic non-vacuolated agranular cytoplasm. **(Figure 1).** Cytochemical myeloperoxidase was negative in blasts.

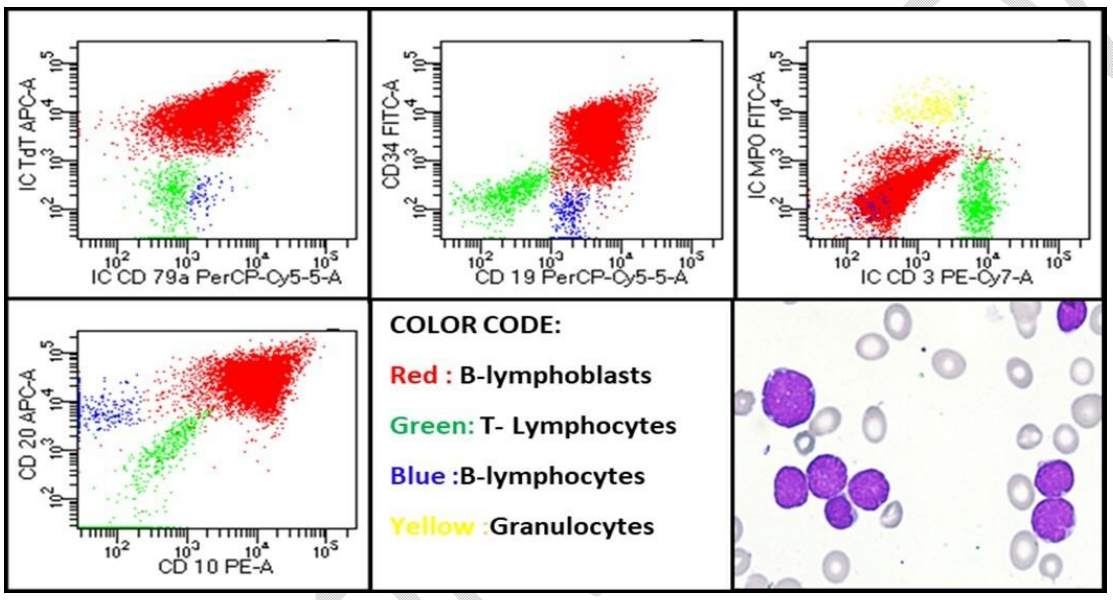

Figure 1: Immunophenotypic analysis performed on peripheral blood showing blasts and bright expression of Tdt, CD34, CD19, CD10 and CD20.

The immunophenotype analysis was performed on peripheral blood by 8-color flowcytometry which shows 77% small to medium sized blasts (forward light scatter properties) exhibiting following phenotype; TdT (+), CD34 (+), CD45 (Dim+), CD19 (+), CD79a (+), CD20 (+), CD10 (+), CD38 (+), CD58 (+), CD9 (+), CD123 (+), CD73 (+), Intracytoplasmic Myeloperoxidase (-), and ICCD3 (-). **(Figure 1)** In addition, it shows 3.3% benign B-lymphocytes, 7.3% benign T - lymphocytes and 7.6% granulocytes. The diagnosis of B-Lymphoblastic Leukemia was thus made. Cerebrospinal fluid examination at the time of diagnosis was consistent with CNS1 status.

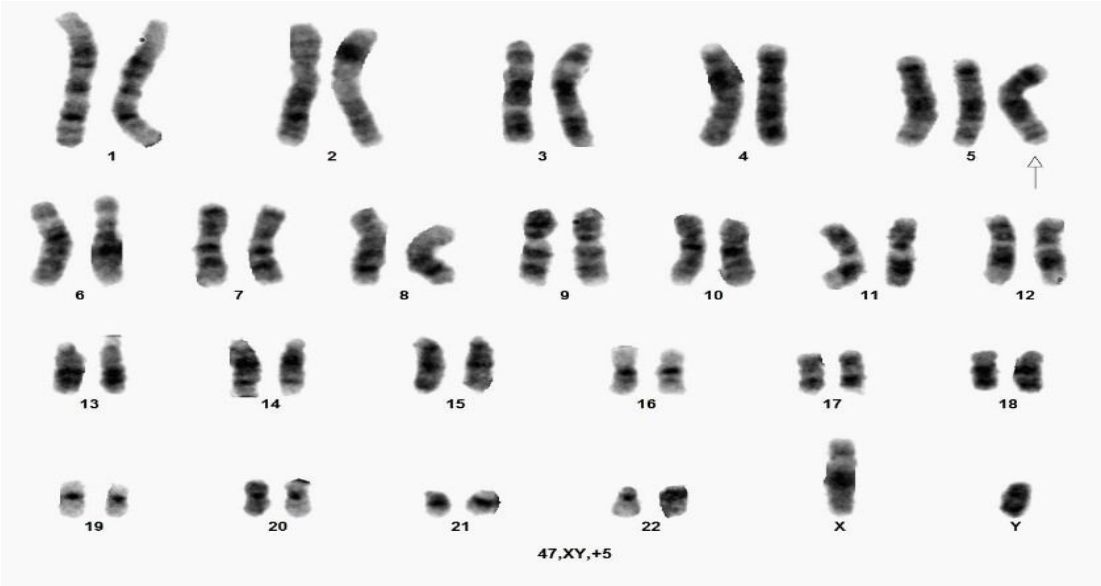

Figure 2: Karyotype performed by GTG banding

In addition, bone marrow specimen was received for conventional cytogenetics and fluorescence in situ hybridization (FISH) analysis. It was cultured in RPMI. Cells were harvested after 24hours, treated with Colcimid for mitotic arrest, KCL and Carnoy's fixative. Chromosomes were G-banded using trypsin and Giemsa stain. The case was analyzed and subsequently karyotyped showing a gain of chromosome 5 as a sole anomaly. Furthermore, FISH test for *BCR::ABL1, ETV6::RUNX1*, and *KMT2A* gene showed normal results. The case was labelled as NCI high risk (HR) based on age and WBC. Hence, HR induction chemotherapy was started as per protocol.

Discussion

In childhood ALL, trisomy 5 is usually seen in cases with hyper diploidy and with other structural cytogenetic aberrations. Trisomy 5 is thought to contribute to leukemogenesis; however, the exact mechanism is yet unclear. The acquisition of an entire chromosome is thought to have the ability to cause a dosage effect or the duplication of a mutation with a carcinogenic potential. Although only a few cases of trisomy 5 are reported to date, however it is linked to a worse clinical outcome. [4] According to the literature, three reported ALL cases with trisomy 5 as the sole finding, two (one case each of adult and pediatric ALL) demonstrated short survival while one adult ALL case demonstrated event-free survival of four years. [6] Trisomy 5 as a sole abnormality has also been reported in T-lymphoblastic leukemia. [7]

We can stratify our patients and choose the best course of treatment with the aid of a better understanding of the genetics of B-ALL. It can also help us in the development of new, targeted treatments. Our information on trisomy 5 as the only chromosomal aberration in B-ALL is currently insufficient to draw any firm conclusions about prognostic and therapeutic implications. [8,9] However, based on our case and the reported literature, we can state that trisomy 5 as the sole numerical abnormality is very rare in pediatric age group, published cases were more commonly reported in more than 10 year old age group and may be associated with an inferior outcome. This chromosomal aberration may represent a distinct, albeit rare, cytogenetic subgroup in ALL. [10]

Conclusion

Cytogenetic findings play an important role in determining the treatment choice as well as predicting disease course. Since, there is limited literature available regarding this abnormality, this report would add some significant knowledge to existing data. Lastly, the significance of this unique cytogenetic entity would come to light as more cases of this sort are reported.

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Consent

The parents of the patient provided written informed consent to the publication of the case details.

Ethical approval

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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Competing interest

Authors have declared that no competing interests exist.

References

1. Huang FL, Liao EC, Li CL, Yen CY, Yu SJ. Pathogenesis of pediatric B-cell acute lymphoblastic leukemia: Molecular pathways and disease treatments. Oncol Lett. 2020 Jul;20(1):448-454. doi: 10.3892/ol.2020.11583. Epub 2020 May 4. PMID: 32565969; PMCID: PMC7285861.
2. Alaggio, R., Amador, C., Anagnostopoulos, I. *et al.* The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia* **36**, 1720–1748 (2022). https://doi.org/10.1038/s41375-022-01620-2
3. Inaba H, Mullighan CG. Pediatric acute lymphoblastic leukemia. Haematologica 2020;105(11):2524-2539; https://doi.org/10.3324/haematol.2020.247031.
4. Roberts KG. Genetics and prognosis of ALL in children vs adults. Hematology Am Soc Hematol Educ Program. 2018 Nov 30;2018(1):137-145. doi: 10.1182/asheducation-2018.1.137. PMID: 30504302; PMCID: PMC6245970.
5. Makongoro, M., Abu Rakhey, M.M.M., Yu, Y. *et al.* A new case of trisomy 5 with complex karyotype abnormalities in B-cell prolymphocytic leukemia: a case study. *Egypt J Med Hum Genet* **23**, 39 (2022). https://doi.org/10.1186/s43042-022-00257-1
6. Vaswani PPM, Dumagay TE. Trisomy 5 as the sole chromosomal anomaly in acute lymphoblastic leukaemia. BMJ Case Rep. 2018 Aug 20;2018: bcr-2018226006. doi: 10.1136/bcr-2018-226006. PMID: 30131405; PMCID: PMC6109723.
7. P. Nagesh Rao, David Buss, Sue Brown, Michael O'Connor, David Hurd, Mark J. Pettenati. Trisomy 5 as the sole abnormality in acute lymphoblastic leukemia: A second case and review, Cancer Genetics and Cytogenetics. Volume 75, Issue 2, 1994, Pages 117-119,ISSN 0165-4608. https://doi.org/10.1016/0165-4608(94)90162-7.
8. Edmond Ma; Thomas Wan *+5 or trisomy 5* Atlas Genet Cytogenet Oncol Haematol. 2002-05-01. Online version: http://atlasgeneticsoncology.org/haematological/1255/+5-or-trisomy-5
9. Shawahna, R., Mosleh, S., Odeh, Y. *et al.* Clinical characteristics and outcomes of patients with pediatric acute lymphoblastic leukemia after induction of chemotherapy: a pilot descriptive correlational study from Palestine. *BMC Res Notes* **14**, 259 (2021). https://doi.org/10.1186/s13104-021-05678-6

10. RL Harris, CJ Harrison, M Martineau, KE Taylor, AV Moorman. Is trisomy 5 a distinct cytogenetic subgroup in acute lymphoblastic leukemia? Cancer Genet Cytogenet, 148 (2004), pp. 159-162.