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A T-cell adult acute lymphoblastic leukemia harboring a rare near-tetraploid karyotype

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Abstract:

Blast ploidy is a distinctive cytogenomic feature related to the prognostic outcome of acute lymphoblastic leukemia (ALL) patients. Near tetraploidy (NT) (81–103 chromosomes) is a very rare ploidy anomaly in (ALL). It is observed in approximately 1% of childhood B-cell precursor ALL (BCP-ALL). In T-ALL specifically in adult T-ALL, it is furthermore rare entity. Only few case reports are found in the existing literature. Compared to BCP-ALL, T-ALL lacks recurrent genetic anomalies with independent prognostic value. Although B-cell ALL associated with NT is related to a standard cytogenomic risk, the prognostic outcome of NT in T-cell ALL is yet to be determined. Conventional karyotyping of this entity is difficult to perform and interpret. Thus, it is recommended that karyotype results should be supplemented by fluorescence *in situ* hybridization. Herewith, we present an adult T-ALL case detected with NT karyotype with emphasis on prognostic significance.

Keywords:

Adult, near tetraploidy, T-cell acute lymphoblastic leukemia

Introduction

Detection of recurrent genetic abnormalities is one of the most effective ways to approach acute lymphoblastic leukemia (ALL) cases and determine diagnosis, prognosis, and therapeutic decisions. Studies have shown that clinical features, morphological, and immunophenotyping presentations are inextricably linked with genetic composition of the disease. Blast cell ploidy is found to be an important prognostic factor directing the progression and response of ALL.[1] Near tetraploid (NT) (81–103 chromosomes) karyotypes which are a rare ploidy anomaly are found in around 1% of childhood B-cell precursor ALL (BCP-ALL) and occasionally in T-ALL.[2] Incidence in adult T-ALL is even more rare. Due to the rarity of presentation, the prognostic significance of NT is yet to be established. Here, we are presenting a middle-aged adult male diagnosed as T-cell ALL with NT on karyotype.

Case Report

A 44-year-old male with type 2 diabetes mellitus on regular oral hypoglycemic agents presented with symptoms of easy fatigability, unintentional severe weight loss, and dyspnea on exertion of 1-month duration. There was no history of fever, headache, chest pain, cough, hemoptysis, night sweats, or seizures. Clinically, the patient had tachycardia (heart rate of 110/min) and mild splenomegaly. On evaluation, the patient was found to have anemia, thrombocytopenia, and leukocytosis with 37% blasts on peripheral blood smear examination. Further, peripheral blood flow cytometry was performed on Fluoresence activated cell sorting (FACS) Canto II using Diva software. 65% of cells were gated using CD45 dim and low-side scatter gating

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strategy. The cells in the gated region were positive for CD34 (subset), CD99, Human leucocyte antigen DR isotype (HLA-DR), cytoplasmic CD3, CD5 (small subset), CD7, and CD33. These blasts were negative for CD1a, CD2, sCD3, CD4, CD8, CD56, TCRα_β, and TCRɣ. Overall, flow cytometric findings were consistent with T-cell ALL with aberrant expression of myeloid marker (CD33 subset). Morphological evaluation of bone marrow (BM) revealed features suggestive of ALL with 56% blasts [Figure 1]. Cerebrospinal fluid showed only occasional lymphocytes and no blast cells were present. Ultrasonography abdomen revealed the presence of splenomegaly. Contrast-enhanced computed tomography neck, chest, abdomen, and pelvis showed small cervical and retroperitoneal lymphadenopathy with mild splenomegaly. Cytogenetic analysis from unstimulated cultures using BM aspirate sample was carried out at diagnosis following standard protocol. G banding with trypsin using Leishman stain G band by trypsin using Giemsa (GTG banding) was performed on metaphases obtained from two unstimulated overnight BM cultures processed with and without colcemid. Metaphase chromosomes were analyzed using an automated karyotyping system (MetaSystems GmbH, Altlussheim, Germany) and reported following the International System for Human Cytogenomic Nomenclature 2020. The analysis revealed a neoplastic clone characterized by the presence of NT as a composite karyotype in eight metaphases with Modal karyotype: 87~88, XY, +X, +Y,−3, −9, −9, −15, +21, +22[2]/46, XY[6] [Figure 2]. Fluorescence *in situ* hybridization (FISH) ALL panel performed on BM sample which was negative for translocation t(9;22)(q34;q11.2), t(4;11)(q21–22;q23), t(1;19)(q23;q11.3), and t(12;21)(p13;q22). Two extra signals for ABL1, AFF1, TEL (ETV6), PBX1, MLL, TCF3, and RUNX1 genes were seen in 86%, 88%, 82%, 88%, 80%, and 82% cells, respectively, supporting the presence of NT clone. At diagnosis, preinduction chemotherapy was started followed by 4 weeks of induction chemotherapy under the adult GMALL protocol. The patient achieved a complete hematological and morphological response on BM examination at the end of induction; however, he had measurable residual disease (MRD) on flow cytometry. His disease relapsed after re-induction phase and was switched on to second-line chemotherapy protocol for high-risk disease, and a donor search for hematopoietic stem cell transplant was started. He continued to be refractory to the subsequent chemotherapy and developed multiple complications. No stem cell donor being available, and due to personal domiciliary issues in addition to financial constraints, the patient presently decided to continue further on palliative low-dose maintenance treatment only and ultimately succumbed to disease.

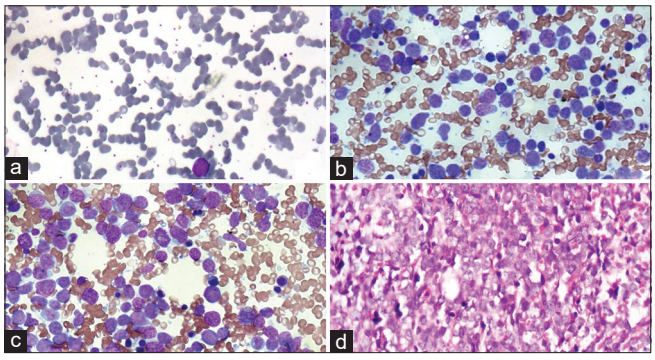

Figure 1: (a) PB smear (LG, ×100): Large atypical cells with a high nucleocytoplasmic ratio, scant cytoplasm, irregular nuclear margin, open chromatin, and prominent nucleoli. (b and c) BMA (LG, ×100): Hypercellular marrow with numerous large blasts scattered. Atypical mitotic figures also noted. (d) BM biopsy (H and E, ×100): Dense hypercellular marrow with sheets of large blasts exhibiting cellular and nuclear pleomorphism, pale-stained irregular nuclei, and open chromatin. PB = Peripheral blood, BMA = Bone marrow aspiration, BM = Bone marrow, LG = Leishman -Giemsa

Discussion

NT-ALL is defined by a diagnostic karyotypic abnormality presenting 81–103 chromosomes without atypical diploid or near-diploid metaphases.[2] NT is a rare cytogenetic aberration (0.7%–2.2%) in T-ALL.[3] While NT B-cell ALL is associated with standard cytogenomic risk,[4] NT subcategory in T-cell ALL is deliberated controversially in the existing literature. Some of the previous studies described T-cell lineage NT as a poor prognostic marker.[5] On the contrary, Lemez *et al*. described it as a favorable outcome indicator in T-ALL. This improvement bias can be due to modification in T-ALL treatment intensification and availability of MRD stratification analysis during the past decades.[2] Modified Medical Research Council – Eastern Cooperative Oncology Group puts this category in intermediate-risk group.[6] A recent large study on Philadelphia-negative adult allogeneic HCT-specific cytogenetic risk classification recommended NT as an adverse karyotype.[7] The presence of NT at diagnosis in acute myeloid leukemia (AML) patients with t(8;21)(q22;q22) and other adult AMLs is found to be associated with poor prognosis.[8]

Previous studies suggested that NT cases are associated with morphologically French–American–British Classification subtype L2 and appeared to have a high frequency of myeloid-associated antigen expression. Expression of myeloid-associated markers in ALL is well known, and in adults, it is reported as a poor prognostic indicator. Myeloid antigen expression is found to be less common in the cases of T-ALL compared to BCP ALL.[9] In our case also, we found that there is aberrant expression of the myeloid marker. Further studies can explore this finding to develop diagnostic model for screening.

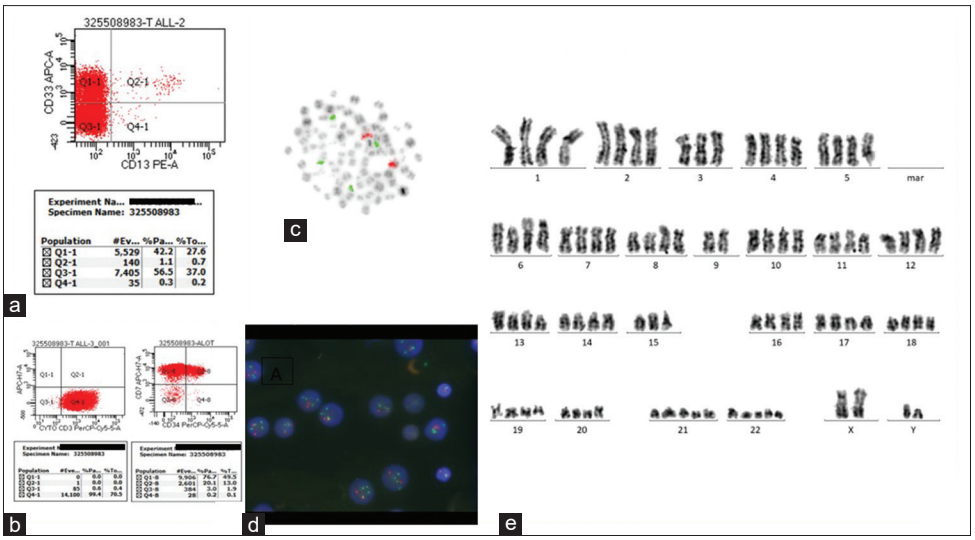

Figure 2: (a) PB flow cytometry: Aberrant expression of CD33. (b) Cells in the gated region showing positive expression for CD34 in a subset of cells and bright expression of cytoplasmic CD3 and CD7. (c) Dual-color dual-fusion metaphase FISH analysis with BCR-ABL1 probe on showing four green signals and 2 red signals. (d) Dual-color dual-fusion FISH analysis with BCR-ABL1 probe on interphase cells showing four green signals and two red signals. (e) BM aspirate karyogram with near tetraploidy. FISH = Fluorescence *in situ* hybridization. PB = Peripheral blood, BM = Bone marrow, BCR-ABL1 = Breakpoint cluster region- Abelson gene

Several molecular mechanisms have been proposed for the NT generation, which includes nondisjunction, hypodiploid cell duplication, loss of chromosomes from initially developed tetraploid cells, and multipolar mitosis of effected tetraploid cells. Out of which endoreduplication with or without subsequent gain or loss of chromosomes is the most accepted feasible mechanism.

Detailed conventional karyotyping of this entity is difficult due to culture failure or selective growth of clones. Thus, FISH is routinely utilized by clinical diagnostic laboratories to overcome this limitation.[10] In our case, we supplemented our karyotyping findings with FISH panel.

In our case, the patient was put on intermediate-risk category but did not respond well. The therapy needs to get augmented and ultimately succumbed to the disease. Our study suggests that contrary to pediatric NT ALL, adult cases should be considered as a distinct entity from other hyperdiploidy types. Therefore, we suggest that further prospective and retrospective studies should be conducted to explore the final risk stratification improvement in therapy and study the origins of adult NT ALL.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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