A rare case of near-haploid acute lymphoblastic leukemia

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ABSTRACT

Near-haploid acute lymphoblastic leukemia is seen in <1% of cases and carries an unfavorable prognosis. We report a case in an 18-year old male. He presented with two abnormal clones, one with 27−28 and one with 54−56 chromosomes. Near-haploidy (27−28) carries a poor prognosis and hyperdiploidy (>50) has a good prognosis. The correct diagnosis was critical for this patient's prognosis and treatment. The patient achieved remission after a bone marrow transplant from a 10/10 HLA matched sibling donor. He relapsed six months later and expired seven months later. This case illustrates the need for careful standard and molecular cytogenetic analysis for accurate diagnosis and treatment for this rare type of ALL.

1. Introduction

Hypodiploidy is seen in only 5−8% of B-lymphoblastic leukemia (B-ALL) cases. The near-haploid sub-type (23−29 chromosomes) is seen in <1% of cases and carries an extremely unfavorable prognosis [1−3]. These cases may also have a second hypodiploid cell line that undergoes duplication of their entire chromosome complement resulting in doubling of the chromosome number. The correct diagnosis is critical for patient prognosis and treatment as this could lead to possible misdiagnosis of hyperdiploid B-ALL, which has a good prognosis [4]. We present a case of near-haploid B acute lymphoblastic leukemia in a patient that achieved temporary remission after bone marrow transplant. The patient relapsed 6 months later with recurrence of the near-haploid clone.

2. Patient

We present a case of near-haploid pre-B-ALL in an 18-year-old male with a karyotype of 27−28<1n>,XY,+8,+14,+21[cp20]/54−56<2n>,XY,+X,+Y,+8,+14,+14,+21,+21[cp22] [Figs. 1 and 2A, B and Table 1]. The patient achieved remission and six months later received an allogeneic hematopoietic stem cell transplant from a 10/10 HLA matched sibling donor. However, six months later, he relapsed and expired seven months later. This case illustrates the importance of careful standard and molecular cytogenetic analysis for accurate diagnosis, prognosis and treatment for this rare type of B-cell ALL.

3. Materials and methods

Cytogenetic G-band metaphase analysis and fluorescence in situ hybridization (FISH) were performed using standard cytogenetic techniques on bone marrow (BM). G-banding was performed on 15–20 metaphase cells per analysis. FISH analysis was performed on 200 nuclei and/or 10 metaphase cells (Table 1). FISH probes: CEP 4 (4p11-q11), LSI BCR/ABL1/ASS TC DF (9q34,22q11.2), CEP 10 (10p11-q11.1), LSI MLL (KMT2A) DC BAR (11q23), LSI ETV6/RUNX-1(ES(12p13/21q22) (Fig. 1 and Table 1). All probes were supplied by Abbott Molecular, Des Plaines, IL, USA.

Flow cytometry was performed using a Becton Dickinson FACSCalibur using BD antiCD10, antiCD19, antiCD20, antiCD22, anti CD38, anti CD79a, anti CD34, anti CD3, anti HLA-DR, anti TdT, and anti CD123 (Table 2).

4. Results

An 18-year old male presented to our institution in August 2016 with fever, headaches, night sweats, bone pain and malaise of one month duration. A complete blood count (CBC) showed leukocytosis, thrombocytopenia and increased peripheral blood blasts (13%). A bone marrow aspirate smear and biopsy showed pre-B acute lymphoblastic leukemia with complete replacement of marrow elements by small to medium sized blasts exhibiting large nuclei, open chromatin, prominent nucleoli and scant cytoplasm [5,6] (Tables 2 and 3). Flow cytometry showed 93% blasts co-expressing CD19, CD34, CD38, TdT, HLA-DR, CD123, CD79a and CD10(calla) (Table 2).

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G-banded chromosome analysis of 22 bone marrow (BM) metaphase cells revealed a near-haploid karyotype of 27∼28<1n>,XY,+8,+14,+21[cp20]/54∼56<2n>,XY,+X,+Y,+8,+8,+14,+14,+21, +21[cp2] (Figs. 1 and 2A). No structural abnormalities were observed. Fluorescence in situ hybridization (FISH) demonstrated a signal pattern consistent with one copy of chromosomes 4, 10, 11, 12 and 22 and two copies of chromosome 21 (Fig. 2A and B). This confirmed the cytogenetic results. FISH and G-banding also revealed metaphases with a hyperdiploid chromosome number of between 54 and 56 chromosomes (Fig. 2A and B). These cells were endoreduplicated and represented a doubling of the haploid cell line. One month later, after induction therapy, the patient achieved remission and chromosome analysis of bone marrow revealed a normal 46,XY[20] male karyotype.

The patient received an allogeneic hematopoietic stem cell transplantation (HSCT) from a 10/10 HLA matched male sibling donor in January 2017. Follow up studies by Flow three months after revealed 0.39% minimal residual disease (MRD). In April 2017 cytogenetic and FISH analysis revealed a normal 46,XY karyotype in 20G-banded cells. FISH analysis for 11q23 (KMT2A) was also normal (Table 1). In July 2017, the patient presented with intermittent fever, pancytopenia and jaundice. Bone marrow biopsy revealed relapsed B-ALL with 33% blasts that were shown by flow cytometry to be positive for CD10, CD34, TdT, CD79a, CD22, and CD20 (Tables 2 and 3). The hypodiploid karyotype was seen in 4/12 cells. FISH confirmed the presence of one copy of KMT2A (11q23) in 95% of the nuclei (Figs. 1 and 2A, B and Table 1). Re-induction was attempted with a treatment regimen that included cyclophosphamide and etoposide. Clinical course was complicated by liver dysfunction, neutropenic fever, bacterial and fungal sepsis, and worsening pain. After stabilization, the patient returned home to receive palliative end-of-life care, where he expired shortly thereafter.
chromosomal translocation and copy number increases [8]. Activated by mutations including regulatory or promoter regions, metabolism, protein synthesis and response to stress [7]. MYC can be several target genes involved in the cell cycle, DNA damage, repair, 8q24. MYC is a transcription factor which regulates the expression of advantage for being retained. Our patient had disomies of 8, 14, and 21. Y, 6, 8, 10, 14, 18 and 21. These chromosomes may have a specific 46 to 23. In near-haploid ALL, most reported cases have two copies of X, near-haploid ALL is associated with an extremely unfavorable near-haploid ALL. Studies have shown that the b9;13(karyotype is unknown. ALL often presents with sheets of primordial blast cells. Blast cells are immature precursor cells. These cells may react like gonadal cells undergoing meiosis, where chromosome number is reduced from 46 to 23. In near-haploid ALL, most reported cases have two copies of X, Y, 6, 8, 10, 14, 18 and 21. These chromosomes may have a specific advantage for being retained. Our patient had disomies of 8, 14, and 21. The retention of chromosome 21 may be related to RUNX1 located 21q22. RUNX1 is a hematopoietic regulator which instructs the more mature progenitor cell. The retention of chromosome 21 may be related to RUNX1 located 21q22. RUNX1 is a hematopoietic regulator which instructs the more mature lymphoid cells. Alteration of IKZF3 was seen in 13.2% of near-haploid cases [10]. This suggests that near-haploid ALL may arise from a more mature progenitor cell. More than 70% of near-haploid ALL cases had alterations known to activate RAS signaling. Those involved deletions, amplifications and/or sequence mutations of NF1, NRAS, KRAS, MAPK1, FLT3 or PTPN11. Several of these genes have been reported in various hematological disorders and appear to play a role in near-haploid ALL [12]. IKZF3 is part of the IKAROS lymphoid transcription factor family that encodes zinc-finger transcription factors involved in lymphoid development and differentiation. IKZF3 expression is highest in more mature lymphoid cells. Alterations of IKZF3 were seen in 13.2% of near-haploid cases [10]. This suggests that near-haploid ALL may arise from a more mature progenitor cell. In a genomic profiling study of 50 hypodiploid (24–31 chromosomes) ALL cases it was found that there were alterations targeting IKZF3 (13%) receptor kinase signaling (RTK) and RAS signaling (71%) [12]. IKZF3 is part of the IKAROS lymphoid transcription factor family that encodes zinc-finger transcription factors involved in lymphoid development and differentiation. IKZF3 expression is highest in more mature lymphoid cells. Alterations of IKZF3 were seen in 13.2% of near-haploid cases [10]. This suggests that near-haploid ALL may arise from a more mature progenitor cell. More than 70% of near-haploid ALL cases had alterations known to activate RTK or RAS signaling. Those involved deletions, amplifications and/or sequence mutations of NF1, NRAS, KRAS, MAPK1, FLT3 or PTPN11. Several of these genes have been reported in various hematological disorders and appear to play a role in near-haploid ALL [12]. RAS signaling, and the lymphoid transcription factor IKZF3 have been implicated in near-haploid ALL. Studies have shown that the leukemia cells in these patients showed activation of RAS signaling and P13K (Phosphoinositide 3-kinase) signaling pathways and were proliferation. It is involved in various translocations and gene rearrangements that correlate with clinical morphological and immunophenotypic features [9]. Table 1
Cytogenetic results.

| Analysis | Specimen | G banding | FISH |
|----------|----------|-----------|------|
| #1 Date  | **BM**   | (number of cells in brackets) | 4p11-q11(CEP 4 x 1) [179/200], 9q34(ABL1,ASXL1) [178/200] |
| 08/2016  | #2       | BM 46,XY[20] | 10p11-q11.1(CEP10×1) [162/200] |
| 09/2016  | #3       | BM 46,XY[20] | Not performed |
| 12/2016  | #4       | BM 46,XY[20] | Not performed |
| 04/2017  | #5       | BM 46,XY[20] | 11q22(RMT2/AX1) [177/200], 12p13(ETV6 × 1) [179/200] |
| 07/2017  |          | BM 46,XY[20] | 21q22(RUNX1 × 1) [179/200], 21q22(RUNX1 × 4) [21/200] |

**# - number; **BM - bone marrow.

Table 2
Flow cytometry and pathology results.

| Analysis | Specimen | Flow cytometry | Pathology |
|----------|----------|----------------|-----------|
| #1 Date  | **BM**   | 93% lymphoid blasts expressing CD19, CD34, CD38, TdT, HLA-DR, CD123, CD79a and CD10 | Precursor B cell acute lymphoblastic leukemia |
| 08/2016  | #2       | BM 46,XY[20] | No immunophenotypic evidence of pre-B ALL |
| 09/2016  | #3       | BM 46,XY[20] | No immunophenotypic evidence of pre-B ALL |
| 12/2016  | #4       | BM 46,XY[20] | 1% hematogones and 1% lymphoblasts with a different phenotype from the original leukemic cells (expressing CD45, dimmer CD34, higher intensity TdT, and do not express CD123) |
| 04/2017  | #5       | BM 46,XY[20] | 33% lymphoid blasts (with the same immunophenotype as original study) positive for CD10, CD34, TdT, CD19, CD79a, CD22, CD38, and CD20. |

**# - number; **BM - bone marrow;

Table 3
Hematology results.

| Date         | White Blood Cells (k/mcl) | Hemoglobin (g/dl) | Platelets (k/mcl) | Blasts (%) |
|--------------|---------------------------|-------------------|------------------|-----------|
| 08/29/2016   | 30.56                     | 12.6              | 41               | 13        |
| 09/27/2016   | 0.6                       | 8.2               | 48               | 0         |
| 12/13/2016   | 0.82                      | 8.7               | 394              | 0         |
| 04/27/2017   | 2.9                       | 9.8               | 104              | 0         |
| 07/13/2017   | 1.86                      | 7.5               | 25               | 34        |

5. Discussion

Near-haploid ALL is associated with an extremely unfavorable prognosis. Even after bone marrow transplantation, most patients relapse within 2 years [1,2,5]. The mechanism for this rare karyotype is unknown. ALL often presents with sheets of promordial blast cells. Blast cells are immature precursor cells. These cells may react like gonadal cells undergoing meiosis, where chromosome number is reduced from 46 to 23. In near-haploid ALL, most reported cases have two copies of X, Y, 6, 8, 10, 14, 18 and 21. These chromosomes may have a specific advantage for being retained. Our patient had disomies of 8, 14, and 21. The retention of chromosome 14 homologs may be related to IGH located at 14q32. IGH is the immunoglobin heavy chain gene. It is most likely a transcription factor that affects genes regulating cellular development and differentiation. IKZF3 is part of the IKAROS lymphoid transcription factor family that encodes zinc-finger transcription factors involved in lymphoid development and differentiation. IKZF3 expression is highest in more mature lymphoid cells. Alterations of IKZF3 were seen in 13.2% of near-haploid cases [10]. This suggests that near-haploid ALL may arise from a more mature progenitor cell.
sensitive to P13K inhibitors [12]. These findings may be useful in the development of novel therapeutic strategies for this very aggressive and often fatal leukemia.

6. Conclusion

As the mechanisms for this rare abnormality are unknown, further studies are necessary to determine the efficacy of targeted therapies and more specific classification of the near-haploid sub-type of B-ALL. Since near-haploid ALL has an extremely poor prognosis and hyperdiploid ALL has a good prognosis careful standard and molecular cytogenetic analysis is crucial for diagnosis, prognosis and patient treatment of this rare type of B-cell ALL.

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