MLL-SEPT6 Positive Acute Myeloid Leukemia Patients Often Co-occur With *NRAS* Mutations?

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Research

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Abstract

Background

The *MLL-SEPT6* fusion gene is a relatively rare genetic event in leukemia. Its clinical characteristics, prognosis, especially the profile of co-occurring gene mutations remain unclear.

Methods

We retrospectively analyzed four rare leukemia cases carrying *MLL-SEPT6* in our hospital from laboratory examination, diagnosis, treatment and prognosis, and provided a comprehensive and detailed description on clinical profile of *MLL-SEPT6*-positive AML patients in the literature.

Results

All the four patients were diagnosed with acute myeloid leukemia (AML) and harbored X chromosome and 11 chromosome rearrangements. Three of four cases occurred *NRAS* mutation while the rest one with congenital AML did not. Of the four cases, one developed drug-resistant, one suffered relapse after bone marrow transplantation (BMT) and one died. Combined with other cases reported in literatures, we found that of all patients diagnosed with AML, 90.9% were children (≤ 9 years old) and 54.5% were infants (≤1 year old). The survival time between infant group (≤1 year old) and pediatric group (>1 and <18 years old), patients that received BMT and that received chemotherapy alone did not show significant differences (P>0.05).

Conclusions

MLL-SEPT6 was more commonly observed in pediatric AML patients, some of which may co-occur with *NRAS* mutations. The prognosis was inconclusive and may not be related to age or BMT. More information needs to be accumulated and summarized from additional cases to confirm the underlying connection between *NRAS* mutations and *MLL-SEPT6* in order to better understand the profile in *MLL-SEPT6*-positive AML.

Background

Acute myeloid leukemia (AML) is a malignant tumor that originates from the myeloid blood cells, characterized by abnormally increased leukemic cells in bone marrow or peripheral blood [1]. Cytogenetic and molecular abnormalities occur commonly in AML patients. Based on genetic mutations and specific chromosomal rearrangements, the World Health Organization (WHO) divides AML with recurrent genetic abnormalities into 11 subgroups [2]. The mixed-lineage leukemia (*MLL*) gene rearrangements is one of the most common chromosomal abnormalities in AML [3, 4].

The *MLL* gene at 11q23 has many partner genes, of which over 80 have been identified [5]. Among them, the *SEPTIN6* (*SEPT6*) gene located at Xq24 involving in the formation of MLL arrangement t(X;11)(q22-24;q23) is extremely rare in AML [6], a limited number of cases have been documented in literatures. To our knowledge, most cases are children while only one adult case has been reported [6–16]. The exact role of *MLL-SEPT6* in hematopoietic cells and its effect on leukemogenesis are still unknown. There is little information on clinical features, treatment strategies and prognosis of such patients, accompanied gene mutations carried by such patients have not been described.

We retrospectively analyzed data on four acute leukemia patients carrying the *MLL-SEPT6* fusion gene that treated in our hospital, especially of the gene mutations information. Additionally, we reviewed cases in literatures together with our cases to provide evidence for potential therapeutic strategies.

Materials And Methods

Case selection

We collected four patients harboring *MLL-SEPT6* gene from a pool of 1656 leukemia patients within our hematological diseases database in the past four years, which were referred as case 1-4. The diagnostic criteria were according to WHO classification of tumors of haematopoietic and lymphoid tissues [17]. We conducted a retrospective analysis and systematic summary with information of morphology, flow cytometric analysis, cytogenetics, molecular biology and other related laboratory tests results.

Literature review

We conducted literature search on PubMed with the keywords "*MLL-SEPT6*", "*MLL-SEPTIN6*" or "t(X;11)" to gather related case reports.

Statistical Analysis

Kaplan–Meier method was used for survival evaluation. Log-rank test was used to assess the difference between groups. $P < 0.05$ was considered statistically significant. All data were analyzed with SPSS Statistics, version 21 (StatSoft).

Results

Clinical presentation

All *MLL-SEPT6* positive cases (case 1-4) were male with ages ranging from 0 to 57 years and a median of 5.2 years, their detailed information was summarized in Table 1. All cases had manifestations of fever and pale complexion. The three pediatric cases (cases 2, 3, and 4) were accompanied by hepatosplenomegaly, and two cases (cases 3 and 4) had scattered petechiae and ecchymoses. The case 1 is an elderly male patient with perianal abscess and diabetes in addition to the above symptoms. The case 2 was accompanied by pain in both lower limbs, tenderness of the sternum and hypertrophy of tonsils. In the case 3, multiple lymph nodes were palpable on bilateral neck, he was positive of sternal tenderness, he also had hyperuricemia and acute bronchial pneumonia. The case 4 is a newborn delivered by cesarean section due to "decreased fetal heart rate". The birth weight was 3100g. The infant had no spontaneous breath at birth and was generally cyanotic, he restored spontaneous respiration under assisted ventilation, he developed persistent pulmonary arterial hypertension and neonatal pneumonia. His parents were healthy and with no history of genetic disease.

Table 1
Clinical features of 4 cases of AML patients with *MLL-SEPT6* positive

Items	Case 1	Case 2	Case 3	Ca
Sex	Male	Male	Male	Ma
Age	57 years	9 years	16 months	0 r
Physical examination	Perianal abscess	Lower limbs pain, sternal tenderness and tonsil hypertrophy	Scattered petechiae on the neck, cervical lymphadenopathy and sternal tenderness (+)	Sc pe ec
Hepatomegaly/ Splenomegaly	No/No	Yes/Yes	Yes/Yes	Ye
CNS involvement	No	Yes	No	Nc
WBC/Hb/PLT ($\times10^9$/L/g/L/ $\times10^9$/L)	12.3/79.0/105.0	3.0/93.0/245.0	123.8/41.0/39.0	11
Serum LDH (U/l)	NA	966	2080	NA
D-Dimer (ug/L(DDU))	13117.0	3149.0	2469.0	62
Blood blasts (%)	69.0	2.0	52.0	17
Bone marrow blasts (%)	92.0	27.5	56.0	20
Morphological diagnosis	AML-M5	AML-M2	AML-M4	AM
Immunophenotype	The leukemic cells expressed HLA-DR, CD117, CD33, CD13, CD38, CD15, CD64 and CD4	The leukemic cells expressed HLA-DR, CD33, CD38, CD15, CD64 and CD4	The leukemic cells expressed HLA-DR, CD33, CD13, CD38, CD15 and CD64	Th ce HL CD an
Karyotype	46, Y, t(X;11)(q24;q23)[4]/46,XY[6]	45,Y,del(X)(q21),der(11)t(X;11)(q24;q23),-20,add(22)(q13)[3]	46, Y, t(X;11)(q24;q23), del(7)(q21q31)[13]/46,XY[2]	46 (q2 [10
Gene mutations	NRAS: NM_002524:exon2:c.G35T:p.G12V rs121913237, VAF = 0.0369; ASXL1: NM_015338:exon12:c.2464dupA:p.D821fs, VAF =0. 3585	NRAS: NM_002524:exon2:c.G35T:p.G12V rs121913237, VAF = 0.0300	NRAS:NM_002524:exon4:c.G436A:p.A146T, VAF = 0.4411	Ne
Treatment protocol	IA regimen (resistance); then changed to decitabine combined with half-dose CAG regimen (once) + high dose cytarabine	MAE regimen + intrathecal chemotherapy + BMT	HA regimen	Nc ch
CR	Yes	Yes	Yes	NA
Follow-up (mo)	9	38	34	0.5
Outcome	Alive	Alive	Alive	Di

Footnotes: CNS, central nervous system; WBC, white blood cells; Hb, hemoglobin; PLT, platelets; LDH, lactate dehydrogenase; VAF, variant allele frequencies; IA + cytosine arabinoside; CAG, cytarabine + aclacinomycin + granulocyte colony stimulating factor; MAE, Mitoxantrone + cytarabine + etoposide; BMT, bone ma transplantation; HA, homoharringtonine + cytarabine; CR, complete remission; mo, month; NA, not available.

Laboratory results showed that three cases (cases 1, 3, and 4) had high white blood cells (WBC) count, anemia, and low platelet count. One case (case 2) had low level of hemoglobin and WBC count but normal platelet count, and two cases (case 2 and 3) had increased level of serum lactate dehydrogenase. The D-dimer level of all four patients were increased.

Morphological evaluation

All cases exhibited morphological characteristics of AML (Figure 1). The French American British (FAB) morphological classification of each case was M5 (case 1 and 4), M2 (case 2) and M4 (case 3). Three cases (cases 1, 3, and 4) showed hypercellular bone marrow and the other case (case 2) had severe hypocellular bone marrow. The case 1 and case 4 were evaluated as M5 and revealed of 92.0% and 20.4% blasts in marrow aspirate, 69.0% and 17.0% in peripheral blood respectively (Table 1, Figure 1A and 1D). The case 2 was evaluated as M2, the marrow aspirate revealed 27.5% myeloblasts and the peripheral blood exhibited 2.0% blasts (Table 1, Figure 1B). The case 3 was evaluated as M4, the marrow aspirate showed 56.0% blasts and the peripheral blood exhibited 52.0% blasts (Table 1, Figure 1C).

Flow cytometric analysis

The flow cytometric analysis revealed the presence of myeloid blasts in bone marrow samples from all four patients (Table 1, Figure 2). The percentage of blasts was highest of 92% in the case 1 and lowest of 4.2% in the case 3. All cases were positive for CD33, CD15, CD64 indicating myeloid lineage, CD13 was positive only in the case 1 and case 2. All the cases were positive for CD38 and HLA-DR. CD117 was positive only in the case 3, CD34 was negative in all the four cases.

Cytogenetic analysis

The results showed that all four cases had clonal abnormalities of X chromosome and chromosome 11 or complex karyotype abnormalities (Table 1, Figure 3). In case 1, the metaphase cells exhibited abnormalities of t(X;11)(q24;q23) (Figure 3A). The metaphase cells collected in the case 2 showed 45, Y, del(X)(q21), der(11)t(X;11)(q24;q23), -20, add(22)(q13) (Figure 3B). In the case 3, in addition to the abnormal karyotype of t(X;11)(q24;q23), thirteen metaphase cells had del(7)(q21q31) (Figure 3C). The metaphase cells in case 4 showed abnormal karyotype of 46, Y, ins(X;11)(q23;q24q12) (Figure 3D).

Molecular analysis

We performed molecular biology tests including screening of fusion genes and next-generation sequencing (NGS) analysis on all cases (Table 1). The *MLL-SEPT6* fusion gene was detected in all four cases. The NGS panel included a total of 20 frequently mutated genes in AML which were *ASXL1*, *CEBPA*, *DNMT3A*, *EZH2*, *FLT3*, *IDH1*, *IDH2*, *KIT*, *NPM1*, *PHF6*, *RUNX1*, *TET2*, *TP53*, *BCOR*, *GATA2*, *MLL*, *KRAS*, *NRAS*, *PDGFRA* and *WT1*, the sequencing depth was 2000×. The results showed that three cases (cases 1-3) harbored *NRAS* (NM_002524) mutations, the mutation sites of the case 1 and 2 were both *NRAS* G12V, with variant allele frequencies (VAF) of 0.3585 and 0.0300 respectively. In addition, the case 1 was also accompanied by an insertion mutation of ASXL1 D821 with a VAF of 0.3585. The reexamination results on the third month showed that the *MLL-SEPT6* gene remained positive but its expression level dropped from 100−24.4%. The *ASXL1* D821 VAF dropped to 0.0068 and *NRAS* G12V gene mutation was not detected. Four month later, the patient achieved complete remission (CR), the *ASXL1* D821 VAF dropped to 0.0032 and this time both the *NRAS* mutation and *MLL-SEPT6* fusion gene were negative. The *NRAS* A146T mutation in the case 3 occurred in exon 4 with a VAF of 0.4411. *MLL-SEPT6* gene and *NRAS* gene mutations both turned negative on the ninth month after diagnosis. The patient relapsed on the twenty-seventh month with positive *MLL-SEPT6* and *NRAS* A146T mutation (VAF = 0.2662). In the case 4, no pathogenic gene mutations were detected.

Clinical Course

The treatment and follow-up information of all cases (case 1-4) was shown in Table 1. Three cases (case 1-3) received chemotherapy, the case 2 subsequently received a bone marrow transplantation (BMT), the case 4 was a newborn and did not receive any chemotherapy. The clinical follow-up period ranges from 0.5 to 38 months with a median of 21.5 months. The case 1 initially received IA (idarubicin + cytosine arabinoside) regimens, which didn't make him reach CR. Then he began a new chemotherapy regime with decitabine combined with half dose CAG (cytarabine + aclacinomycin + granulocyte colony stimulating factor) and achieved CR. He also received an intrathecal injection (cytarabine + dexamethasone + methotrexate) for central nervous system infiltration prevention. After the chemotherapy, the bone marrow aspiration of the patient revealed a normal karyotype and negative molecular results of *MLL-SEPT6* rearrangement and *NRAS* mutation. The case 2 received MAE (mitoxantrone + cytarabine + etoposide) regimens and reached CR one month later. In the following six months, the patient received BMT. Nineteen months after the transplantation he was re-admitted for headache. A flow cytometry analysis of the cerebrospinal fluid revealed 81.9% leukemia cells which indicated central nervous system leukemia, following five courses of intrathecal injection, the child's headache relieved and no leukemia cells were detected in his cerebrospinal fluid. The case 3 received HA (homoharringtonine + cytarabine) regimens and intrathecal injection (cytarabine + dexamethasone + methotrexate), he reached CR four weeks after the diagnosis. This patient relapsed 27 months later, after receiving HAI (homoharringtonine + cytarabine + idarubicin) regimen he reached and remained CR status. The case 4 had dyspnea at birth, he was on assisted ventilation and given blood infusion to improve anemia and thrombocytopenia. The newborn's condition did not improve during the treatment. His parents refused the follow-up treatment, and the child died a week later.

Literature review

A total of 22 *MLL-SEPT6* positive cases were included in this literature review, including four cases in our report and eighteen cases from literatures [6–16]. Table 2 and Table 3 listed the detailed laboratory results and clinical information of all cases.

Table 3
Clinicopathologic features of evaluable patients

Characteristic	N (%)
Gender	N=22
Male	16 (72.7%)
Female	6 (27.3%)
Age (years)	N=22
≤1	12 (54.5%)
>1 and <18	8 (36.4%)
≥18	2 (9.1%)
WBC count (×10^9/L)	N=15
≥20.0	9 (60.0%)
<20.0	6 (40.0%)
Symptom at presentation	N=10
Hepatosplenomegaly	5 (50.0%)
CNS involvement	3 (30.0%)
Lymphadenopathy	3 (30.0%)
Skin involvement	2 (20.0%)
FAB classification	N=22
M1	1 (4.5%)
M2	8 (36.4%)
M4	5 (22.7%)
M5	5 (22.7%)
Unknown	3 (13.6%)
Chromosomal abnormalities	N=22
Translocations	11 (50.0%)
Insertions	9 (40.9%)
Complex abnormalities	3 (13.6%)
Treatment protocol	N=19
Chemotherapy alone	8 (42.1%)
BMT	9 (47.4%)
No chemotherapy	2 (10.5%)
Survival outcome	N=19
Alive	13 (68.4%)
Died	6 (31.6%)
Footnotes: WBC, white blood cells; CNS, central nervous system; BMT, bone marrow transplantation.	

The age of the patients ranged from 0 to 57 years (median = 1 year), with a male–female ratio of nearly 3:1 (16 males vs. 6 females). Twenty patients (90.9%) were children (≤ 9 years old), including twelve (54.5%) infants (≤1 year old). The majority of the patients manifested leukocytosis (range 1-608 × 10^9/L), anemia (range 41-109 g/L) and low platelet counts (range 9-254 × 10^9/L). According to the high WBC index [18], nine (60.0%) of the fifteen cases with WBC count information were defined as high WBC levels. Twelve cases were not provided with description of clinical features. Of the remaining ten cases, five children (50.0%) were observed of splenomegaly and hepatomegaly and three patients (30.0%) had lymphadenopathy. Central nervous system involvement was observed in three children (30.0%) and skin involvement was observed in two (20.0%).

All patients were diagnosed with AML (twenty children and two adults) according to the former FAB classification: five patients (three children and two adults, 22.7%) of M5, five children (22.7%) of M4, eight children (36.4%) of M2, one child (4.5%) of M1, and three children (13.6%) unknown.

All the cases had available cytogenetic information, chromosomal translocations (eleven cases) were the most common chromosomal rearrangements, followed by chromosomal insertions (nine cases). Among them, Xq24 (nine cases) and 11q23 (fourteen cases) were the most frequently involved chromosomal bands. Seven cases (31.8%) demonstrated complex abnormalities.

Of all 22 cases, 18 cases had clinical follow-up with median period of 27.7 months (0.5-101.5 months). Table 3 showed the clinicopathologic features of evaluable patients. Eight patients (42.1%) received chemotherapy alone. Nine patients (50%) received BMT. Six of eighteen patients died during the period of follow-up. Kaplan-Meier survival analysis was performed on eighteen cases with complete follow-up information (Figure 4A). As of the final follow-up, median survival time has not been reached. In order to understand the impact of age and BMT on survival time, the patients were divided into infant group (≤1 year old, n=10), pediatric group (>1 and <18 years old, n=7), and adult group (≥18 years old, n=1). At the time of the last observation, there was no statistically significant differences in survival time between infant group and pediatric group (hazard ratio for infant-pediatric = 0.26, 95% confidence interval = 0.07 to 1.67, P = 0.1822, Figure 4B). The adult group was not included in the statistical analysis because there was only one case with complete follow-up information in this group. Meanwhile, the patients were also divided into receiving chemotherapy alone (n=6, one without survival information was excluded) and receiving BMT (n=9) treatment groups according to the treatment protocol. Survival time between the patients received chemotherapy alone and BMT did not show significant differences neither (hazard ratio for chemotherapy alone-BMT = 1.04, 95% confidence interval = 0.18 to 6.19, P = 0.9647, Figure 4C).

Discussion

The *MLL* gene is a frequent target of rearrangement in human leukemia, especially in infant and pediatric leukemia [9, 19, 20]. It is well established that the rearrangement heralds poor prognosis [5, 21]. These rearrangements include fusions with many partner genes, but rarely involve the X chromosome. *SEPT6* is a member of the septin family of GTPases. Members of this family are involved in cell polarity, cytokinesis and oncogenesis [22, 23]. The *MLL* gene and *SEPT6* gene are vulnerable to damage to form translocations associated with infant AML.

In this study, we described four cases of AML with *MLL-SEPT6* fusion gene. The FAB subtypes were mainly M2, M4 and M5, which was consistent with literatures. Most cases that have been reported were children. As far as we know, only two adult patients have been reported including one case in our series and 54.5% (12/22) were infant patients (≤1 year old). Among these cases, 60.0% were with high level of WBC, and 30% manifested central nervous system involvement, which were similar to the clinical features of *MLL*-rearranged AML patients. The findings of Balgobind BV et al. showed that *MLL*-rearranged AML patients usually exhibit high tumor burden, including organomegaly, high median WBC and central nervous system involvement [24]. The present study included the largest number of *MLL-SEPT6* cases to date. The patients' NGS test results were not provided except ours, and we also tracked the patients' molecular biological examination results. Three of four cases in our series occurred *NRAS* mutation while the rest one with congenital AML did not.

The *NRAS* mutations has very important roles in pathogenesis and progression of human leukemia, which have been frequently reported in AML patients [25, 26]. *NRAS* G12V is required in leukemia self-renewal process, independent of its effects on growth and survival [27]. Compared with other subtypes of leukemia, acute leukemia with *MLL*-translocations (such as *MLL-AF4* and *MLL-AF9*) harbored the fewest number of mutations, in which *NRAS* mutations commonly co-occur [27, 28]. In our series, we identified *NRAS* mutations in *MLL-SEPT6* positive AML patients for the first time, and most of the mutation sites appeared at codon 12 and 145. The former site is a hotspot mutant of *NRAS* and the latter site has also been reported [25, 29]. The VAF of NARS mutation decreased as the patients condition improved. When the patients achieved CR, it also turned negative. The underlying connection between *NRAS* mutations and *MLL-SEPT6* and whether non-congenital *MLL-SEPT6*-positive AML patients all have *NRAS* mutations remain to be further studied in a larger cohort in the future.

MLL gene rearrangement in AML usually indicates poor prognosis. The prognostic significance of *NRAS* mutations in AML patients remains unclear [30–33]. Of the four cases in our series, one developed drug-resistant at first, one suffered relapse after BMT and one died, showing unsatisfactory therapeutic effect. However, whether the outcomes of patients with *MLL-SEPT6* were aggravated by the concurrence of *NRAS* mutations needs a follow-up study. Kaplan–Meier curve demonstrated that pediatric group (>1 and <18 years old) did not show better survival time compared with infant group (≤1 year old). Age may not be an independent prognostic factor for survival. Most of the patients received chemotherapy, nine of them received BMT, but three of them eventually died. The survival time of patients between the chemotherapy alone group and the BMT group did not show a significant difference, which suggested that BMT may not improve the survival time of such patients. This was consistent with several studies and meta-analyses that suggesting BMT does not improve survival in patients with *MLL* rearrangement [34, 35]. But the prognosis and its factors of *MLL-SEPT6*-positive AML patients need further analysis in more cases.

Our study has some limitations. Firstly, this was a retrospective study, coupled with limited number of reported cases and incomplete clinical information, which makes it impossible for us to obtain the median survival time of patients through statistical methods. On the other hand, the small sample sizes of some subgroups may lead to false negative results. Secondly, our NGS detection only covers the twenty most frequently mutated genes in AML, and prognostic effects of some critical genes may be neglected. Thirdly, gene mutation information in the reported cases was not available and cases in our series are detailed but limited by sample size. Therefore, our findings need to be combined with more cases to further explore the correlation between *MLL-SEPT6* and *NRAS* mutations.

Conclusions

In conclusion, the *MLL-SEPT6* fusion gene was more commonly observed in pediatric patients diagnosed with AML. *NRAS* mutations were observed in these patients, most frequently of the *NRAS* G12V hotspot mutation. Whether *NRAS* mutations are related to the occurrence of *MLL-SEPT6*-positive AML is currently unclear. The prognosis was inconclusive and may not be related to age. BMT may not improve survival in these patients. More cases should be accumulated and summarized to better understand the profile in *MLL-SEPT6*-positive AML. Our findings provide a basis for better understanding the mechanisms of leukemogenesis and the development of potential therapeutic targets for *MLL-SEPT6*-positive AML.

Abbreviations

AML: acute myeloid leukemia

BMT: bone marrow transplantation

WHO: World Health Organization

WBC: white blood cells

FAB: French American British

NGS: next-generation sequencing

VAF: variant allele frequency

CR: complete remission

IA: idarubicin + cytosine arabinoside

CAG: cytarabine + aclacinomycin + granulocyte colony stimulating factor

MAE: mitoxantrone + cytarabine + etoposide

HA: homoharringtonine + cytarabine

HAI: homoharringtonine + cytarabine + idarubicin

CNS: central nervous system

Hb: hemoglobin

PLT: platelets

LDH: lactate dehydrogenase

NA: not available

Declarations

Ethics approval and consent to participate

This study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Shengjing Hospital of China Medical University (No. 2021PS122K). All patients provided written informed consents.

Availability of data and materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Consent for publication

Written informed consent for publication of their clinical details and clinical images was obtained from the patient/parent of the patient.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

Shuang Fu and Fang Chen performed study concept and design; Shuang Fu, Fang Chen and Ying Yang performed development of methodology and writing, review and revision of the paper; Fang Chen and Ying Yang provided acquisition, analysis and interpretation of data, and statistical analysis. All authors read and approved the final paper.

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Table

Due to technical limitations, table 2 docx is only available as a download in the Supplemental Files section.

Figures

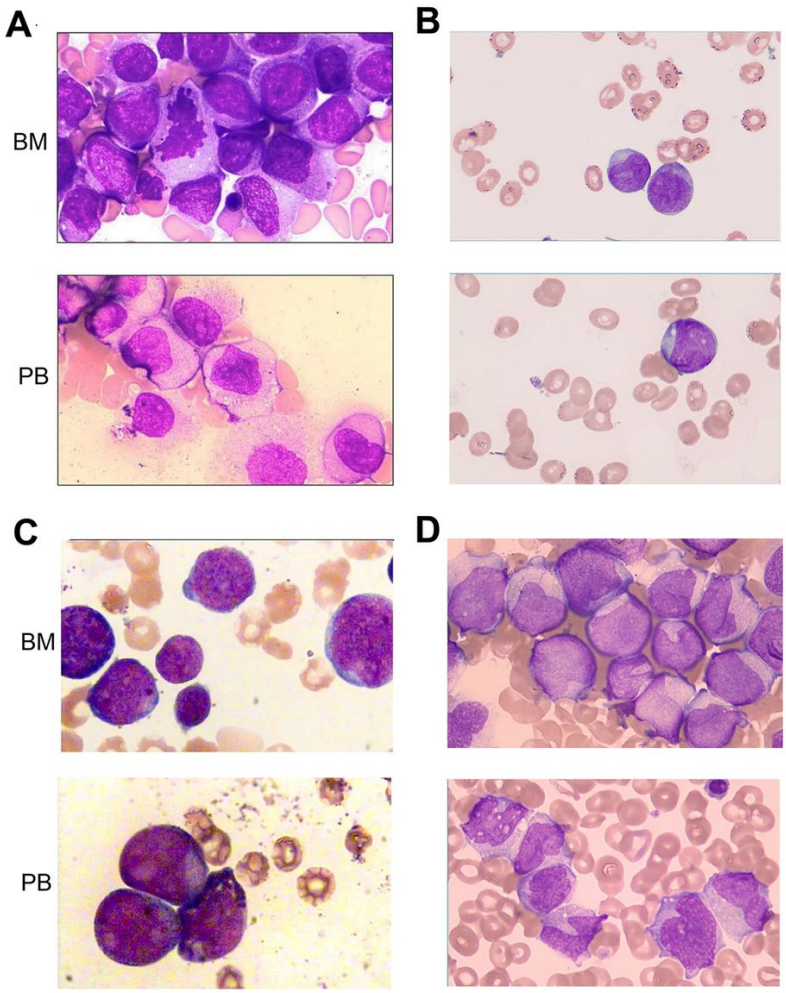

Figure 1

Morphologic evaluation of leukemic cells at diagnosis (Wright–Giemsa stain, ×1000). (A), (B), (C) and (D) represented the case 1, 2, 3 and 4, respectively. BM, bone marrow; PB, peripheral blood.

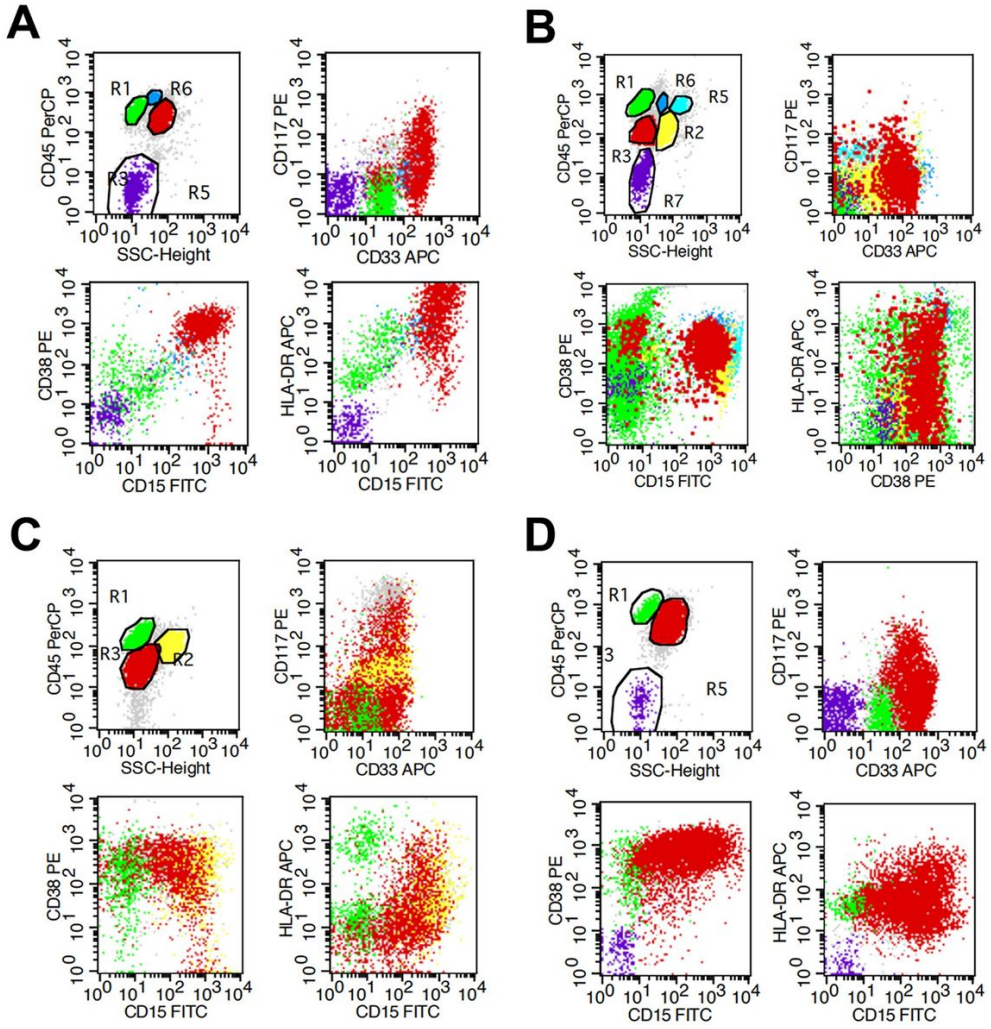

Figure 2

Flow cytometry results of bone marrow. (A), (B), (C) and (D) represented the case 1, 2, 3 and 4, respectively.

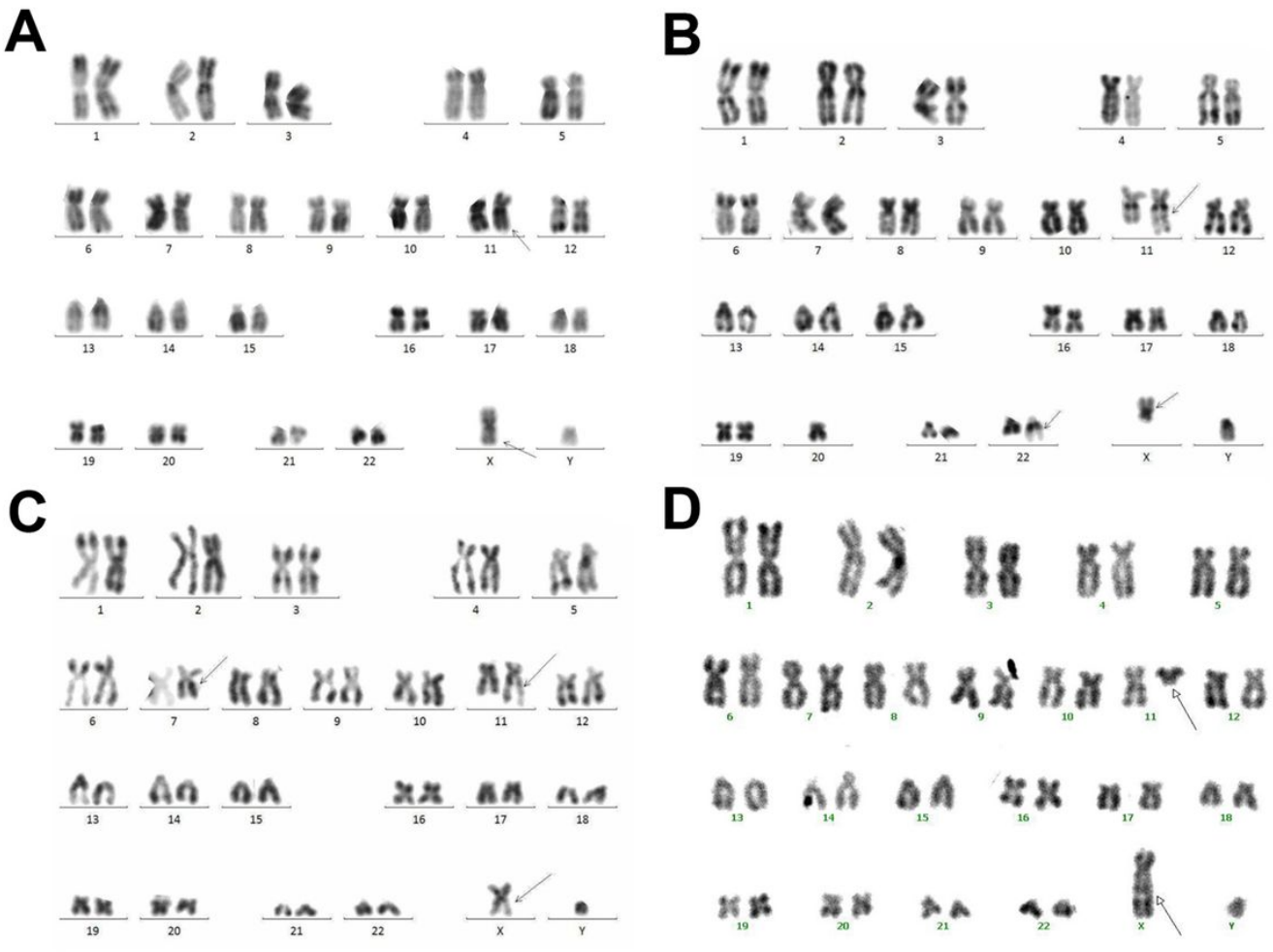

Figure 3

Karyotype analysis results of bone marrow. (A), (B), (C) and (D) represented the case 1, 2, 3 and 4, respectively.

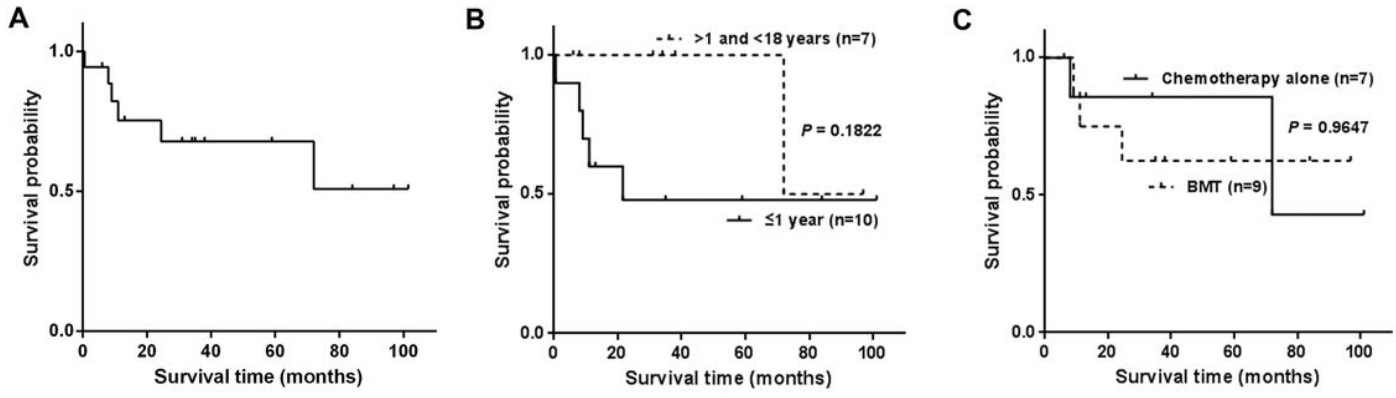

Figure 4

Kaplan–Meier survival analysis of eighteen cases with complete follow-up information. These included fourteen reported cases with clinical follow-up, and four cases in our series. (A) Survival months of eighteen cases. (B) Infant group (≤ 1 year) vs. pediatric group (>1 and <18 years old). Hazard ratio for infant-pediatric = 0.26, 95% confidence interval = 0.07 to 1.67, P = 0.1822. (C) Chemotherapy alone vs. BMT. Hazard ratio for chemotherapy alone-BMT = 1.04, 95% confidence interval = 0.18 to 6.19, P = 0.9647.

Supplementary Files

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- Table2.doc