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A Case of Acute Lymphocytic Leukaemia with t(3;13) and Central Nervous System Leukemia after Allogenic Cord Blood Transplantation

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is a neoplastic cancer characterized by clonal expansion of leukemic cells in lymph organs and bone marrow. Lots of kinds of different chromosomal translocations can be found in those leukemic cells. However, the role of abnormal chromosomes and genes in leukemogenesis is not yet fully understood. Identifying new chromosomal translocations can facilitate a better understanding of pathogenesis of this disease. **Case presentation:** We report a rare case of acute lymphocytic leukaemia with t(3;13)(q29, q21). The patient was diagnosed pre-B-ALL with no abnormal chromosomal or gene fusion and achieved complete remission (CR) after induction chemotherapy; 10 months later, she relapsed in the consolidation, with cytogenetics tests showing 46, XX, t(3;13)(q29, q21). Given no CR after two chemotherapy regimens, the patient received salvage cord blood transplantation. Regular intrathecal methotrexate was applied to prevent central nervous system leukemia. Good graft versus leukemia was induced by daily injection of a low dose of IL-2 2 months post-transplantation. Minimal residual disease negativity was maintained until central nervous system (CNS) leukemia was found 8 months after transplantation. A whole exome sequencing was performed. Nine driver mutation genes and seven tumor genes were found. **Conclusions:** We highly suspect that the relapse in the CNS after transplantation is associated with a rare chromosomal translocation.

Keywords

cord blood transplantation, central nervous system leukemia, translocation, integrin, acute lymphocytic leukaemia

Introduction

Acute lymphoblastic leukemia (ALL) is a cancer of the lymphoid line characterized by the development of large numbers of immature lymphocytes[1]. The prognosis of the disease in adults remains poor[2–4]. ALL oncogenes include gene fusions and translocations of transcription regulators and other chromatin-associated factors. Many chromosome translocations present in ALL, of which the majority result in fusion genes encoding fusion proteins, such as BCR/ABL. Chromosomal abnormalities can affect oncogenes; they cause either malignant transformation or help proliferation[3]. Therefore, chromosomal abnormalities are related to disease prognosis. Various chromosome translocations in ALL have been identified, which facilitates a better understanding of pathogenesis of this disease[4,5]. However, the role of abnormal chromosomes and genes in leukemogenesis is not yet fully understood, and identification of new chromosome translocations in ALL is needed.

Central nervous system leukemia, especially central nervous system acute lymphoblastic leukemia (CNS-ALL) is a major problem in the clinic. All subtypes of ALL can metastasis into the CNS[6]. It is reported that this metastasis is due to integrin expression, which is common in ALL. This expression allows leukemia cells to use neural migratory pathways to invade the CNS[7]. ALL patients who relapse in the CNS have poor outcomes. And regular prevention methods are

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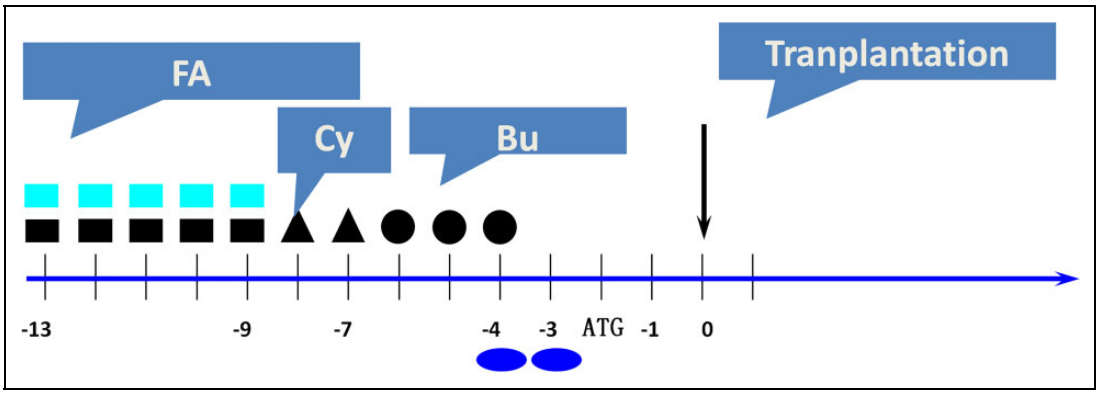

Fig 1. Conditioning Regimen: Myeloablative FA5-CYBU protocol.

included in the clinical standard operating procedures to minimize relapse in the CNS[1].

Hematopoietic stem cell transplant (HSCT) is a curative treatment for hematologic malignancies[8]. Salvage transplantation can be performed on those patients with refractory/relapse leukemia. Unrelated cord blood transplantation (CBT) serves as a valuable curative option for patients who have no matched related donors[9]. Post-transplant patients are in immunocompromised status and infection is common after HSCT, especially after CBT[10]. Graft versus host disease (GVHD) is another common lethal complication after HSCT[11]. One of the advantages of CBT is a reduced severity of GVHD without reducing graft-versus-tumor effects[12–14].

Herein, we report a rare case of ALL with t(3;13)(q29, q21). The patient developed CNS leukemia after allogenic transplantation. A whole exome sequencing suggested the relapse in CNS could be associated with a rare chromosomal translocation.

Case Report

A 33-year-old Chinese Han female with relapse of B-ALL was admitted to Fujian Medical University Union Hospital to perform allo-HSCT (CBT). The patient was diagnosed pre-B-ALL with no abnormal chromosomal or gene fusion and achieved complete remission (CR) after induction chemotherapy. She had nothing special in her family, surgical, medical, medication, or psychosocial histories. She had a 10-month CR time from Pre-B-ALL [flow cytometry: CD34, CD19, CD38, HLA-DR, cCD79a positive and CD3, CD4, CD56, CD2, CD5, CD7, CD14, CD33, CD15, CD11b, cd117, sIgM, cMPO negative, karyotype: 46 XX (30)] after a regimen of vincristine, daunorubicin, cyclophosphamide, L-asparaginase, and prednisone (VDCLP, vincristine 1.5 mg/m^2/day, days 1, 8, 15, and 22; daunorubicin 45 mg/m^2/day, days 1–3 and days 15–17; cyclophosphamide 800 mg/m^2/day, days 1 and 15; prednisone 60 mg/m^2/day, days 1–19; and L-asparaginase 10,000 U/m^2/day, days 19–28). Regular consolidation was given as well as intrathecal methotrexate treatment (10 mg, X4). However, she relapsed in the consolidation, suffering from fever and bone pain. There was a positive sternal compression test in the physical examination. The cytogenetics test of bone marrow (BM) sample showed 46, XX, t(3;13)(q29, q21). With two courses of HyperCVAD(A: Cyclophosphamide 300 mg/m^2 days 1–3; Doxorubicin 50 mg/m^2 day 4; Vincristine, 1.4 mg/m^2 d4, 11; Dexamethasone 40 mg days 1–4/days 11–14 B Methotrexate 1g/m^2 day 1; Cytarabine 3g/m^2 days 2–3) regimen chemotherapy, the disease still showed progression. Accordingly, without an HLA-matched sibling available, a salvage CBT from a male donor (HLA 5/10) in a public cord blood bank (Zhejiang) was performed.

An intensified conditioning of fludarabine (30mg/m^2 qd for 5 days), busulfan (9.6 mg/kg separated into 3 days), cytosine arabinoside(2.0/m^2 qd for 5 days), cyclophosphamide (3.6 g/m^2 separated into 2 days), and rabbit antithymocyte globulin (ATG-Fresenius; 10 mg/kg) was selected to treat the patient (Fig 1). HLA mismatched (5/10) male cord blood cells (nucleated cells: 2.5 x 10^7/kg, containing 1.5 x 10^5/kg of $CD34^+$ cells) were transplanted. After CBT, mycophenolate mofetil (MMF) and cyclosporin (CsA) were used to prevent GVHD. The time to neutrophil engraftment and plantlet engraftment were 19 days and 38 days, respectively. Full donor chimerism was found after engraftment by short tandem repeat (STR) detection. Intrathecal methotrexate (10 mg, X4, 1- to 2-month interval) was applied to prevent CNS leukemia.

The complications of CBT included cytomegalovirus viremia, pneumonia, and hemorrhagic cystitis. After treatment with ganciclovir, Imipenem, vancomycin, Voriconazole, and hydration, alkalizing diuresis as well as withdrawal of immunosuppressant, the patient recovered from those complications.

Given the complication after CBT, to avoid severe GVHD and to enhance GVL, low dose IL-2 (1 million units, qd) was given 2 months post-transplantation after withdrawal of all immunosuppressants. Accordingly, minimal residual disease (MRD) measured by 10-color flow cytometry was determined monthly. Good GVL was observed after daily injection of low dose IL-2. MRD negativity was maintained until CNS leukemia was found 8 months after transplantation.

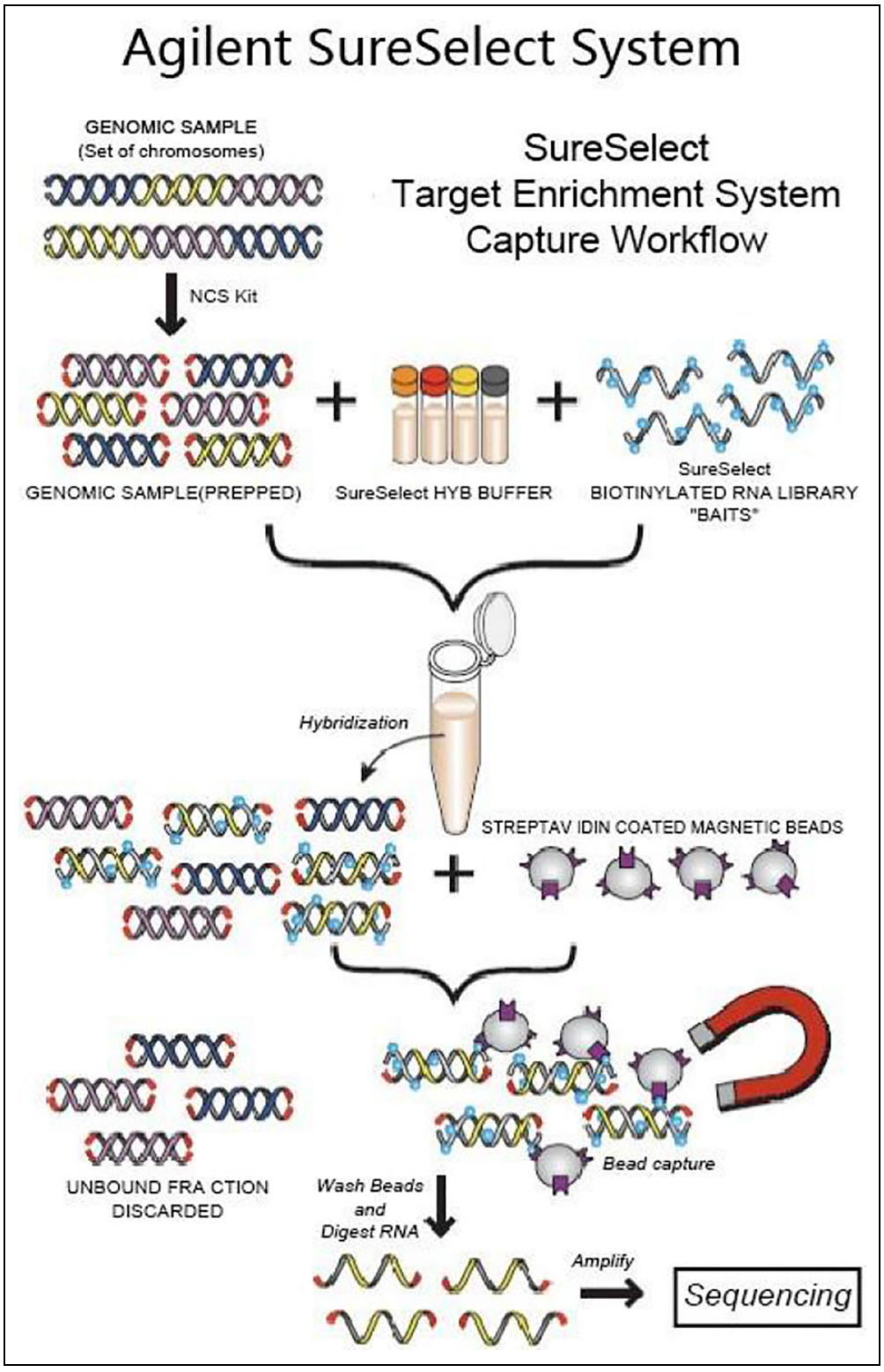

Fig 2. Flowchart of sequencing system.

After the patient's death, a whole exome sequencing of the BM sample was performed. Briefly, germline control DNA was used for normalization of the whole exome sequencing. After capture with the Agilent Sureselect system, a sequencing quality check was performed (Q30 = 92.48%); 96.84% of the acquired data matched the HG19 genome exactly. The 1000 Genomes Project and ESP6500 database were used to filter no pathogenic mutation (Fig 2).

Table 1. Whole Exome Sequencing COSMIC Reports Results.

COSMIC_ID	COSMIC_DIS
COSM1744914	2(biliary_tract)
COSM676615	1(lung)
COSM246232	1(prostate);1(large_intestine)
COSM1422593	1(large_intestine)
COSM3846357	1(breast)
COSM1264485	1(oesophagus)
COSM1059929	1(endometrium)
COSM3951019	1(lung)
COSM1131716	1(prostate)
COSM3662914	2(liver)
COSM1453549;COSM1453550	1(large_intestine)
COSM1720142;COSM1720143; COSM1720144	2(NS)
COSM752250	1(lung)
COSM1460093	1(large_intestine)
COSM1472170;COSM1472169; COSM3745836	1(prostate);1(liver)
COSM3769077	1(pancreas)
COSM3397024	1(central_nervous_system)
COSM1347109	1(large_intestine)
COSM914595	1(endometrium)
COSM1704569	1(skin)
COSM541695	1(lung)
COSM3706758	2(liver)
COSM434917	1(breast)
COSM1726597	1(liver)
COSM3796037	1(urinary_tract)
COSM148603	1(stomach)
COSM1467376	2(liver);2(large_intestine)
COSM3363959	1(kidney)

Table 2. Mutation Genes and Tumor Genes.

Driver mutation genes	Gene in Cancer Gene Census	Gene in KEGG cancer pathway
ABL1, KDR, TGA2B, SC1, MLH1, COL4A2, GF22, SMD2, OL6A3	ABL1, KDR, TSC1, MLH1, DNM2, NUP98 CBFA2T3	ITGA2B COL4A2 FGF22 ARNT2 DAPK1

We found 28 COSMIC reports (Table 1) as well as the driver mutation genes and tumor genes (Table 2).

Discussion and Conclusion

ALL has a poor prognosis in adults[4]. Translocation in ALL can serve as a prognosis factor, either favorable or adverse[5]. Translocation usually results in gene fusion and a fusion protein[3]. This has been documented in the acute leukemia database. For example, translocation between 9:22, causing BCR/ABL protein, is common among adult ALL and carries a poor prognosis. Therefore, identifying more chromosome translocations in ALL can facilitate a better understanding of the disease. Herein, we report a rare case of acute lymphocytic leukaemia with t(3;13)(q29, q21), as well as whole exome sequencing. However, with the limitations of our laboratory, we cannot find the fusion protein caused by this chromosome abnormality. A more in-depth research of this chromosome translocation is needed.

Like majority of ALL cases, treatment involving a combination of common chemotherapeutic drugs was given to the patient, and achieved CR after the first case. There was no abnormal rearrangement at initial diagnosis. The karyotype at diagnosis was normal with the absence of the t(3;13) translocation at diagnosis. We viewed 30 metaphases. Thus, the chance that the translocation was simply missed is very low. It was still possible that the translocation was perhaps present at low level, and, consequently, began to expand during treatment. It is also possible that the translocation was therapy-induced or developed from clone evolution. The patient relapsed during the consolidation, with the novel translocation t(3;13)(q29, q21) present. The disease progressed after two courses of HyperCVAD. Thus, salvage transplantation was needed.

There has been much progress in CBT in recent years. It is reported that the curative effect of CBT on acute leukemia is similar to that of haplo-identical transplantation, unrelated BM transplantation[4,12,14]. The advantage of CBT in treating hematological diseases is the abundant source. The great improvement in the umbilical blood bank in China has made CBT convenient for the treatment of a variety of diseases. The HLA matching requirement of CBT is low. Given the fact that there was no CNS involvement at the time of transplantation, we chose a male cord blood as the source of allostem cells using a radiation-free conditioning regimen. Also, the incidence of GVHD after CBT is low and easy to control, even after being induced by IL-2, as in this case. CBT can maintain GVL, high GRFS, and better quality of life after transplantation. In this case, MRD was negative for 6 months until CNS leukemia was found, which could be due to the genetic abnormality of the leukemia blasts.

CNS leukemia is an inherent feature of ALL of all genetic subtypes. We gave intrathecal methotrexate four times during the consolidation stage. Although a useful CNS leukemia prophylaxes measure, it is still possible that the leukemic clone had already migrated to the CNS before CBT and remained dormant in this 'sanctuary site', especially since total body irradiation was not used. Usually, we take samples for MRD analysis after consolidation. We have no data for MRD before relapse. Also, we acknowledge that the large amount of blasts in peripheral tissues might get into the CNS via the puncture; we did not examine the CNS before performing CBT. Some papers have reported that late relapse is still possible from host pre-leukemic (e.g. BCR-ABL1+) progenitor cells that can lie dormant in the BM even after irradiation. Therefore, presumably the leukemia cells can also hide in the CNS and may emerge many years later.

The major disadvantage of CBT in the treatment of acute leukemia is the low number of umbilical cord blood cells and

its slow immune reconstruction (especially T-cell-related immunity). Thus, early transplantation can easily become infected, which leads to a higher mortality associated with transplantation. In the present case, with antibiotic treatment, the patient recovered quickly from infection.

Moreover, for this salvage CBT case, the most challenging part is how to enhance graft versus leukemia (GVL) and to prevent relapse after CBT. Due to differences in the response in newborns and adults to cytokine, anti-tumor activity seems to be stronger after CBT[15]. The potential for augmenting GVL with IL2 has been reported in recent decades[16,17]. Treatment of leukemic relapse following CBT with high dose IL2 can induce both GVL and GVHD[18]. Given the patient's complication after CBT, to better enhance GVL without increasing GVHD, low dose IL-2 (1 million units qd) was given 2 months post-transplantation after withdrawal of all immunosuppressants. After administration of IL-2, we found the patient developed mild GVHD, manifesting as a skin rash over about 35% of total body surface area. After treatment with methylprednisolone, the IL-2 induced GVHD was controlled. Good GVL was observed by monitoring MRD monthly. This MRD negativity was maintained until CNS leukemia was found 8 months after transplantation, indicating that low dose IL-2 early after CBT could be a potential method to enhance GVL without lethal GVHD. This low-dose IL-2 treatment could be helpful for such patients after salvage CBT.

Different tumors may have the same mutation, and a COSMIC record may appear in different tumors. In the whole exome sequencing, we found 28 COSMIC reports, mostly of majority epithelial tissue origin. Recently, Munch et al. showed expression data that CNS involvement may be mediated by vascular endothelial growth factor. Although as yet there is no convincing evidence that a particular mutation profile increases the incidence of CNS leukemia, it is interesting to find that there is one record (COSM3397024) with CNS. Also, in Table 2, we found some genes related to CNS leukemia. DNM2 mutation was found to be related with oncogenesis in ALL[19]. A KDR mutation has been reported previously in angiosarcomas[20]. ABL1 is associated with clonal evolution[21]. It is also reported that ALL blasts migrate into the CNS along vessels that pass directly between vertebral/calvarial BM and the subarachnoid space. This study showed convincingly that α6 integrin-laminin (ITGA6-laminin) interactions mediate the migration of ALL cells towards the CNS. Thus integrin–laminin interactions mediated the migration of ALL cells towards the cerebrospinal fluid[7]. In this case, the gene we found to be mutated, ITGA2B, forms one part (alpha2b) of the alpha2b/beta3 (α2bβ3). This receptor integrin is usually found on the surface of platelets that control blood clotting. The integrin (ITGA2B) in the present study can be associated with the complications of hemorrhagic cystitis early after CBT.

The major limitation of this case is that one might argue that the CNS leukemia could have developed after the CBT, but it is likely that these cells were already present in the CNS before the CBT. This could be proved by cloning the translocation at the DNA level from final relapse DNA and backtracking through the various samples collected. With the limitation of our laboratory, we cannot perform those experiments, or identify the fusion protein caused by this chromosome abnormality. Without protein level functional data, until now, no clear answer regarding the function of t(3;13)(q29, q21) can be obtained from the whole exome data.

We report a rare case of ALL with t(3;13)(q29, q21). Whole exome sequencing could explain, at least to some extent, the reason for CNS leukemia relapse after CBT. We report this case to create awareness among clinicians of the chromosome translocation; although uncommon, it could be a cause of relapse. In patients with chromosome translocation, attention should be paid to CNS leukemia even after transplantation.

Availability of Data and Materials

The data is available from the corresponding author upon reasonable request (morningshiplee@sina.com).

Authors' Contributions

XFL and NNL participated in data collection, interpretation, drafting and review of article. XFL, YQH, JFH and NNL participated in the laboratory work. XFL and NNL contributed to data interpretation, and also revised the manuscript. All authors revised and approved the final version of the manuscript.

Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

Consent for Publication

Written informed consent was obtained from the patient's husband for publication of this case report as well as carrying out the whole exome sequencing of the bone marrow sample. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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