ZNF384 Gene Rearrangement in Acute Lymphocytic Leukemia with Kidney Involvement as the First Manifestation is Associated with Poor Prognosis: A Case Report

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Case Report

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Abstract

Background: Novel fusion genes such as ZNF384 have been identified in B-cell precursor acute lymphoblastic leukemia (BCP-ALL) in recent years. Patients harboring ZNF384 rearrangement have a distinctive immunophenotype with weak CD10 and aberrant CD13 and/or CD33 expression, which makes ZNF384-rearranged ALL a unique subtype of BCP-ALL. However, research on the prognostic significance of ZNF384 rearrangement has been limited to date.

Case presentation: We described a 17-year-old young woman who was diagnosed with ALL and had kidney involvement as the first manifestation, which was very rare in the existing studies. FISH analysis indicated a rearrangement of ZNF384 according to its probe. The patient had a typical characteristic immunophenotype of ZNF384 rearrangement with CD10 being negative but CD13 and CD33 being positive. She had an unfavorable prognosis since she responded poorly to chemotherapy and developed a relapse shortly after reaching CR.

Conclusion: The importance of the ZNF384 gene rearrangement in terms of prognosis remains unclear. We reported a young woman harboring ZNF384 rearrangement in ALL with kidney involvement. She experienced different treatments, but her prognosis remained poor. Since ZNF384 rearrangement may act as a negative prognostic predictor, early detection based on its characteristic immunophenotype is of great necessity.

Background

Acute lymphocytic leukemia (ALL) is a malignant neoplasm of lymphoid cells experiencing differentiation blocked at an early stage, with extensive infiltration in the bone marrow, peripheral blood, and other organs. Over 80% of ALL cases are B-cell precursor acute lymphoblastic leukemia (BCP-ALL). In 2020, 6,150 new cases of ALL were diagnosed in the United States, accounting for 0.3% of all new cancer cases(1). ALL usually occurs in children and young adults, with a peak age ranging from 2 to 5(2).

Gene rearrangement and fusion are common in BCP-ALL, playing an important role in determining therapeutic targets and predicting prognosis. With the advance of the genome and transcriptome sequencing, novel gene fusions such as zinc-finger protein 384 (ZNF384) rearrangement were found. The ZNF384 gene encodes a zinc finger protein that functions as a transcription factor and regulates the expression of matrix metalloproteinases(3). Patients harboring ZNF384 rearrangement have a distinctive immunophenotype, with weak CD10 and aberrant CD13 and/or CD33 expression, making ZNF384-rearranged ALL a separate subtype of BCP-ALL(4). Recent data have shown that up to 6% of children and 15% of adults with BCP-ALL harbor ZNF384 gene rearrangement, while the outcomes of these patients remain unclear.

Herein, we report a case of ZNF384-rearranged ALL with a poor clinical prognosis.

Case Presentation

A 17-year-old young woman was admitted to our hospital in December 2019 because of increased urine foam and fatigue for 3 weeks.

Laboratory examinations showed protein(3+) and occult blood(2+) in urine. The blood urea nitrogen was 5.39mmol/L, the serum creatinine was 69μmol/L, and the lymphocyte ratio was 62.01%. Kidney color Doppler ultrasound showed increased volume in both kidneys as well as enhanced parenchymal echo. Then kidney biopsy was performed, indicating lymphoblastic lymphoma or leukemia with kidney involvement(Fig. 1A and 1B)and immunohistochemistry showed TdT(+), CD99(+), CD3(-), CD20(part +),CD73(-), PAX5(+), and LCA(part +). Fluorescence in situ hybridization (FISH) result of the kidney biopsy sample showed ZNF384 rearrangement (Fig. 1E). Then bone marrow aspiration and biopsy was performed, revealing disappearance of fat vacuoles and appearance of immature lymphoid cells. A suspected diagnosis of ALL was made, with extreme lymphocyte proliferation and the proportion of lymphoblasts was 50.8% (Fig. 1C and 1D). Flow cytometry(FCM) of bone marrow revealed CD34(+),CD117(-),CD33(+),CD64(-),CD13(+),CD14(-),CD274(-),TSLPR(-),CD11b(-),IgM(+),CD71(-),CD56(+),CD2(-),CD7(-),CD5(-),CD10(+),CD3(-),CD4(-),CD8(-),CD3DR(+),CD19(+),CD22(+),CD20(+),cMPO(-),cCD3(-), cCD79a(+),TDT(+),CD58(+),CD61(-),CD235a(-),CD11c(-), which was compatible with BCP-ALL(Fig. 2). Next generation sequencing (NGS) showed STAG2 gene mutation in bone marrow and reverse transcription-polymerase chain reaction (RT-PCR) showed negative for leukemia fusion gene.

Her medical history was unremarkable. On physical examination, the patient had an anemic appearance without ecchymosis. The initial laboratory evaluation revealed lymphocytosis ($2.37 \times 10^9/L$) and moderate anemia (Hb78 g/L, Vitamin B12 164pg/mL, folic acid3.00ng/mL and serum ferritin426.7ug/L). She was diagnosed with BCP-ALL with both kidneys involvement.

After a cycle of VCDLP regimen, the bone marrow was obviously hyperplastic and active, and immature lymphocytes were occasionally observed. FCM showed the ratio of lymphoblasts was 42% with CD34(+),CD10(-),CD19(+),CD38(+),HLA-DR(+),CD64(-),CD13(+),CD20(-),and CD33(+). Since the patient did not achieve remission, a cycle of FLAG salvage treatment was administrated, then the patient was assessed as complete remission(CR). No lymphoblasts were seen in the bone marrow. FCM showed the ratio of lymphoblasts was 0.8% with CD34(+),CD10(-),CD19(+),CD38(+),HLA-DR(+),CD13(+) and STAG2 gene mutation. The volume of both kidneys returned to normal according to color Doppler ultrasound. After the patient achieved CR, an intrathecal drug injection was performed for consolidation therapy. Eight months after the continued complete remission(CCR), the disease relapsed according to bone marrow smear revealing 55.2% of lymphoblasts and FCM showing ALL with the partial expression of CD33. FISH showed ZNF384 rearrangement (39%) according to its probe (Fig. 1F) and positive for IgH rearrangement (37%). The leukemia fusion gene and mutation panel were both negative. But there was no remission in the bone marrow after she was treated with chidamide and a dose-adjusted FLAG plus VP chemotherapeutic regimen, as well as highly sensitive treatment, HAD. The percentage of lymphoblasts was 14.4% and ZNF384 was positive (17.6%) according to FISH. Now the patient has been admitted to the hospital and is receiving chemotherapy regularly. The details of the treatment process were summarized in Supplement Table 1.

Discussion And Conclusions

ZNF384-rearranged ALL defines a new subtype of leukemia that may be classified as BCP-ALL(5). Patients with BCP-ALL harboring ZNF384 are likely to possess the characteristic immunophenotype of a dull or negative CD10 and aberrant expression of one or more myeloid antigens, which should be the hallmark of ZNF384 rearrangement. CD10 was negative in our case, while CD13 and CD33 were positive, which was consistent with previous studies. The Tokyo Children's Cancer Study Group (TCCSG) came up with a similar outcome to ours. TCCSG tested 91 samples from BCP-ALL patients, revealing an incidence of a weak or negative expression of CD10, ranging from 0.39–67.34% (mean: $19.44 \pm 18.23\%$), and 31.82% and 77.27% expression of CD13 and CD33 respectively in 22 patients with ZNF384-related fusion genes(6).

Unlike the mechanism that subclonal genomic variation drives clonal evolution in disease progression of ALL(7), mutational variegation does not determine immunophenotype within individual patients harboring ZNF384 rearrangement and the immunophenotypic aberrancy arises from inherent lineage plasticity(5). Moreover, fusion partners for ZNF384 are commonly involved in BCP-ALL, which is responsible for leukemia development. Preclinical studies found out the initial effect of fusion proteins was the inhibition of B-cell differentiation by introducing EP300, one of the fusion genes, and ZNF384 into mouse pro-B cells, resulting in the stasis of cell differentiation(8, 9).

Although a few reports support a generally favorable prognosis for patients with ZNF384 rearrangement(10, 11), others suggest a poor clinical outcome. A higher recurrence rate of over 2% was reported in some ZNF384 gene fusion cases(6). Additionally, CD10 negativity was found to be an independent adverse prognostic factor in ALL because CD10-negative lymphoblastic leukemia cells had lower cycling capacities and were resistant to apoptosis(12, 13). A cohort study in China investigating 92 adults and 111 pediatric patients with BCP-ALL revealed that leukemic cells from patients with ZNF384 fusions had more possibilities to be CD10-negative than those from other patients both in adults (15.8% vs. 5.3%, $P = 0.04$) and children (18.8% vs. 2.9%, $P = 0.02$)(14). This finding may explain why patients with ZNF384 rearrangement are related to unfavorable outcomes. The patient in our case had the distinct immunophenotype of negative CD10 and she developed disease relapse approximately eight months after she reached CR despite receiving consistent consolidation chemotherapy. She also had poor responses to chemotherapeutic treatment, necessitating frequent adjustments to more effective and powerful regimens.

In conclusion, we reported a BCP-ALL case with ZNF384 gene rearrangement. The patient showed a very typical immunophenotype with CD10 being negative but CD13 and CD33 being positive. She responded poorly to chemotherapy and developed a relapse shortly after reaching CR. Owing to the low incidence and variety of treatment protocols from institution to institution, the statistical significance of clinical outcome in ZNF384 rearrangement has not been analyzed so far. But it has been linked to an unfavorable prognosis in some small studies, which still needs to be replicated on a larger scale to be confirmed. Furthermore, ZNF384 probes are not commonly included in screening leukemia translocations, which could cause a delay in diagnosis and later treatment. Therefore, we suggest that when the rearrangement of ZNF384 is suspected based on its characteristic immunophenotype, it should be tested and confirmed as soon as possible.

Abbreviations

ALL, acute lymphocytic leukemia

BCP-ALL, B-cell precursor acute lymphoblastic leukemia

ZNF384, zinc-finger protein 384

FISH, fluorescence in situ hybridization

FCM, flow cytometry

NGS, next generation sequencing

RT-PCR, reverse transcription-polymerase chain reaction

CR, complete remission

CCR, continued complete remission

TCCSG, the Tokyo Children's Cancer Study Group

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the experimental design and edited the manuscript. JM contributed to the explanation of morphology and laboratory data. JG wrote the manuscript. BC was responsible for supervising the data analysis.

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Not applicable.

References

1. National Cancer Institute. SEER. Cancer Statistics, Review. 1975–2020 [Available from: <https://seer.cancer.gov/statfacts/html/alyt.html>].
2. Gurney JG, Severson RK, Davis S, Robison LL. Incidence of cancer in children in the United States. Sex-, race-, and 1-year age-specific rates by histologic type. *Cancer*. 1995;75(8):2186–95.
3. Nakamoto T, Yamagata T, Sakai R, Ogawa S, Honda H, Ueno H, et al. ClZ, a zinc finger protein that interacts with p130(cas) and activates the expression of matrix metalloproteinases. *Mol Cell Biol*. 2000;20(5):1649–58.
4. Gocho Y, Kiyokawa N, Ichikawa H, Nakabayashi K, Osumi T, Ishibashi T, et al. A novel recurrent EP300-ZNF384 gene fusion in B-cell precursor acute lymphoblastic leukemia. *Leukemia*. 2015;29(12):2445–8.
5. Alexander TB, Gu Z, Iacobucci I, Dickerson K, Choi JK, Xu B, et al. The genetic basis and cell of origin of mixed phenotype acute leukaemia. *Nature*. 2018;562(7727):373–9.
6. Hirabayashi S, Ohki K, Nakabayashi K, Ichikawa H, Momozawa Y, Okamura K, et al. ZNF384-related fusion genes define a subgroup of childhood B-cell precursor acute lymphoblastic leukemia with a characteristic immunotype. *Haematologica*. 2017;102(1):118–29.
7. Ma X, Edmonson M, Yergeau D, Muzny DM, Hampton OA, Rusch M, et al. Rise and fall of subclones from diagnosis to relapse in pediatric B-acute lymphoblastic leukaemia. *Nat Commun*. 2015;6:6604.
8. Yasuda T, Tsuzuki S, Kawazu M, Hayakawa F, Kojima S, Ueno T, et al. Recurrent DUX4 fusions in B cell acute lymphoblastic leukemia of adolescents and young adults. *Nat Genet*. 2016;48(5):569–74.
9. Yaguchi A, Ishibashi T, Terada K, Ueno-Yokohata H, Saito Y, Fujimura J, et al. EP300-ZNF384 fusion gene product up-regulates GATA3 gene expression and induces hematopoietic stem cell gene expression signature in B-cell precursor acute lymphoblastic leukemia cells. *Int J Hematol*. 2017;106(2):269–81.
10. Berg HE, Blackburn PR, Smadbeck JB, Swanson KE, Rice CS, Webley MR, et al. Detection of a Cryptic EP300/ZNF384 Gene Fusion by Chromosomal Microarray and Next-Generation Sequencing Studies in a Pediatric Patient with B-Lymphoblastic Leukemia. *Lab Med*. 2021;52(3):297–302.
11. McClure BJ, Heatley SL, Kok CH, Sadras T, An J, Hughes TP, et al. Pre-B acute lymphoblastic leukaemia recurrent fusion, EP300-ZNF384, is associated with a distinct gene expression. *Br J Cancer*. 2018;118(7):1000–4.
12. Reaman GH, Spoto R, Sensel MG, Lange BJ, Feusner JH, Heerema NA, et al. Treatment outcome and prognostic factors for infants with acute lymphoblastic leukemia treated on two consecutive trials of the Children's Cancer Group. *J Clin Oncol*. 1999;17(2):445–55.
13. Cutrona G, Tasso P, Dono M, Roncella S, Ulivi M, Carpaneto EM, et al. CD10 is a marker for cycling cells with propensity to apoptosis in childhood ALL. *Br J Cancer*. 2002;86(11):1776–85.
14. Liu YF, Wang BY, Zhang WN, Huang JY, Li BS, Zhang M, et al. Genomic Profiling of Adult and Pediatric B-cell Acute Lymphoblastic Leukemia. *EBioMedicine*. 2016;8:173–83.

Figures

Figure 1

Pathological results of kidney biopsy and bone marrow aspiration smear and results of FISH (A)(B)The result of kidney biopsy shows the increased lymphocytes, indicating lymphoblastic lymphoma or leukemia with kidney involvement(A: HE staining; original magnification, 400× and B: PAS staining; original magnification, 400×). (C) The result of the Wright-Giemsa staining of the bone marrow smear sample is shown. Bone marrow hyperplasia is extremely active with lymphoblasts accounting for 50.8% before treatment(Wright-Giemsa staining; original magnification, 1000×) (D)Lymphoblasts were negative for myeloperoxidase(red arrows), suggesting the possible diagnosis of acute lymphocytic leukemia (POX staining; original magnification, 1000×). (E) ZNF384 rearrangement in the kidney biopsy sample is revealed according to its probe by fluorescence in situ hybridization(FISH). The white arrow represents a single red signal, a single green signal, and a yellow signal (1R1G1Y), which is a positive signal for ZNF384 rearrangement. (F) Figure 1F describes ZNF384 rearrangement (39%) in the bone marrow sample, indicating the homology with the rearrangement of ZNF384 in the kidney biopsy sample. The yellow arrow on the left represents a negative signal and the white arrows on the right represent positive signals(1R1G1Y).

Figure 2

Results of the flow cytometry. The results of the flow cytometry indicate acute lymphocytic leukemia. (A) The proportion of primary cells is 68.45% according to the SSC/CD45 gating. (B) The CD22 fraction is shown as 22.8%. (C)CD19 is positive with a proportion of 81.1% and CD10 is positive with a proportion of 20.9%. (D) CD34 is positive with a proportion of 98.2% and CD13 is positive with a proportion of 55.8%. (E) CD20 is positive with a proportion of 35.0%. (F) CD33 is positive with a percentage of 69.8%.

Supplementary Files

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