Case Report

Coexistence of *ETV6-RUNX1* and *MLL* aberration among pediatric acute lymphoblastic leukemia: case reports and a literature review

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Background: It is known that *ETV6-RUNX1* is usually related to favorable prognosis, but *MLL* aberration has been associated with poor prognosis among pediatric acute lymphoblastic leukemia (ALL). However, the outcome of coexistence of *ETV6-RUNX1* and *MLL* aberration in pediatric ALL patients is unknown. Herein, we report 4 cases of the coexistence of *ETV6-RUNX1* and *MLL*-partial tandem duplications (*MLL*-PTD) in pediatric ALL patients and show the favorable outcome, which was never reported before.

Case Description: The frequency of coexistence of *ETV6-RUNX1* and *MLL* aberration at our children's medical center was calculated as 0.98% (4/410). All of them were *ETV6/RUNX1*-positive cases that exhibited *MLL*-PTD, and the 10-year event-free survival (EFS) and overall survival (OS) were both 75%. With the following keywords of "*ETV6-RUNX1*", "*MLL*", "children" and "acute lymphoblastic leukemia", a literature search of coexistence of *ETV6-RUNX1* and *MLL* aberration was conducted in the database of PubMed, and 4 articles were retrieved finally, involving 16 cases of children. Among the 16 cases of pediatric ALL, the age ranged from 2 to 7 years old, including 9 males and 7 females and the white blood cell (WBC) count was (2.66–68.6)×10^9/L. In terms of fusion genes, they all had positive *ETV6/RUNX1*. Among them, *MLL* deletion was exhibited among 8 *ETV6/RUNX1*-positive patients, and 2 cases of der(21) duplication. *MLL* allelic deletions were shown among the remaining *ETV6/RUNX1*-positive patients. All patients showed a favorable outcome.

Conclusions: The results of our analysis primarily provide compelling evidence that cases with an *MLL*-PTD or other types of *MLL* aberration are in fact a distinct subentry among *ETV6-RUNX1* B-cell ALL (B-ALL).

Keywords: Acute lymphoblastic leukemia (ALL); children; *MLL* aberration; *ETV6/RUNX1*; case report

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Introduction

In pediatric acute lymphoblastic leukemia (ALL), *ETV6-RUNX1* is the most common genetic abnormality, which is found in 25% of pediatric ALL cases, and it is usually related to favorable prognosis (1-3). *MLL* aberrations have been described in a small number of ALL cases and are considered a poor prognostic marker (4-6). However, the coexistence of *ETV6-RUNX1* and *MLL* aberrations in pediatric ALL patients is rare. Herein, we report 4 cases of pediatric ALL with the coexistence of *ETV6-RUNX1* and *MLL* aberration who were diagnosed from February 2008 to June 2016. We present this article in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-142/rc).

Case presentation

Case reports

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patients' parents/legal guardians for publication of these case reports. A copy of the written consent is available for review by the editorial office of this journal. The study protocol and informed consent were approved by the Ethics Committee of Sun Yat-Sen Memorial Hospital (No. SYSKY-2022-333-01).

Highlight box

Key findings

- Cases with an *MLL*-partial tandem duplications (*MLL*-PTD) or other types of *MLL* aberration are in fact a distinct subentry among *ETV6-RUNX1* B-cell acute lymphoblastic leukemia (B-ALL).

What is known and what is new?

- It is known that *ETV6-RUNX1* is usually related to favorable prognosis, but *MLL* aberration has demonstrated poor prognosis among pediatric ALL.
- Herein, we reported 4 cases of the coexistence of *ETV6-RUNX1* and *MLL*-PTD in pediatric ALL patients and showed the favorable outcome.

What is the implication, and what should change now?

- This result also indicates a simple explanation for the good clinical characteristics and good prognosis about coexistence of *ETV6-RUNX1* and *MLL* aberration.

Case 1

An 8-year-old male presented with a week of pallor and coughing on February 28, 2012. Blood routine test showed white blood cell (WBC) count 5×10^9/L, hemoglobin (Hb) 104 g/L, and platelet (PLT) 28×10^9/L. Flow cytometry (FC) on bone marrow (BM) revealed findings consistent with a B-cell ALL (B-ALL) and CD10 was positive. A normal male karyotype was shown by cytogenetic analysis, and fluorescence in situ hybridization (FISH) studies showed that (12;21) (p13;q22)/*ETV6-RUNX1* in 92% of the interphase nuclei and *MLL* aberration was negative. However, reverse transcription-polymerase chain reaction (RT-PCR) showed an *MLL* exon 6–2 fusion. The case was included in the Guangdong-2008-ALL protocol for induction chemotherapy. He exhibited prednisone good response (PGR) on day 8, and FC performed on day 15 BM showed minimal residual disease (MRD) B-ALL (4% lymphoblasts) and on day 33 was negative for residual disease. Later, the patient was unable to continue treatment because a lack of family financial resources, and treatment was abandoned 1 month after diagnosis.

Case 2

In case 2, another 8-year-old male childhood patient was admitted to hospital for a month of pallor and a 5-day of fever on April 14, 2011. The results of routine blood examination revealed a WBC of 22.58×10^9/L, Hb of 50 g/L, and PLT of 22×10^9/L. BM indicated that primitive lymphoid and immature lymphocytes accounted for 98.5%. The result of BM FC was consistent with that of B-ALL and CD10 was positive. We used an *ETV6-RUNX1* probe and an *MLL* probe with FISH analysis on metaphase and interphase cells revealed *ETV6-RUNX1* (82% of cells), whereas FISH analysis revealed negative *MLL* aberration. Nevertheless, RT-PCR showed an *MLL* exon 5–2 fusion. He exhibited PGR on day 8, and FC performed on day 15 and on day 33 BM were negative for MRD. The patient was also treated with Guangdong-2008-ALL protocol and achieved complete response (CR), which, at the time of writing, had been maintained for 10 years.

Case 3

This child was a 3-year-old male who developed fever for 6 days and abnormal hemogram for 2 days on March 23, 2012. Blood routine examination showed Hb 62 g/L, PLT 32×10^9/L, and WBC 4.67×10^9/L, but 96.5% of the primordial cells were of different sizes. BM FC confirmed

Table 1 Clinical and laboratory features of the patients with coexistence of *ETV6-RUNX1* and *MLL* aberration among pediatric ALL patients in our pediatric department

Case	Age (years)	Gender	WBC	Prednisone response	BM blasts on day 15	BM blasts on day 33	Fusion gene		Outcome (time since diagnosis)
							ETV6/RUNX1	*MLL*	
1	8.3	M	5×10^9/L	PGR	M1	M1	92% (+)	*MLL*-PTD (ex6/MLLex2)	Abandon treatment
2	8.2	M	22.58×10^9/L	PGR	M1	M1	82% (+)	*MLL*-PTD (ex5/MLLex2)	CR for 10 years
3	3.3	M	4.67×10^9/L	PGR	M2	M1	86% (+)	*MLL*-PTD (ex5/MLLex2)	CR for 9 years
4	5.2	M	3.5×10^9/L	PGR	M1	M1	80% (+)	*MLL*-PTD (ex5,6/MLLex2)	CR for 11 years

M1: bone marrow blast <5%; M2: bone marrow blast of 5–25%. "+" means positive. ALL, acute lymphoblastic leukemia; WBC, white blood cell; BM, bone marrow; M, male; PGR, prednisone good response; PTD, partial tandem duplications; CR, complete remission.

that he had B-ALL and CD10 was positive. *ETV6-RUNX1* were positive with 86% by FISH analysis, and no *MLL* was found, but RT-PCR confirmed exon 5–2 of *MLL* was fused. The patient received induction chemotherapy with Guangdong-2008-ALL regimen. He exhibited PGR on day 8, BM FC showed little B-ALL residue on day 15 (6% of lymphoblasts), and MRD was negative on day 33. Consolidation chemotherapy was well tolerated and there was no acute reaction. He was in remission during a 9-year follow-up and is still in remission.

Case 4

Case 4, a 5-year-old male patient hospitalized due to swelling and pain in the right wrist for 2 weeks on October 21, 2010. Routine blood examinations showed that WBC 3.5×10^9/L, Hb 88 g/L, PLT 124×10^9/L. BM cytology indicated that blast cells accounted for 98%. Cytogenetic analysis showed a normal male karyotype; FISH analysis showed *ETV6-RUNX1* was positive, *MLL* aberration was negative, and CD10 was positive. Nonetheless, RT-PCR showed an *MLL* exon 5, 6–2 fusion. The patient was treated with Guangdong-2008-ALL protocol for induction chemotherapy. He exhibited PGR on day 8, and BM FC performed on day 15 showed MRD (4% lymphoblasts) and on day 33 was negative for MRD. To date, he has been in CR for 11 years since diagnosis. *Table 1* shows the patients' characteristics.

Literature review

Using the keywords "*ETV6-RUNX1*", "*MLL*", "children" and "acute lymphoblastic leukemia", a literature search of coexistence of *ETV6-RUNX1* and *MLL* aberration was performed in the database of PubMed, and 4 articles were retrieved finally [Attarbaschi *et al.* (7), 2007; Amare Kadam *et al.* (8), 2008; Matthew C. Hiemenz *et al.* (9), 2011; Gagnon *et al.* (10)]. Among the 4 reports, the patient age range was from 2 to 7 years, including 9 males and 7 females and the WBC count was $(2.66–68.6)\times10^9$/L. When it comes to fusion genes, they all had *ETV6/RUNX1*-positive (39–94% of cells). Among them, 8 *ETV6/RUNX1*-positive cases exhibited *MLL* deletion, and 2 cases had der(21) duplication.

Attarbaschi *et al.* (7) reported that 7 cases of concurrent *ETV6-RUNX1* and *MLL* aberration (case 1 to case 7 in *Table 2*) among a cohort of 824 B-ALL between 22 September 1986 and 31 May 2005 in 4 center trials of Berlin-Frankfurt-Münster (BFM) group, and the frequency of coexistence of *ETV6-RUNX1* and *MLL* aberration was 0.8% (7/824). The 8-year RFS and OS were 86%±13% and 100% for the 7 cases, respectively.

Amare Kadam *et al.* (8) reported 7 cases (case 8 to case 14 in *Table 2*) among 428 childhood B-cell precursor ALL (BCP-ALL) patients (including 76 *ETV6/RUNX1*-positive cases) who were treated at their center from 2000 to 2006, and the frequency of coexistence of *ETV6-RUNX1* and *MLL* aberration was 1.6% (7/426). The 3-year event-free survival (EFS) and overall survival (OS) were both 85.7%.

Hiemenz *et al.* (9) described a 3-year-old male who presented with 3 days of fever, pallor, and lymphadenopathy. Laboratory examination revealed Hb of 77 g/L, PLT of 60×10^9/L, and normal WBC of 10.7×10^9/L, but with 41% blasts of variable cell size. FC on BM revealed findings consistent with a B-ALL. Cytogenetic analysis showed

Table 2 Clinical and laboratory features of the patients with coexistence of ETV6-RUNX1 and MLL aberration among pediatric ALL cases from a literature review

Case	Age (years)	Gender	WBC	Prednisone response	BM blasts on day +15	BM blasts on day +33	Fusion gene		Outcome (time since diagnosis)
							ETV6/RUNX1	MLL	
1	5	F	25×10^9/L	PGR	M2	M1	83% (+)	MLL deletion	Relapse in ovary (4.13 yr)
2	2	F	29×10^9/L	PGR	M1	M1	75% (+)	MLL deletion	Secondary AML (4.5 yr)
3	4	F	15×10^9/L	PGR	M1	M1	83% (+)	MLL deletion	CR (8 yr)
4	7	F	7×10^9/L	PGR	M2	M1	80% (+)	MLL deletion	CR (8 yr)
5	3	M	5×10^9/L	PGR	M2	M1	75% (+)	MLL deletion	CR (8 yr)
6	5	M	10.1×10^9/L	PGR	M2	M1	92% (+)	MLL deletion	CR (8 yr)
7	2	M	13.5×10^9/L	PGR	M1	M1	86% (+)	MLL deletion	CR (8 yr)
8	5	M	13.3×10^9/L	PGR	M1	M1	75% (+)	MLL deletion	CR (1 yr 3 mo)
9	4	M	17.9×10^9/L	PGR	M1	M1	39% (+)	Southern-positive MLL aberration	CR (6 yr 8 mo)
10	7	M	2.6×10^9/L	PGR	M2	M1	79% (+)	27% monoallelic loss	CR (10 mo)
11	2	M	8×10^9/L	PGR	M1	M1	72% (+)	41% monoallelic loss	Induction death
12	3	M	2.5×10^9/L	PGR	M1	M1	70% (+)	26% monoallelic loss	CR (2 yr 4 mo)
13	4	F	4.9×10^9/L	PGR	M1	M1	90% (+)	66% monoallelic loss	CR (3 yr 5 mo)
14	4	F	68.6×10^9/L	PGR	M1	M1	94% (+)	15% monoallelic loss	CR (2 yr 5 mo)
15	3	M	10.7×10^9/L	PGR	M1	M1	58% (+)	Southern-positive MLL aberration	CR (6 mo)
16	3	F	10.95×10^9/L	PGR	M1	M1	42% (+)	AF9	CR (3 mo)

ALL, acute lymphoblastic leukemia; WBC, white blood cell; BM, bone marrow; F, female; M, male; PGR, prednisone good response; yr, years; mo, months; AML, acute myeloid leukemia; CR, complete remission.

a normal male karyotype; FISH studies showed (12;21)(p13;q22)/*ETV6-RUNX1* in 58% of the interphase nuclei and a small clonal population (3% of the cells) with an *MLL* rearrangement.

Gagnon *et al.* (10) described a 3-year-old female patient with ALL for whom complete blood count revealed significant cytopenia with a Hb level of 18 g/L and total WBC count of 10.95×10^9/L. FISH studies using a dual color fusion probe for *MLL-AF9* were performed and revealed *MLL-AF9* fusion signals in 40% of interphase nuclei and in 2 metaphase cells. Additional abnormalities were also observed including an *ETV6-RUNX1* fusion in 42% of nuclei.

Discussion

In general, *ETV6-RUNX1* and *MLL* aberration are considered disease-initiating primary genetic lesions in B-ALL with prevailing mutual exclusivity. However, we found that the frequency of coexistence of the 2 fusion genes in our hospital was 0.98%, which was consistent with Attarbaschi *et al.*'s report (7) (0.8%), but was lower than reported by Amare Kadam *et al.* (8) (1.6%). Our exploration of the reason revealed that it was not only due to different

sample sizes, but also the respective screening approaches. The detection of *MLL* cases relies on the diagnostic procedures used in studies, because traditional cytogenetics or *MLL* FISH technology (which will show typical *MLL* translocations) would confirm them, whereas examining *ETV6-RUNX1* with RT-PCR or FISH alone would miss those (11). Our study showed that children who showed co-expression of fusion gene were *MLL* aberration-negative for FISH, but *MLL*-partial tandem duplications (PTD) was detected by RT-PCR.

The *MLL* dichromatic break aberration/separation aberration probe used in this study can only detect all translocation aberrations of 11q23 *MLL* gene, and cannot be used for detection of other aberration types such as deletion, inversion, and repetition. Conversely, RT-PCR can quickly and accurately detect multiple fusion genes, detect the fusion gene type formed by chromosome translocation in *MLL* gene aberration, PTD, and detect the coexistence of many fusion genes at the same time, which is a feasible method to detect *MLL* gene aberration (12). Thereby, we suggest that the joint detection of fusion genes by the 3 methods should be recommended.

Considering the coexistence of 2 recurrent genetic abnormalities, the clinical course of these cases is expected to be poor because the clinical outcome of ALL patients with *MLL* aberration is poor (13-15). However, combining the cases in our study and those reported in the literature, the 20 patients revealed favorable clinical and laboratory features at diagnosis. The association between these patients is that they were all between age 2 to 8 years, with low WBC and PGR on day 8, day 15, and day 33, with a similar favorable EFS and OS rate. This result of coexistence of the 2 fusion genes seemed to be related to *ETV6-RUNX1* rather than *MLL* aberration, which indicated that *ETV6-RUNX1* was dominant, whereas *MLL* aberration was inhibited. Based on the current data, we suggest that the interaction and expression of *ETV6-RUNX1* protein with various cellular signaling pathways may affect pharmacological reaction, but have nothing to do with any minor events of *MLL*. The interaction between *ETV6-RUNX1* protein products and abnormal *MLL* and its effect on cell environment, and if *MLL* plays a cancer inhibitory role due to allele deletion in *ETV6-RUNX1* positive environment warrants further study (16). Another possible explanation for the good outcome of coexistence of *ETV6-RUNX1* and *MLL* aberration is that *MLL* aberration merely represents a highly specific nonrandom secondary genetic abnormality that should always provide an alert to the potential presence of an *ETV6/RUNX1*-associated pathology that is rarely identified with conventional cytogenetic means only. In contrast to the previous study, Gagnon *et al.* (10) used whole genome sequencing to elucidate and characterize this case of coexistence, and they revealed that the apparent fusion between *MLL* and *AF9* by FISH was not predicted to result in a bona fide *MLL-AF9* fusion and would not be expected to alter the intrinsic *MLL* regulatory mechanisms and confer leukemogenic potential, whereas it would be expected to result in a lack of protein production from this allele.

The biggest difference between our study and the previous literature was that in the previous literature, *MLL* aberration involved *MLL* deletion, southern-positive *MLL* aberration, and monoallelic loss, but our study showed that 4 *ETV6/RUNX1*-positive cases had *MLL*-PTD. *MLL*-PTD is one of the common forms of *MLL* gene aberration, which is the product of partial insertion of the 5' end of the *MLL* gene into the genome and self-fusion (17). It has been reported that *MLL*-PTD positive patients easily relapse after the first CR, the survival time is short, and the prognosis is very poor (18,19). *MLL*-PTD can be detected in peripheral blood, BM, and umbilical cord blood of healthy individuals, which indicates that *MLL*-PLD is not a decisive factor in the occurrence of *MLL*-PTD-related leukemia, and may provide a genetic background for subsequent changes in key genes of ALL (20). In our study, 3 patients who exhibited coexistence of *ETV6-RUNX1* and *MLL* aberration achieved CR and had a long-term EFS, which is inconsistent with the previous studies (7-10).

Conclusions

We believe that the results of our analysis primarily provide compelling evidence that cases with an *MLL*-PTD or other types of *MLL* aberration comprise a distinct subentity among *ETV6-RUNX1* B-ALL. Therefore, this finding also indicates a simple explanation for their good clinical characteristics and good prognosis.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-142/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-142/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patients' parents/legal guardians for publication of these case reports. A copy of the written consent is available for review by the editorial office of this journal. The study protocol and informed consent form were approved by the Ethics Committee of Sun Yat-Sen Memorial Hospital (No. SYSKY-2022-333-01).

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