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A Pediatric Acute Promyelocytic Leukemia With a Rare Karyotype of $ider(17)(q10)t(15;17)$ and Favorable Outcome

A Case Report

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Abstract: Acute promyelocytic leukemia (APL) is a specific malignant hematological disorder with a diagnostic hallmark of chromosome translocation $t(15;17)(q22;q21)$. As a very rare secondary cytogenetic aberration in pediatric APL, $ider(17)(q10)t(15;17)$ was suggested to be a poor prognostic factor based on previous case reports.

Here, we report a pediatric APL case with a rare karyotype of $ider(17)(q10)t(15;17)$. Bone marrow aspiration, immunophenotyping, molecular biology, cytogenetic, and fluorescence in situ hybridization (FISH) analyses were performed at initial diagnosis and during the treatment.

A 6-year-old boy was brought to our hospital with the chief complaint of bleeding gums twice and intermittent fever for 3 days in January 2013. He was diagnosed as low-risk APL according to the 2012 NCCN guideline on APL, with the expression of PML-RARA (bcr3 subtype) and the karyotype of $46,XY, der(15)t(15;17)(q22;q21), ider(17)(q10)t(15;17)$, which was further verified by FISH. The patient was treated through combination all-trans retinoic acid (ATRA) and arsenic with daunorubicin according to the 2012 NCCN guideline for APL. Continuous hematological completed remission (HCR) and major

molecular remission (MMR) were achieved with normal karyotype for >28 months after induction chemotherapy.

Different from previously reported cases, this pediatric APL patient with $ider(17)(q10)t(15;17)$ displays favorable clinical outcomes, which might be related to the low-risk classification and arsenic treatment during the treatment. It suggests that $ider(17)(q10)t(15;17)$ may not be the sole determinant for worse outcomes in pediatric APL and implies that more contributed factors should be considered for pediatric APL prognosis.

(*Medicine* 94(41):e1778)

Abbreviations: APL = acute promyelocytic leukemia, ATRA = all-trans retinoic acid, CR = completed remission, FISH = fluorescence in situ hybridization, HCR = hematological completed remission, MMR = major molecular remission, MRD = minimal residual disease, NCCN = national comprehensive cancer network, RT-qPCR = real time quantitative polymerase chain reaction.

Editor: Martin Staeger.

Received: May 26, 2015; revised: August 18, 2015; accepted: September 14, 2015.

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This research was supported by grants-in-aid from the National Young Scientist's Programs of China (No. 81100356, 81202093, 81201552).

The authors have no conflicts of interest to disclose.

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DOI: 10.1097/MD.0000000000001778

INTRODUCTION

The fusion gene PML-RARA generated from chromosome translocation $t(15;17)(q22;q21)$ has been identified as a distinguished marker for acute promyelocytic leukemia (APL).¹ Classic cytogenetics combined with fluorescence in situ hybridization (FISH) indicates 90% of typical $t(15;17)$ and some rare case of atypical translocations such as $t(5;17)$, $t(11;17)$, and $dup(17)(q21q23)$ in APL.² In the past decades, owing to the utilization of all-trans-retinoic acid (ATRA) in combination with arsenic and other chemotherapies, APL has been one of most curable leukemia types.^{3–5} As high as 95% of newly diagnosed APL patients with the PML-RARA fusion gene could achieve completed remission (CR) after the treatments, in which ~80% reaches long-term event-free survival. However, a small population of APL patients still show poor outcomes after post-remission chemotherapy, which may be attributed to some featured genetic abnormalities as well as changes in treatment response, relapse, and clinical pathological characters.^{6–9}

The $ider(17)(q10)t(15;17)(q22;q12)$ ^{6,10–15} is one of the rare secondary genetic abnormalities in APL. To the best of our knowledge, only 4 pediatric APL cases with $ider(17)(q10)t(15;17)(q22;q12)$ were reported in the literature and all of them died in 1 to 21 months after diagnosis.^{16–19} These data suggest that $ider(17)(q10)t(15;17)(q22;q12)$ is likely to be a poor prognostic marker for pediatric APL. Different from previous reports, we first report a pediatric APL case with the rare karyotype of $ider(17)(q10)t(15;17)$, which still remains CR for 28 months until now.

MATERIALS AND METHODS

Case Report

A 6-year-old boy was brought to our hospital with the chief complaint of bleeding gums twice and intermittent fever for 3 days in January 2013. He had a fever of 38.2 Celsius, multiple cervical lymphadenopathy, scattered bleeder in both lower limbs and enlarged liver at 2 cm of the subcostal. No special contact, allergies, medicine, or family history were present. No more positive signs were found. The initial blood count showed pancytopenia (Hb, 95 g/L; red blood cell count, $3.18 \times 10^{12}/L$; platelet count, $57 \times 10^9/L$; and white blood cell count, $2.23 \times 10^9/L$). The bone marrow morphology displayed a hypercellular marrow with increased abnormal promyelocytes, which were variable in the cell size and nucleolus, rich in cytoplasm and varying granules, and visible of round or oval, distorted, folded nucleus, accounting for 87.5% of all nucleated cells. Bone marrow specimens were also positive for myeloperoxidase and nonspecific esterase staining (Fig. 1). Flow cytometry analysis (Fig. 2) with the bone marrow showed that ~91.5% of blasts were strongly positive for CD9, CD13, CD15, CD33, CD45, CD64, CD123, Myeloperoxidase, with partial expression of CD38, CD117, HLA-DR, CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11b, CD14, CD16, CD19, CD20, CD22, and CD34, whereas CD56, CD71, GlyA, cCD79a, cCD3, TdT were negative (Tables 1 and 2). Cytogenetic studies showed a karyotype of 46,XY, der(15)t(15;17)(q22;q21), ider(17)(q10)t(15;17) according to ISCN2009²⁰ (Fig. 3A and B). Fluorescence in situ hybridization (FISH) with Vysis LSI PML/RAR α dual color, dual fusion translocation probe (Abbott Molecular, IL) revealed nuc ish (nuclear in situ hybridization) (PML \times 4)(RARA \times 4)(PML con RARA \times 3)[400] (Fig. 3C and D). The fusion PML-RARA gene in this patient was further characterized as bcr3 subtype by real-time quantitative polymerase chain reaction (RT-qPCR). Therefore, the patient was diagnosed as APL according to bone marrow morphology, immunophenotyping, cytogenetics, and molecular biology studies. Subsequently, the patient was administrated with induction chemotherapy consisting of ATRA at a dose of 45 mg/m²/d for 33 days, arsenic trioxide 0.15 mg/kg/d for 27 days, and daunorubicin 60 mg/m²/d for 3 days.

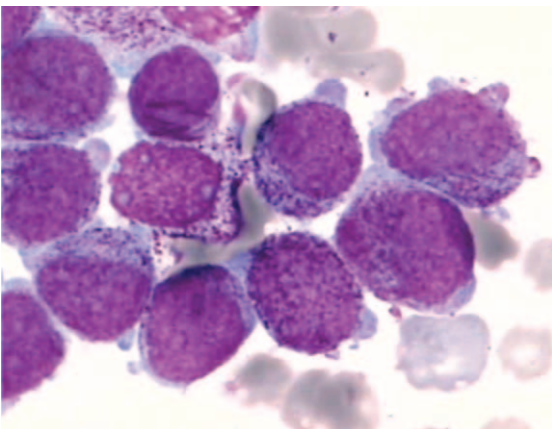


FIGURE 1. Bone marrow morphology at initial diagnosis. Bone marrow aspiration showed a hypercellular marrow with increased abnormal promyelocytes, which were variable in the cell size and nucleolus, rich in cytoplasm and varying granules, and visible of round or oval, distorted, folded nucleus.

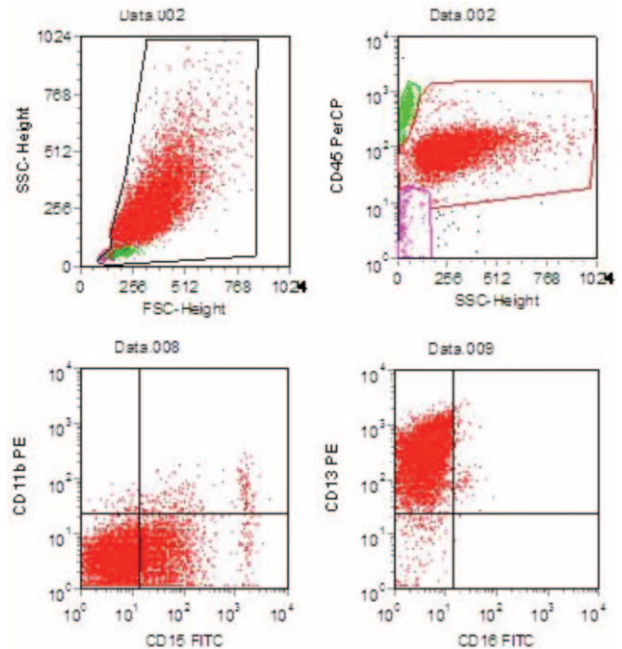


FIGURE 2. Immunophenotyping of bone marrow at initial diagnosis. In the dot plot of CD45/side scatter (SSC), the abnormal APL leukemia cells were continuously distributed from immature to mature granulocytes cells area. The abnormal promyelocytes comprised 91.5% of the nucleated cells and expressed CD9, CD13, CD15, CD33, CD45, CD64, CD123, Myeloperoxidase (MPO), also with partial expression of CD38 and CD117. APL = acute promyelocytic leukemia.

After the induction chemotherapy, the blood cell counts came back to normal levels and bone marrow aspirate showed hematological completed remission (HCR) but not major molecular remission (MMR) with detection out of PML-RARA by RT-qPCR. Then, one cycle of DA regimen (Daunorubicin 60 mg/m²/d, d1-3; cytarabine 200 mg/m²/d, d1-7) and another cycle of DA regimen (Daunorubicin 45 mg/m²/d, d1-3; cytarabine 1 g/m²/12 h, d1-4) were administrated to the patient as the consolidation chemotherapy. After the consolidation therapy, the patient achieved MMR (the PML-RARA was undetectable by RT-qPCR) under HCR. Maintenance chemotherapy was still continued following the consolidation chemotherapy according to the 2012 NCCN guideline for APL. No serious side reactions occurred in the chemotherapy process. During and after the maintenance chemotherapy, this patient was always under persistent MMR and HCR without any clinical symptoms or signs till now.

The patient provided written informed consent for the publication of this case details and the consent procedure was approved by the ethic committee for Drug Clinical Trial of Huazhong University of Science and Technology.

DISCUSSION

The ider(17)(q10)t(15;17) is a derived isochromosomal abnormality on the long arm of chromosome 17 with APL unique reciprocal translocation of t(15;17). It is also a rare cytogenetic abnormality in APL. From January 2013 to December 2014, we detected 12 cases with the karyotype of ider(17)(q10)t(15;17) in 635 APL patients with t(15;17) in our center.

TABLE 1. Comparison Between Previous 4 Reports and Present Study With ider(17)(q10)t(15;17)(q22;q12) Positive APL

	Simmers et al¹⁹	Prigogina et al¹⁸	Chou et al¹⁶	Kim et al¹⁷	Present Case
Sex/age (year)	M/15	F/10	M/17	M/13	M/6
WBC ($\times 10^9/L$)	NA	NA	4.04	1.67	2.23
Morphology	NA	NA	Hypogranular type	Hypergranular type	Hypergranular type
Karyotype	46,XY,der(15)t(15;17)(q22;q21),ider(17)(q10)t(15;17)	46,XX,t(15;17)(q22;q21)/47,idem,+8/47,XX,+8,der(15)t(15;17)(q22;q21),ider(17)(q10)t(15;17)	ider(17)(q10)t(15;17)(q22;q21)	47,XY,+8,der(15)t(15;17)(q22;q21),ider(17)(q10)t(15;17)	46,XY,der(15)t(15;17)(q22;q21),ider(17)(q10)t(15;17)
Immunophenotyping	NA	NA	NA	CD45+, CD13+, CD33+, CD117+, HLA-DR-, CD7-, CD10-, CD14-, CD34-, CD41-, CD56-, TdT-	CD45+, CD9+, CD13+, CD15+, CD33+, CD64+, CD123+, MPO+, CD38p+, CD117p+, HLA-DR-CD7-, CD10-, CD14-, CD34-, CD41-, CD56-, TdT- (details seen in Table 2)
PML-RARA rearrangement	NA	NA	Positive (FISH, RT-qPCR)	Positive (FISH, RT-qPCR)	Positive (FISH, RT-qPCR)
HCR (month)	Y	N	12	15	28
MMR (month)	NA	NA	NA	NA	28
Relapse	Y	N	Y	Y	N
Survival (month)	21 (dead)	< 1 (dead)	13 (dead)	16 (dead)	29 (alive)
ATRA therapy	No	No	Yes	Yes	Yes

APL = acute promyelocytic leukemia, ATRA = all-trans retinoic acid, FISH = fluorescence in situ hybridization, HCR = hematological completed remission, MMR = major molecular remission, NA = not available, RT-qPCR = real time quantitative polymerase chain reaction, WBC = white blood cell.

TABLE 2. The Percentages of the Detected Antigens in this Patient by Flow Cytometry

Antigens	Percentages in Blast (%)	Antigens	Percentages in Blast (%)
HLA-DR	0.50	CD20	Negative
CD2	Negative	CD22	Negative
CD3	Negative	CD33	96.02
CD4	Negative	CD34	0.39
CD5	Negative	CD38	12.76
CD7	Negative	CD56	Negative
CD8	Negative	CD64	45.29
CD9	96.34	CD71	Negative
CD10	Negative	CD117	18.34
CD11b	3.29	CD123	84.68
CD13	97.45	MPO	92.32
CD14	Negative	cCD79a	Negative
CD15	20.79	TdT	Negative
CD16	Negative	cCD3	Negative
CD19	Negative		

They are at the average age of 29.6 years (from 6 to 75 years old). The incidence of *ider(17)(q10)t(15;17)* in our center is 1.89%, which is consistent with previous report.⁶ Although previous studies^{11,21} reported that the *ider(17q)(q10)t(15;17)* had a slightly higher frequency in APL patients with

PML-RARA *bcr1* subtype, which might be related to delayed CR and lower sensitivity to ATRA treatment, we found no significant correlation between *ider(17)(q10)t(15;17)* and 3 isoforms of PML-RARA gene (*bcr1*, *bcr2* and *bcr3* subtypes) in our center, which may be caused by the rarity of *ider(17)(q10)t(15;17)* since we only have 12 *ider(17)(q10)t(15;17)* positive cases until now.

To the best of our knowledge, only 4 pediatric APL cases with the *ider(17q)(q10)t(15;17)* have been reported in the literature so far.²¹⁻²³ The role of the *ider(17q)(q10)t(15;17)* in APL is still an ongoing investigation and all of the previous studies considered it as a poor prognosis maker for APL especially in pediatric APL patients.^{2,6,10,17,21} As shown in Table 1, no matter the variable clinical and laboratory features as well as different treatments, 1 of the 4 reported pediatric patients did not achieve CR at all and died in the first month from the initial diagnosis, whereas the remained 3 cases relapsed and died within 13 to 21 survival months.¹⁶⁻¹⁹ Interestingly, Hu and colleagues²¹ showed that the *ider(17)(q10)t(15;17)* had a proliferation and growth advantage, which might be mediated by loss of a tumor suppressor TP53 allele. However, no drug-sensitive analysis has been performed in the *ider(17)(q10)t(15;17)* positive clones and the detailed role of TP53 copy number variation in these clones is still mysterious. The sensitivity of these clones containing the *ider(17)(q10)t(15;17)* to ATRA, arsenic trioxide and other chemotherapy drugs is still unknown and need further studies.

Interestingly, the case we presented here displayed encouraging clinical outcomes until now. He was treated with

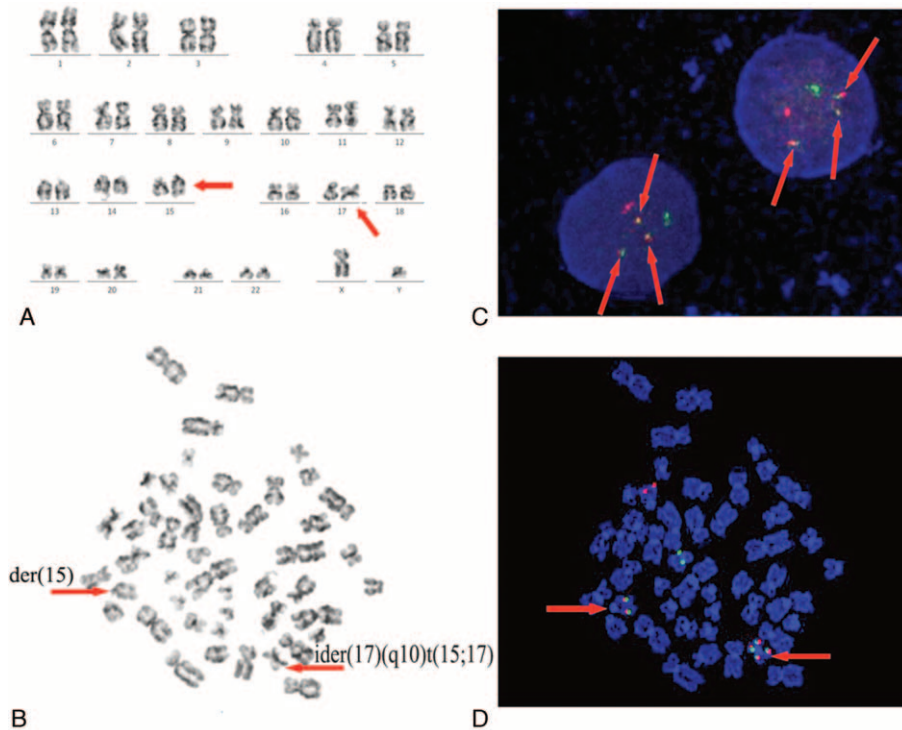


FIGURE 3. Karyotype and FISH analysis at initial diagnosis. A: the karyotyping from 20 bone marrow metaphase cells showed 46,XY,der(15)t(15;17)(q22;q21),ider(17)(q10)t(15;17). The arrows indicate abnormal chromosomes. B: one of the metaphase karyograms of the bone marrow cells at initial diagnosis. The arrows indicate der(15) and *ider(17)(q10)t(15;17)*. C: the FISH study using an LSI PML-RARA dual-color, dual-fusion translocation probe (Abbott Molecular/Vysis) at diagnosis. The arrows indicate positive PML-RARA fusion signals (3 fusion signals in a cell). D: karyotyping and PML-RARA FISH analysis in the same metaphase cell. FISH = fluorescence in situ hybridization.

both ATRA and arsenic and achieved HCR after induction therapy and MMR after consolidation therapy. After consolidation chemotherapy, this patient was still under continuous HCR and MMR for >28 months until now by detection of MRD every 3 months. Besides, no serious complications and side effects (such as the ATRA syndrome) of chemotherapeutic agents occurred during and after serials of therapies. This is the first case report of pediatric APL with *ider(17)(q10)t(15;17)* showing favorable outcomes after chemotherapy. It suggests that the *ider(17)(q10)t(15;17)* may not be the sole determinants for worse outcomes in pediatric APL and more contributed factors need to be considered for pediatric APL prognosis.

As an inference, we think the encouraging clinical outcomes from this case may be attributed to 2 important factors. First, this patient was classified in the low-risk group at the initial diagnosis stage according to the 2012 NCCN guideline for APL. The risk classification is very important for APL, especially pediatric APL, and it correlates very well with the therapeutic effects, clinical outcomes, and relapse. Basically, low-risk classification means better response to treatment and less relapse. Second, we think the patient may also benefit from the early usage of arsenic trioxide. As one of the most famous Chinese traditional medicaments, arsenic trioxide has been shown powerful therapeutic effects in APL and has been the standard treatment for APL patients in both induction and maintenance chemotherapies. Combination of ATRA and arsenic also has synergistic effects in APL patients during induction therapy due to their different pharmacology targets (ATRA targets RAR α and arsenic targets PML).^{24,25} For the 4 previously reported pediatric APL cases with the *ider(17)(q10)t(15;17)*, 2 of them^{18,19} were reported in 1986 and 1987, which were before the starting of ATRA treatment in 1988. The remaining 2 cases also did not involve the combination of ATRA and arsenic in the induction chemotherapy.^{16,17} Therefore, we infer that the patient reported here may benefit from the combination of ATRA and arsenic in the induction chemotherapy. However, more case reports and systematic analysis are needed to study the role of ATRA and arsenic in the treatment of pediatric APL patients with the *ider(17)(q10)t(15;17)*.

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