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LETTER TO THE EDITOR

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CASE REPORT

Pediatric acute myeloid leukemia patients with i(17)(q10) mimicking acute promyelocytic leukemia: Two case reports

Hong-Xia Yan, Wei-Hua Zhang, Jin-Quan Wen, Yan-He Liu, Bao-Juan Zhang, A-Duo Ji

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Abstract

BACKGROUND

Chromosome i(17)(q10) abnormality is mainly associated with chronic myeloid leukemia (CML), myelodysplastic syndrome/myeloproliferative tumors (MDS/MPD), and acute myeloid leukemia (AML). The role of i(17)(q10) in AML is still unknown, the differences between AML and acute promyelocytic leukemia (APL)-like AML with i(17)(q10) need more research. This study aimed to investigate the clinical characteristics and laboratory evidence of 2 AML cases with i(17)(q10), similar to APL phenotype.

CASE SUMMARY

Both pediatric patients were males; case 1 had newly diagnosed AML, and case 2 showed relapsed tumor after 1 year of drug withdrawal. Bone marrow cell morphology, chromosome karyotype analysis, Fully-instrumented submersible housing test, immunological assays, molecular biological methods, and blood tumor panoramic gene test were performed. All-trans retinoic acid (ATRA) combined with arsenic acid (As2O3) were used in the first course of treatment. Bone marrow was dominated by abnormal promyelocytic granulocytes. Karyotype test revealed i(17)(q10) isochromosome. Immunological phenotype mainly included positive expressions of CD9, CD13, CD33, and CD38. Case 1 suffered intracranial hemorrhage after re-chemotherapy and died on D162. For case 2, on D145 and D265, bone marrow promyelocytic granulocytes accounted for 2%. Flow cytometric residual lesion detection showed no abnormal immuno-

phenotype cells. The copy number of WT1 gene in two cases were 1087 and 1010, respectively, and the expression rates were 55.29% and 59.5%, respectively.

CONCLUSION
ATRA, As2O3, and chemotherapy may be ineffective in treating APL-like AML with i(17)(q10) but without t(15;17) and PML-RARA fusion gene.

Key Words: Chromosome; i(17)(q10); Gene mutations; Acute promyelocytic leukemia; Acute myeloid leukemia; Case report

Core Tip: Herein we reported two cases of acute myeloid leukemia (AML) mimicking APL after the same treatment protocols. A rare chromosomal abnormality, i(17)(q10), was observed in two pediatric patients, which mimicked acute promyelocytic leukemia (APL) phenotype. Both patients showed no responses to all-trans retinoic acid and arsenic trioxide induction therapy. One patient with i(17)(q10) died after 5 mo, and the other patient with i(17)(q10) add (14)14 had been medication free more than 10 mo and achieved complete tumor remission for 3 years since drugs were withdrawn. Pediatric AML mimicking APL is difficult to treat and additional cases should be studied to provide better treatment strategies for these patients.

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INTRODUCTION

Chromosome i(17)(q10) abnormality is described as any unreasonable damage or breakage of the centromeres of chromosome 17, resulting in absence of the short arm and an iso-arm of the long arm[1]. Isochromosome 17 i(17)(q10) is mainly associated with chronic myeloid leukemia (CML)[2,3], myelodysplastic syndrome/myeloproliferative tumors (MDS/MPD)[4-6], and acute myeloid leukemia (AML)[6,7]. Genetic mutation analysis showed that 95% of patients with chromosome karyotype i(17)(q10) carried at least one mutation, and on average three mutations. The three most commonly mutated genes were *ASXL1*(66%), *SRSF2*(65%), and *SETBP1* (48%)[8,9]. In acute promyelocytic leukemia (APL), chromosome karyotype i(17)(q10) was often accompanied by t(15;17) and PML-RARa fusion gene with an incidence of 1.9% and 4.1%, respectively[10,11]. APL children with i(17)(q10) have poor prognosis [12]. In a group study of 478 children with AML, chromosome karyotype analysis showed only one i(17)(q10) abnormality case, without morphological description and prognostic evaluation[13]. A 10-year-old African Black APL child carrying i(17)(q10) karyotype but without t(15;17) abnormality, who was in serious condition at admission, did not get tumor remission after treatment, and died within 2 wk[14]. A Chinese i(17)(q10) AML adult with a similar phenotype to APL was reported[15]. In the present case study, we treated 1 AML child with i(17)(q10) and 1 AML child with i(17)(q10) and (14)(p11) who had a phenotype similar to APL in our department. These two cases were investigated and followed up, and their clinical significance was discussed.

CASE PRESENTATION

Chief complaints

Case 1: A 3-year-old boy of Han nationality, was admitted to the Pediatric Hematology Department of Xianyang Caihong Hospital, China on December 19, 2016. The boy had paleness and fever for more than half a month, as well as exophthalmos and pain in the right knee joint due to unknown reasons for two weeks.

Case 2: A 12-year-old Han boy was admitted to our hospital with a history of a pale complexion for one month and skin bleeding for 10 d.

History of present illness

Case 1: He had a fever of 38.2 °C, moderate anemia, scattered red bleeding spots on the skin, protruded eyeballs, and no swelling of the superficial lymph nodes.Initial blood tests showed the following: Hb 75 g/L, white blood cell (WBC) count 5.82 × 10^9/L, and platelet (PLT) count 73 × 10^9/L.

Case 2: He had moderate anemia and bleeding spots on the skin and mucosa throughout the body. Initial blood test results showed the following: Hb 68 g/L, WBC count 17.53 × 10^9/L, and PLT count 60 × 10^9/L.

History of past illness

Case 1: There is no history of past illness.

Case 2: He was diagnosed with APL 3 years ago in a local hospital based on bone marrow morphology and immunological classification, with negative PML-RARa fusion gene at the time of diagnosis.The patient received all-trans retinoic acid (ARAT) and arsenic trioxide (ATO) as induction therapy, and bone marrow examination showed no tumor remission on D29. He then received three cycles of consolidation therapy (DA, HA, and MA regimen) and maintenance therapy, bone marrow evaluation showed complete remission, and the treatment was stopped.

Personal and family history

Case 1: He had been in good health condition, with no family history of inherited blood disorder, no history of tumor-associated genetic abnormalities, and no history of drug or food allergies.

Case 2: There is no personal and family history.

Physical examination

Case 1: Upon examination, he had a fever of 38.2 °C, moderate anemia, scattered red bleeding spots on the skin, protruded eyeballs, and no swelling of the superficial lymph nodes. On auscultation, his heart and lung were normal, and the liver and spleen were not examined.

Case 2: He had moderate anemia and bleeding spots on the skin and mucosa throughout the body. Auscultation of the heart and lung showed no abnormalities. Subcostal areas of the liver and spleen were not examined.

Laboratory examinations

A volume of 0.1 mL bone marrow fluid was extracted from the posterior superior iliac spine (sampling was very difficult), a bone marrow smear was prepared and submitted for examination. Chromosome G-banding karyotype analysis: 3 mL of sterile bone marrow fluid was taken from the patient, and g-banding technique was employed to detect the chromosomes in trypsin-digested short-term cell culture. Karyotype results were analyzed according to the international system for human cytogenetic nomenclature (ISCN, 1991).

Immunophenotype: 2 mL of bone marrow fluid with heparin anticoagulant was obtained, 5x10^5-5×10^6/mL cells were isolated using FACSort flow cytometry (BD Biosciences) and analyzed with CellQuest software > The expression levels of leukemia related antigens in the cell population were analyzed and calculated. Monoclonal antibodies used included HLA-DR, CD2, CD3, CD4, CD7, CD8, CD9, CD11b, CD13, CD14, CD15, CD16, CD19, CD22, CD33, and CD34 Labeled by FITC, PE, and PerCP, or APC-CD38, CD56, CD64, CD71, CD117, CD123, and MPO. All antibodies were purchased from BD Biosciences.

PML-RARa fusion gene was detected by real-time quantitative PCR: A volume of 2 mL bone marrow fluid with heparin anticoagulant was collected to isolate the mononuclear cells, and total DNA of mononuclear cells was extracted.

Imaging examinations

There is no imaging examinations.

FINAL DIAGNOSIS

Acute promyelocytic leukemia -like acute myeloid leukemia with i(17)(q10).

TREATMENT

Phase I: Two children were treated with ATAR combined with ATO to induce remission: ATAR (30 mg/M2/d), divided 3 times, orally, D1-30; ATO (0.02 mg/Kg), 1 time/day, intravenous infusion, D1-28.

Then they were treated with low molecular weight heparin anticoagulant correction therapy based on the coagulation test. Bone marrow cell morphology and leukocyte residual lesions were detected on D29. Blood WBC count was 27.53 × 10^9/L. Considering the possibility of retinoic acid syndrome, dexamethasone tablets were administered orally at 1.5 mg/time, 3 times a day. With fever regression, WBC was reduced to 12.27 × 10^9/L on D7. Case 2 showed fever on D2 of treatment, with a temperature of 38.5 ℃, and still had a fever on D3. Blood routine test showed a WBC count of 27.53 × 10^9/L. Considering the possibility of the retinoic acid syndrome, dexamethasone tablet was taken 1.5 mg/time, 3 times a day. With fever regression, WBC decreased to 12.27 × 10^9/L in D7.

Phase II: On D33, case 1 was treated with the DAE regimen, which including the following: DNR (40 mg/M2/d), D1, 3 and 5, intravenous infusion, once a day; Ara-c (200mg/M2/d), D 1-7, q12h, subcutaneous injection; and Vp-16 /E (100mg/M2/d), D 5, 6, 7, intravenous infusion, once a day. Reexamination of bone marrow cell morphology on D 65 showed no remission. The pediatric patient gave up treatment and discharged themselves. On D154, he came to the hospital again with fatigue, sallow complexion, skin hemorrhagic spots, bone pain, and eyeball herniation. Bone marrow examination showed 85% abnormal promyelocytic granulocytes. D156 Chemotherapy with MAH protocol: M (10 mg/M2/d), D1, 2 and 3; A (200 mg/M2/d), D1-7, q12h, subcutaneous injection; and H (3 mg/M2/d),D 1-7, subcutaneous injection. Case 2 was treated with the MAH regimen on D 47 and D80. The doses and methods were as above. On D115, he was treated with IDA (10mg/M2/ D1-3); intravenous infusion; once a day. The dosage and usage of the ara-C and H were the same as before. On D145, bone marrow cell morphology was evaluated, residual lesions were detected by flow cytometry, and WT1 gene copy number was detected by molecular biological techniques (See Methods). On D175, he was treated with HD ara-C (2.0 g/M2/d); D1, 3, 5 and 7; q12h. The dose and usage of HD ara-C were the same as above. On D205, HD ara-C dose and usage were the same as above: Vp-16 (100 mg/M2/d), D1-5; intravenous infusion. On D 235, he received HD ara-C (3.0g/M2/d); D1, 3, 5, 7; q12h; the dose and usage were the same as above. During D265-730, 6-MP [50 mg/M2/d (D1-21)] plus low-dose ara-C (40mg/M2) were given. D1-4 (D22-28) maintenance therapy: Bone marrow cell morphology was returned one year after drug discontinuation, residual lesions were detected using flow cytometry, and WT1 gene copy number was detected by molecular biological tools (See methods).

OUTCOME AND FOLLOW-UP

Bone marrow smear: Case 1 showed active bone marrow with nucleated cell hyperplasia. Case 2 originally had granulocyte at 1.0%, and abnormal early young granulocyte at 83.0% and 85.0%, respectively. The cytoplasm was bulky and filled with azure particles. Plasma particles were visible both inside and outside some cells, with less outside the cells. Round or oval nucleus, coarse chromatin, and indistinct nucleoli were observed. Acute promyelocytic leukemia is shown in Figure 1.

Karyotype analysis

The following results were revealed: Case 1: 46XY, i(17)(q10)[9]/46, XY[11], long equi arm of chromosome 17; Cases 2: 46XY, Add(14)(P11), i(17)(q10)[4]/46, XY[1], a short arm of chromosome 14 with an additional fragment of unknown origin and a long arm of chromosome 17, as shown in Figure 2.

Fully-instrumented submersible housing detection

Case 1: The nuclear in situ hybridization (nuc ish) (PML × 2, RARA × 3) (180/400) showed no fusion signal by PML/RARA translocation probe, and the copy number of RARA (located at 17q21) site increased, accounting for about 45%.

Case 2: The nuc ish (PML × 2, RARA × 2) showed no abnormal signal in the PML/RARA locus, and the detection result was negative as shown in Figure 3.

Immune typing

Abnormal cells were accounted for 88% in Case 1 and 78% in Case 2. Flow cytometric analysis on CD45/SSC dot plot showed that CD9, CD13, CD33, and CD38 were mainly expressed in all analyses, while CD64, CD123, and MPO were only expressed in some analyses. CD58 was expressed in case 1 and CD15 was expressed in case 2, as shown in Figure 4. Molecular biological detection: PML/RARa, PLZF/RARa, NPM/RARa, STAT5b/RARa, NuMA1/RARa, PRKARIA/RARa, and FIPIL1/RARa fusion-gene tests showed negative results.

Detection of gene (exon) variation related to myeloid and gonorrhea hematologic malignancies was performed by targeted capture method. Mutation sites were clearly associated with the disease, and all of them had mutations of WT1 (Wilms Tumor 11). Case 1 WT1: NM_024426: exon9:c.G1367C:p.C456s; mutation frequency 49.2%. Case 2 WT1: NM_024426:exon1:c.410_413del:p.137_138del; mutation frequency 100%. Case 1 with EP300 (E1A Binding Protein p300) mutations: NM_001429: exon31:c.C5449T:p.Q1817X; mutation frequency 72.1%.

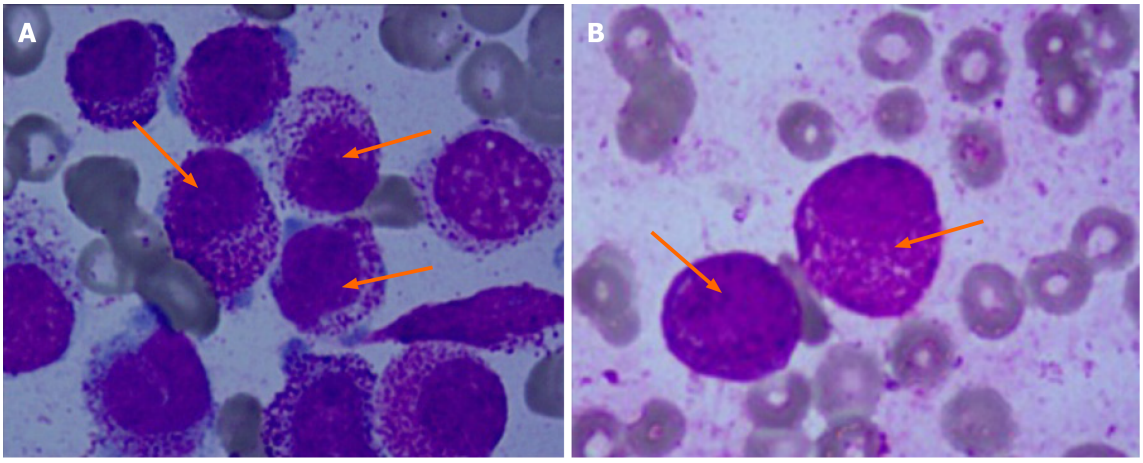

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Figure 1 Morphology of the bone marrow. A: Case 1; B: Case 2.

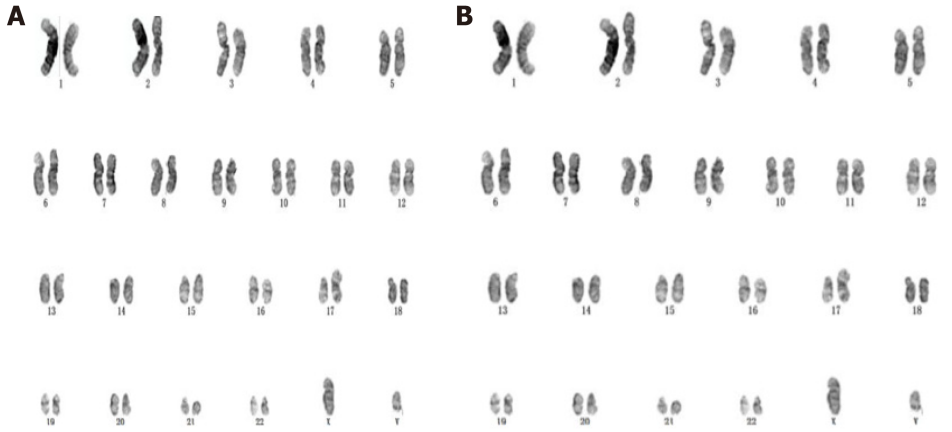

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Figure 2 The karyotype of the bone marrow. A: Case 1; B: Case 2.

For case 1, the following mutation sites might be associated with the disease: (1) USP6 (NM_004505:exon12:c.854delG:p.W285fs) was a frameshift mutation, with a mutation frequency of 32.6%; (2) NUTM2G (NM_001170741:exon7:c.C2102T:p.701L) was a missense mutation, with a mutation frequency of 78.8%.

For case 2, the following mutation sites might be associated with the disease: (1) TAL1 (T-Cell Acute Lymphocytic Leukemia genemutation (NM_003189:exon6:c.821_822insGGGGGGGGG-GGGGG:p.G274fs), with a mutation frequency of 44.2%; (2) TTN mutation in the titin gene (NM_001267550:exon96:c.C27746T:p.T9249M), with a mutation frequency of 53.5%; (3) PHLPP1 (PH Domain And Leucine Rich Repeat Protein Phospatase1) gene mutation (NM_19449:exon1: c.77_78insTCTGG:pA26fs), with a mutation frequency of 35.3%; (4) OR5B12 (Olfactory Receptor Family 5 Subfamily B Member 12) gene mutation (NM_001004733:exon1:c.597delT:p.199fs), with a mutation frequency of 83.5%; (5) DDX11 (DEAD/H-BOX Helicase 11) genemutation (NM_152438: exon7:c.G778A:p.R263Q), with a mutation frequency of 18.8%.

Treatment outcome

Case 1 review of bone marrow on D29 and D65: It was still very difficult to collect bone marrow; myelodysplastic hyperplasia was pronounced; abnormal promyelocytic granulocytes were 33% and 78%, respectively; the treatment was ineffective on D156; MAH regimen was used for chemotherapy; the patient died of intracranial hemorrhage on D162.

Case 2 review of bone marrow on D29: It was still very difficult to obtain bone marrow samples; myelodysplasia decreased and promyelocytic granulocytes accounted for 32%. On repeated examination of bone marrow on D46, D145, D265 to D730, it was still very difficult to obtain bone marrow samples; reduced myelodysplasia was observed; abnormal morphology of promyelocytic granulocytes accounted for 2%; cytoplasm contained a large number of arrocysts; nuclei had lumps and

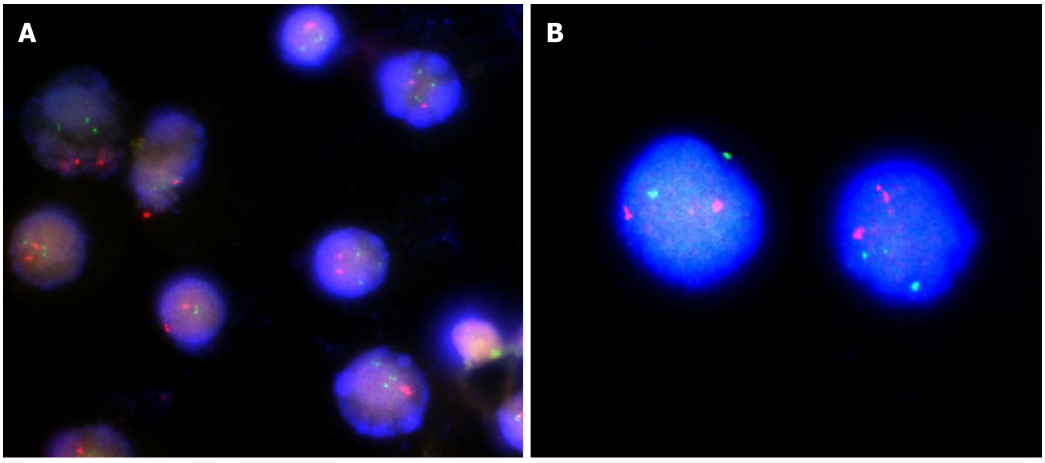

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Figure 3 Fully-instrumented submersible housing images of the bone marrow. A: Case 1; B: Case 2.

no nucleolus. Residual leukemia detection revealed no immunophenotypic abnormal cell population (residual leukemia cells < 10^4); complete remission occurred. Up to now, the drug has been discontinued for 1 year, and the clinical, morphological, and flow cytometry results continued to show complete remission. However, the copy number of the *WT1* gene was 1010-1087, and the expression rate was 51.95%-55.29%, which indicated the risk of recurrence, and allogeneic hematopoietic stem cell transplantation was necessary.

DISCUSSION

APL is a rare subtype of AML and has different morphological and immunological characteristics compared with other myeloid leukemia cells. Karyotype t (15;17) is a unique chromosome translocation in APL. At the molecular level, PML/RARα fusion gene is formed by translocation of PML gene at 15q and RARα gene at 17q.Therefore, it is a highly specific cytogenetic marker for this type of leukemia. In this case study, the phenotype of 2 children showed typical APL characteristics, especially some cells had inner and outer plasma membrane, with thick azinophilus granules (Figure 1). Immunophenotypic markers mainly included CD9, CD13, CD33, CD38 (Figure 2), and CD64, CD123, MPO were also expressed in case 1. In addition, case 1 also had the expression of CD15, which was consistent with the immunophenotype of APL[16,17] and the isolated i(17)(q10) AML with similar APL morphology.

Previously, 4 isolated i(17) (q10) cases were reported, including 2 children[13,14], 1 adult[15], 1 case without age information[18], and 3 cases with M3 (APL) FAB classification. There were no t(15;17) and PML-RARa fusion gene detected and patients had no responses to ATRA treatment[15]. One case did not respond to chemotherapy and the survival time was less than 1 mo[14]. The other 2 cases did not mention prognosis[13,19]. In this study, there were 2 cases examined, case 1 was isolated i(17)(q10), case 2 was isolated i(17)(q10) add(14)(p11). The t(15;17) was not present, and PML-RARa fusion gene was not detected by Fully-instrumented submersible housing and second-generation sequencing, which rendered ATRA and As_2O_3 combined chemotherapy ineffective. Case 1 survived 5.5 mo. Case 2 achieved sustained complete remission after intensive chemotherapy with acute non-eluting regimen. The difference might not be related to isolated i(17)(q10) add(14)(P11), which was speculated to contribute to the transport of chemotherapeutic drugs. Similar studies have not been reported on leukemia patients, and the underlying specific mechanism needs further exploration. However, with the high expression of *WT1* gene, the risk of recurrence is still very high[20]. Further clinical follow-up is required, and hematopoietic stem cell transplantation is necessary. However, this case was different from occult APL and APL with i(17)(q10) and PML-RARa fusion gene, for which the ATRA and As_2O_3 combined chemotherapy was effective[2,18].

Patients with myeloid tumor i(17)(q10) are mostly MDS/MPO+ patients with a chronic history, and often have pathological hematopoiesis in granulocyte, erythrocyte, and megakaryocyte lines, with an average of 3 gene mutations, mainly *ASXL1*, *SRF2*, and *SETP1*[8,9]. In this study, 2 patients had a short course of the disease, with no history of MDS/MPO+, and no erythrocyte or megakaryocyte pathological hematopoiesis except granulocyte lineage, which was similar to a 27-year-old female APL-like AML patient with a short course of the disease, having no chronic history and multi-family pathological hematopoiesis[15].

Gene mutations in these APL-like AML cases were reported for the first time, and there were 5 mutations in case 1, including WT EP300 c.854delg: P w285fs frame-shift mutation and C.C2102T: P

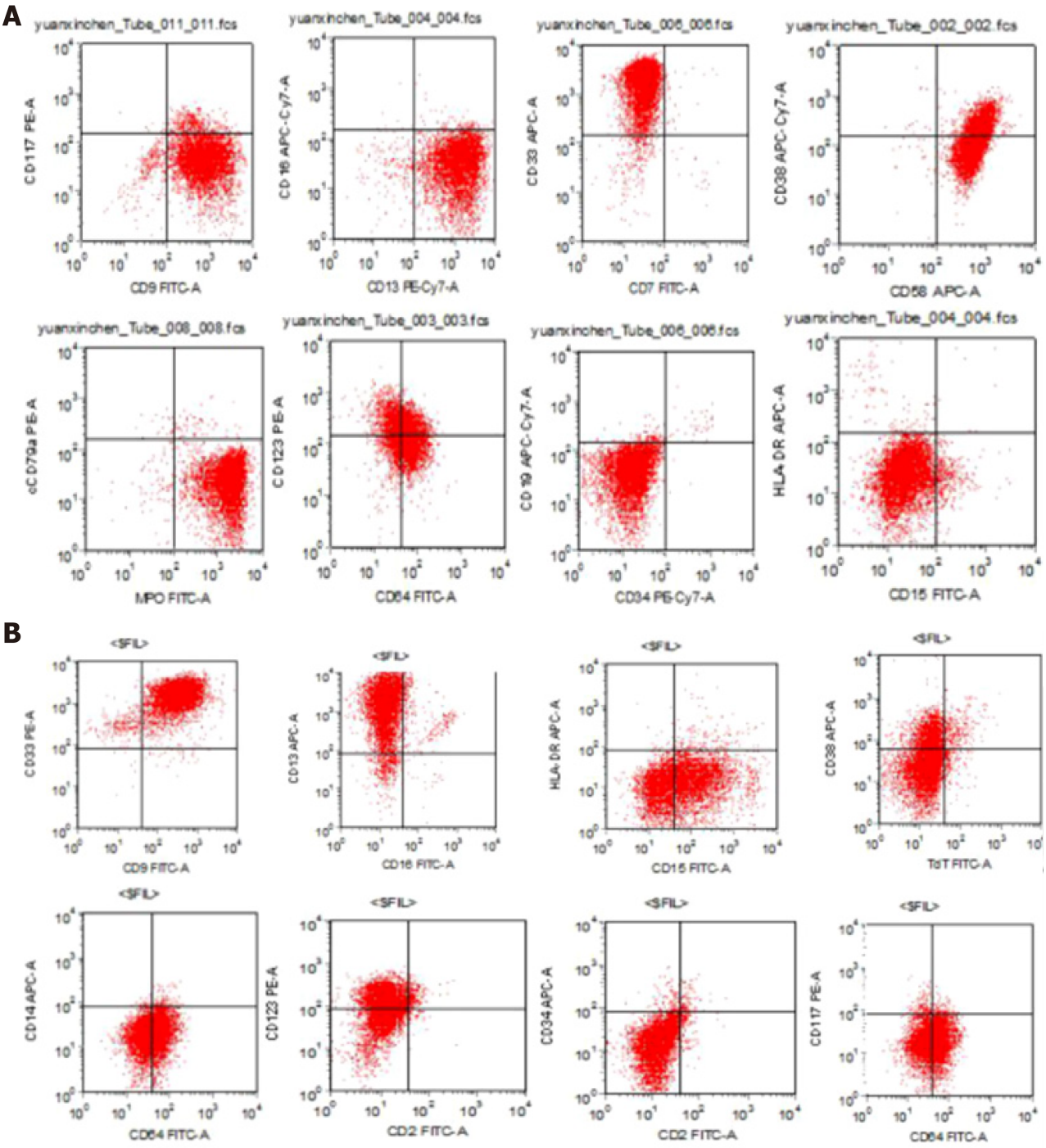

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Figure 4 Immunophenotyping results. A: Case 1; B: Case 2.

701L missense mutation. *WT1*, *TAL1*, *TTN*, and *DDX11* mutations were found in case 2. Both cases had *WT1* gene mutations, which were consistent with the characteristics of i(17)(q10) gene mutations (0-6) in MDS/MPO+ patients, but the gene mutation points were completely different. Therefore, case with i(17)(q10) was clinically diagnosed. The morphological diversity was probably due to different mutation patterns, and the number and order of the mutations might play a key role[8]. Therefore, both morphologic and immunological manifestations of APL were found in 2 children without t(15;17) and PML-RARa fusion-gene expression. Though preliminary diagnosis of AML morphologically similar to APL[15] were made for both children, the treatment failed in case 1, and case 2 with add(14)(p11) achieved sustained complete remission after chemotherapy, which might be related to the different gene mutation points.

Through literature review, 6 patients with i(17)(q10) have been known (including 2 in this group), 5 morphologically similar to AML, 1 without FAB classification mentioned[13], 5 with isolated TYPE i(17)(q10), 1 with add(14)(p11), and 3 patients (including 2 in this group) had CD33 immunophenotype

Table 1 Motivational interviewing case management genotyping of the cases

Number	Age	Sex	FABtyping	Karyotype	Immunological phenotype	Genemutation	Therapeutic reaction	Prognosis	Ref.
1	27	F	M3	i(17)(q10)	$CD33^{+/}CD13^{+/}$ MPO	PML-RARa (-)	Retinoic acid (-)	Die (survival 1 mo)	Yan *et al* [15], China
2	10	M	M3	i(17)(q10)	-	-	NR	Die (survival < 1 mo)	Bernstein *et al*[14], South Africa
3	Child	F	-	i(17)(q10)	-	-	-	-	Raimondi *et al*[13], Mexico
4	-	-	M3	i(17)(q10)	-	-	-	-	Becher *et al*[19]
5	3 (Case 1)	M	M3	i(17)(q10)	CD9/CD13/CD33/ CD38/CD64/CD123/CD58/MPO	WT1/EP300/C.854delG: P w285fs Frame shiftC.C2102T: P.701LMissense	-		Wen JQ, China
6	12 (Case 2)	M	M3	i(17)(q10) Add(14) (p11)	CD9/CD13/CD33/ CD38/CD64/CD123/CD15/MPO	WT1/TAL1/TTN/DDX11	+	CR 36 months, WT1 copy: 1010-1087	Wen JQ, China

F: Female; M: Male.

with CD3 MPO expression[15]. Using existing genetic and molecular biological techniques, t(15;17) among the 6 patients with PML-RARa fusion gene were not detected, 3 patients failed to respond toATRA-As_2O_3 and chemotherapy and died (survival shorter than 5.5 mo), 1 patient achieved sustained complete response after chemotherapy, and 2 patients did not show prognosis[13,18].

Morphology, immunology, chromosomal karyotype, and molecular biological genotyping of 6 cases with i(17)(q10) in different periods and their prognosis are shown in Table 1.

CONCLUSION

APL-like AML with i(17)(q10) has morphological and immunological characteristics similar to APL, without t(15;17) and PML-RARa fusion gene expression. ATRA-As_2O_3 and chemotherapy were not effective in treating the patients, with short survival period. If a chromosomal addition occurred, a sustained complete remission should be achieved and related clinical manifestations should be revealed. It is necessary to further strengthen the molecular biological study and collect a large number of cases to provide better treatment strategies.

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FOOTNOTES

Author contributions: Yan HX and Wen JQ contributed to conception and design of the study; Yan HX and Zhang WH are the co-first author; Zhang WH organized the database; Yan HX wrote the first draft of the manuscript; all authors contributed to manuscript revision, read, and approved the submitted version.

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