A RARE CASE OF HIGH-RISK ACUTE PROMYELOCYTIC LEUKEMIA WITH T (1; 17) (Q21; Q21)

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ABSTRACT

Objectives: *Acute promyelocytic leukemia (APL) is characterized by t (15; 17) (q24; q21). This translocation results in a PML-RARA fusion gene. To date, 16 cytogenetic variants of APL have been identified, including t (11; 17) (11q23; q12)/PLZF-RARA, t (5; 17) (5q35; q12)/NPM1-RARA, t (11; 17) (q13; q21)/NUMA-RARA, etc. Most of variant APL exhibited resistance to all-trans retinoic acid (ATRA) and arsenic trioxide. Variant APL is subject to relapse and its prognosis is poor. This study aims to present a rare case of high-risk APL with t (1; 17) (q21; q21), which is different from the above APL in karyotypes. APL is characterized by t (15; 17) (q24; q21). This translocation results in a PML-RARA fusion gene.*

Methods: *A 49-year-old male suffered fever for five days, strength lacking in his right lower extremity for three days. With bone marrow (BM) aspirate, flow cytometry, RT-PCR and karyotype, the case is diagnosed with variant high-risk APL. The patient received large-dose idarubicin for induction treatment.*

Results: *The patient achieved complete molecular remission. However, the case relapsed 18 months later, though ARA-C+aclarubicin +granulocyte colony-stimulating factor (GCF) (CAG) +ATRA have been administered to him. CR2 wasn't achieved. He refused to be transferred to a higher-level hospital and voluntarily gave up all the treatment, then died.*

Conclusion: *The present study identified a novel t (1; 17) (q21; q21), a novel variant translocation. High-risk plus the fusion gene PML-RARa (bcr3) might partly contribute to the refractory APL. In many aspects, the high-risk APL with t (1; 17) (q21; q21) showed many characteristics invariant APL. APL with t (1; 17) (q42; q21) is ATO resistance and DNR resistance during induction therapy but can obtain CR1 with large-dose idarubicin. APL with t (1; 17) (q42; q21) is vulnerable to relapse and is hard to obtain CR2. Its prognosis was poor, probably due to its variant karyotype. After CR1 has been achieved, further chemotherapy might be unnecessary and Allo-HSCT might be the only effective therapy to treat it.*

Keywords: *Acute promyelocytic leukemia, high-risk, t (1; 17) (q21; q21), PML-RARa (bcr3).*

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Introduction

Acute promyelocytic leukemia (APL) is a biologically and clinically distinct subtype of acute myeloid leukemia (AML) with unique molecular pathogenesis, clinical manifestations and treatment that is cytogenetically characterized by a balanced translocation t (15; 17) (q24; q21[(1)]. This translocation involves the retinoic acid receptor alpha (RARA) gene on chromosome 17 and the promyelocytic leukemia (PML) gene on chromosome 15 that results in a PML-RARA fusion gene[(2)]. High-risk APL is defined as APL with a WBC>10×109/L[(3)]. In roughly 1% to 2% of APL patients, novel translocations other than t (15; 17) have been identified. To date, 16 genetic variants involving RARA of APL have been identified, including t (11; 17) (11q23; q12)/PLZF-RARA, t (5; 17) (5q35; q12)/NPM1-RARA, t (11; 17) (q13; q21)/NUMA-RARA, etc[(4)]. Here, a rare case of high-risk APL with t (1; 17) (q21; q21), which is different from the above APL in karyotypes, is presented. The details are described as follows.

Cases report

On June 21, 2017, a 49-year-old male welder was admitted to our hospital for "fever for five days, strength lacking in his right lower extremity for three days". He had five years of hypertension: 190/80mmHg, but 130/80 mmHg could be kept after metoprolol tartrate tablets were orally taken. Five days ago, he caught a cold, then had a fever, about 38.5°C, accompanied with petechiae and ecchymosis and had been treated with anti-inflammation therapy in a local hospital for 3 days. After 3 days, blurred vision in his right eye and strength lacking in his right lower limb occurred.

Then he was transferred to another larger hospital where he was treated with anti-inflammation therapy for 2 days. Laboratory test: WBC 40.6×109/L, PLT 30×109/L, D-dimer levels increased; CT: bilateral low density lesions around basal ganglia of internal capsule. Then on June 21, he was transferred to our hospital. Physical examination: T: 38.3°C, P: 128/min, R: 18/min, BP: 170/90mmHg, conscious, soft neck, sternum tenderness (+), the examinations of his lungs and heart weren't abnormal, obvious hepatomegaly and splenomegaly: both 4 fingers under the rib cages with medium texture but without tenderness, both low limbs weren't swelling but petechiae and ecchymosis appeared in four limbs and the blood-drawing site. Laboratory tests: WBC 45.64×109/L, RBC 4.11×1012/L, Hb 125g/L, PLT 30×109/L, prothrombin time (PT): 16.2s, prothrombin activity (PTA): 50.5%, fibrinogen (FIB): 1.34g/L, D-dimer (D-Di): 3.4mg/L, Bone marrow (BM) aspirate showed hypercellularity with approximately 52% promyelocytes and Auer rods (Figure 1).

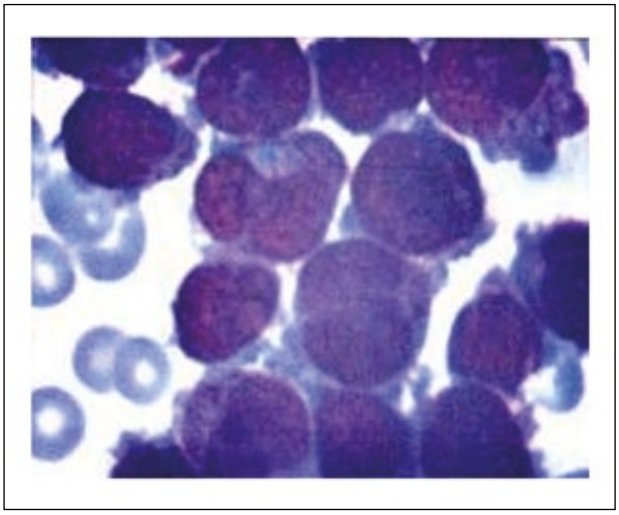

Figure 1: Bone marrow examination at diagnosis.

Flow cytometry on the aspirate revealed 87% immature cells expressing CD2+ CD13+ CD33+ CD34+ CD38+ CD56+ CD58+ CD64+ CD117+ CD123+ MPO. The detection of karyotype analysis with bone marrow aspirate revealed: 46, XY, t (1; 17) (q21; q21) (Figure 2).

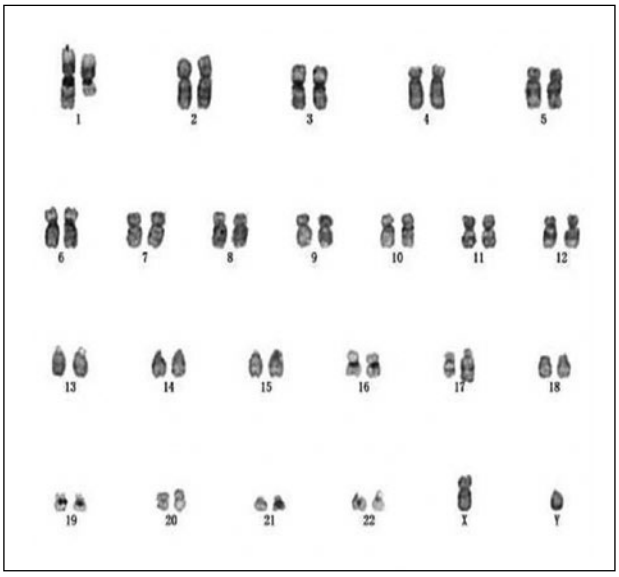

Figure 2: Chromosome karyotype analysis at first diagnosis: 46, XY, t (1; 17) (q21; q21).

The detection of fusion genes with bone marrow aspirate with reverse transcription-polymerase chain reaction (RT-PCR) showed: PML-RARa (bcr3) (+) [Appendix]. CT: bilateral low density lesions around basal ganglia of internal capsule. He was diagnosed with high-risk APL, DIC, cerebral lacunar infarction, and hypertension. He was treated with low molecular weight heparin sodium, felodipine and induction therapy: On June 22, arsenic trioxide (ATO) 10mg Qd*1d+daunorubicin (DNR) 40mg*4d were administered to induce his PML.

On June 24, cytarabine (Ara-C) 0.075g, Q12h was administered to him and dexamethasone (DXM) 5mg Q12h*1d was administered to prevent APL differentiation syndrome. On July 2, WBC decreased to 8.85×10^9/L, PLT increased to 55×10^9/L, but on July 3, WBC increased to 33×10^9/L and PLT decreased to 33×10^9/L. On this day, DNR 60mg*1d was administered to him. But the effect wasn't good: WBC increased to 45×10^9/L and PLT decreased to 26×109/L. So on July 4, idarubicin (IDA) 10mg*3d was administered to him. Then in July 7, Ara-C 0.1g Q12h*1d was administered to him. In July 10, 2017, his DIC and cerebral lacuna infarction were cured. He achieved the first complete remission (CR1): WBC 3.04×10^9/L, PLT 150×10^9/L. His fusion genes with bone marrow aspiration: PML-RARa(bcr3) (-),

bone marrow karyotype analysis: 46, XY, minimal residual disease (MRD): (-). Ara-C+DXM intrathecal injection was administered to him as well. He was discharged in August 1, 2017.

In August 11, 2017, he was readmitted for consolidation therapy. Initial IA regime: IDA 10mg*4d +Ara-C 0.075g Q12h*1d were administered to him. In September 19, 2017, for economic reason, DA regime: DNR40mg*3d +Ara-C 0.1g, Q12h*1d were administered to him. Then idarubicin 10mg*3d was used. Ara-C+DXM intrathecal injection was administered to him again. On October 8, 2017, when he was discharged, his condition was good: his symptoms were improved, normal body temperature, normal heart, lungs and abdomen, BM: CR1, moderate anemia.

In October 25, 2017, eight cycles of maintenance therapy, each of which included ATO 10mg QD*22d in the 1st month + MTX 20mg qw*4w in the 2nd month+ ATRA 20mg Bid*30d in the 3rd month, was administered to him. His WBC, Hb and PLT became normal, his BM: CR1, PML-RARa(bcr3) (-), karyotype analysis: 46, XY, MRD: (-). He didn't have any symptoms.

In January, 2019, when ATO chemotherapy as a part of the sixth cycles was administered to him, His fusion genes of PML-RARa(bcr3) with bone marrow aspiration became positive, but BM: CR1, karyotype: 46, XY, MRD: (-). The maintenance therapy for him was still administered to him as scheduled plan. In April 2019, his fusion genes of PML-RARa(bcr3) with bone marrow aspiration became negative. But in July 2019, his fusion genes of PML-RARa(bcr3) with bone marrow aspiration became positive again. So, in August, 2019, a new regime: ARA-C+aclarubicin +granulocyte colony-stimulating factor (GCF) (CAG) +ATRA was administered to him. In September, 2019, the copy numbers of PML-RARa(bcr3) decreased. But in December, 2019, CAG+ATRA were still administered to him. But his PML-RARa was still positive, his WBC and PLT decreased, so large-dose Ara-C (2.5g, i.v.gtt) was administered to suppress the deteriorating APL. Then his WBC and PLT increased. In April, 2020, swelling and aching of gum, chilling fever 39°C, WBC: 12.97×10^9/L, PLT: 7×10^9/L, BM: promyelocyte 56%, occurred to him, so he was readmitted for relapse of APL and pulmonary infection. CAG+ATRA were still administered to him. The supportive therapy was administered to him. His swelling and aching of gum relieved. But his fever was still recurrent even anti-inflammation therapy was administered. In May 7, 2020, BM: promyelocyte 47%, CR2 wasn't achieved after chemotherapy. For economic reason he refused to be transferred to a higher-level hospital and voluntarily gave up all the treatment and was discharged, then in May 12, 2020, died at home.

Discussion

The present patient was a welder and the long-term professional exposure to radiation might to an important pathogenic factor to his PML. His WBC was more than 10×10^9/L. His BM smear showed classic APL morphology. This case exhibited classic immunophenotype of promyelocyte (CD13, CD33, CD64, CD117, MPO-positive, and HLA-DR-negative). The detection of PML-RARa (bcr3) was positive. Different from the typical t (15; 17) (q24; q21) of typical APL, his karyotype was t (1; 17) (q21; q21), a novel variant translocation that have never been reported before. So he was diagnosed with high-risk APL and DIC, a common complication of APL, presenting petechiae and ecchymosis and blurred vision in his right eye. He had a long history of hypertension which led to his cerebral lacuna infarction presenting strength lacking in his right lower extremity and CT imaging. Thus, he was regularly treated with low molecular weight.

Heparin sodium, felodipine and induction therapy. Fortunately, the complications related to APL were cured. ATRA plus ATO with the addition of some cytoreductive chemotherapy is a treatment option for high-risk patients[5]. So, ATO+ DNR was administered, but WBC increased. So ATO resistance and DNR resistance were proved. Gemtuzumab ozogamicin (GO), or IDA, should be added early during induction therapy in patients with high-risk APL[6]. So IDA regime was administered and molecular CR1 was achieved. Therefore, APL with t (1; 17) (q42; q21) is ATO resistance, just like many variant APL[4, 7], and DNR resistance but large-dose IDA could induce it to CR1. With initiation of treatment, patients are at risk for developing a rapidly rising WBC and potentially life-threatening differentiation syndrome, hemorrhage, and DIC. Therefore, the National Comprehensive Cancer Network (NCCN) guidelines recommend prophylactic administration of corticosteroids in all APL patients with a WBC $>10\times10^9$/L[8]. So in this case, DXM was administered to prevent APL differentiation syndrome[9]. Ara-C+DXM intrathecal injection was administered to prevent central nervous

system leukemia (CNS-L). Then consolidation therapy (IA regime, DA regime) and eight cycles of maintenance therapy were conducted. The patient's condition looked better and better. However, in the 18th month after his CR1 (January, 2019), positive PML-RARa(bcr3) indicated the relapse of his APL. Though changed regimes (CAG +ATRA) have been administered to him[10]. PML-RARa(bcr3) was still positive and molecular CR2 wasn't achieved. Finally the patient died of the relapse of high-risk APL.

High WBC count is the most important risk factor in APL[11]. Moreover, some reports have shown that bcr3 PML-RARA isoform patients would have a poor prognosis and an aggressive disease course[5, 12]. So, high-risk plus the fusion gene PML-RARa(bcr3) might partly contribute to the refractory APL. Moreover, in many aspects, the high-risk APL with t (1; 17) (q21; q21) showed many characteristics invariant APL. For example: ATO resistance[13]. Variant APL preferred to fall in high-risk group and develop to relapsed disease during the clinical course[4]. The high-risk APL with t (1; 17) (q42; q21) was also vulnerable to relapse and was hard to obtain CR2. So, just like many variant APL[5], its prognosis is also poor, probably due to its variant karyotype. After CR1 has been achieved, further chemotherapy might be unnecessary. Variant APL patients could be candidates for hematopoietic stem cell transplantation (HSCT)[14]. Moreover, once remission has been achieved, consolidation with autologous HSCT for APL patients with negative minimal residual disease (MRD) status, and with allogeneic HSCT for APL patients with positive MRD status appear to offer the best long-term outcomes[15]. Hence, allogenic hematopoietic stem cell transplantation (Allo-HSCT) might be the only effective therapy to treat it.

In conclusion, the present study, to the best of our knowledge, identified a novel t (1; 17) (q21; q21), a novel variant translocation, in an adult patient with high-risk APL. High-risk plus the fusion gene PML-RARa(bcr3) might partly contribute to the refractory APL. In many aspects, the high-risk APL with t (1; 17) (q21; q21) showed many characteristics invariant APL. APL with t (1;17) (q42; q21) was ATO resistance and DNR resistance during induction therapy but could obtain CR1 with large-dose idarubicin. APL with t (1; 17) (q42; q21) was vulnerable to relapse and was hard to obtain CR2. Its prognosis was poor, probably due to its variant karyotype. After CR1 has been achieved, further chemotherapy might be unnecessary, and Allo-HSCT might be the only effective therapy to treat it. The study involved only one APLs with t (1; 17) (q21; q21). More apps with t (1; 17) (q21; q21) are needed to be found and to be studied.

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