

Does acute promyelocytic leukemia patient with the STAT5B/RARa fusion gene respond well to decitabine?

A case report and literature review

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Abstract

Rationale: Most acute promyelocytic leukemia (APL) patients respond to all-trans-retinoic acid (ATRA) and have a good prognosis. However, variants APL who carry PLZF/RARa, STAT5B/RARa, and STAT3/RARa are insensitive to ATRA and have poor prognoses. The standard treatment for variants APL is still unclear due to the small sample size.

Patient concerns: Here we reported a Chinese male who was admitted to our hospital with the complaint of rib pain, dyspnea, and fever (37.5°C). Blood tests showed leukopenia ($1.83 \times 10^9/L$), anemia (hemoglobin 73 g/L), and thrombocytopenia ($54 \times 10^9/L$). Prothrombin time and activated partial thromboplastin time were normal.

Diagnoses: The patient was diagnosed as STAT5b-RARa-positive APL based on the clinical and laboratory findings.

Interventions: ATRA was used immediately for induction treatment, then he was treated with ATRA + arsenic trioxide and got the severe cardiac insufficiency. Subsequently, consolidation chemotherapy was added with ATRA + Huangdai tablets + idarubicin and decitabine, cytarabine, aclamycin (DCAG).

Outcomes: The patient relapsed soon after his first molecular complete remission (CRm), fortunately, he got a second CRm with DCAG. He has survived for more than 9 months and remains CRm, now he is looking for a suitable donor to prepare for hematopoietic stem cell transplantation (HSCT).

Lessons: APL patients with STAT5B-RARa is not only resistant to ATRA, but also to conventional combination chemotherapy such as daunorubicin and cytarabine/idarubicin and cytarabine or other regimens. Relapse and extramedullary infiltration is common, HSCT is a effective treatment, and the best time for HSCT is after the first CR. It should be noted that this patient got CRm with DCAG after relapse, so the role of decitabine in APL with STAT5B-RARa needs to be considered.

Abbreviations: APL = acute promyelocytic leukemia, ATO = arsenic trioxide, ATRA = all-trans retinoic acid, CR = complete remission, CRm = molecular complete remission, DA = daunorubicin and cytarabine, DCAG = decitabine, cytarabine, aclamycin, G-CSF, DIC = disseminated intravascular coagulation, HSCT = hematopoietic stem cell transplantation, IA = idarubicin and cytarabine.

Keywords: acute promyelocytic leukemia, all-trans retinoic acid, PML-RARA, prognosis, STAT5B/RARa

1. Introduction

More than 98% of acute promyelocytic leukemia (APL) patients have classic $t(15,17)(q22;q12-23)$ and promyelocytic leukemia-retinoic acid receptorA (PML-RARA) fusion genes; they respond to all-trans retinoic acid (ATRA) and have a good prognosis.

However, RARa fuses with other partner genes in patients with variants APL (1%–2%), and some new fusion proteins have been formed, such as PLZF/RARa, NPM/RARa, NuMA/RARa, STAT5B/RARa, FIP1L1/RARa, PRKAR1A/RARa, and BCOR/RARa. APL patients with PLZF/RARa, STAT5B/RARa, and

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The patient had provided informed consent for publication of the case.

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

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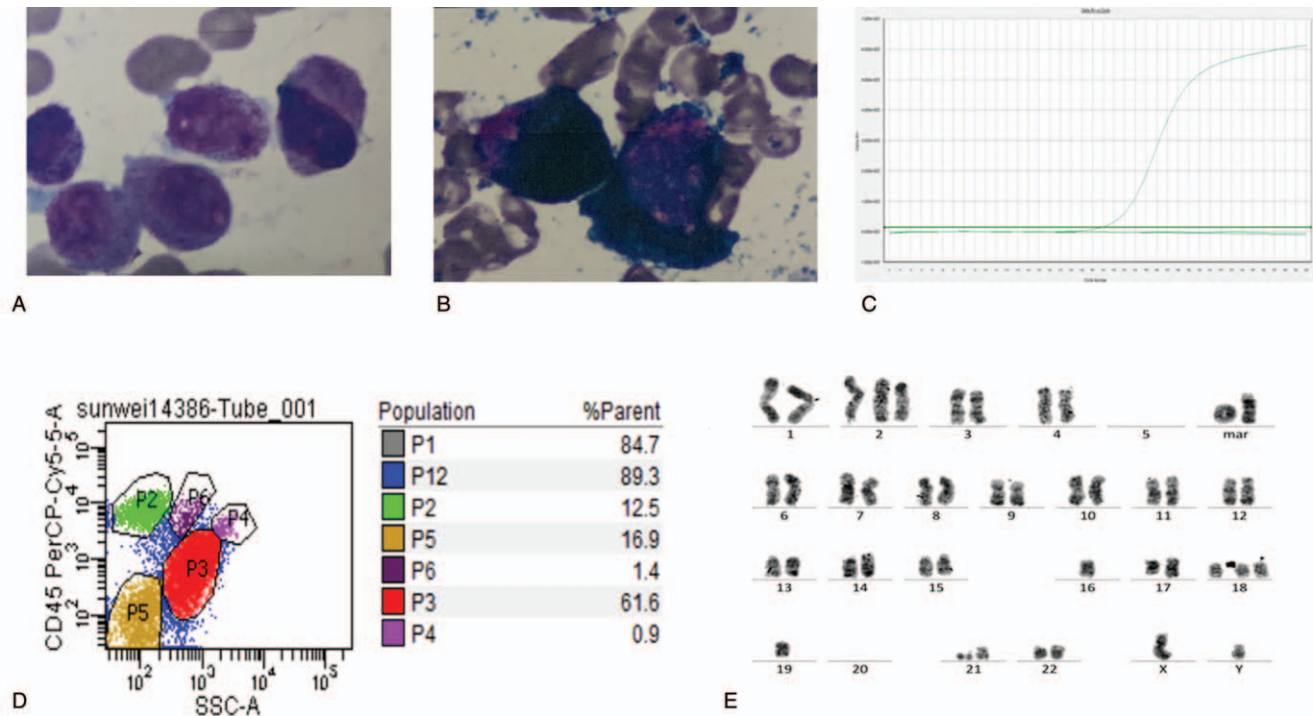


Figure 1. Laboratory examination result of this patient. (A) Abnormal promyelocyte in bone marrow (100× oil objective), (B) Peroxidase staining of bone marrow (100× oil objective), (C) Flow cytometric analysis of BM cells showing a population of abnormal cell (P3: 61.6%). (D) STAT5B-RARα fusion transcript detected by RT-PCR analysis in this patient. (E) Karyotype of this patient:43,-46,XY,+2,-5,+8,14p+,-16,17q-,17q+,+18,-19,-20,-21,+mar1,+mar2[CP5]/46,XY[15]. BM = bone marrow, RT-PCR = reverse transcription–polymerase chain reaction.

STAT3/RARα are insensitive to ATRA.^[1] Patients with variants APL often have poor prognoses. The STAT5B/RARα fusion gene is rare in APL and was first reported in 1996.^[2] To date, 16 cases have been reported. The standard treatment for variants APL is still unclear due to the small sample size. Here, we report a 62-year-old man diagnosed as APL with STAT5B/RARα and summarize the clinical features and effective treatment, hoping to improve the prognosis of these patients.

2. Case report

A 62-year-old man was admitted to the hospital with the complaint of rib pain, dyspnea, and fever (37.5°C). Blood tests showed the following results: white blood cell count $1.83 \times 10^9/L$, hemoglobin 73 g/L, platelet count $54 \times 10^9/L$, prothrombin time 13.6 seconds, activated partial thromboplastin time 38.8 seconds, fibrinogen 5.8 g/L, D-dimer 2.4 μg/mL, fibrinogen degradation products 8.15 μg/mL. Abnormal promyelocyte in bone marrow aspiration showed 80.4% of blast, and flow cytometry indicated mainly positivity for CD33 and myeloperoxidase, partially positivity for CD117, CD9, CD11b, CD13, CD15 and CD64; negativity for CD7, CD19, CD10, cCD3, cCD79a, CD16, CD123, HLA-DR, CD14, CD56, CD3, CD4, CD8, CD2, and CD11c. Cytogenetics showed 43,-46,XY,+2,-5,+8,14p+,-16,17q-,17q+,+18,-19,-20,-21,+mar1,+mar2[CP5]/46,XY[15] (Fig. 1A). STAT5B/RARα fusion transcript was detected by reverse transcription–polymerase chain reaction. Given the clinical and laboratory findings, he was diagnosed as APL with STAT5B/RARα and treated with ATRA monotherapy for the first course, and no granulocyte differentia-

tion was observed. However, his fibrinogen degradation product and D-dimer levels improved and he got a complete remission (CR) after the first course. Then he was treated with ATRA + arsenic trioxide (ATO) during the second course. But unfortunately, he was transferred to the intensive care unit because of severe cardiac insufficiency (BNPmax 1361 pg/mL) on the 14th day of the second course. However, STAT5B/RARα was still positive (17.96%) after the second course. He received 3 courses of ATRA + Huangdai tablets (ATO oral forms) + idarubicin in the following consolidation treatment and got molecular complete remission (CRm) after the fourth course, but STAT5B/RARα turned to be positive (0.6%) again after the fifth course. Fortunately, he got a second CRm with DCAG (decitabine [15 mg/m², D1-5], cytarabine [10 mg/m², q12, D3-9], aclamycin [8 mg/m², D3-6], G-CSF [200 ug/m², D0-1, till white blood cell count $>20 \times 10^9/L$]). This patient is now looking for a suitable donor to prepare for hematopoietic stem cell transplantation (HSCT).

3. Discussion

STAT5B is located on chromosome (Chr)17q21.1-21.2 and mainly distributed in the cytoplasm and nucleus. It regulates cell proliferation and induces leukemia through JAK-STAT signaling pathways. STAT5B plays a role in preventing further differentiation of hematopoietic cells together with the corepressor complex of deacetylase, this complex cannot be released by ATRA. This may explain the resistance of APL with STAT5B/RARα to ATRA.

The current case showed a complex karyotype and an unsatisfactory treatment process. He was responsive to ATRA

Table 1

Clinical characteristics of APL patients with ATAT5B/RARa reported in the literature.

Case	Author's name, year of publication	Age	Gender	Karyotype	FAB	WBC ($\times 10^9$)	PLT ($\times 10^9$)	DIC	FDP, D-D	ATRA improve	ATRA-induced granulocytoc differentiation	Therapy	Course	Outcome	Effective treatment	OS (mo)
1	Arnould C, 2015 ^[3]	67	M	45,X,-Y,add(17)(q2)[40]	M1/M3v	6.7	NA	+	NA	NO	NO	ATRA	1	NR	None	NA
2	S. Strehl, 2013 ^[4]	57	M	46,XY,t(10;1)(q22;q25),i(17)(q10)	M3	23.8	NA	+	NA	NO	NO	ATRA DA Gentuzumab ozogamicin allo-SCT	1	NR CR, First relapse: BM at 9 mo Second CR, Dead at 18 mo	None DA gentuzumab ozogamicin	18 mo
3	Kusakabe M, 2008 ^[5]	42	M	46,X,-Y,+11[9]/46,XY,[11]	M3	3.6	125	+	YES	NO	NO	ATRA DA + MIT + vp16 HD-Ara-C	1	NR	DA + Mit + VP16	21 mo
4	Iwanaga E, 2009 ^[6]	41	M	47,XY,(del9)(q?),add(17)(q12),+mar1 [3],48,XY, idem,mar1[17]	M3	77.8	95	+	NA	NO	NO	ATRA + IA ATRA + IA HD-Ara-C + intrathecal chemotherapy + whole brain irradiation	5 1 2	CR CR First relapse: meningeal Second CR for 6 mo Second relapse: BM, Died	ATRA + IA ATRA + IA	17 mo
5	Jovanovic JV, 2011 ^[7]	29	F	46,XX,t(8;17)(q26;q21)	M3	5.6	NA	+	NA	NO	NO	ATRA + IA FLA allo-BMT	1 1	CR (no CRm) NR CR; Dead of BMT-related complications;	ATRA + IA allo-BMT	15 mo
6	Qiao C, 2011 ^[8]	32;	M	46,XY	M3	3.8	282	+	NO	NO	NO	ATRA + ATO + MIT FLAG FLAG allo-HSCT	1 1 1	NR CR CR CR	FLAG allo-HSCT	96 d after allo-HSCT; ongoing
7	Chen H, 2012 ^[9]	26	M	46,XY	M3	6.6	94	+	NA	NA	NA	ATRA IA ATRA + ATO ATRA IA + VP16 ATRA + IA VP16 + HD-AraC + ATRA MA + ATRA ATO fludarabine + Ara-c + daunoxome FLA + auto-HSCT FLA	1 1 1 1 1 1 1 1	NR NR NR First relapse: testis at 24 mo NR Second CR Second relapse: BM at 40 mo NR Dead at 53 mo	None None ATRA, IA, VP16	NA NA 53 mo
8	Strehl S, 2013 ^[10]	17	M	46,XY,?der(13),?der(17q)	M3	2.8	NA	+	NO	NA	NA	ATRA ATRA + ATO ATO fludarabine + Ara-c + daunoxome FLA + auto-HSCT FLA FLA + amsacrine ATRA ATO + IA Refused further therapy	1 1 1 1 1 1 1	CR CR CR First relapse: testis at 24 mo NR Second CR Second relapse: BM at 40 mo NR Dead at 53 mo	ATRA, IA, VP16	53 mo
9	Wang YY, 2015 ^[11]	22	M	46,XY,inv.(9)(p13q13)c[18]/44-45,XY,inv.(9)(p13q13)c[cp4]/ [22]	M3	2.3	125	+	YES	NO	NO	ATRA ATO + IA Refused further therapy	1 1	NR NR Dead	None	9 mo

(continued)

Table 1
(Continued).

Case reference number	Author's name, year of publication and gender	Age	Gender	Karyotype	FAB	WBC (×10 ⁹)	PLT (×10 ⁹)	DIC	FDP	D-D	ATRA improve	ATRA-induced granulocytoc differentiation	Therapy	Course	Outcome	Effective treatment	OS (mo)
10	Liu Lirong, 2016 ^[2]	49	M	46,XY[20]	M3	19.7	24	+	NA	NA		ATRA + ATO + idarubicin	1	CRm	ATRA + ATO + idarubicin	More than 15 mo	
												IA	4	First relapse: BM	IA		
												HHT + MD-Ara-C;	1	NR	HHT + MD-Ara-C;		
												idarubicin + MD-Ara-C	1	NR			
												FLAG	1	NR			
												HHT + MD-Ara-C;	1	NR			
												ATO	1				
												ATRA	1				
11	Zhang C, 2018 ^[3]	28	F	46,XX[20]	M3	1.95	196	+	NA	NA		ATRA + idarubicin	1	NR	None	2 mo	
												ATO/ATRA + DA	1	NR			
												HA + ATRA	1	Dead			
												ATRA	1	NR	HSCT	9 mo	
												DA	1	NR			
												HSCT	1	CR			
												ATRA/mitoxantrone + ATO,	1	NR	Decitabine + AAV/IA	12 mo; ongoing	
												IA;	1	NR			
												decitabine + AAV/IA	6	CRm			
												ATRA	1	NR	FLAG-IA + ATRA	NA	
14	Ciangola G, 2019 ^[6]	47	M	46,XY,der(5)(5:8)	M3	1.6	229	-	NO	NO		DA	1	NR			
												FLAG-IA + ATRA	1	NR			
												Allo-HSCT	1	CR			
														CR, dead of multiple organ failure			
15	Peterson JF, 2019 ^[7]	27	M	46, XY	M3	52	24	+	NA	YES		ATRA + Hydroxyurea	1	Dead	None	3.5 d	
16	Pessina C, 2017 ^[8]	32	M	45,X,Y,der(17)inv(17)(p11.2q21)del(17)(q21)/46,XY	M3	6.8	126	+	NA	NA		IA	1	NR	Allo-HSCT	12 mo after HSCT; Ongoing	
												FLAG-IDA	2	NR			
												Allo-HSCT		CR			
												ATRA,	1	CR	ATRA ATO,	8 mo;	
												ATRA + ATO	1	CRm at 4 mo,	idarubicin,	Ongoing	
												ATRA + ATO + idarubicin	4	but molecular relapse at 5 mo	decitabine + CAG		
												decitabine + AA	1	CRm			

AA = aclarubicin and cytarabine, APL = acute promyelocytic leukemia, ATO = arsenic trioxide, ATRA = all-trans retinoic acid, CAG = cytarabine, G-CSF = granulocyte colony-stimulating factor, DA = daunorubicin and cytarabine, DIC = disseminated intravascular coagulation, F = female, FAB = French-American-British classification, FLAG = fludarabine, cytarabine and recombinant human granulocyte colony-stimulating factor (G-CSF), IA = idarubicin and cytarabine, M = male, MA = mitoxantrone and cytarabine, NA = not available, NR = no response, OS = overall survival measured as time from date of disease diagnosis to death (failure) or alive at last follow-up (censored), PLT = platelet count, VP-16 = etoposide, WBC = white blood cell count.

and ATO at the beginning and achieved CRm after the fourth course; however, he relapsed quickly (molecular biology relapse). To date, a total of 16 cases of APL with STAT5B/RARA have been reported worldwide; this disease is extremely rare (Table 1). Only 3 patients were female, and more samples are needed to explain the sex-bias phenomenon. The age at onset was generally young; only 2 patients were over 60 years old. STAT5B/RARA is often accompanied by complex karyotypes (13 cases) and a high frequency of DIC (16 cases). ATRA can improve coagulation function in some patients (case 3, 9, 17), but granulocyte differentiation was observed in only 1 patient (case 15). Extramedullary infiltration in APL with PML/RARA is a rare event; even in patients without CR, 2 cases reported developed into extramedullary infiltration after CR (case 4 was CNS relapse, case 8 was testis relapse) (Table 1). Most patients received ATRA (monotherapy (n=9) or combined with ATO/chemotherapy (n=7)) in the first course of treatment (Table 1), but only 1 (ATRA monotherapy) and 3 patients (ATRA combined with ATO/chemotherapy) achieved CR after the first course. The CR rate is obviously lower in APL patients with STAT5B/RARA than in those with PML/RARA. After treatment with DA, IA (idarubicin and cytarabine), FLAG (fludarabine, cytarabine, and G-CSF), CAG (cytarabine, amlastin, G-CSF), medium dose Ara-C, and DCAG, 12 patients achieved once CR at least in the whole course of treatment, 5 patients relapsed (case 2, 4, 8, 10, and 17), 5 patients died (case 2, 4, 5, 8, and 14) (Table 1). The CR rate and total mortality rate were 35.3% (6/17) and 47.1% (8/17) in APL with STAT5B-RARA, in contrast to 95% and 5% in APL with PML-RARA, respectively (Table 1). The main reasons of death were infections, progressive disease, cerebral hemorrhage or transplantation-related complications. Notably, 6 patients remained relapse-free until the report, 3 of them received combined chemotherapy (case 3, 13, 17), and another 3 received HSCT (case 6, 12, and 16). Among the 17 patients in Table 1, 7 patients received HSCT, and 4 patients died (the longest OS was 53 months). Patients failed to get CR when HSCT after relapse (case 2, 8), the best time for HSCT is after CR1. Until now, the standard treatment for variants APL was still unclear due to the small sample size. Therefore, it is critical to improve the prognosis of patients with new treatment methods. It should be noted that 2 patients (case 13, 17) got CR with decitabine + AA/IA or DCAG after relapse, and the role of decitabine in APL with STAT5B-RARA needs to be considered.

We can conclude that APL patients with STAT5B-RARA is not only resistant to ATRA, but also to conventional combination chemotherapy such as DA/IA or other regimens. Relapse and extramedullary infiltration is common, HSCT is a effective treatment, and the best time for HSCT is after the first CR.

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