Am J Blood Res 2015;5(2):91-94
www.AJBlood.us /ISSN:2160-1992/AJBR0020219

Case Report

Therapy-related myelodysplastic syndrome: a case study

Masahiro Manabe[1], Katsuya Wada[2], Dai Momose[1], Yasuyoshi Sugano[1], Masayuki Hino[3], Takahisa Yamane[4], Eiwa Ishida[5], Ki-Ryang Koh[1]

[1]Department of Hematology, Osaka General Hospital of West Japan Railway Company, 1-2-22 Matsuzaki-cho, Abeno-ku, Osaka 545-0053, Japan; [2]Department of Hematology, Matsushita Memorial Hospital, 5-55 Sotojima-cho, Moriguchi, Osaka 570-8540, Japan; [3]Department of Hematology, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan; [4]Department of Hematology, Osaka City General Hospital, 2-13-22 Miyakojimahondori, Miyakojima-ku, Osaka 534-0021, Japan; [5]Department of Pathology, Osaka General Hospital of West Japan Railway Company, 1-2-22 Matsuzaki-cho, Tennoji-ku, Osaka 545-0053, Japan

Received November 21, 2015; Accepted December 15, 2015; Epub December 25, 2015; Published December 30, 2015

Abstract: We present a case of therapy-related myelodyspastic syndrome in which the t(3;8)(q26;q24) translocation appeared, even though no chromosomal abnormalities were found at the initial diagnosis of acute myeloid leukemia. To the best of our knowledge, there have only been around 20 reported cases of myeloid malignancies involving t(3;8)(q26;q24). We discuss the characteristics of t(3;8)(q26;q24) along with a review of literature.

Keywords: Therapy-related myelodyspastic syndrome, t(3;8)(q26;q24), dysmegakaryopoiesis

Introduction

Chromosomal analysis is important for diagnosing myeloid malignancies such as acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), particularly for the classification of disease subtypes and prognostic prediction. Chromosomal abnormality involving 3q has been described in 3.5-4.7% of all AML cases [1, 2]. The most representative rearrangements including 3q26 are inv(3)(q21q26) and t(3;3)(q21;q26), which result in the production of increased numbers of megakaryocytes with monolobed or bilobed forms [3]. Among 3q abnormalities, t(3;8)(q26;q24) is reported to be extremely rare rearrangement and has only been described in about 20 patients [1, 2, 4-15]. Herein, we report the case of a patient with therapy-related MDS associated with the t(3;8)(q26;q24) translocation.

Case presentation

A 73-year-old male was referred to our hospital because of anemia and thrombocytopenia. Peripheral blood analysis showed a white blood cell count of 4300/μL (46% blasts), a hemoglobin level of 6.9 g/dL, and a platelet count of 54000/μL. Bone marrow aspiration revealed marked proliferation of blast cells, which accounted for 83.7% of bone marrow cells, and surface marker analysis demonstrated that the blasts were CD2-, CD3-, CD4+, CD5-, CD8-, CD10-, CD19-, CD20-, CD13+, CD14-, CD33+, CD34+, and human leukocyte antigen (HLA)-DR+. No dysplasia was observed. A chromosomal study of the patient's bone marrow cells showed a karyotype of 46, XY [20]. A diagnosis of AML without maturation was made. The patient received chemotherapy involving 20 mg/m^2 cytosine arabinoside on days 1 to 35 and 300 μg of filgrastim on days 1 to 35, resulting in complete remission. There afer, he was subjected to consolidative chemotherapy involving the abovementioned regimen. Then, he underwent surveillance consultations, including peripheral blood examinations, once a month, which confirmed that he remained in remission. However, he developed anemia at 36 months after the initial diagnosis. Peripheral blood analysis revealed a white blood cell count of 2100/μL with 43% neutrophils, 49% lymphocytes, 6% monocytes, and 2% blastoid cells. His hemoglobin level was 9.5 g/dL, and his platelet count was 178000/μL. His serum lactate dehydrogenase level was not elevated (172 U/L; reference range, 106-211 U/L). Bone marrow aspiration revealed marked dysmegakaryopoiesis, e.g., small monolobulated mega-

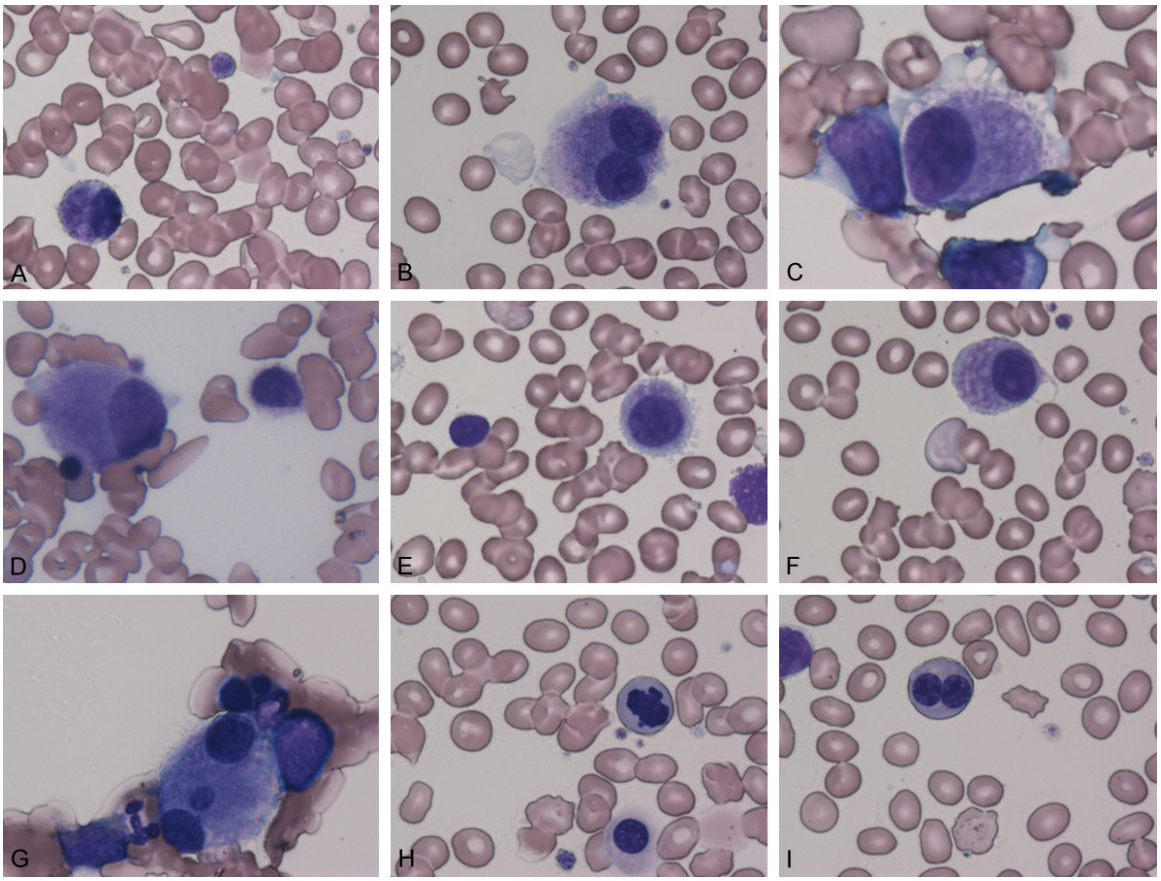

Figure 1. May-Giemsa-stained bone marrow cells with dysplasia. Small mononuclear megakaryocytes (A-G), erythroblasts with karyorrhexis (H), and binuclear erythroblasts (I) were seen.

karyocytes, and that blasts accounted for 8% of his bone marrow cells (**Figure 1**). Surface marker analysis demonstrated changes compared with the initial diagnosis; i.e., the blasts expressed CD7, but were negative for CD4; no changes were detected in the expression of other markers. A chromosomal study of the patient's bone marrow cells revealed the following karyotype: 46, XY, t(3;8)(q26;q24)[11]/48, XY, +X, t(3;8)(q26;q24), +12 [9]. Based on the appearance of dysplasia and that fact that blasts now accounted for less than 10% of the patient's bone marrow cells, a diagnosis of therapy-related MDS (refractory anemia with excess of blasts-1) was made. The patient was administerd azacitidine monotherapy (100 mg/m^2 on 7 days every 4 weeks) because of his poor performance status; however, he died from pneumonia at 46 months after the initial diagnosis.

Discussion

Here, we describe the case of a patient with therapy-related MDS harboring t(3;8)(q26;q24), who had initially been diagnosed with AML without maturation and exhibited a normal karyotype. To the best of our knowledge, about 20 cases of myeloid malignancies involving reciprocal t(3;8)(q26;q24) translocations have been reported (**Table 1**) [1, 2, 4-15]. 3q abnormalities are recurrent, but not frequent; it is estimated that they are seen in 3.5-4.7% of all AML cases [1, 2]. Among them, the t(3;8)(q26;q24) translocation is extremely rare, exhibiting an estimated incidence of 3.5% of myeloid malignancies involving 3q rearrangements [1]. The t(3;8)(q26;q24) translocation is considered to be the rarest of the many types of chromosomal translocations associated with 3q26 [14]. Lin et al. reported that hematological malignancies involving this translocation exhibit common characteristics including trilineage dysplasia and a poor prognosis and are predominantly seen in therapy-related cases. As for its morphological effects, our patient's cells displayed dysplasia, especially marked dysmegakaryopoiesis, which is consistent with previous reports about this cytogenetic translocation.

Table 1. Cytogenetic findings of previously reported cases involving t(3;8)(q26;q24)

Case no.	Age/ Sex	G-banded Karyotype including t(3;8)(q26;q24)	Diagnosis	Reference
1	62/M	46, XY, t(3;8)(q26;q24)	RAEB-t[a]	Martens et al (1987)
2	66/F	46, XX, t(3;8)(q26;q24), -7[b]	sAML[a]	Charrin et al (2002)
3	69/F	46, XX, t(3;8)(q26;q24), del(5)(q14q34), -7, -18[b]	AML(FAB M2)	Charrin et al (2002)
4	46/F	46, XX, t(3;8)(q26;q24), -7, +mar	t-AML	Lin et al (2006)
5	68/F	46, XX, t(3;8)(q26;q24)	t-AML	Lin et al (2006)
6	57/M	45, XY, t(3;8)(q26;q24), -7	t-MDS	Lin et al (2006)
7	82/M	47, XY, t(3;8)(q26;q24), +13	AML with maturation	Lin et al (2006)
8	73/M	46, XY, t(3;8)(q26;q24)	AMML	Lin et al (2006)
9	52/F	46, XX, t(3;8)(q26;q24), -7/45, idem, inv(7)(q22q34)	AML	Bobadilla et al (2007)
10	54/F	46, XX, t(3;8)(q26;q24)	AML	Bobadilla et al (2007)
11	28/M	46, XY, t(3;8)(q26;q24)/45, idem, -7	AML	Schroeder et al (2008)
12	47/F	46, XX, t(3;8)(q26;q24), t(9;22)(q34;q11)/46, idem, t(4;5)(p16;q31)/46, idem, del(6)(q21q27)	CML-BC	Lin et al (2009)
13	60/F	46, XX, t(3;8)(q26;q24)/46, idem, t(8;21)(q13;q22)/45, idem, -7	CMML	Isoda et al (2009)
14	NR/M	46, XY, t(3;8)(q26;q24)	AML	Lugthart et al (2010)
15	84/M	47, XY, t(3;8)(q26;q24), +14	AML	Danilova et al (2013)
16	51/M	46, XY, t(3;8)(q26;q24)	AML	Xu et al (2014)
17	41/M	46, XY, t(3;8)(q26;q24)	RCMD	Xu et al (2014)
18	71/F	46, XX, t(3;8)(q26;q24)/46, idem, del(7)(p11p15)/45, idem, i(7)(q10)	AML	Xu et al (2014)
19	64/M	46, XY, t(3;8)(q26;q24)	AML	Xu et al (2014)
20	52/M	46, XY, t(3;8)(q26;q24), t(9;22)(q34;q11)/92, idem x2	CML-BC	Xu et al (2014)
21	79/M	46, XY, t(3;8)(q26;q24), -7, +21	AML	Lavallée et al (2015)
22	73/M	46, XY, t(3;8)(q26;q24)/48, XY, +X, t(3;8)(q26;q24), +12	t-MDS	Present case

RAEB-t, refractory anemia with excess of blasts in transformation; AML, acute myeloid leukemia; s, secondary; t-, therapy-related; MDS, myelodysplastic syndrome; AMML, acute myelomonocytic leukemia; CML-BC, chronic myelogenous leukemia in blast crisis; CMML, chronic myelomonocytic leukemia; RCMD, refractory anemia with multilineage dysplasia; NR, not reported. [a]The diagnosis and [b]karyotype were obtained from the original study.

Although we could not assess whether ecotropic viral integration site 1 (*EVI1*) was involved in the present case because no specimen was preserved, the morphological characteristics of the patient's bone marrow cells; i.e., the presence of small mono- or bi-lobulated forms, were consistent with those of *EVI1*-associated leukemia [3]. Concerning the partner of 3q26 in this translocation, 8q24, it was reported that candidate genes on the 8q24 locus are difficult to identify, because this band contains many genes [8]. Hence, further accumulation of cases is necessary to evaluate the genetic relationship between this abnormality and leukemogenesis. As for its diagnostic impact, the t(3;8)(q26;q24) aberration has mainly been reported in myeloid malignancies such as AML, MDS, and chronic myelogenous leukemia (CML). Among them, there have been several cases in which the t(3;8)(q26;q24) translocation was not present at the initial diagnosis, but subsequently appeared after progression to the CML-blastic phase [11], transformation from low grade MDS [4, 12], or the development of late-appearing myelofibrosis [13]. It seems that the t(3;8)(q26;q24) translocation plays a specific role in clonal evolution. On the other hand, some papers have reported that t(3;8)(q26;q24) is predominantly found in therapy-related cases [8, 14]. Recently, our knowledge of the crucial roles played by genetic mutations in therapy-related myeloid neoplasms has improved. Hence, it might be possible to determine the genetic mutations responsible for therapy-related leukemigenesis, even in cases in which the discrimination between clonal evolution and therapy-related disease is distressing.

Finally, azacitidine was recently reported to be effective against 3q-harboring AML and MDS [16]. In the latter study, it was shown that patients with lower bone marrow blasts counts, higher platelet counts, or non-complex cytogenetics and those who had not received prior intensive chemotherapy achieved better outcomes. Although t(3;8)(q26;q24) tends to have a poor prognosis [14], we suggest that a therapeutic strategy including azacitidine therapy might be suitable, especially in patients with the abovementioned clinical characteristics.

Address correspondence to: Masahiro Manabe, Department of Hematology, Osaka General Hospital of West Japan Railway Company, 1-2-22 Matsuzaki-cho, Abeno-ku, Osaka 545-0053, Japan. Tel: 81-6-6628-2221; Fax: 81-6-6628-4707; E-mail: m1153-564@med.osaka-cu.ac.jp

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