Journal of clinical and experimental hematopathology
Vol. 59 No.2, 96-97, 2019

Letter to the Editor

Spontaneous remission of acute monocytic leukemia with trisomy 8 and trisomy 18

Keywords: Spontaneous remission, trisomy 8, immune responses against leukemic cells

TO THE EDITOR

A 67-year-old male with no medical history presented with fever and visited a general practitioner. Based on the complete blood count, he had leukocytosis (white blood cell [WBC] count, 46,000/μl) and thrombocytopenia (platelet count, 29,000/μl), and was thus referred to our hospital (Day 1). His temperature ranged from 37.1°C to 37.8°C, but the physical examination results were unremarkable. No evidence of hepatosplenomegaly, gingival hypertrophy, or petechiae was found. Laboratory findings were as follows: WBC count, 33,000/μl; hemoglobin level, 11.8 g/dl; platelet count, 8000/μl; C-reactive protein level, 3.89 mg/dl; and lactate dehydrogenase level, 1,124 U/l. Serum and urine lysozyme levels were high (46.4 mg/μL [normal range, 5.0-10.2] and 0.03 mg/μL [0.0], respectively). Peripheral blood contained 28% blasts, including promonocytes. Bone marrow aspiration smear revealed 55.6% blasts, including promonocytes, with monocytic differentiation; some blasts had many small vacuoles, a few large vacuoles, or honeycomb-like vacuoles in the wide cytoplasm. A few monocytes and macrophages exhibited hemophagocytosis. On cytochemical staining, 31% of blasts, including promonocytes, were positive for myeloperoxidase activity, 71% were positive for non-specific esterase reactions, and all blasts were negative for naphthol AS-D chloroacetate esterase activity. Non-specific esterase reactions were inhibited by sodium fluoride. On flow cytometry, the blasts expressed cluster of differentiation (CD) 13, CD14, CD33, and CD56; the blasts weakly expressed myeloperoxidase but were negative for CD34. Cytogenetic analysis revealed trisomy 8 and trisomy 18 in 5/20 metaphases (Table 1). A diagnosis of acute monocytic leukemia was established according to the World Health Organization (WHO) classification 4th revised edition (2017) (French-American-British [FAB] classification: AML M5b).[1]

He was transfused with irradiated platelets once on Day 3 and once on Day 7. Monoblasts and promonocytes in the peripheral blood decreased from 28% (Day 1) to 2% (Day 7) and then to 1% (Day 10); his leukocytosis also normalized (Day 10; WBC count, 6220/μl). Thrombocytopenia improved gradually (Day 12; platelet count, 37,000/μl; Day 18; platelet count, 44,000/μl). Therefore, chemotherapy was postponed and he was discharged. Bone marrow examination on Day 21 revealed improvement, with 7.2% blasts, including promonocytes. Fluorescence in situ hybridization demonstrated that the proportion of abnormal clones with trisomy 8 decreased from 62% (61%+1%) (Day 1) to 16% (13%+1%+2%) (Day 21) (Table 1). Partial spontaneous remission (SR), but not complete SR, of acute monocytic leukemia was observed, which was hematological and cytogenetic in nature.

As monoblasts and promonocytes in the peripheral blood increased to 7% of the WBCs (11,200/μl) on Day 42, we examined his bone marrow. Monoblasts and promonocytes had increased to 54.2% of the nucleated cells. Cytogenetic analysis revealed an increasing number of clones with trisomy 8 and trisomy 18. Furthermore, these clones had accumulated additional chromosomal abnormalities (Table 1). Based on fluorescence in situ hybridization for chromosome 8, the number of clones with 3 or more signals had increased

Table 1. Bone marrow examination

	Blasts	Chromosome analysis		FISH (signals for chromosome 8)
Day 1	55.6%	48, XY, +8, inv(9)(p12q13)*, +18	[5]	3 signals: 61.0%
Admission		46, XY, inv(9)(p12q13)*	[15]	4 signals: 1.0%
Day 21	7.2%	48, XY, +8, inv(9)(p12q13)*, +18	[2]	3 signals: 13.0%
Partial SR		49, idem, +8	[1]	4 signals: 1.0%
		46, XY, inv(9)(p12q13)*	[17]	6 signals: 2.0%
Day 42	54.2%	48, XY, +8, inv(9)(p12q13)*, +18	[1]	3 signals: 54.0%
Relapse		48, idem, -inv(9),+mar1	[5]	6 signals: 16.0%
		48, idem, add(10)(q22),add(16)(p11.2)	[6]	7 signals: 1.0%
		46, XY, inv(9)(p12q13)*	[8]	

*inv(9)(p12q13) is thought to be a normal change; FISH, fluorescence in situ hybridization; SR, spontaneous remission

(Table 1). Due to the rarity of 4 and 5 signals for chromosome 8, 6 signals were considered to originate from tetraploidy of the clone with 46, XY, +8, inv(9)(p12q13), +18, although metaphase chromosomes were not obtained after incubation for chromosome analysis.

Monoblasts and promonocytes in peripheral blood steadily increased in number. Anemia and thrombocytopenia worsened (day 54; hemoglobin level, 7.9 g/dl; platelet count, 6,000/μl). As spontaneous remission did not occur again, we started induction chemotherapy with daunorubicin-cytosine arabinoside (DNR/AraC) on Day 57. On Day 65, monoblasts were not detected in peripheral blood. However, the patient developed pneumonia and died on Day 68.

SR of acute myeloid leukemia (AML) in adults is a rare clinical phenomenon that usually occurs for a short duration. It was first described following typhoid infection by Eisenlohr in 1878.[2] Immune responses induced by severe systemic infections or non-irradiated blood transfusions have been reported to play an important role in the development of SR. However, the exact mechanisms of SR have yet to be determined. On Day 1, we detected many macrophages in the patient's bone marrow aspiration smear. We thought that SR had started prior to irradiated platelet transfusion (performed once on day 3 and once on day 7) in this case. SR may be more likely in the FAB subtypes M4/M5. These subtypes account for approximately half of all reported cases of SR of AML.[3] SR has been reported in several cases of AML with trisomy 8, but the role of trisomy 8 in SR development remains unclear. Furthermore, we were unable to elucidate the relationship between cytogenetic abnormality, especially +8 and +18, and SR. SR usually lasts for a short duration, with an average of 5-7 months, ranging from as short as 2 weeks to more than 10 years.[3,4] Based on the results of ex vivo experiments performed at the 10-year follow-up of sustained SR in an *MLL/AF-9*-positive AML patient, Müller *et al*. speculated that AML-specific CD8 T-cells and humoral mechanisms direct early clearing of myeloblasts, whereas long-term remission may be due to natural killer-mediated disease control.[4] In this case, no marked increase in lymphocyte or granular lymphocyte counts was observed. We found no evidence of disease control that was mediated by certain AML-specific CD8 T-cells or natural killer cells. As SR occurs even in patients with high disease burden, relapsed/refractory disease, or AML with complex/adverse genetic abnormalities, it is of interest because it demonstrates the strength of the immune system in inhibiting leukemia. In the past decade, the field of cancer immunotherapy has seen marked success with the introduction of immune checkpoint inhibitors. We consider the appearance of resistant clones (Table 1) to be associated with the development of immune responses against leukemic cells.

ACKNOWLEDGMENTS

SRL, Inc. performed chromosome analysis and fluorescence in situ hybridization (chromosome 8), and interpreted the results of the analyses.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest. There was no funding.

REFERENCES

1 Arber DA, Peterson LC, Brunning RD, *et al*. Acute myeloid leukemia, NOS. In: Swerdlow SH, Campo E, Harris NL, *et al*. (eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed, Geneva, WHO Press. 2017; pp. 156-166.

2 Eisenlohr C. Leukemia lienalis, lymphatica et medullaris mit multiplen Gehimnerveinlahmungen. Virchows Arch. 1878; 73 : 56-73.

3 Rashidi A, Fisher SI. Spontaneous remission of acute myeloid leukemia. Leuk Lymphoma. 2015; 56 : 1727-1734.

4 Müller-Schmah C, Solari L, Weis R, *et al*. Immune response as a possible mechanism of long-lasting disease control in spontaneous remission of MLL/AF9-positive acute myeloid leukemia. Ann Hematol. 2012; 91 : 27-32.

Takahiro Suyama,[1] Kaoru Hasebe[2]

[1]Department of Hematology, Ebina General Hospital, Ebina, Kanagawa, Japan, present address: Department of Internal medicine, Nippon Koukan Hospital, Kawasaki, Kanagawa, Japan, [2]Department of Clinical Laboratory, Ebina General Hospital, Ebina, Kanagawa, Japan

Corresponding author: Takahiro Suyama, 1-2-1, Kawasaki-ku, Kawasaki, Kanagawa, 210-0852 Japan.
E-mail: takahiro-suyama@koukankai.or.jp

Received: February 7, 2019.
Revised: March 4, 2019.
Accepted: March 26, 2019.
Onlune Published: June 28, 2019
DOI:10.3960/jslrt.19005