A case of acute promyelocytic leukemia with morphologic multilineage dysplastic changes

Setsuki Isono,¹ Katsuyasu Saigo,²
Keiko Nagata,¹ Keiko Numata,¹
Toshiaki Kojitani,¹ Akiharu Okamura,³
Akihiko Nishizawa,⁴ Masafumi Takata,²
Mariko Takenokuchi,⁴ Eiji Tatsumi⁵

¹Clinical Laboratory, Kakogawa West City Hospital; ²Faculty of Pharmacological Sciences, Himeji Dokkyo University; ³Section of Pathology, Kakogawa West City Hospital; ⁴Section of Internal Medicine, Kakogawa West City Hospital; ⁵Department of Nutrition and Health, Sagami Women's University, Japan

Abstract

Although reports of typical acute promyelocytic leukemia (APL) cases rarely mention dysplastic changes, this report concerns a rare case of APL with tri-lineage dysplastic changes resembling the characteristic features of myelodysplastic syndrome (MDS). The patient, a 77-year-old Japanese male, was diagnosed as having pancytopenia with hematologic morphological abnormalities comprising micro-megakaryocytes, neutrophils with hypo-granulation and negative peroxidase activity, and erythroblasts containing nuclei with abnormalities such as karyorrhexis. Although there is one report of a case of transformation of de novo MDS into APL and several reports of cases of therapy-related MDS transformed into APL, our patient had no history of cytopenia or of either chemo or radiation therapy. Our case can thus be considered to constitute a rare case of APL with dysplastic morphology.

Introduction

Myelodysplastic syndrome (MDS) frequently transforms into acute myelogenous leukemia, but rarely into acute promyelocytic leukemia (APL).¹ We experienced a rare case of elderly APL featuring various morphological abnormalities resembling characteristics of MDS, although the patient did not go through a stage perceptibly complicated with any form of cytopenia before the diagnosis of APL.

Case Report

A 77-year-old male was suffering from low-

grade fever and general fatigability in April 2011. After the possibility of pancytopenia was pointed out by a general physician, he was referred to Kakogawa West City Hospital, Japan. A chest X-ray indicated the presence of pneumonia and yielded the following laboratory findings: leukocyte count, $0.84 \times 10^9/L$; red blood cell count, $2.75 \times 10^{12}/L$; hemoglobin value, 8.5 g/dL; hematocrit value, 26.5%; platelet count, $55 \times 10^9/L$; prothrombin time, 13.8 sec; fibrinogen level, 372 mg/dL and fibrin degradation product (FDP) level, 88.7 micro g/mL. These findings pointed to the presence of pancytopenia and a hyperfibrinolytic state.

Differential leukocyte counts were 10% for neutrophils, 83% for lymphocytes and 1% for basophils. Morphological examination detected frequent hypo-granular and peroxidase (POX)-negative neutrophils (Figure 1A and B).

Blood chemistry test findings were: CRP, 20.45 mg/dL; AST, 20 IU/L; ALT, 8 IU/L; LD, 175 IU/L; ALP, 238 IU/L; BUN, 55 mg/dL; creatinine, 2.74 mg/dL and uric acid, 8.7 mg/dL, indicating severe inflammation due to pneumonia and renal dysfunction.

Iliac bone marrow aspiration produced a total nucleated cell count of $59 \times 10^9/L$ and a megakaryocyte count of $25 \times 10^6/L$, while the differential count showed the bone marrow consisted of 28.2% myeloblasts and 55.2% abnormal promyelocytes, frequently containing Auer rods or faggot cells (Figure 2A and B). These cells were strongly positive for POX staining (Figure 2C). Micromegakaryocytes and megakaryocytes with non-lobulated nuclei or isolated multi-nuclei (Figure 3A-D) as well as erythroblasts showing karyorrhexis or nuclei with abnormal configuration (Figure 3E and F) were also detected. Surface marker analysis produced positive results for CD13 (88.9%), CD33 (98.7%), CD64 (70.8%), CD65 (42.9%), CD71 (51.8%), CD117 (84.8%) and negative results for CD2, CD7, CD19, CD14, CD15, CD11b, CD34, HLA-DR, and glycophorin-A. RT-PCR detected the presence of a PML-RARA chimeric mRNA of 2.0×10^4 copies/micro g RNA, and chromosome analysis showed 46XY, t(15;17)(q22;q12) in 25% of the cells analyzed. These results indicated the patient had APL with MDS-like morphological abnormalities complicated with disseminated intravascular coagulation (DIC), pneumonia and renal insufficiency.

Although treatment with all-trans-retinoic acid (ATRA) combined with antibiotics therapy was started immediately, renal insufficiency deteriorated and the patient died on the 14th day after admission. The renal insufficiency was considered to be result of pre-existing dysfunction and adverse effects of antibiotics or anti-inflammatory drugs, although the possibility of differentiation syndrome could not be completely excluded. After the initiation of ATRA administration, the leukocyte counts

Correspondence: Katsuyasu Saigo, Faculty of Pharmacological Sciences, Himeji Dokkyo University, 7, Kami-ohno, Himeji, Hyogo 670-8524, Japan.

Tel. +81.79.2236844 - Fax: +81.79.2236853.

E-mail: ksaigo@himeji-du.ac.jp

Contributions: SI, AO, concept and design, data acquisition and interpretation; KS, concept and design, data interpretation, drafting of article; MTake, data interpretation, drafting of article; ET, concept and design, data interpretation; KNa, KNu, TK, data acquisition; MTaka, AN, data interpretation.

Conflict of interests: the authors declare no conflict of interests.

Key words: acute promyelocytic leukemia, dysplasia, all-trans retinoic acid.

Received for publication: 19 September 2012.

Revision received: 27 November 2012.

Accepted for publication: 7 January 2013.

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Hematology Reports 2013; 5:e5

doi:10.4081/hr.2013.e5

increased from $1 \times 10^9/L$ to $5.7 \times 10^9/L$ and the neutrophil percentage from 21% to 62%. Because mature neutrophils with Auer rods were observed in peripheral blood (Figure 1C), the patient's leukemia was considered to be responsive to ATRA treatment.

Discussion and Conclusions

Initially, our patient was thought to have MDS complicated with pneumonia and DIC, but the laboratory findings disclosed he was suffering from APL. There are three possible explanations for the morphological abnormalities resembling the characteristic features of MDS. First, this was possibly a rare case of MDS transformed into APL. Ogawa *et al.* reported a case of RAEB in transformation with 15% t(15;17),² which changed to APL after several months and is the only case report of de novo MDS transformed into APL. On the other hand, there are no reports of even APL cases with chromosome 7 abnormalities that possess morphological abnormalities.³ Although Varma *et al.* reported that variant forms of APL cases frequently express myelodysplastic abnormalities, our patient was a typical APL.⁴ However, the diagnosis of MDS

Figure 1. Peripheral blood leukocytes. A) peroxidase (POX) negative neutrophil; B) hypogranular neutrophil (May-Giemsa staining); C) neutrophil containing Auer body after initiation of ATRA treatment (May-Giemsa staining).

Figure 2. Typical acute promyelocytic leukemia (APL) cells in bone marrow. A) and B) APL cells with hypergranular cytoplasm and Auer body or faggot cells (May-Giemsa staining); C) strongly positive staining for peroxidase.

Figure 3. Atypical cells in bone marrow smear (May-Giemsa staining). A) and B) micro megakaryocytes; C) megakryocyte with non-lobulated nucleus; D) megakaryocyte with isolated multi-nuclei; E) erythroblast showing karyorrhexis; F) erythroblast with a nucleus showing abnormal configuration.

could not be confirmed in our case because there was no past history of cytopenia.

There are several reports of cases of therapy-related MDS transformed into APL. Anderson *et al.* reported three such cases among 41 secondary APL cases.⁵ Furthermore, Wolach *et al.* reported a case responsive to treatment with ATRA and arsenic trioxide that developed APL from therapy-related MDS over the course of several years.⁶ However, our patient had no history of chemotherapy or irradiation.

The third possibility is that, according to the WHO classification of tumors of hematopoietic and lymphoid tissues, our patient could have been classified as acute myelogenous leukemia (AML) with myelodysplasia-related changes.⁷ Although this specific category excludes cases characterized by genetic abnormalities of AML accompanied by recurrent abnormalities such as t(15;17), our case might be classified in this category.

According to Haferlach *et al.*, morphologic dysplasia in de novo AML reportedly does not correlate with prognosis.⁸ Although our patient also seemed to respond to ATRA, he died from complicating renal insufficiency and infection.

To summarize, we encountered an elderly case with APL associated with dysplastic changes resembling myelodysplastic syndrome.

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