Acute Myelomonocytic Leukemia in a Patient with Multiple Myeloma: Evidence for Different Clonal Origin

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A case of 77-year-old female with multiple myeloma (IgG-k) developed acute myelomonocytic leukemia (AMMoL) following a myelodysplastic stage after chemotherapy with melphalan-cyclophosphamide combinations for 6 years. The leukemic blast cells expressed both myeloid antigens (CD11b, CD13, CD14, CD15, CD33 and CD34) and T/B lymphoid antigens (CD2, CD4, CD22 and PCA1). Cytogenetic analysis revealed a chromosome deletion -7. Analysis of immunoglobulin genes showed the heavy chain genes in germ line configuration. These findings indicate that the AMMoL was a therapy-related stem cell leukemia and was a clonal origin genetically different from multiple myeloma irrespective of plasma cell phenotype.
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Key words: therapy-related leukemia, monosomy 7

Introduction

Multiple myeloma and acute myelomonocytic leukemia (AMMoL) are generally considered to be unrelated diseases. However, several cases of coexistence of multiple myeloma and AMMoL (1, 2) or multiple myeloma terminating in AMMoL (3, 4) have been previously described. It is known that BALB/c mice develop plasmacytoma or AMMoL by injecting mineral oil into the peritoneal cavity (5). Whether these two diseases arise from same or different clonal origins is controversial. Recently, Akashi et al (6) reported the presence of two identical rearrangement bands of immunoglobulin heavy chain gene in both myeloma cells and AMMoL cells and described the involvement of common leukemic progenitors providing both myeloma and AMMoL cells. Here, we describe a case of multiple myeloma developing AMMoL which was considered to be a genetically different clone from myeloma.

Patient and Methods

Case report

A 77-year-old female was admitted to our hospital in October, 1982 because of lumbago. Peripheral blood showed a slight anemia and erythrocyte sedimentation ratio was as high as 81 mm per hour. The serum level of total protein was increased to 10 g/dl. Serum IgG was 6,750 mg/dl and the other immu-

noglobulin classes were markedly depressed. Serum immunoelectrophoresis showed a monoclonal IgG-k bow. The bone marrow was hypercellular with 78.9% atypical plasma cells (Fig. 1). A diagnosis of multiple myeloma was made and the patient was treated with daily oral melphalan (2-6 mg/day, a total dose of 694 mg) with or without added prednisolone (10 mg/day) until February 1987. Following this, she also received daily oral cyclophosphamide (50 mg/day, a total dose of 14,200 mg) and prednisolone (5-10 mg/day). In October 1988, she developed a pancytopenia with white blood cell of 900/cmm, red blood cell of 153×10^4 /cmm and platelet of 0.9×10^4 /cmm. The bone marrow puncture revealed a nuclear cell count of 12.6×10^4 /cmm with the appearance of 7.2% myeloid blastic cells and plasma cells were decreased to 1.6%. We ceased cyclophosphamide and prednisolone treatments and observed her with no chemotherapy. This myelodysplastic stage continued until April 1989, when the white blood cell count rapidly increased to 15,200/cmm with 27% monocytoid cells and 13% myeloid blastic cells. Monoblasts accounted for 20% and myeloblasts for 62% of all the nucleated cells in the bone marrow (Table 1), and a diagnosis of acute myelomonocytic leukemia was made (Fig. 2). Though there was an absence of atypical plasma cells, serum immunoelectrophoresis showed a faint band in the IgG-k region. Treatment with low-dose cytarabine was not effective and she died on December 23, 1989. Autopsy was not done.

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Figure 1. Myeloma cells in bone marrow (May-Giemsa staining, $\times 600$).

Figure 2. AMMoL cells in bone marrow (May-Giemsa staining, $\times 600$).

Table 1. Hematological Findings on the Occurrence of AMMoL

	Peripheral blood (%)	Bone marrow (%)
Myeloblast	13	62
Promyelocyte	0	1
Myelocyte	0	2
Metamyelocyte	0	5
Neutrophil-stab	34	6
Neutrophil-seg	18	2
Eosinophil	0	0
Basophil	0	0
Monocytoid cell	27	20
Lymphocyte	8	1
Erythroblast	0	1
Nuclear cell count (/cmm)	15,200	480,000

Cell characterization

Immunophenotyping. Mononuclear cells were obtained from peripheral blood by Ficoll-Hypaque density gradient centrifugation and applied for the following studies. These collected mononuclear cells consisted of over 90% leukemic cells on the cytospin preparation. Surface marker analysis was performed by the indirect immunofluorescence method as previously described (7). Before immunostaining, the cells were treated with 5% heat aggregated human AB serum for blocking of binding due to receptors for the IgG Fc portion. CD11b (recognized by OKM1), CD13 (MCS2), CD14 (My4), CD15 (LeuM1), CD33 (My9), CD34 (My10) and CD41 (J15) were tested as myeloid markers; CD2 (T11), CD3 (Leu4), CD4 (Leu3), CD7 (Tp40) and CD8 (Leu2) as T-cell markers; CD10 (J5), CD19

(Leu12), CD20 (B1), CD22 (Leu14) and PCA1 as B-cell markers. CD38 and HLA-DR were detected by Leu17 and OKIa1, respectively. Anti-Tac was used to detect interleukin-2 receptor alpha chain (CD25). Specimens were evaluated by flow cytometry (Cytron; Ortho Diagnostic Systems, Tokyo, Japan). We focused on the blastic fraction of the cytogram to clarify the phenotype of the leukemic cells. Specimens were considered positive for a monoclonal antibody (MoAb) if more than 15% of the cells showed specific labeling above the level of the control. Contaminated T-cells or B-cells were judged by considering the expression of T-cell antigen, CD3 or B-cell antigen, CD20. In fact, the contaminated T-cells or B-cells made up less than 4% of the leukemic cells.

DNA study. Southern blot analysis was performed as described previously (8). DNA probe was JH for Ig heavy chain (IgH) genes.

Cytogenetic analysis. A chromosome study was performed on aspirated bone marrow cells as previously described (9).

Results

Cellular characteristics

The leukemic cells morphologically consisted of both myeloid blastic cells and monocytoid cells (Fig. 2), and were cytochemically stained for myeloperoxidase and alpha-naphthyl butyrate esterase. Immunophenotypic studies showed that the leukemic cells were positive for CD11b, CD13, CD14, CD15, CD33, CD34, CD2, CD4, CD22, PCA1, CD38, HLA-DR and CD25 (Table 2). The IgH genes were germ line configuration. Cytogenetic analysis of marrow cells revealed a complex abnormality of 45 XX, -7, 12q-, 21q+ in 19 of 20 metaphases. The remaining one metaphase was normal karyotype.

Discussion

In this study, we report the development of AMMoL in a

Table 2. Surface Markers

Immunophenotype	Positive cells (%)
Myeloid	
CD11b	19
CD13	54
CD14	0
CD15	7
CD33	45
CD34	70
CD41	0
T-lymphoid	
CD2	18
CD3	0
CD4	28
CD7	3
CD8	0
B-lymphoid	
CD10	2
CD19	0
CD20	4
CD22	39
PCA1	15
Others	
CD25	18
CD38	85
HLA-DR	95

patient after long-term (6 years) alkylating therapy for multiple myeloma. The occurrence of AMMoL supervening on multiple myeloma following alkylating therapy is well recognized (10, 11). The patient had a myelodysplastic stage prior to AMMoL and showed a karyotype of -7 abnormality. Monosomy 7 is well recognized to be seen in secondary leukemia (12). Therefore, it is suggested that the current case was therapy-related secondary leukemia (13). There have been various descriptions of the relationship between multiple myeloma and AMMoL. Some investigators described myeloma cells with monocytic features such as phagocytosis (14) or myelomonocytic antigen expression (15). Synchronous or metachronous coexistence of myeloma and AMMoL irrespective of prior therapy was also reported (1–4). This situation resembles biphenotypic or bilineal subtypes of immature acute leukemia and such leukemia cells are considered to have originated from multipotential stem cells (16). In fact, Akashi et al (6) showed the identical IgH gene rearrangements in both AMMoL cells and myeloma cells, and described the involvement of common leukemic progenitors. In addition, other investigators reported multiple myeloma cells expressing surface markers of multiple hematopoietic-cell lineages (17). However, genetically myeloma cells have rearranged genes of not only IgH but also Ig light chain, suggesting

that myeloma cells originated from early B-cells or more differentiated cells (18). Therefore, concerning neoplastic target cells of multiple myeloma, further investigations are needed.

In the present case, when AMMoL occurred, a faint IgG-k monoclonal protein was still recognized, indicating the coexistence of occult neoplastic plasma cells producing IgG-k. However, unlike the case of Akashi et al (6), monoclonal IgH gene rearrangement was not detected in the AMMoL cells of our case. These AMMoL cells possessed, in addition to myeloid antigens, stem cell antigen CD34 and T/B lymphoid antigens such as CD2, CD4, CD22 and PCA1. CD25 expression is also an immature characteristic (19). Though PCA1 is a plasma cell phenotype, it is known to be rarely expressed even on myeloid lineage cells (20). Therefore, the AMMoL cells may be derived from primitive stem cells capable of both lymphoid and myeloid differentiation. In conclusion, as mentioned above, we regard the AMMoL as a therapy-induced secondary leukemia which had immature properties and was of a different clonal origin than multiple myeloma. Genetically, few cases have been proved to be different clonal diseases in the disorder like the present case. In the coexistence of AMMoL and myeloma, whether two diseases are derived from identical or different clones may be considered to vary from case to case. However, since we do not know the genetic marker expressed prior to the Ig gene rearrangement, further studies are necessary to precisely clarify the clonality of this type of disease.

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