Paraproteinemia in a Patient with Acute Myelogenous Leukemia Derived from the Myelodysplastic Syndrome —— A Case Report ——

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ABSTRACT. Severe paraproteinemia was found in a 75-year-old female with acute myelogenous leukemia (AML) derived from refractory anemia with an excess of blasts, a type of the myelodysplastic syndrome (MDS). Immunoglobulin G-κ and G-λ paraproteins had increased in accordance with the proliferation of myeloblasts in her bone marrow. When the diagnosis of AML was made, a severe bleeding tendency and disturbance of consciousness due to the hyperviscosity syndrome were noted, although there was no significant increase in plasma cells in her bone marrow. An ultrasonogram disclosed multiple hyperechoic nodular lesions in the spleen. Cytoreductive therapy for AML was begun after plasma exchange, but she died of acute renal failure, subarachnoid hemorrhage, and the disseminated intravascular coagulation syndrome. Autopsy findings revealed clusters of plasma cells in the spleen and lymph nodes. The possibility that this coexistant paraproteinemia and AML were related to the evolution of a transformed clone in MDS is discussed.

Key words : paraproteinemia — AML — MDS

Among malignancies of myelomonocytoid lineage, chronic neutrophilic leukemia is frequently associated with multiple myeloma (MM).[1,2] In addition, MM or paraproteinemia has also been reported in some cases of the myelodysplastic syndrome (MDS)[3,4] and in several cases of acute myelogenous or myelomonocytoid leukemia (AML or AMMoL).[5-8] Simultaneous occurrence of AML and MM, however, is considered quite uncommon and, in a critical review of reported cases,[9] has been suggested to represent a coincidental or chance association.

Recently, it has been suggested that a malignantly evolved clone in MDS might be not only in myeloid and/or monocytoid lineage but also in lymphoid lineage.[10]

In this report, a case of AML derived from MDS and characterized by the severe hyperviscosity syndrome due to paraproteinemia, with multiple nodular lesions of plasmocytes in the spleen, is described. Its possible relation to the malignant clone in MDS and the proliferating plasmocytes is discussed.

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CASE REPORT

A 75-year-old female with a two-year history of bronchiectasis first consulted our division on January 24, 1989. She had pancytopenia (Hb, 7.4 g/dl ; platelet count, $69\times10^9/\ell$; WBC count, $4.7\times10^9/\ell$) and 2% myeloblasts in peripheral blood. A bone marrow smear disclosed a marked increase in cellularity with a moderate decrease in megakaryocytes. Moderate nuclear maturation defects were seen in her erythroid series, and myeloblasts accounted for 11.6% of the total nuclear cell count (NCC). Plasmocytes made up only 2% of the NCC. The results of karyotypical analysis of her bone marrow cells were: 47, XX, +8, −11, −12, 9q+, 21q+, +2 markers. A diagnosis of the myelodysplastic syndrome (MDS) — refractory anemia with an excess of blasts (RAEB) — was made according to the FAB classification.[11] Serum protein electrophoresis showed total protein to be 9.0, albumin 4.0, α_1 globulin 0.24, α_2 globulin 0.5, β globulin 0.67, and γ globulin 3.59 g/dl with a small notch in the γ region. Serum immunoglobulin (Ig) levels were as follows: IgG 3,749, IgA 294, and IgM 600 mg/dl. She was discharged with 1 μg/body of 1α-hydroxy vitamin D_3.

One month later, she was readmitted to our hospital due to increasing fatigue, pyrexia, and anorexia. Her peripheral blood smear showed an increased WBC of $20.7\times10^9/\ell$ with 25% myeloblasts. A bone marrow smear disclosed a marked increase in cellularity with 45% myeloblasts. Plasmocytes in her bone marrow acounted for 0.6% of the NCC. The results of a chromosome analysis were: 50, XX, +8, +11, +14, +19. The serum γ globulin was elevated to 6.1 g/dl with elevation of Ig levels. The IgG was 6,281, the IgA 399, and the IgM 563 mg/dl, and serum immunoelectorophoresis revealed M-bows at anti-IgG, anti-κ, and anti-λ (Fig. 1). Electrophoresis of urinary protein showed a leakage of γ globulin of 5.76 g/day. Based on these findings in peripheral blood and bone marrow, a diagnosis of acute myelogenous leukemia (AML-M2) derived from RAEB was made according to the FAB classification.[11] Neither lymphadenopathy nor hepatosplenomegaly was observed. An ultrasonogram of the spleen disclosed multiple hyperechoic nodules approximately 10 mm in diameter. A radiological examination of the bones revealed neither osteolytic lesions nor pathological fractures.

During treatment for pneumonia, a severe bleeding tendency and disturbance of consciousness developed with an increase in blasts in the peripheral blood and elevation of total serum protein to 11.2 g/dl (the IgG was 6,869 mg/dl). A diagnosis of the hyperviscosity syndrome was made clinically, and 1.8 ℓ of plasma exchange (PEx) was done using the centrifugation type of pheresis system ; V50 (Hemonetics, U.S.A.) with fresh frozen plasma as the substituting fluid. Immediately after PEx, a dramatic improvement in the bleeding tendency and disturbance of consciousness was observed. Then, cytoreductive therapy, including cytosine arabinoside, daunorubicin, 6-mercaptopurine, and prednisolone, was started. Although disappearance of blasts from her peripheral blood was observed and no elevation of serum immunoglobulin was seen five days after the start of chemotherapy, disseminated intravascular coagulation (DIC), acute renal failure, and subarachnoid hemorrhage occurred. Although number and size of the multiple nodular lesions of the spleen were reduced, she died of respiratory failure five months after the diagnosis of RAEB.

The main autopsy findings were as follows; hypercellular marrow which was compatible with AML, nodular infiltration of plasmocytes in the spleen (Fig. 2) and the paraaortic lymph node, general bleeding, and multiple hemorrhagic infarctions of both kidneys due to DIC. The weight of the spleen was 480 g. The size of the lymph node was approximately $25 \times 6 \times 10$ mm. The plasmocytes in the spleen showed polyclonality with Ig-κ being more dominant than Ig-λ with PAP staining.

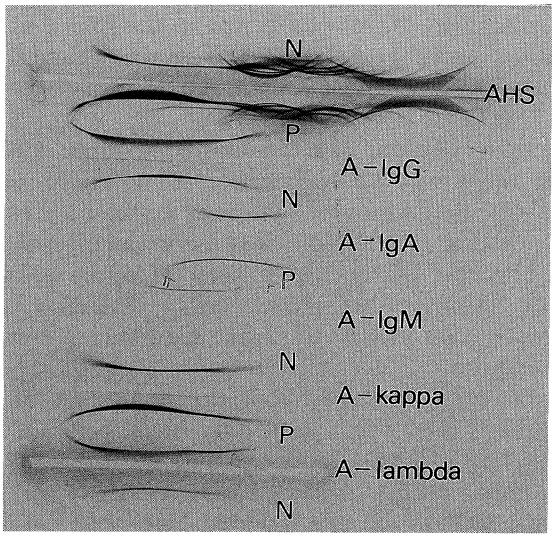

Fig. 1. M-bows at anti-IgG, anti-κ, and anti-λ detected by serum immunoelectrophoresis at diagnosis of AML.

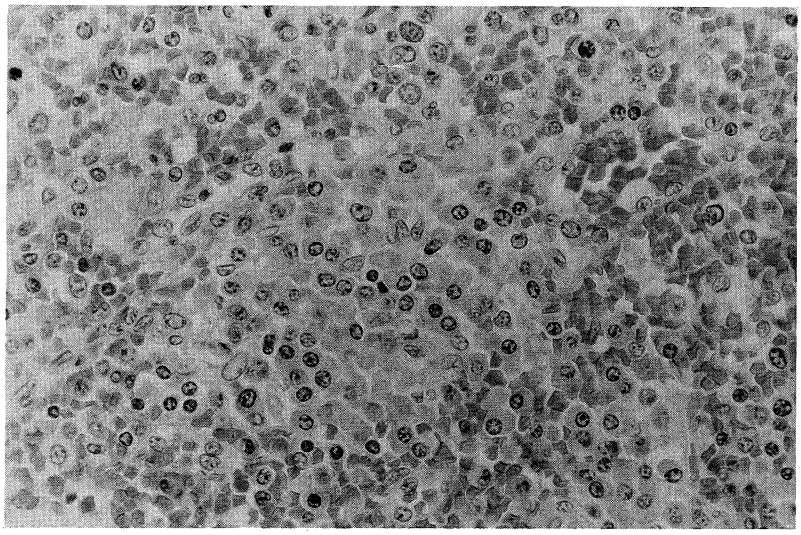

Fig. 2. Cluster of plasmocytes in the spleen at autopsy.

DISCUSSION

The coexistance of AML and paraproteinemia in the present case different in several ways from that in previously reported cases.[3-8] First, the serum immunoglobulin level, which exceeded 6 g/dl, was higher than that in any other reported cases. The hyperviscosity syndrome had developed and it was necessary to carry out PEx due to its severe clinical manifestation in the form of a bleeding tendency and a disturbance of consciousness. Second, there was no increase in plasma cells in her bone marrow (less than 2% of the NCC), although plasma cells might have proliferated in the spleen as multiple nodular lesions. In addition, there have been no cases in which the progression of paraproteinemia has paralleled the proliferation of myeloblasts of the leukemic clone.

The paraproteinemia in our case was not compatible with typical multiple myeloma, because there was no suppression of albumin or other immunoglobulins, or any osteolytic lesions. It must be categorized as plasma cell dyscrasia, however, rather than simple secondary gammopathy associated with malignant disease, because of the higher level of serum paraproteins and the existence of splenic lesions of the plasma cells. Therefore, these proliferated plasma cells may be considered to have acquired a certain capacity for malignant transformation.

Recently, Yunis *et al.* proposed that the occurrence of *ras* mutation in MDS extended to all cell types; not only stem cells of myeloid and/or monocytoid lineage but also those of lymphoid cell lineage.[10] If the model of this theoretical proposal occurs in certain cases of MDS and/or AML derived from MDS, patients, such as the one reported here, with concomitant AML or MDS and paraproteinemia, may have a malignantly transformed clone in at least two lineages, one myeloid and one B-lymphoid, due to unknown but common genetic events.

In this case, regrettably, there was no opportunity to examine the *ras* mutation in leukemic cells or to carry out karyotypical analyses of the plasma cell tumor in the spleen. Moreover, the possibility remains that the evoluted leukemic cells produce immunoglobulins. Although some researchers believe that the coexistence of AML/MDS and paraproteinemia represents a coincidental or chance association,[9] the above-mentioned possibility suggests clonal expansion of the transforming events to other lineages. Before any definite conclusion can be made, however, additional cases of concomitant leukemia and gammopathy must be accumulated and studied in greater detail.

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