Multiple Myeloma with Coexistent Myelofibrosis: Improvement of Myelofibrosis Following Recovery from Multiple Myeloma after Treatment with Melphalan and Prednisolone

Kiyotaka KAWAUCHI, Haruki MORI, Hajime SUGIYAMA*, Kazuo OSHIMI** and Akira HIRAYAMA***

We describe a case of multiple myeloma associated with myelofibrosis. This patient had hepatosplenomegaly, moderate anemia with anisocytosis and nucleated red blood cells, and Bence-Jones protein (κ) in the urine. A bone marrow biopsy showed extensive marrow fibrosis and proliferation of numerous immature plasma cells containing κ light chain in the cytoplasm. Melphalan-prednisolone therapy not only facilitated the disappearance of the immature plasma cells but also resulted in an improvement of myelofibrosis in the bone marrow. The immature plasma cell proliferation and marrow fibrosis in the bone marrow were seen again after interruption of chemotherapy. Therefore, this myelofibrosis may be secondary to the coexistent multiple myeloma.

Key words: Multiple myeloma, Myelofibrosis, MP therapy

Myelofibrosis (MF) is characterized by splenomegaly and fibrotic bone marrow. It is usually the primary form of one of the chronic myeloproliferative disorders. However, sometimes it is secondary to hematological or non-hematological neoplasms, infections, or exposure to drugs or radiation (1). Although marrow fibrosis associated with plasma cell dyscrasia such as multiple myeloma (MM) is reported occasionally, it has not been clearly demonstrated whether coexistent MF in untreated bone marrow is secondary to MM or not (2). In this paper we report a patient in whom MF improved with the recovery from MM after treatment with melphalan and prednisolone (MP).

CASE REPORT

A 67-year-old woman was admitted to our hospital in November 1984 with complaints of dyspnea from exertion. A right hemicolecction was performed for Crohn’s disease in 1981. On admission a physical examination revealed hepatosplenomegaly. Peripheral blood showed normocytic-normochromic anemia of Hb 7.6 g/dl with anisocytosis, white blood cell count of 4.7 × 10⁹/l with 1% melocytes, 0.5% metamyelocytes, 3% bands, 51% polymorphonuclear leukocytes, 33.5% lymphocytes, 8.5% monocytes, and 5 nucleated RBCs/100WBC, and platelet count of 132 × 10⁹/l. Peripheral neutrophilic granulocytes exhibited a normal alkaline phosphatase activity. Blood chemical analysis showed an elevation of lactate dehydrogenase and hypogammaglobulinemia. Urine immunoelectrophoresis revealed the presence of Bence-Jones protein (BJP) (κ). An attempt to
Aspirate bone marrow was unsuccessful. A bone marrow biopsy showed numerous immature plasma cells with prominent nucleoli in the hematoxylin-eosin stained section and extensive fibrosis surrounding tumor cells in the reticulin stained section (Figs. 1, 2). Peroxidase/antiperoxidase complex immunostaining revealed the presence of immature plasma cells containing cytoplasmic \( \kappa \) light chain (Fig. 3). A bone survey was normal. A diagnosis of plasma cell myeloma and myelofibrosis was made.

Intermittent chemotherapy was initiated with 12 mg/day of melphalan and 100 mg/day of prednisolone administered orally for 4 days at intervals of 4 to 5 wk. The patient received a total of 41 cycles of MP during 46 months as a maintenance therapy. After 15 cycles of MP therapy, daily dosages of melphalan and prednisolone were reduced to 6 mg and 60 mg, respectively. BJP in urine was gradually reduced and was barely detectable after 14 cycles of MP therapy, however it never disappeared during maintenance chemotherapy. The hemoglobin level was restored from 7.6 g/dl to 15.2 g/dl and the IgG level rose from 628 mg/dl to 1,070 mg/dl. Hepatosplenomegaly was no longer observed in an ultrasonographic study. MP therapy was discontinued October 4, 1988, because a bone marrow biopsy revealed hypocellular bone marrow. At this time successful bone marrow aspiration revealed a nucleated cell count of \( 25 \times 10^9/\text{l} \) without immature plasma cell infiltration and a bone marrow biopsy showed no evident marrow fibrosis (Fig. 4). Seven months later, bone marrow biopsy revealed moderate marrow fibrosis and immature plasma cell proliferation again with normal trilineage hematopoiesis (Fig. 5). The urine BJP also gradually increased in amount. She received MP therapy again on January 23, 1990. Bone marrow biopsy revealed a decreased number of plasma cells and improved

![Fig. 1. Bone marrow biopsy showing diffuse proliferation of immature plasma cells (Hematoxylin-Eosine stain, \( \times 1000 \)).](image1)

![Fig. 2. Pretreatment bone marrow showing extensive fibrosis (silver impregnated reticulin stain, \( \times 200 \)).](image2)

![Fig. 3. Bone marrow biopsy showing numerous immature plasma cells containing cytoplasmic \( \kappa \) light chain (peroxidase/antiperoxidase complex immunostain, \( \times 400 \)).](image3)

![Fig. 4. Marrow fibrosis improvement after chemotherapy (silver impregnated reticulin stain, \( \times 200 \)).](image4)
Fig. 5. Marrow fibrosis developed again after interruption of chemotherapy (silver impregnated reticulin stain, ×200).

myelofibrosis. At this time measurement of platelet-derived growth factor (PDGF) by radioimmunoassay revealed a high value (4,100 pg/ml) in bone marrow supernatant compared with that in peripheral blood in healthy donors (<800 pg/ml).

**DISCUSSION**

In recent retrospective studies the incidence of the presence of idiopathic MF in patients with MM and that of MM in patients with idiopathic MF were estimated to be 8.8% and 4.3%, respectively, in the scattered reports associating MF with MM (3, 4). Vandermolen and colleagues described a classification of MM with coexistent MF, categorizing them into two groups: plasma cell dyscrasia-marrow fibrosis syndrome and coincident myeloma and myelofibrosis (5). In the present case, except for the absence of tear drop red blood cells, the hematological condition seems to be compatible with coincident myeloma and myelofibrosis, according to Vandermolen et al. Interestingly, it was observed that the MF and MM simultaneously improved after treatment with alkylating agents. This observation has not been described in previously reports except by Patterson et al, as far as we can ascertain (6). This finding supports the hypothesis that the development of MF was secondary to MM in the present patient.

The pathogenesis of bone marrow fibrosis in myeloproliferative disorders and other underlying conditions such as hairy cell leukemia, carcinoma and myeloma is not yet clear. Recently it has been demonstrated that interleukin 6 (IL-6), known as B-cell stimulatory factor 2, is produced by fresh myeloma cell and may play a role in autocrine generation of multiple myelomas (7). IL-6 with IL-3 not only acts synergistically in the proliferation of megakaryocytes in vitro but IL-6 also stimulates platelet production in vivo (8, 9). In addition, various growth factors known as PDGF, transforming growth factor (TGF)-β, and epidermal growth factor (EGF), which stimulate the proliferation of fibroblasts are contained in platelets (10–12). It has been demonstrated that megakaryocytes stimulate the proliferation of bone marrow fibroblasts by growth-promoting factor similar to PDGF which increases collagen synthesis by target mesenchymal cells (13, 14). Therefore, we may assume the possibility in the pathogenesis of myelofibrosis associated with multiple myeloma that cytokine such as IL-6 derived from myeloma cells stimulates the secretion of fibroblast proliferation factors as PDGF in bone marrow and extracellular matrix protein derived from fibroblasts results in marrow fibrosis. The fact that PDGF activity of bone marrow in this case revealed a high value compared with that of plasma in healthy donors may support this assumption. The interaction between these factors and bone marrow cells should be investigated further.

**REFERENCES**

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