Multiple Myeloma Associated with Thrombocytopenia Caused by Immunological Destruction

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ABSTRACT. Herein we report a case of multiple myeloma (MM) with thrombocytopenia associated with a shortened half-life of platelets and improvement following splenectomy, with a transient increase in platelet counts as a result of chemotherapy including predonisolone (PSL). This thrombocytopenia may have been caused by immunological destruction of platelets related to the immunoglobulin produced by myeloma cells. We also discuss previously reported cases resembling the present patient.

Key words: multiple myeloma — thrombocytopenia

Multiple myeloma (MM) remains an incurable hematological malignancy characterized by various clinical manifestations such as hyperproteinemia, anemia, renal dysfunction, bone lesions, and immunological deficiencies.[1,2] In addition, MM associated with hyperamylasemia[3-5] and hyperammonemia[6-8] has been reported mainly in Japanese patients. These complications have been recognized as myeloma-related complications because of the excess production and secretion of amylase or ammonia from malignant myeloma cells analyzed *in vitro* using established cell lines.[9,10] Thrombocytopenia associated with MM is usually caused by marrow-occupying by malignant myeloma cells. However, immunological thrombocytopenia, the mechanism of which resembles idiopathic thrombocytopenic purpura (ITP), has been reported.[11-13] In these cases, it appears that M-protein produced by myeloma cells has acted as an anti-platelet antibody.

Herein, we describe an MM patient with thrombocytopenia associated with a shortened half-life of platelets and improvement in thrombocytopenia following splenectomy, with a transient increase in platelet counts as a result of chemotherapy including prednisolone (PSL).

CASE NOTES

A 69-year-old-Japanese man was admitted to our hospital on July 31, 1989, with easy fatigability and detected anemia and M-proteinemia. Although only anemic pale skin and conjunctiva were noted on physical examination, laboratory findings revealed mild anemia (Hb 10.4 g/dl), severe thrombocytopenia (platelets 27×10^3 /μl), hyperproteinemia (serum globulin 6.6 g/dl) with an abnormal M-peak, and M-bows against immunoglobulin (Ig)-G

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and κ-light chain in an immuno-electrophoresis assay. In addition, his bone marrow had been infiltrated by malignant myeloma cells (8.4% in total nucleated cells). Interestingly, there was also an increased number of megakaryocytes (MGK) with no platelet-producing morphologies as shown in Fig 1, despite severe thrombocytopenia in peripheral blood. No other autoantibodies, such as anti-nuclear antibodies, or anti-DNA antibodies were detected, and neither direct nor indirect Coombs tests were positive. He was diagnosed as having Ig-G type MM, and multidrug combined chemotherapy including vindesine sulfate, melphalan, and PSL was carried out. He showed a good response to the chemotherapy and went to maintenance therapy using Interferon-α. His thrombocytopenia improved after splenectomy performed eight months after the initial diagnosis. Unfortunately, he died due to pulmonary metastasis of myeloma seven years after initial diagnosis.

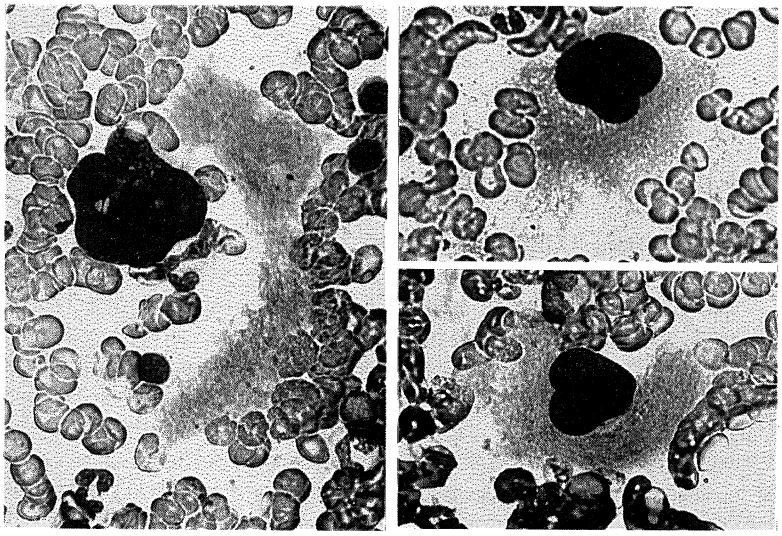

Fig 1. Morphologies of bone marrow megakaryocytes (MGK) at diagnosis showing no productive figures of platelets compatible with the MGK-morphology found in idiopathic thrombocytopenic purpura (original magnification ; $\times$1,000).

When his thrombocytopenia was considered at the initial diagnosis, it did not seem to be caused by marrow-occupying due to the involvement of myeloma cells, because of the discrepancy in severity between his anemia and thrombocytopenia, and the low percentage of myeloma cells in bone marrow. The finding of MGK was compatible with ITP, in which platelets are destroyed by an immunological mechanism. In addition, the peripheral platelet count remarkably increased during initial chemotherapy and rapidly decreased when PSL administration ceased, although the decrease in M-protein was slight, as shown in Fig 2. In addition, splenectomy, which is a standard therapy for ITP, caused clinical remission of his thrombocytopenia. Based on these findings and a high level of platelet-associated Ig G (PA-Ig G ; 85.9 ng/10^7 cells), it appeared that his platelets might have been destroyed by an immunological mechanism. Therefore, the ^{51}Cr platelet life span was examined. As shown in Fig 3, his platelets showed a remarkably shortened half-life, less than half-day

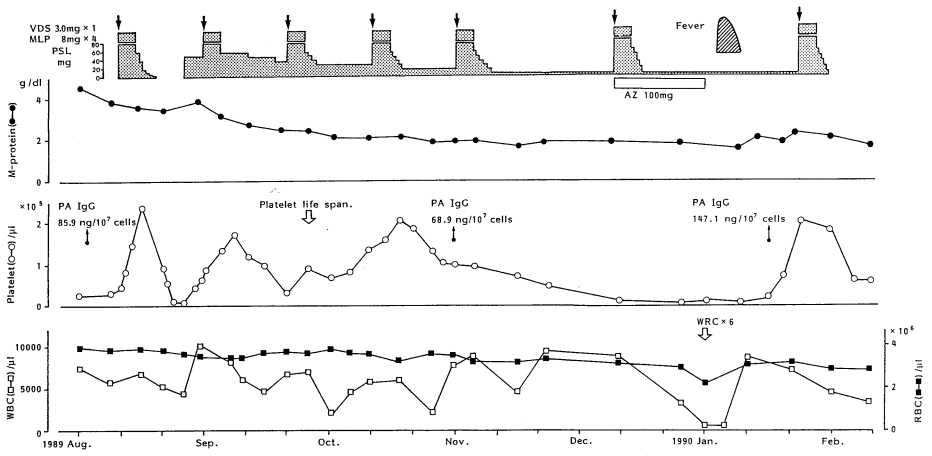

Fig 2. Clinical course of the present patient in the early phase. The abbreviations used in this figure are as follows. VDS, vindesine; MLP, melphalan; PSL, prednisolone; AZ, azathiopurine; A IgG, platelet-associated immunogulobulin G; WBC, white blood cells; RBC, red blood cells; WRC, whole red cell transfusion.

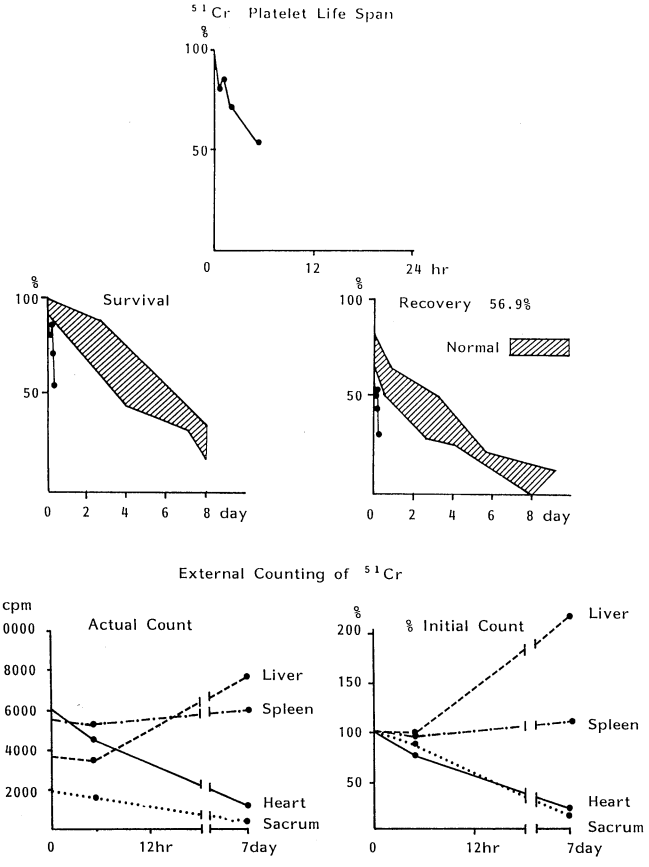

Fig 3. ^{51}Cr platelet Life span assay showing a remarkable shortened half life, less than half-day (normal range was 3 to 5 days), and transportation of destroyed platelets to the liver.

(the normal range is three to five days), and the destroyed platelets were transported to the liver for phagocytic disposition.

DISCUSSION

We experienced a case of MM with severe thrombocytopenia which seemed to be caused by an immunological mechanism. Although we were unfortunately unable to analyze the platelet-binding actevity of the Ig-G produced by his myeloma cells, his thrombocytopenia clinically improved after splenectomy. His clinical course also strongly suggested that the thrombocytopenia was caused by an immunological mechanism.

There have been several reports of patients with myeloma associated with immunological thrombocytopenia.[11-13] Verdirame *et al* described two patients who both had Ig G type myeloma with thrombocytopenia that improved after splenectomy following PSL administration, in a similar manner to the present patient. However, these authors reported that their patients showed thrombocytopenia after chemotherapies against myeloma.[11] Instead of measuring the PA-Ig G titer, they measured anti-platelet-antibody titers and noted higher values in both patients. Another case of thrombocytopenia with myeloma kidney was described by Kayhan *et al*.[12] However, they did not discuss the immunological aspects of thrombocytopenia. In addition, Muroi *et al* described an MM patient with hemolytic anemia and thrombocytopenia.[13] They observed that the immunoglobulin produced by myeloma cells was of the same class of that which binds to red cells, but partially purified Ig from the patient's serum did not agglutinate with autologous red cells. Because their patient was treated with alminoprofen for two months prior to the diagnosis of MM, they discussed the possibility that an autoantibody against this drug might have crossreacted with autologous red cells and platelets. They also considered the possilility of immunological destruction of platelets caused by tumorous Ig produced by myeloma cells.

Based on these reports and the clinical findings of the present patient, it appears difficult to confirm that Ig produced by myeloma cells induces the immunological destruction of autologous platelets and causes severe thrombocytopenia clinically. However, Fritz *et al* reported shortened platelet half-life in MM patients.[14] Therefore, we should be careful treating MM patients who show severe thrombocytopenia which cannot be explained only by marrow involvement by tumor cells, and consider the possibility of immunological destruction of platelets.

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