Abstract

A 57-year-old man was admitted with severe anemia and hypergamma globulinemia. After a diagnosis of multiple myeloma and autoimmune hemolytic anemia was made, chemotherapy rapidly decreased the M-protein level and improved his anemia with normalization of the direct Coombs test. The immunoglobulin binding to the patient's red cells was immunoglobulin G kappa chain like the myeloma M-protein. However, monoclonal immunoglobulin G derived from short-term culture of the patient's bone marrow mononuclear cells did not bind to a panel of red cells. Therefore, the relationship between the M protein produced by his myeloma cells and hemolysis remained unclear.

Key words: hemolytic anemia, M-protein, multiple myeloma

Introduction

Anemia associated with myeloma has been reported to arise from disordered maturation of the erythroblastic series, shortening of the lifespan of erythrocytes, and iron deficiency associated with an increased tumor cell mass, while hemolytic anemia has rarely been reported (1–3). Here, we report a case of multiple myeloma complicated by severe autoimmune hemolytic anemia at presentation, and discuss the relationship between the M-protein and the onset of such anemia.

Case Report

A 57-year-old man, with a non-contributory past history and family history attended a local clinic because of excessive fatigue on exertion. Anemia was diagnosed in early September 2000. Further investigation showed M-proteinemia, thus he was hospitalized for detailed assessment and treatment on October 27. He had no history of taking prescription drugs and no symptoms suggesting viral infection.

Physical findings on admission

The patient was 166.5 cm tall and weighed 68.5 kg. His blood pressure was 120/64 mmHg, his pulse rate was 80/min (regular), and his temperature was 36.5°C. No abnormalities were observed on physical examination, except for marked conjunctival pallor. His liver and spleen were not palpable.

Laboratory findings on admission (Table 1)

Peripheral blood examination showed severe anemia with a hemoglobin of 4.2 g/dl. Smears showed atypical cells resembling plasma cells, as well as erythroblasts and microspherocytes. Various findings that suggested a diagnosis of autoimmune hemolytic anemia (AIHA) were observed, including an increase of the reticulocyte count, high levels of indirect bilirubin and lactate dehydrogenase (LDH), a low haptoglobin level, and a positive direct Coombs test. The Ham test, sugar-water test, Donath-Landsteiner test, cold agglutinin reaction, and test for cryoglobulins were all negative, while the serum complement level was normal. The total protein level was 11 g/dl, and immunoglobulin (Ig) G was increased to 8,010 mg/dl, but IgA and IgM levels were low. Serum immunoelectrophoresis showed that the M-protein was the IgG kappa chain (IgG-k). Urinary M-protein excretion was 0.4 g/day. On aspiration, hyperplasia of the
bone marrow was observed and 40% of the marrow cells were atypical plasma cells that showed expression of the following antigens: CD38+CD19–CD56–CD49e–CD126–. No chromosomal abnormalities were detected. The adjusted serum calcium level was 9.9 mg/dl (corrected for albumin). The skeletal survey revealed no abnormalities.

Clinical course (Fig. 1)

Based on the above findings, he was diagnosed as having stage IIIA multiple myeloma with an M-protein of the IgG-TypeOne0 type. Red cell transfusion was performed for his advanced anemia. In addition, treatment of the myeloma with MCNU-VMP therapy (4) was started on hospital day 5, while prednisolone was administered at 25 mg/day to control his AIHA. After chemotherapy was commenced, the M-protein level decreased rapidly and his anemia improved. There was also improvement of the hemolytic findings and normalization of the direct Coombs’ test. Accordingly, he was discharged at the end of December 2000. He was rehospitalized due to exacerbation of multiple myeloma in August 2002, but AIHA was not detected at that time and it did not recur before the patient died of myeloma in April 2003.

Relationship between M-protein and AIHA

When the direct anti-globulin test was performed with blood cells from the patient, it showed positivity for anti-IgG, anti-IgG1, anti-κ, and anti-C3d (Table 2). To determine the blood type specificity of the autoantibody, absorption-elution studies were performed. It was determined that the autoantibody had no blood type specificity because antibody elution from patient’s red blood cells and panel red blood cells (lot number: 484) reacted.

To investigate whether the immunoglobulin binding with the patient’s red blood cells was derived from the myeloma, the IgG subclass of the antibody binding to the red cell membrane was compared with that of the M-protein, and it was found that both were IgG1-TypeOne0. Next, bone marrow mononuclear cells were cultured in serum-free medium for 72 hours and the supernatant was harvested. After the presence of IgG in the supernatant was confirmed, it was used to examine agglutination of a panel of red blood cells by the low ionic strength saline anti-globulin method, Ficin anti-globulin method, Ficin method at 37°C, albumin method at 37°C, and saline solution method (at 20°C and 37°C). As a result, agglutination was not detected by any of these techniques, thus no antibody binding red blood cells were detected in the culture supernatant.

Discussion

Patients with secondary AIHA often have underlying collagen diseases or hematologic malignancies (5). In particular, AIHA is often associated with lymphoproliferative disorders.
IgG-κ Myeloma and AIHA

and it has been reported to precede the onset of chronic lymphocytic leukemia. Although patients with malignant lymphoma often show a positive Coombs’ test, they rarely develop AIHA (5). In addition, a previous study showed that only about 4% of AIHA patients had myeloma (5), while other reports have stated that myeloma is rarely associated with hemolytic anemia (6, 7). Since 1987, there have only been 6 case reports (including the present patient) of AIHA associated with myeloma (6, 8–11) (Table 3), and none of these cases provided conclusive evidence that the antibody responsible for AIHA was the myeloma M-protein.

The myeloma cells of the present patient were considered to be at an early stage of differentiation in which cell growth was greater than antibody production because they were negative for CD49e (very late antigen 5) (12). Both the M-protein produced by the myeloma cells and the IgG that bound to the patient’s red cells were of the IgG1 subclass. In addition, resolution of hemolytic anemia and normalization of the Coombs’ test occurred in association with a reduction of IgG levels after the start of chemotherapy, suggesting that the M-protein may have been a cause of hemolysis. However, this could not be confirmed because an antibody binding to the panel of red blood cells was not detected in the culture supernatant obtained from the patient’s bone marrow mononuclear cells (including myeloma cells). There is a possibility that nonspecific binding may have occurred due to high levels of M-protein or some abnormality of the patient’s red cells, but further investigations to confirm this were not performed.

It is also possible that this patient may have developed multiple myeloma as a complication of pre-existing AIHA, although there was nothing suggestive in the medical history. Assuming that his chemotherapy including prednisolone and an immunosuppressive agent achieved the long-term remission of AIHA, this would explain why hemolytic anemia did not occur.

Table 2. Characteristics of the Autoantibody to the Patient’s Red Cells

<table>
<thead>
<tr>
<th>Direct anti-globulin test</th>
<th>Anti-IgG</th>
<th>4+</th>
<th>Anti-C3c</th>
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<tbody>
<tr>
<td>Anti-IgM</td>
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<td></td>
<td>Anti-C3d</td>
<td>2+</td>
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<tr>
<td>Anti-Igl</td>
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<td>Anti-κ</td>
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<td>Anti-IgG1</td>
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<td>Anti-λ</td>
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<td>Anti-IgG4</td>
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Figure 1. Clinical course of the patient. MCNU-VMP: ranimustine vindesine melphalan prednisolone, VMP: vindesine melphalan prednisolone, MP: melphalan prednisolone, LDH: lactate dehydrogenase, MAP: packed red cells in mannitol-adenine phosphate (each arrow indicates two units of red blood cells). #: first visit to his local doctor, *admission to our division.
not recur despite the recrudescence of multiple myeloma. It is rare for AIHA to develop in patients with multiple myeloma and further studies are necessary to understand the mechanism of hemolysis in this disease.

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References