Acquired Amegakaryocytic Thrombocytopenic Purpura with Humoral Inhibitory Factor for Megakaryocyte Colony Formation

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A 67-year-old man with thrombocytopenia, and amegakaryocytic but otherwise normal bone marrow, was evaluated. Antibody against thrombocytes was negative and the half-life of thrombocytes was normal. In vitro clonal culture of the patient's bone marrow cells yielded no megakaryocyte colony with normal granulocyte-macrophage and erythroid colony formation. Megakaryocyte colony formation of the control bone marrow cells was significantly suppressed by the addition of the patient's serum to the culture, suggesting the existence of humoral inhibitory factor(s) for megakaryocyte colony formation. Therapeutic trials with plasma exchange, cyclosporine, prednisolone, and cyclosporine plus prednisolone were all unsuccessful, but serious bleeding has been absent.

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Introduction

Acquired amegakaryocytic thrombocytopenic purpura (AATP) is characterized by thrombocytopenia, markedly decreased or complete absence of bone marrow megakaryocytes and minimal changes in other hematopoietic cell lines (1-3). The clinical course is highly variable and no standard treatment is available (1-3). It may precede overt leukemia (1, 2, 4) and other hematologic diseases (1, 2, 4, 5) in some patients. On the other hand, the disease state may remain unchanged for as long as 15 years (6). Bleeding tendency is often serious and patients with fatal bleeding have been reported (7). We recently encountered a patient with AATP with humoral inhibitory factor(s) for megakaryocyte colony formation (1, 8). Therapeutic trials with plasma exchange (2), cyclosporine (4, 9, 10), prednisolone (2-4), and cyclosporine plus prednisolone (9) were all ineffective in this patient.

Case Report

A 67-year-old man was referred to the Shinshu University Hospital for the evaluation and treatment of thrombocytopenia which was first noticed at the age of 62, but had been left untreated as there were no symptoms related to the thrombocytopenia. The family history and the patient's past history were unremarkable.

Physical examination revealed many petechiae and small ecchymoses on the extremities and abdominal wall and a few bleeding spots on the retinae. Hepatosplenomegaly was absent and physical findings were otherwise normal. Hematuria and occult blood of the stool were negative, however superficial bleeding was found in the stomach by an endoscopic examination. The platelet count was 8×10^9/l; the blood count was otherwise normal. Bone marrow examination showed an absence of megakaryocytes with the erythroblastic and granulopoietic series normally present. A bone marrow cytogenetic study showed a 46XY normal karyotype. The Coombs' test, the antinuclear antibody, and the platelet-associated IgG were negative, as well as serological tests for toxoplasma, brucella, syphilis, human immunodeficiency virus, Epstein-Barr virus, and hepatitis B and C viruses. Fibrinogen and partial thromboplastin time, and folic acid were normal and serum vitamin B12 level was 2,830 pg/ml (normal range 230-1,200). There was mild liver dysfunction possibly due to...
excessive drinking in the past but the blood chemistry was otherwise normal. Adrenal and thyroid functions were normal. A neoplastic process elsewhere was ruled out by appropriate tests.

The half-life of the platelet was normal (11) (t1/2, 7.34 days, performed on July 23, 1991). An in vitro methylcellulose culture of the patient’s bone marrow mononuclear cells (12) yielded no megakaryocyte colony in the presence of 100 U/ml recombinant human interleukin 3 (IL-3), 10 ng/ml recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF), 2 U/ml recombinant human erythropoietin (Epo) and 80 mg/ml recombinant human IL-6 (performed on July 15, 1991). On the other hand, other colonies including granulocyte-macrophage, eosinophil and mixed hemopoietic colonies, and erythroid bursts colonies were formed normally. Addition of the patient’s serum to the culture of the control bone marrow nonphagocytic mononuclear cells (NPMNC) derived from a patient with essential thrombocytosis resulted in significant suppression of megakaryocyte colony formation: 20.7±3.3/2×10^4 NPMNC vs 41.3±11.9/2×10^4 NPMNC, with patient’s sera and control sera, respectively (p<0.05, n=3 for each condition, performed on July 30, 1991).

Clinical course and results of therapeutic trials (Fig. 1)

On July 13, 1991, platelet concentrates (8 packs) were transfused for the first time. The platelet count was >13×10^9/L with no treatment for the next 7 months. On March 2, 1992, the platelet count decreased to 8×10^9/L and the second platelet transfusion was performed. Because the patient was asymptomatic except for petechiae on the skin, platelets were infused only when the platelet count decreased to fewer than 8×10^9/L. The platelet-associated IgG was weakly positive on April 7, 1992; we considered the appearance of platelet-associated IgG as due to the repeated platelet transfusions. However, the disappearance rate of transfused platelets remained constant (t1/2, 2.6–5.4 days) before and after the appearance of the IgG, indicating that excessive destruction of the platelets did not take place.

Plasma exchange (1,500 ml each time) was performed three times on March 18, 26 and 27, 1992, but the platelet count did not increase significantly. From April 15, 1992, 5 mg/kg BW/day (BW 53 kg) p.o. cyclosporine was started. During the next 75 days, the platelet count was more than 10×10^9/L suggesting some beneficial effect from the drug. Side effects of cyclosporine such as liver and kidney dysfunction, leukocytopenia and gingival hypertrophy were not observed. However, on July 3, 1992, the platelet count decreased to 9×10^9/L. Cyclosporine was discontinued because the therapeutic effect of the drug was eventually judged to be absent, and 50 mg/day prednisolone was started p.o. on July 14, 1992. The prednisolone therapy was not clearly effective and frequent platelet transfusion was needed. Finally, 20 mg/day prednisolone plus 5 mg/kg BW/day cyclosporine was administered from August 26, 1992 to October 12, 1992, however, the combination therapy did not significantly raise the platelet count. Thereafter, the patient has been receiving a small amount of prednisolone (3.75–10 mg/day) alone, with the platelet count being 9–22×10^9/L and no serious bleeding episodes.

Discussion

AATP is a rare hematologic disorder characterized by the isolated absence of bone marrow megakaryocytes and consequent thrombocytopenia (1–3). According to a literature search, there has been only one case reported of the disease in Japan (13, 14). Its etiology is not well understood and seemingly diverse; alcoholic abuse, abnormality in the megakaryocytes or its progenitors themselves, and suppression of the megakaryocytes or its progenitors by autoimmune mechanism have been listed as possible causes of the disease (1, 2). On the other hand, transitions from AATP to leukemia, myelodysplastic syndrome and aplastic anemia have also been reported (1, 2, 4), indicating that AATP might well be a syndrome rather than a single disease. Therapeutic trials including immune suppress-
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In the previous literature, the youngest and eldest patients were 15 (1, 2) and 83 (5) years of age, respectively, and the age at the development of the disease does not appear to be important. The platelet count in this disorder reportedly ranged from 2.5-70x10^9/l (1, 2, 5), and was highly variable. Thus, the age and the degree of thrombocytopenia in the present case were within the reported range. There is a high likelihood that the present patient possessed some humoral factor(s) against megakaryocyte colony formation. Although we did not purify the humoral factor(s), it might have been IgG as described by Hoffman (7). Such factor(s) were present in 13% (2 of 15) of the patients in whom the presence of it was searched for in the previous literature. In a patient reported by Nagasawa and colleagues (14), in vitro suppression of colony-forming unit-megakaryocytes by the patient’s T cells was found. We did not perform such a cytotoxicity assay in the present case.

Regarding treatment, plasma exchange (2), immune suppression with steroids (2, 3, 5, 6), cyclosporine (9) and other drugs, and anti-thymocyte immunoglobulin (9) have been tried in patients with AATP, and possible beneficial effects have been reported in a small number of patients (4, 9). More specifically, Hoffman (7) proposed prednisone, plasmapheresis, cyclophosphamide and/or cyclosporine for patients with AATP due to abnormal IgG production and antithymocyte globulin, and cyclosporine and/or cytokine therapy for those with T-cell mediated suppression of thrombocyte formation. However, Manoharen and colleagues concluded that treatment of any kind appeared to be ineffective (4). Unfortunately, this was also the case in the present patient. We tried all of the previously reported treatments except for antithymocyte immunoglobulin and found none of them to be effective. Spontaneous fluctuation in the platelet count has been reported in AATP (15), and we believe the data shown in Fig. 1 exhibits such a fluctuation rather than a change due to treatment.

Thrombocytopenia was first incidentally discovered at the age of 62 in the present patient and, until now, the clinical course was benign without serious bleeding episodes. However, careful follow-up of the condition is required due to the frequent transition of AATP to leukemia and other more malignant conditions (1, 2, 9).

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References