CASE REPORT

Synchronous Fluctuation of Interleukin-6 and Platelet Count in Cyclic Thrombocytopenia and Thrombocytosis

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We describe a case of cyclic thrombocytopenia and thrombocytosis, whose cytokine levels, granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin-6 (IL-6) in plasma, fluctuated in synchrony with platelet count. The levels of the two cytokines correlated significantly with the platelet count for 11 observations over an 8-month period (r=0.79, p<0.01 for GM-CSF and r=0.87, p<0.001 for IL-6). No inverse relationship between platelet-associated immunoglobulin G (PAIgG) and platelet count was observed (r=0.39, p>0.20). These findings suggest that the fluctuation of platelet count in this case may result from an aberration of the cytokine network regulating megakaryopoiesis and platelet formation.

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Key words: menstrual cycle, megakaryopoiesis, GM-CSF, TGF-β, stimulatory cytokine, inhibitory cytokine

Introduction

Cyclic thrombocytopenia and thrombocytosis is a rare disorder characterized by regular fluctuations in platelet counts ranging from severely thrombocytopenic levels to as high as 1 million per microliter (1, 2). In women, these fluctuations occur often in phase with the menstrual cycle (2, 3). We describe a case of this disorder, in whom plasma levels of granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin-6 (IL-6) fluctuated in synchrony with the platelet count.

Case Report

A 43-year-old Japanese female was in good health until the age of 40 years in 1989, when she started to bruise easily and developed genital bleeding. She was found to be thrombocytopenic, but an apparently spontaneous recovery and thrombocytosis occurred followed by recurrent episodes of thrombocytopenia and thrombocytosis, which correlated with menstruation. Her platelet count fell at the mid-cycle of menses and peaked at or just after the onset of menses with a 28- to 30-day cycle. For this reason, her condition was diagnosed as menstrual cyclic thrombocytopenia and thrombocytosis. Between July 1989 and April 1992, she was admitted four times for severe genital bleeding emergency. Her platelet count and clinical course over a 7-month observation period from February to August 1990 are shown in Fig. 1. The platelet count was 0.1×10⁴/µl on February 5, 1990 and 0.5×10⁴/µl on July 2, 1990, while it was 72.0×10⁴/µl on February 16, 1990 and 70.2×10⁴/µl on July 14, 1990. Bone marrow examinations performed at the peak of the platelet cycle showed megakaryocytic hyperplasia with a large-sized mature picture, and at the nadir megakaryocytic hypoplasia with a small-sized immature picture, indicating the cyclic changes of megakaryopoiesis. Hypochromic anemia (hemoglobin levels 8–9 g/dl, MCH 21–24 pg) and mild monocytosis (white blood cell counts, 4.4–6.9×10⁴/µl; monocyte differentials, 10–18%) were recorded but did not accompany the cyclic changes. Antinuclear antibody test and rheumatoid factor were positive and quantitative immunoglobulin determinations showed elevated IgA levels (630–780 mg/dl). Results of repeated examinations of immune complex levels, serum complements C3, C4, and CH50 were all within normal ranges. Lymphocyte surface marker analysis consistently showed a normal CD4/8 ratio (1.6–2.6), a decrease in CD16+ cells (4.1–5.7%), and an increase in CD20+ cells (25.1–33.3%) without any cyclic fluctuation. Corticosteroid therapy, high-dose γ-globulin, and splenectomy were all ineffective for her cyclic fluctuation of platelet counts. In April 1992, she presented with severe anemia (hemoglobin level, 4.9 g/dl) due to

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thrombocytopenia and massive genital bleeding. Subtotal hysterectomy and bilateral salpingo-oophorectomy was performed in June 1992 in an attempt to prevent the coming life-threatening genital bleeding. However, the surgery failed to affect the fluctuations. Examination of the resected uterus and the ovaries showed no pathological findings. The fluctuation repeated itself for more than four years until the time of her death due to pulmonary infarction in September 1993.

During the 8-month observation from April to November 1992, platelet-associated IgG (PAIgG), plasma interleukin-3 (IL-3), GM-CSF, and IL-6 levels were measured repeatedly with enzyme-immunoassay (EIA) (Shionogi Biomedical Osaka Laboratory for PAIgG and Mitsubishi Yuka BCL Company, Tokyo, for IL-3, GM-CSF, and IL-6). No inverse relationship between PAIgG and platelet count was observed \((r=0.39, p>0.20)\) (Fig. 2). The levels of IL-3 remained within the normal laboratory level \(<31\, \text{pg/ml}\) throughout the cycles. Both GM-CSF and IL-6 levels showed an increase from the nadir phase to the peak phase of the platelet counts, and a decrease from the peak phase to the nadir phase. On May 4, 1992, before the hysterectomy, the GM-CSF level was 8.5 pg/ml and the IL-6 level was 250 pg/ml with a platelet count of 24.2×10⁴/µl at the mid-cycle of menses. After 16 days, the GM-CSF level was 10.8 and the IL-6 level was 481 with a platelet count of 57.2×10⁴/µl just after the onset of menses. On November 10, after the surgery, the GM-CSF level was 7.2 and the IL-6 level was <10.0 with a platelet count of 3.3×10⁴/µl. After 14 days, the GM-CSF level was 8.6 and the IL-6 level was 120 with a platelet count of 36.6×10⁴/µl. Normal laboratory levels were <5.0 pg/ml for GM-CSF and <40.6 pg/ml for IL-6. The levels of the two cytokines correlated significantly with the platelet count for 11 observations made during the 8-month period; the relationships between GM-CSF levels and platelet counts (Fig. 3) and between IL-6 levels and platelet counts (Fig. 4) were linear \((r=0.79, p<0.01 \text{ for GM-CSF and } r=0.87, p<0.001 \text{ for IL-6})\).

**Discussion**

There are several possible explanations for the pathogenesis
of cyclic thrombocytopenia and thrombocytosis. Menitove et al (4) and Kosugi et al (5) suggested that the cycling of platelets is mediated by autoantibodies and that the underlying abnormalities might be a defect in the regulation of autoantibody production. Tomer et al (6) reported that hormonal changes during the menstrual cycle might alter the Fcγ receptor-mediated clearance of antibody-coated platelets by macrophages, modulate platelet survival, and cause cyclic thrombocytopenia. Hoffman et al (7), on the other hand, reported that cyclic amegakaryocytic thrombocytopenia might be due to an antibody that selectively blocks the action of GM-CSF on megakaryocyte progenitor cells. Numerous factors concerning the regulation of megakaryopoiesis by various cytokines have been reported. (i) The survival, proliferation and differentiation of progenitor cells into immature megakaryocytes are regulated mainly by IL-3 and GM-CSF (8, 9); (ii) the maturation of immature megakaryocytes to produce platelets is regulated primarily by IL-6 and thrombopoietin (10), (iii) transforming growth factor β (TGF-β) exerts as an inhibitory regulator in megakaryocyte colony formation, megakaryocyte growth and endomitosis (11, 12) and (iv) abnormalities of these cytokine levels may result in an abnormal megakaryopoiesis (13, 14). Taking these in vitro and in vivo findings into account, it seems reasonable to consider that physiologically the platelet count may be maintained within a certain range through the antagonistic actions of these stimulatory and inhibitory cytokines regulating megakaryopoiesis and platelet formation. In the present case, no inverse relationship between PAIgG and the platelet count was observed. The bone marrow examinations revealed that both the number of megakaryocytes and the degree of maturation corresponded with the platelet count, and plasma IL-6 levels correlated significantly with the platelet count. These results suggest that the fluctuation of platelet counts above the normal range observed during the thrombocytotic phase may be mainly due to the fluctuating levels of the stimulatory cytokine, IL-6. On the other hand, the fluctuation of platelet counts below the normal range observed during the thrombocytopenic phase may presumably be correlated with the fluctuating levels of inhibitory cytokine(s) such as TGF-β rather than with those of stimulatory cytokine(s) such as IL-6. Unfortunately as we did not measure the plasma TGF-β levels of the present case, we could not confirm the assumption concerning the relationship between thrombocytopenia and inhibitory cytokine levels. Plasma GM-CSF levels ranging from 5 pg/ml to 10 pg/ml were physiologically too low to affect megakaryopoiesis. Therefore, it seems unlikely that the fluctuations of GM-CSF levels contributed to the pathogenesis of this case, even though the correlation between the plasma GM-CSF level and the platelet count was statistically significant.

Cyclic thrombocytopenia occurs predominantly in women and in the majority of women these fluctuations are in phase with the menstrual cycle. The high platelet counts occur typically at mid-cycle and the low platelet counts during menses (6). However, in some women the opposite pattern has been described (3). In the present case, the platelet count fell at the midcycle of menses and peaked at or just after the onset of menses.
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Her platelet counts continued to fluctuate after the hysterectomy and bilateral salpingo-oophorectomy. Therefore, we conclude that the hormonal changes in the menstrual cycle did not play a pivotal role in the fluctuations of the platelet count in this case.

Our study indicates that the aberration of cytokine networks regulating megakaryopoiesis and platelet formation may be involved in the pathogenesis of some cases with cyclic thrombocytopenia and thrombocytosis. Furthermore, it may provide some insight into the regulation mechanism of megakaryopoiesis and platelet formation by various cytokines in vivo.

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References