Cyclic Thrombocytopenia of Apparent Autoimmune Etiology

By Jay E. Menitove, Jaime Pereira, Ronald Hoffman, Tom Anderson, Walter Fried, and Richard H. Aster

Serial studies were performed in two patients with cyclic thrombocytopenia to investigate the pathogenesis of this disorder. Mean life span of autologous platelets when platelet levels were declining was normal (2.4 and 0.8 days), and megakaryocytes were abundant in the bone marrow during thrombocytopenia. Megakaryocyte colony-stimulating activity could not be detected in the serum of either patient at any point of their cycles. In each patient, total platelet-associated IgG varied inversely with platelet levels. Surface platelet-associated IgG was measured only in patient 2 and was significantly elevated (>1,280 IgG molecules per platelet) at all stages of the cycle, even during thrombocytopenia. However, the highest values were observed during thrombocytopenia. Platelet-bindable IgG in plasma declined to normal immediately before platelet levels began to rise. IgG eluted from the platelets of this patient reacted strongly with autologous and homologous platelets in contrast to a "mock eluate" prepared from platelets of a normal subject. The eluate from the patient's platelets reacted strongly with immobilized autologous and homologous glycoprotein IIb/IIIa complex and weakly with GP Ib but not with isolated GP IIla alone. In each patient the decline in platelet levels was significantly delayed following administration of intravenous gamma globulin 0.4 g/kg body weight for five days. These findings suggest that platelet-reactive autoantibodies are of pathogenic significance in some patients with cyclic thrombocytopenia.

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CYCLIC THROMBOCYTOPENIA is a rare disorder characterized by regular fluctuations in platelet levels ranging from severely thrombocytopenic to as high as 1 million per microliter. In women, the platelet cycles often occur in synchrony with menstruation, but exceptions have been described, and the condition has been reported in otherwise normal men. It is generally thought that cyclic thrombocytopenia results from periodic failure of effective platelet production, possibly reflecting a perturbation of normal feedback control mechanisms. Several reports have suggested that platelet destruction may be important in the pathogenesis of this disorder.

A similar disorder of apparent infectious etiology has been described in dogs.

We recently encountered two patients with cyclic thrombocytopenia, a man and a woman, whose platelet counts varied between 1,000 and 900,000 per µL in 10- to 25-day cycles and performed studies to test the possibility that immunologic factors might be involved in the pathogenesis of their disorders. Our findings are consistent with the possibility that cycling of platelets in these individuals is mediated by autoantibodies and suggest that the underlying abnormality may be a defect in the regulation of autoantibody production. These findings were previously reported in abstract form.

CASE REPORTS

Case 1. A 31-year-old white female was diagnosed as having idiopathic thrombocytopenic purpura (ITP) at the age of 19 years. She failed to respond to corticosteroids and underwent splenectomy, after which her platelet count increased to 50,000 to 75,000 per µL. She became pregnant at the age of 24 years and was noted to have oscillations in platelet levels ranging from 5,000 to 500,000 per µL. A child with a normal platelet count was delivered by cesarean section when the patient's platelet level was normal. At the age of 25 years serial studies showed that her platelet count varied between 2,600 and 640,000 per µL in 10- to 19-day cycles, which did not correlate with menstruation, and the diagnosis of cyclic thrombocytopenia was made. The patient failed to respond to cyclophosphamide (100 mg/d) or azathioprine (50 to 100 mg/d). Bone marrow aspirates performed at the peak and nadir of the platelet cycle were judged to contain normal numbers of megakaryocytes. At the age of 27 years, colchicine (0.6 mg/d) was given without benefit. At the age of 28 years the patient was found to have enlarged cystic ovaries bilaterally. Shortly thereafter, life-threatening hemorrhage from the ovaries necessitated an emergency abdominal hysterectomy and bilateral salpingo-oophorectomy. Pathologic examination of the ovaries demonstrated bilateral endometriomas. Surgery was complicated by profound thrombocytopenia (2,000 per µL) and significant blood loss. Following surgery there was no further cycling of platelets, and the platelet level remained in the range of 10,000 to 30,000 per µL. Except for thrombocytopenia, the patient's hematologic profile has been consistently normal. A typical pattern of platelet counts during a 95-day period of observation in 1982 is shown in Fig 1.

Case 2. A 30-year-old white male was well until the age of 24 years when he developed epistaxis. About 4 months later, petechiae appeared on his tongue, he was found to be thrombocytopenic, and a diagnosis of ITP was made. There was an apparent response to prednisone therapy. About 1 month later, the platelet count again decreased, and a splenectomy was performed, after which platelets increased to 700,000 per µL. During the next year the patient was treated with various doses of prednisone until it was realized that fluctuations of platelet levels were occurring at about 4-week intervals, independent of therapy. A 4-month course of danazol, 400 mg daily, failed to influence platelet levels. Bone marrow aspirates performed when platelet levels were 6,000 and 240,000 per µL were judged to contain normal numbers of megakaryocytes. Two intravenous (IV) injections of 1.0 mg vincristine were without benefit. At this time the pattern of platelet cycling continues unchanged 6 years after the initial onset of thrombocytopenia. Despite the periodic fluctuations of platelet levels, a man and a woman, whose platelet counts varied between 1,000 and 900,000 per µL in 10- to 25-day cycles and performed studies to test the possibility that immunologic factors might be involved in the pathogenesis of their disorders. Our findings are consistent with the possibility that cycling of platelets in these individuals is mediated by autoantibodies and suggest that the underlying abnormality may be a defect in the regulation of autoantibody production. These findings were previously reported in abstract form.

From the Blood Center of Southeastern Wisconsin and the Medical College of Wisconsin, Milwaukee; the Department of Medicine, Catholic University of Chile, Santiago; Indiana University School of Medicine, Indianapolis; and Rush Medical College, Chicago.

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Address reprint requests to J.E. Menitove, MD, The Blood Center of Southeastern Wisconsin, 1701 West Wisconsin Ave, Milwaukee, WI 53233.

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Sensitization was performed by lysis of platelets lysed in 0.1% Triton X-100 detergent using a modification and IgM was measured by nephelometry performed on washed platelets are solubilized after being sensitized by a modification of the antigen capture assay (below), in which immunospecific assay (ELISA) and intact platelets immobilized in microtiter trays by enzyme-linked fluorescence test (PSIFT) was performed as described by von dem Borne et al. Measurement of the binding of serum antibody to intact platelets immobilized in microtiter trays by enzyme-linked immunospecific assay (ELISA) and the \(^{51}Cr\) release test were performed as previously reported.

In patient 2, platelet-binding IgG in plasma was also measured by a modification of the antigen capture assay (below), in which platelets are solubilized after being sensitized with test plasma. Sensitization was performed by incubating \(4 \times 10^7\) platelets with 0.5 mL plasma at room temperature for 30 minutes. The platelets were then washed and solubilized in 1% Triton X-100 in Tris-saline at 4°C for 30 minutes. Lysate equivalent to \(1 \times 10^7\) platelets was applied to the wells of a microtiter tray, each containing 0.5 \(\mu\)g fixed AP-1 or AP-2 MoAb. After incubation for 60 minutes at 37°C, the trays were washed, and captured IgG was detected with biotin-labeled monoclonal HB-43 as described below (antigen capture ELISA). The conditions of this assay allow antibody in test plasma to bind to antigen on glycoproteins while they are in their normal state in the platelet membrane, allowing for the possibility that epitopes will be recognized (and stabilized) by antibody that would otherwise be lost after solubilization. Assays differing in detail but based on the same principal were described recently by two other groups.

Antigen capture ELISA. In this assay the glycoprotein IIb/IIIa complex in detergent-solubilized platelets is “captured” by MoAb AP-2 immobilized in the wells of a microtiter plate. The immobilized GP1b/IIIa complex is incubated with serum to test for antibodies reactive with determinants on GP1b/IIIa. After washing, bound IgG is detected with biotin-labeled HB-43 specific for the Fc portion of human IgG. Bound HB-43 is then quantitated with avidin-biotin-alkaline phosphatase complex. The same approach is used to detect IgG antibodies specific for the GP1b/IX, a glycoprotein complex of platelets using a GPIb-specific murine monoclonal, AP-1, for glycoprotein immobilization. Details of the assay and properties of these MoAbs have been reported previously.

Elution of IgG from platelets. Platelets from patient 2 were obtained by apheresis using a Fenwal CS-3000 Blood Cell Separator (Fenwal Division, Baxter Healthcare Corp, Deerfield, IL) at a time when his platelet count was 640,000 per \(\mu\)L and falling. About 9.9 \(\times 10^{11}\) platelets were obtained. These were washed three times, and platelet-associated antibody was eluted at pH 3.0 as previously described. A “mock eluate” was prepared from 2.8 \(\times 10^{11}\) platelets from a normal subject isolated in the same way. IgG in the patient eluate and the mock eluate was partially purified and concentrated by chromatography on Protein A-Sepharose to a volume of about 1.0 mL. Protein content of the final preparation was determined by absorbance at 280 nm.

Survival time of autologous platelets. Survival time of autologous, \(^{51}Cr\)-labeled platelets was measured as previously described. Recovery and mean life span of the labeled cells were determined using computer-assisted analysis based on the “multiple hit” model of Murphy.

Megakaryocyte colony stimulating activity. Serum samples from each patient were assayed for their ability to promote megakaryocyte colony formation by normal human marrow cells.
Marrow aspirates were obtained from normal paid volunteers who gave informed consent. Colonies derived from megakaryocyte progenitor cells (CFU-MK) were cultured from marrow mononuclear cells as previously described. Serum obtained from patients with severe aplastic anemia was used as a source of megakaryocyte colony stimulating factor. Serum samples to be tested for megakaryocyte colony-stimulating activity (MK-CSA, i.e., activity in excess of that found in normal type A,B serum) were sterilized by ultrafiltration and were heat inactivated at 56°C for 30 minutes. When individual serum samples were added to the culture medium, they were substituted for an equal volume of normal human A,B serum.

RESULTS

Direct assays of platelet-associated IgG and IgM. Total platelet-associated IgG (PAIgG) and IgM was measured repeatedly during seven platelet cycles in patient 1 and four cycles in patient 2. An inverse relationship between PAIgG and platelet count was observed in 51 observations made at various points in the cycles when platelet levels ranged from 2,000 to 950,000 per μL. Sporadic elevations of PAIgM were also seen, but these were not as consistent as the changes in PAIgG and did not exceed 5 fg per platelet.

Platelet surface IgG (radiolabeled HB-43 binding) was measured only in patient 2 because this assay was not available when patient 1 was studied (1982). During one cycle, when the platelet count was normal or elevated (five samples), platelet surface IgG ranged from 1,280 to 1,823 molecules per platelet (Fig 2). These values were significantly higher than those obtained with ten matched samples from normal subjects (average 600 ± 207, range 254 to 954 molecules per platelet; *P* < .001). During the same cycle when the platelet count was very low (four samples), the patient’s platelets carried 2,218, 2,380, 9,280 and 4,219 molecules of IgG (Fig 2).

Indirect assays of platelet-bindable IgG and IgM. Serum from patient 2 obtained at different phases of the

![Fig 2.](image-url) Platelet surface IgG (monoclonal HB-43 binding) and platelet counts during one cycle in patient 2. Range of platelet surface IgG values obtained on platelets from 10 matched normal control subjects is shown by the horizontal bars (average value 600 ± 207 SD mol/platelet). In the patient, platelet surface IgG was greater than normal even during periods of thrombocytosis, but was highest during thrombocytopenia. Values shown are the averages. Brackets indicate the range of triplicate, independent determinations. On days 5, 7, and 10, only enough platelets were obtained for a single independent determination. The value shown is the average of triplicate measurements performed on the single samples.

![Fig 3.](image-url) (A and B) Reactions of plasma samples from patient 2 against autologous (A) and homologous platelets (B) obtained on day 16. Platelet bindable IgG was measured by modified antigen capture ELISA (MACE). Optical density (OD) measurements, reflecting IgG bound to GPIIb/IIIa glycoprotein complex, is depicted by open squares. Values shown are the averages of triplicate determinations ± 1 SEM. Dashed horizontal lines indicate the range of OD values obtained simultaneously with autologous (A) and homologous (B) platelets incubated with normal plasma. The higher control OD values obtained with autologous platelets and normal plasma (A) appear to reflect autoantibody already bound to the patient’s platelets in vivo (Fig 2).
platelet cycles yielded negative results against normal target platelets using the PSIFT, the ELISA against immobilized normal target platelets, and the $^{51}$Cr release test. Serum from patient 1 reacted variably with different target preparations. This was felt to reflect HLA-reactive antibodies stimulated by her multiple previous blood transfusions.

Using the modified antigen capture ELISA (MACE), antibody reactive with the GPIIb/IIIa complex was detected during the thrombocytopenic phase in patient 2. As shown in Fig 3, antibody activity against both autologous (Fig 3A) and homologous (Fig 3B) GPIIb/IIIa declined and became undetectable just before platelet levels began to rise. Antibody reappeared as platelet levels reached their peak and remained elevated throughout the next two weeks. A transient decline in activity against both target glycoprotein preparations was observed on day 23.

Studies with IgG eluted from platelets of patient 2. A total of 0.40 mg of IgG was isolated from the eluate prepared from 9.9 x $10^{11}$ platelets of patient 2 when his platelet count was 640,000 per $\mu$L and falling. A “mock eluate” obtained from 2.8 x $10^{11}$ platelets of a normal subject yielded 0.08 mg IgG. As shown in Fig 4, the eluate prepared from the patient’s own platelets caused dose-dependent IgG binding to autologous platelets, in contrast to IgG in the mock eluate. Comparable reactions were obtained with normal homologous target platelets.

Similar results were obtained when the two eluates were reacted with immobilized glycoprotein IIb/IIIa complex. In Fig 5 it can be seen that the patient’s eluate reacted strongly with autologous GPIIb/IIIa immobilized either with MoAb AP-2, specific for the complex, or AP-3, specific for its GPIIIa component. It also reacted less strongly with autologous glycoprotein IIb/IX complex immobilized with MoAb AP-1. Similar reactions were obtained with autologous and homologous GPIIb/IIIa complex. When detergent-solubilized platelets were treated with EDTA at 37°C to dissociate the GPIIb/IIIa complex before it was applied to MoAb AP-2, specific for the complex, or AP-3, specific for its GPIIIa component. It also reacted less strongly with autologous glycoprotein IIb/IX complex immobilized with MoAb AP-1. Similar reactions were obtained with autologous and homologous GPIIb/IIIa complex. The periodicity and severity of thrombocytopenia during later cycles was unchanged.

DISCUSSION

Studies in animals with cyclic hematopoiesis of erythroid and myeloid origin have provided evidence that these conditions result from abnormalities of stem cells.32 The phenomenon has been documented best in a strain of grey collie dogs with spontaneous cycling of granulocytes, monocytes, reticulocytes, and platelets in which normal hematopoiesis can be restored by bone marrow transplantation.33 One human patient transplanted with bone marrow from a donor with cyclic granulocytopenia acquired this condition post-transplant.34 A genetic basis for cyclic neutropenia in man is suggested by a report of the occurrence of this condition in twins.35

Cyclic thrombocytopenia in women occurring in synchrony with menstruation was first described by Minot in 1936.3 A number of similar cases were subsequently reported.3,7 In
Fig 5. Reactions of eluates obtained from platelets of patient 2 and from a normal subject and an alloantibody specific for P^\text{IIb} against glycoproteins from platelets of patient 2 immobilized in microtiter wells by MoAb "capture." EDTA indicates treatment of platelet lysate with EDTA at 37°C to dissociate GPIIb from GPIIIa before monoclonal capture. IgG bound was measured by ELISA. The eluate from platelets of patient 2 reacted with GPIIb/GPIIIa complex immobilized either with AP-2 or AP-3 but failed to react with GPIIla alone captured by AP-3 in the presence of EDTA. Weaker reactions were obtained against the GPIb/IX complex immobilized with AP-1. The eluate prepared from normal platelets failed to react with any of the preparations. Anti-P^\text{IIb} antibody reacted with each preparation containing GPIIIa. Similar reactions were obtained when the two eluates were tested against glycoprotein preparations prepared from platelets of a normal, P^\text{IIb}-positive subject.

several of these patients, platelet levels were lowest in the middle of the menstrual cycle rather than at the time of menstruation,\textsuperscript{5,7} and in another the platelet cycles failed to correlate with menstruation in any apparent way.\textsuperscript{1} At least five men with a seemingly identical disorder have been described.\textsuperscript{8,13} All the reported cases have been sporadic except for an apparently unique family, described by Aranda et al,\textsuperscript{36} in which platelet cycling was observed in four of nine siblings and their father.

Studies undertaken to determine the cause(s) of platelet fluctuations in patients with cyclic thrombocytopenia have yielded different conclusions. In four cases decreases in the numbers of megakaryocytes and changes in their morphology were interpreted to indicate that the decline in platelet levels resulted from a failure of platelet production.\textsuperscript{9,11,12,34} Normal or near-normal survival of labeled autologous platelets when platelet levels were declining was also consistent with this possibility in several patients.\textsuperscript{1,4,5,11} In one woman a decrease in follicle-stimulating hormone levels occurred just before platelets declined, and it was suggested that pituitary factors might be operative.\textsuperscript{5} Minot,\textsuperscript{2} on the other hand, attributed the rapid decline of platelets at the time of menses in three patients to platelet destruction, possibly reflecting platelet consumption in the uterus,\textsuperscript{2} and in a number of reported cases, megakaryocytes were present in normal or increased numbers in the marrow during thrombocytopenia.\textsuperscript{1,4,6,13} Brey observed cyclic thrombocytopenia in a woman with multiple autoantibodies reactive with tissues other than platelets and suggested that immune factors might be active.\textsuperscript{6} Platelet-reactive autoantibodies have not yet been demonstrated in reported cases, however.\textsuperscript{1,4,9,10,12}

Splenectomy\textsuperscript{3,11,36} and corticosteroid therapy\textsuperscript{1,5,7,10,12,13} failed to influence platelet cycles in patients in whom these therapies were instituted. Bilateral hysterectomy and oophorectomy was ineffective in one reported case\textsuperscript{2} and also was without effect on platelet cycling in our patient 1. The only apparent direct response of cyclic thrombocytopenia to treatment occurred in a patient described by Wahlberg et al,\textsuperscript{1} who administered a synthetic estrogen, lynestrenol, to inhibit ovulation and menstruation.

The findings made in our patients provide evidence that platelet-reactive autoantibodies may be of pathogenic significance in some patients with cyclic thrombocytopenia, a speculation made previously by Morley\textsuperscript{77} in a review of cyclic hematopoiesis. Total platelet-associated IgG varied inversely with the platelet count in both cases. Similar findings have been made in patients with chronic ITP, but in itself this finding is not specific.\textsuperscript{38} In patient 2, direct measurements of platelet surface IgG demonstrated a consistent elevation above normal throughout the platelet cycle, with peak levels during the thrombocytopenic phase (Fig 2). The range of platelet surface IgG values observed in this patient (1,280 to 9,280) is similar to that reported by Court et al\textsuperscript{39} using the same technique in a series of patients with idiopathic (au-
Table 1. Effect of Patient Sera on Megakaryocyte Colony Formation by Human Marrow Cells (CFU-MK/5 × 10⁶ Cells Plated)

<table>
<thead>
<tr>
<th>Material Added</th>
<th>None</th>
<th>10% Aplastic Anemia Serum</th>
<th>Patient Serum*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.5 ± 2.1†</td>
<td>36.5 ± 3.5</td>
<td>3.5 ± 2.1 (250)</td>
<td>9.0 ± 7.1 (101)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>18.5 ± 4.1</td>
<td>47.5 ± 1.5 (95)</td>
<td>20.5 ± 4.4 (2.5)</td>
</tr>
</tbody>
</table>

*Platelet level at time each sample was drawn (thousands per μL) is shown in parentheses.
†Each value is the mean ± SD of quadruplicate assays.
CYCLIC THROMBOCYTOPENIA

Platelet-reactive autoantibody was also demonstrated in the eluate prepared from platelets of patient 2. The eluate obtained from the patient's platelets and the mock eluate obtained from normal platelets contained IgG consistent with the amounts expected from partial release of the internal platelet IgG pool under the conditions used for elution. However, only the IgG obtained from platelets of patient 2 reacted with autologous and homologous intact platelets fixed in microtiter trays (Fig 4). The patient's eluate also reacted strongly with autologous glycoprotein IIb/IIa complex immobilized either with AP-2, specific for the complex, or AP-3, specific for glycoprotein IIIa, but failed to react with GPIIIa alone immobilized with AP-3 following dissociation of the GPIIb/IIa complex in EDTA at 37°C (Fig 5). These findings suggest that the autoantibody present in the eluate from platelets of patient 2 is specific either for the GPIIb/IIa complex or for GPIIb. The weaker reactions with autologous GPIb/IX complex suggest the presence of a second autoantibody with specificity for one of those glycoproteins.

The rapid disappearance of radiolabeled autologous platelets in both patients argues strongly for destruction of platelets rather than for failure of platelet production as the cause of thrombocytopenia in these individuals. Clearance of radiolabeled platelets was significantly more rapid than the concomitant decrease in peripheral blood platelet levels. The likely explanation for this is that the drop in total platelets was lessened by platelets newly released from the marrow in an attempt to compensate for developing thrombocytopenia. The short life span of platelets transfused to patient 2 for treatment of intracranial hemorrhage also argues in favor of a platelet-destructive process.

MK-CSA was not detectable in the serum of either patient at any time during their platelet cycles (Table 1). Serum MK-CSA has been shown to be inversely related to marrow megakaryocyte number. Failure to demonstrate increased levels of MK-CSA in these samples is consistent with the view that production of MK-CSA is related to megakaryocyte number rather than to the level of circulating platelets. Failure of plasma obtained during the thrombocytopenic period to avert the drop in platelet levels in patient 1 when transfused at the peak of a platelet cycle is not surprising in view of the absence of detectable MK-CSA. Similar observations were made in other reported cases of cyclic thrombocytopenia. Moreover, the plasma infusion did not hasten the rate of platelet decline in any apparent way, despite its content of platelet-reactive autoantibody. Failure of the transfused autoantibody to augment destruction of already partially sensitized recipient platelets may have been a consequence of its low concentration in plasma and its dilution in the total blood volume and extravascular space.

In both patients a five-day course of IV gamma globulin given when the platelet count was beginning to decline resulted in a significant delay in the onset of thrombocytopenia (Fig 6). This observation is consistent with an immunologic basis for the thrombocytopenia in these patients, as is the eventual reversion of patient 1 to a state of sustained

**Fig 6.** Effect of gamma globulin given IV at a dose of 0.4 g/kg body weight for five successive days (arrows) in patients 1 (above) and 2 (below). In patient 1 the onset of severe thrombocytopenia was delayed significantly (squares) in comparison with the two previous cycles (diamonds). In patient 2 an increase in platelet levels followed IgG administration (squares). The subsequent decline in platelets was delayed, and thrombocytopenia occurred about 1 week later than in the cycle immediately following (diamonds).
thrombocytopenia with clinical and laboratory findings typical of chronic ITP. It is of interest that a previously reported patient with cyclic thrombocytopenia apparently had typical ITP prior to the onset of platelet cycling.1

In summary, our findings provide circumstantial evidence in patient 1 and direct evidence in patient 2 for an association between platelet-reactive autoantibody and cyclic thrombocytopenia. The inverse relationship between platelet levels and platelet surface IgG (Fig 2) and platelet bindable IgG in plasma (Fig 3) of patient 2 suggests that cyclic production of autoantibody caused the periodic destruction of platelets. However, surface PAIgG was significantly increased in this patient even when platelet levels were normal. Reticuloendothelial (RE) function may be an important determinant of platelet destruction in immune disorders.42 Therefore the findings could also be explained by period fluctuations in the ability of the RE system to recognize and destroy sensitized platelets. A recent preliminary report based on studies of two women with menstrual thrombocytopenia is consistent with this possibility.49

Our data do not provide direct evidence for an underlying abnormality of immunoregulation that might account for what appears to be intermittent autoantibody production in these two patients. It is now generally accepted that autoimmune responses are normally held in check by cellular and humoral mechanisms constituting an anti-idiotypic network,44 and it is tempting to speculate that our patients were suffering from an abnormality of this regulatory system. In both animals45,46 and man,47,48 cycling of anti-idiotypic antibodies has been observed. The clinical course of our patients could be explained by regular fluctuations in production of anti-idiotypic antibody capable of neutralizing platelet-reactive autoantibodies. We are applying newly developed, more sensitive methods for autoantibody and anti-idiotyp antibody detection to investigate this possibility.

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