Cell-Mediated Amegakaryocytic Thrombocytopenia Associated With Systemic Lupus Erythematosus

By Toshiro Nagasawa, Tetsushi Sakurai, Heihachiro Kashiwagi, and Tsukasa Abe

We studied a patient with a rare complication of amegakaryocytic thrombocytopenia (AMT) associated with systemic lupus erythematosus (SLE). To investigate the underlying pathogenesis of AMT, the effects of peripheral blood T cells and serum on human megakaryocyte progenitor cells were studied using in vitro coculture techniques. Mononuclear bone marrow cells \(2 \times 10^9\) from normal donors produced \(33.6 \pm 8.8\) (n = 10) colony-forming unit-megakaryocytes (CFU-M) in our plasma clot system. When \(2 \times 10^9\) of the patient's T cells were added to the culture system, the number of CFU-M decreased to only 3.5 ± 0.6/2 × 10^4 bone marrow cells. No evidence of inhibitory effects was found by the addition of the patient's serum and complement to the culture system. The T cells stored at \(-80^\circ C\) on admission were also capable of suppressing autologous CFU-M after recovery from AMT. These results indicate that in vitro suppression of CFU-M from allogenic and autologous bone marrow cells by this patient's T cells provides an explanation for the pathogenesis of AMT associated with SLE.

A variety of hematologic abnormalities has been reported in patients with systemic lupus erythematosus (SLE).\(^1,2\) In SLE patients with thrombocytopenia, the number of bone marrow megakaryocytes, as estimated from bone marrow smears, is frequently increased.\(^3,4\) However, thrombocytopenia associated with decreased megakaryocyte is uncommon in SLE.\(^5\) We studied a patient with amegakaryocytic thrombocytopenia (AMT) associated with SLE. In this study, we attempted to investigate the underlying pathogenesis of AMT associated with SLE using an in vitro clonal assay of human CFU-M and in vitro coculture techniques.

MATERIALS AND METHODS

Patient

A 47-year-old female (S.O.) was diagnosed as having SLE in 1979 on the basis of fever, arthralgia, malar erythema, alopecia, positive antinuclear antibody, and anti-ds DNA antibody. She had been initially treated with 30 mg of prednisolone and continued to make good progress on a lesser amount until three months before admission, when she developed gingival bleeding and ecchymoses. She was found to have thrombocytopenia of 10,000/\(\mu\)L. She was hospitalized elsewhere and then transferred to Tsukuba University Hospital in November 1981 for evaluation of thrombocytopenia. She has no history of blood transfusion. Physical examination on admission revealed numerous petechiae and ecchymoses on both legs. Blood cell count revealed the following: RBC, 3.78 × 10^12/L; Hb, 12.0 g/dL; Hct, 38%; reticulocytes, 0.8%; platelet count, 8 × 10^9/L; WBC, 8 × 10^9/L with normal differentiation. The ratio of T\(\alpha\) to T\(\gamma\) in T cell fraction was 28.5%-63.5%. Bone marrow aspiration and biopsy showed no megakaryocytes. She was treated with 60 mg of prednisolone daily and a pulse therapy (methylprednisolone 1 g intravenously for three days). The platelet count was elevated to the normal range for three weeks after treatment. Furthermore, the ratio of T\(\alpha\) to T\(\gamma\) changed to 53.4%-24.5%. The bone marrow aspirate at this time showed normal cellularity with many mature megakaryocytes. Details of serological tests and clinical course have been previously reported.\(^6\)

Control Subjects

Ten normal subjects, five SLE cases with normal platelet counts (SLE group A), and five SLE cases with thrombocytopenia (less than 50 × 10^9/L) and increased megakaryocytes (SLE group B) were used as a control. All SLE cases were studied before treatment. Informed consent was obtained from prospective marrow donors before collection of blood specimens and aspiration of bone marrows required for this study. The research procedures and informed consents for this study were approved by the institutional research review committee.

Preparation and Freezing of T Cells

Peripheral blood mononuclear cells were separated from freshly drawn heparinized blood by Ficoll-Hypaque density sedimentation\(^7\) from the patient (S.O.), ten cases of SLE, and ten normal donors. A T cell-rich fraction was obtained by E rosette centrifugation through Ficoll Hypaque, and the T cells from the patient (S.O.) were frozen using a programmed freezing apparatus (Cryo-Med, Mount Clemens, Mich). Details of the procedure were previously described.\(^8\) Frozen T cells were stored at \(-80^\circ C\) in a concentration of \(2 \times 10^9/\text{mL}\) in RPMI 1640 (GIBCO, Grand Island, NY) supplemented with 15% fetal calf serum (FCS; Flow Laboratories, Rockland, Md) and 10% dimethyl sulfoxide (DMSO; Merck, Darmstadt, FRG). When further experiments were required, the T cells were thawed and washed twice by RPMI 1640 supplemented with 2% FCS and then checked for viability with the trypan blue dye exclusion test.

T Cell subsets

T cells bearing receptors for the Fc portion of IgG and IgM were detected by rosette formation with ox red blood cells,\(^9\) which were coated with purified rabbit IgG and IgM antioxi red blood cells.

Plasma Clot Megakaryocyte Cultures

Bone marrow cell preparation. Bone marrow mononuclear cells were obtained by density centrifugation with Ficoll-Hypaque. The interface mononuclear cell layer was collected and washed twice by a-medium (Flow) supplemented with 2% FCS. Bone marrow cells were finally resuspended in a-medium supplemented with 10% FCS at a concentration of \(5 \times 10^9/\text{mL}\).

Preparation of phytohemagglutinin-leukocyte conditioned medium (PHA-LCM). Mononuclear cells derived from peripheral blood of the normal subjects were cultured in RPMI 1640 supplemented with 10% FCS and 1% PHA (GIBCO) at a concentration of

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0006-4971/86/6702-0036$03.00/0


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2 x 10^5/mL. The supernatant was harvested after four days of incubation and stored at -20°C as PHA-LCM.

**Culture system.** The following materials were used for the plasma clot system: Bovine serum albumin solution (BSA); bovine serum albumin fraction V (Sigma Chemical Co, St Louis) was used. An 8% (wt/vol) BSA stock solution was prepared as described by McLeod et al. L-Asparagine solution: L-Asparagine (Sigma) was dissolved in α-medium at a concentration of 2 mg/mL, filtered through a 0.45-μm filter, and stored at -20°C until used. This stock solution was diluted 1:10 with α-medium before being added to the culture system. Bovine embryo extract: Bovine embryo extract (BEE) (Step-III, Connaught Laboratories, Willowdale, Ontario) was diluted to 20 U/mL by α-medium. Supplemented Eagle’s minimum essential medium with Hanks’ balanced salt solution (supplemented HMEM): The composition of supplemented HMEM was Dulbecco’s modified Eagle’s medium (Flow), 0.086 g; Hanks’ balanced salts without sodium bicarbonate (Flow), 0.99 g; sodium pyruvate (Flow), 0.011 g; 1 mL of MEM nonessential amino acids (GIBCO, 10 mmol/L, 100 x concentrate); 1 mL of L-glutamine (GIBCO, 200 mmol/L, 100 x concentrate); 0.89 mL of 7% (wt/vol) NaHCO3 solution; 10 mL of heat-inactivated human type AB serum and 88 mL of double distilled water. Complement: Rabbit lyophilized serum (Cappel Laboratories, Cochranville, PA) was diluted by α-medium and used as a source of complement.

The plasma clot system was as follows: The mononuclear bone marrow cell suspensions (5 x 10^6 cells) were mixed with 0.1 mL of BSA, 0.1 mL of BEE, 0.1 mL of L-asparagine, 0.1 mL of PHA-LCM, 0.1 mL of Epo, 0.25 mL of α-medium, 0.05 mL of heat-inactivated human Type AB serum, and 0.1 mL of fresh human type AB citrated plasma. The mixture (0.4 mL) was clotted in a 35-mm culture dish, and 2 mL of supplemented HMEH was placed around the clot as a surrounding medium. The culture dishes were kept for 14 days at 37°C in a 100% humidified atmosphere of 5% CO2 in air. The clots were fixed, in situ with 100% methanol for 1 minute and washed with phosphate-buffered saline (0.01 mol/L, pH 7.2). They were then dried in cool air and stored frozen at -20°C until immunofluorescence staining.

**Identification of megakaryocytic colonies.** Immunofluorescent identification using an antiplatelet glycoprotein antiserum was by the method described previously. Briefly, human platelet glycoproteins (HPG) were purified by lithium diiodoacetyl-carnitine-phenol extraction of human platelets by the method described by Marchesi and Chasis. To prepare antiserum against HPG, New Zealand white rabbits were immunized with a subcutaneous injection of 1 mg of HPG with complete Freund’s adjuvant and then intramuscularly injected with 1 mg of HPG every week for four weeks. Blood was collected by ear vein puncture one week after the final injection. Serum was separated and stored at -20°C. Normal bone marrow smears and frozen sections of lymph node, liver, and spleen were stained to check the specificity of anti-HPG. Megakaryocytes and platelets were intensively fluorescent by this antiserum, although macrophages and eosinophils were slightly stained. Indirect immunofluorescence staining procedure was followed by the method of Hoffman et al. A megakaryocytic colony was defined as an aggregate of more than four fluorescent cells.

**CFU-C and CFU-E Assay**

Colon-forming unit in culture (CFU-C) assay was carried out using the method of Pike and Robinson. Triplicate cultures were prepared for each marrow. Cultures were maintained at 37°C in humidified air with 5% CO2 for 14 days. Cell aggregates of more than 40 cells were called colonies. Colony-forming unit erythroid (CFU-E) assay was carried out using the plasma clot method described by Tepperman et al. in the presence of 2 units of erythropoietin (sheep erythropoietin step III; Connaught). Cultures were maintained at 37°C in humidified air with 5% CO2 for seven days. Cell aggregates of more than eight benzidin-positive cells were counted as a colony.

**Coculture Studies**

Normal bone marrow cells from ABO compatible donors were used for all coculture studies. T cells (2 x 10^5) from the patient (S.O.), ten SLE cases, and ten normal subjects were cocultured with 2 x 10^5 normal allogenic or autologous bone marrow cells to assay CFU-M. α-Medium was substituted when the T cell suspension was added to the culture system. To study humoral inhibitors, 0.1 mL of serum from the patient, normal donors, and ten SLE patients, and 0.1 mL of complement were added to the culture system. After the recovery of megakaryopoiesis, 2 x 10^5 of the patient’s T cells (frozen on admission) were cocultured with 2 x 10^5 autologous bone marrow cells. For the coculture studies of CFU-C and CFU-E, 2 x 10^5 T cells obtained from the patient before treatment and from ten normal subjects were cocultured with 2 x 10^5 normal allogenic or autologous bone marrow cells to assay CFU-C and CFU-E.

**RESULTS**

Table 1 shows the control studies from five SLE patients with normal platelet counts (SLE group A), five SLE patients with thrombocytopenia and increased megakaryocytes (SLE group B), and ten normal subjects. Mononuclear bone marrow cells (2 x 10^5) from five normal donors produced a mean of 33.6 ± 8.8 megakaryocytic colonies by culturing in the presence of PHA-LCM and Epo. Only 2.6 ± 1.3 megakaryocytic colonies were cloned per 2 x 10^5 cells in the absence of PHA-LCM and Epo. The mean of megakaryocytic colonies from five cases of SLE group B was 35.5 ± 7.6/2 x 10^5 cells. However, the mean of megakaryocytic colonies from five cases of SLE group A was 35.5 ± 7.6/2 x 10^5 cells. The addition of 2 x 10^5 T cells from normal donors, five cases with SLE group A, and five cases with SLE group B caused a significant increase in megakaryocytic colony formation from allogenic normal bone marrows to 63.5 ± 10.3, 59.3 ± 11.4, and 60.7 ± 9.5/2 x 10^5 cells, respectively (P < 0.001). Also, an addition of autologous T cells caused a similar increase of megakaryocytic colonies in SLE groups A and B as well as in normal subjects. Furthermore, the number of megakaryocytic colonies from normal subjects, SLE group A, and SLE group B were not influenced by the addition of serum and complement.

Table 2 summarizes the effects of T cells and serum from the patient on megakaryocytic colony formation. Only 1.5 ± 0.4 megakaryocytic colonies were cloned per 2 x 10^5 mononuclear bone marrow cells from the patient. The coculture between 2 x 10^5 of the patient’s T cells and 2 x 10^5 mononuclear bone marrow cells from a normal donor caused a marked decrease of megakaryocytic colonies to 3.5 ± 0.6/2 x 10^5 cells.

When the patient recovered from AMT by combination therapy with a high dose of prednisolone and pulse therapy of methylprednisolone, 2 x 10^5 of the patient’s mononuclear bone marrow cells produced 40.3 ± 8.3 megakaryocytic...
Table 1. Effects of T Cells and Serum From Normal Subjects, SLE Group A, and SLE Group B on Megakaryocytic Colony Formation

<table>
<thead>
<tr>
<th>Coculture Studies</th>
<th>Addition to Culture</th>
<th>Source of Bone Marrow</th>
<th>No. of CFU-M/2 x 10^6 Cells</th>
<th>SD (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>None</td>
<td>Own</td>
<td>33.6 ± 8.8</td>
<td></td>
</tr>
<tr>
<td>(n = 10)</td>
<td>2 x 10^6 T cells</td>
<td>Allogenic normal</td>
<td>63.5 ± 10.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 x 10^6 T cells</td>
<td>Autologous</td>
<td>62.8 ± 11.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1 mL of serum</td>
<td>Allogenic normal</td>
<td>31.7 ± 6.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1 mL of serum</td>
<td>Autologous</td>
<td>32.3 ± 6.6</td>
<td></td>
</tr>
<tr>
<td>SLE group A</td>
<td>None</td>
<td>Own</td>
<td>35.5 ± 7.6</td>
<td></td>
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<tr>
<td>(n = 5)</td>
<td>2 x 10^6 T cells</td>
<td>Allogenic normal</td>
<td>59.3 ± 11.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 x 10^6 T cells</td>
<td>Autologous</td>
<td>61.4 ± 9.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1 mL of serum</td>
<td>Allogenic normal</td>
<td>35.7 ± 7.1</td>
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</tr>
<tr>
<td></td>
<td>0.1 mL of serum</td>
<td>Autologous</td>
<td>36.0 ± 8.2</td>
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<tr>
<td>SLE group B</td>
<td>None</td>
<td>Own</td>
<td>46.8 ± 11.8</td>
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<tr>
<td>(n = 5)</td>
<td>2 x 10^6 T cells</td>
<td>Allogenic normal</td>
<td>60.7 ± 9.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 x 10^6 T cells</td>
<td>Autologous</td>
<td>75.6 ± 8.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1 mL of serum</td>
<td>Allogenic normal</td>
<td>40.7 ± 8.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1 mL of serum</td>
<td>Autologous</td>
<td>45.7 ± 10.4</td>
<td></td>
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</tbody>
</table>

T cells (2 x 10^6) from normal subjects, SLE group A, and SLE group B were cocultured with 2 x 10^6 autologous and allogenic normal bone marrows. Further, 0.1 mL of serum from normal subjects, SLE group A, and SLE group B were added to culture system with 0.1 mL of complement (rabbit lyophilized serum diluted by α-medium). Values for normal subjects were constructed from ten normal subjects by separate experiments (mean ± SD, n = 10). Values for SLE group A and SLE group B were constructed from five SLE group A and SLE group B by separate experiments (mean ± SD, n = 5). All allogenic normal bone marrows were obtained from different donors.

In order to study the effect of the patient’s T cells on autologous bone marrow cells, 2 x 10^6 of the patient’s T cells (frozen on admission) were cocultured with 2 x 10^6 autologous mononuclear bone marrow cells after the recovery of megakaryopoiesis. The number of megakaryocytic colonies was suppressed to 2.7 ± 0.3/2 x 10^6 cells. However, 2 x 10^6 T cells after recovery from AMT failed to suppress the megakaryocytic colonies derived from autologous and allogenic bone marrow cells.

To study the humoral inhibitors influencing megakaryocytic colony formation, the patient’s serum (0.1 mL) and complement were added to the culture system. The numbers of megakaryocytic colonies from the patient, normal donors, SLE group A, and SLE group B were not suppressed by the addition of serum and complement, suggesting no evidence of inhibitor in the serum. These coculture studies indicated that T cells were responsible for severe megakaryocytopenia associated with SLE.

In addition, to determine whether T cells from the patient exhibited suppressive effects on autologous and allogenic CFU-C or CFU-E growth or not, 2 x 10^5 T cells from the patient were cocultured with 2 x 10^5 mononuclear bone marrow cells from autologous or allogenic bone marrow marrows. Mononuclear bone marrow cells (2 x 10^6) from normal subjects yielded 105.4 ± 14.5 (mean ± SD, n = 5) of CFU-C and 185.6 ± 21.5 (mean ± SD, n = 5) of CFU-E. Similarly, 2 x 10^5 mononuclear bone marrow cells from the patient during AMT yielded 125.4 ± 15.2 of CFU-C and 198.3 ± 21.9 of CFU-E. When T cells obtained from the patient before treatment were added, the mean values of CFU-C and CFU-E were increased to 136.6 ± 18.5 and 245.3 ± 47.6/2 x 10^5 cells, respectively, indicating no suppression of autologous CFU-C and CFU-E growth. T cells from normal subjects also enhanced colony formation of CFU-C and CFU-E (data not shown).

DISCUSSION

Much work has been done on the immune suppression of hematopoiesis in SLE, characterized by major alteration of both the humoral and the cellular branches of immunity. In a previous study, Duckham et al reported that a factor in the serum from patients with SLE inhibited granulocytic colony formation in an in vitro agar system. Also, Fitchen et al described one patient having SLE and IgG inhibitor of granulopoiesis and erythropoiesis. However, in a recent
report, the peripheral T cells from SLE patients suppressed the CFU-C growth from allogenic normal bone marrow. These studies indicate that cell-mediated suppression, as well as serum inhibitor, could be responsible for immune cytopenia in SLE.

Acquired AMT is an uncommon disorder that does not represent a single clinical entity. It has been reported in conjunction with SLE without determination of an underlying pathogenesis. It was suggested by Hoffman et al20 that acquired AMT could involve several pathogenetic mechanisms, including (a) failure of terminal megakaryocytic differentiation; (b) an intrinsic cell defect; (c) abnormal interaction between CFU-M and bone marrow regulatory cells; (d) decreased production of a hematopoietic growth factor; and (e) immunologic attachment on megakaryocytic progenitor cells. They also demonstrated, from their analyses of six cases, that acquired AMT could be due to at least one of two alternative mechanisms: either an intrinsic defect at the level of CFU-M or a circulating cytotoxic autoantibody directed against the CFU-M. More recently, Hoffman et al21 reported an unusual case of chronic idiopathic thrombocytopenic purpura with amegakaryocytosis due to a humoral antibody cytotoxic to megakaryocyte progenitor cells.

Our control studies showed that the number of CFU-M in SLE group B was significantly higher than those in SLE group A and normal controls, suggesting that the regulatory response to the thrombocytopenic state is not impaired in SLE group B. Also, we failed to suppress the number of CFU-M by the addition of complement and serum from patients in SLE group B as well as from those in group A, indicating no inhibitory humoral antibody to megakaryocyte progenitor cells. These findings suggest that a humoral antibody to megakaryocyte progenitor cells is uncommon in SLE.

T cells may play an important role in the regulation of megakaryopoiesis at the progenitor cell level, although it is well known that T cells stimulate CFU-E and CFU-C growth. The present study indicates that T cells from normal donors, SLE group A, and SLE group B are capable of enhancing the number of CFU-M from allogenic and autologous bone marrow. We have assumed that T cells may secrete a stimulating factor, like a colony-stimulating factor for megakaryocytes (CSF-Meg). However, we could not find a marked difference in T cells from the three groups for enhancing of CFU-M from allogenic or autologous bone marrow.

In contrast, the CFU-M were strongly suppressed when T cells from this patient were cocultured with normal allogenic bone marrow cells. Also, the patient's T cells (frozen on admission) suppressed CFU-M of autologous bone marrow cells after the recovery of megakaryopoiesis. This is a direct demonstration that the patient's T cells are capable of suppressing autologous hematopoietic stem cells. These results indicate that abnormal cell-to-cell interaction between the patient's T cells and megakaryocytic progenitor cells may be responsible for the underlying mechanism of megakaryocytic colony suppression in vitro.

It has recently become possible to quantify subsets of T cells as helper T cells (T\textsubscript{H}) and suppressor T cells (T\textsubscript{S}). However, this analysis of subsets of T cells in SLE remains controversial. Morimoto et al23 reported a selective decrease in OKT\textsubscript{8} cells (suppressor T cells), whereas Bakke et al24 demonstrated that one half of 28 SLE patients had markedly depressed percentage and absolute number of OKT\textsubscript{4} cells (helper T cells). The patient in the present study showed a decreased number of T\textsubscript{H} cells and a relatively increased number of T\textsubscript{S} cells. Recently, Worman et al25 reported an excess of suppressor T lymphocytes in association with AMT in a case of AML. In the present case, an imbalance of T cell subsets may cause a megakaryocytopenia associated with SLE.

This patient developed AMT during an inactive serologic state of SLE. Cline and Golde26 described a patient having SLE and an IgG inhibitor of granulopoiesis and erythropoiesis and stated that such inhibitors appear to be relatively infrequent in patients with active disease. However, AMT in the present patient responded to a high dose of prednisolone and pulse therapy of methylprednisolone. The analysis of T cell subsets after the recovery of megakaryopoiesis revealed 53.4% of T\textsubscript{S} and 24.5% of T\textsubscript{H}, suggesting the decrease of T\textsubscript{S} cells to be due to combination therapy.

We conclude that T cells from this patient are capable of in vitro suppression of megakaryopoiesis. For some cases, this may explain the association of AMT with SLE.

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