Disseminated Intravascular Coagulation in a Patient with Systemic Lupus Erythematosus with Lupus Anticoagulant

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A 19-year-old female patient with systemic lupus erythematosus (SLE) who had lupus anticoagulant (LA) and concurrently developed disseminated intravascular coagulation (DIC) during an exacerbation of “central nervous system (CNS) lupus”. Since no other indications or causes for DIC could be demonstrated, she was treated with prednisolone and anticoagulants, which rapidly alleviated her DIC condition as well as “CNS lupus”. Although abnormalities of coagulation are frequently reported in SLE patients, DIC rarely occurs in patients with SLE without associated complications. A review of the pathogenesis of DIC in patients with SLE is discussed.

Key words: thrombomodulin, antiphospholipid antibodies, immunoglobulin index

Introduction

A variety of hematostatic abnormalities such as autoimmune thrombocytopenia and/or abnormalities of the coagulation mechanisms have been known to be associated in patients with systemic lupus erythematosus (SLE). It has been suggested that activation of local intravascular coagulation occurs and contributes to tissue injury in patients with SLE (1). Anti-phospholipid antibodies (aPL), especially lupus anticoagulant (LA) is considered as one of the major causes of abnormalities in the coagulation mechanisms and functions as an inhibitor of the prothrombin-activation complex of the clotting cascade and furthermore reacts with the phospholipid molecules of the vascular endothelial cells and platelets to induce arterial/venous thrombosis (2).

Disseminated intravascular coagulation (DIC) is characterized as a systemic intravascular microthrombosis and is involved in ischemic organ damage due to the microthrombosis. DIC is often associated with solid tumors, leukemia, sepsis, intravascular hemolysis, liver diseases and obstetrical complications (3). However, DIC is rarely associated with SLE although minor or low-grade chronic intravascular coagulation abnormalities are frequently observed among patients with active SLE (4).

Here we report a patient with LA-positive SLE who developed DIC during an exacerbation of “CNS lupus” and discuss the mechanism of DIC in SLE patients.

Case Report

A 19-year-old high school female patient was diagnosed as having SLE on the basis of arthritis, butterfly rash, pleuritis, nephritis, LE cells, antinuclear antibody (ANA) (1:20,480, homogeneous), anti-dsDNA antibody (44.1 U/ml; normal range <10 U/ml) and anti-Sm antibody (1:4) in 1986. Activated partial thromboplastin time (APTT) was 44.6 second (control 32.4 second). The prolonged APTT was not corrected by control plasma and positive LA was confirmed by caolin clot test (CCT) as described by Exner et al (5).

On July 23, 1988, the patient was admitted to our hospital with renal failure due to lupus nephritis. She had generalized edema, bilateral pleural effusions and high blood pressure (180/100 mmHg). Biochemical analysis revealed elevated levels of BUN and creatinine, 116 mg/dl and 6.5 mg/dl, respectively. Urinalysis revealed telescoped sediments with 6–12 g/day of proteinuria. GFR was 6.9 ml/min. Despite steroid “pulse” therapy (methylprednisolone sodium succinate 1000 mg/day for 3 days) and 100 mg/day of azathioprine, oliguria and azotemia progressed. Hemodialysis treatment was commenced from August 5, 1988.

Over the subsequent two years, her condition was stable with hemodialysis treatment and betamethasone in doses of 3–4 mg/day. From October 8, 1990, the dose of betamethasone was gradually decreased from 3 mg to 2 mg/day because she had aseptic bone necrosis of both femoral heads and complained of pain at both hip joints even though her SLE condition was...
stable. Ten days after the dose of betamethasone was decreased to 2 mg/day, she developed psychological problems such as crying all day and irritability. No particular causes other than the decrease in the dose of betamethasone could be found for exacerbation of her illness. On November 13, she developed stuporose. There were small petechiae observed on the trunk, purpura and ecchymotic lesions on the extremities and a butterfly rash on her face. The fingers showed multiple small, discrete gangrenous lesions. The laboratory findings are indicated in Fig. 1. ANA was 1:40 and anti-dsDNA antibody was negative. LA was consistently positive but a marked prolongation of APTT (more than 110 second/control 33.6 second) was detected on Nov. 6. Prolonged APTT was not due to the effect of the anticoagulant used during hemodialysis treatment and drugs associated with the possibly of inducing LA had not been administered (6). Anticardiolipin antibody (aCL) (IgG) was 0.6 U (<3.0). Decrease in the levels of C3 from 41 to 28 mg/dl, C4 from 31 to 28 mg/dl and CH50 from 32.5 to 15.8 U/ml were detected on Nov. 14. Plasma ammonia level was within the normal range. Circulating immune complex (CIC; Clq binding assay) was negative. The level of platelet associated IgG (PAIgG), which is frequently detected in patients with idiopathic thrombocytopenic purpura (ITP) and SLE with thrombocytopenia was 22.8 ng/10⁷ cells (9.0–25.0). Plasma thrombomodulin (TM) level was elevated to 119 ng/ml (<20: kindly measured by Dr. M. Kazama, Department of Internal Medicine, School of Medicine, Teikyo University, Tokyo, Japan). Cerebrospinal fluid (CSF) examination revealed a markedly elevated immunoglobulin index of IgG; 6.8 (<0.75), IgM; 1.1 (<0.20) and the level of protein and cells were within normal limits. These findings strongly suggested that this patient had "CNS lupus". There were no abnormal findings except old
DIC in LA Positive SLE

small infarctions observed on CT scan of the brain. Retinal
vascular narrowing was found by fundoscopy but "cytoid bod-
ies", hemorrhage, papillitis and retinal artery thrombosis were
not observed. Extensive examinations of the CSF, blood, spu-
tum, urine, the hemodialysis catheter and the dialysis system
failed to reveal any evidence of bacterial infection.

According to the criteria for DIC (7), the patient satisfied the
DIC score in 8 out of 13 points on Nov. 14. Therefore, on the
basis of clinical manifestations and laboratory findings, she was
diagnosed as having "CNS lupus" and DIC.

High-dose steroid therapy (betamethasone 10 mg/day) and
anticoagulant therapy with heparin (10,000 U/day), nafamostat
mesilate (8) (240 mg/day), and AT III (50 ml/day; 10 ml
included a dosage of 500 times the amount of AT III present in
normal human plasma 1 ml) were administered per day.
Hemodialysis was conducted three times per week. Two days
after commencement of treatment, her consciousness level
gradually improved and the levels of FDP, fibrinogen and AT
III as well as SGOT, SGPT rapidly improved within 4 days (Fig.
1). A week later, she had completely recovered from the DIC
and "CNS lupus". The decreased C3, C4 and CH50 levels
returned to the levels determined on Nov. 6, 2 weeks after the
present episode. The brain CT examination at three weeks after
the episode revealed no additional small infarctions and the
elevated CSF immunoglobulin indices returned to within the
normal range a month after the episode. Over the subsequent 6
months, LA was consistently positive with prolonged APTT
levels (42–76 second: control 26–38 second).

Discussion

According to the criteria for DIC proposed by the DIC
Research Committee of Japan, Ministry of Health and Welfare,
1981 (7), our patient was diagnosed as DIC. Bleeding symp-
toms (purpura and ecchymotic lesions), organ (liver) dysfunc-
tion, prolonged PT, decreased fibrinogen level and platelet
count, increased serum FDP level fulfilled the DIC score in 10
out of 13 criteria (score more than 7 is diagnosed as definite
DIC). In addition to these findings, the decreased AT III level
was a confirmatory finding and very rapid improvement with
anticoagulation treatment including heparin confirmed that she
had DIC. The transient increase of SGOT, SGPT suggested that
intravascular coagulation occurred in the hepatic arteries since
these enzymes normalized within only 5 days by intensive
anticoagulant and steroid therapies. Furthermore, a markedly
increased level of thrombomodulin (TM) suggested that sys-
temic and extensive endothelial injury occurred during the
clinical course (9).

Hemolytic anemia, icterus and appearance of markedly
fragmented red blood cells were not observed. Therefore,
thrombotic thrombocytopenic purpura (TTP) was not likely
associated with this patient. Although the PAIgG level re-
mained within the normal range and antiplatelet antibodies
were not detected, the possibility of association of autoimmune
thrombocytopenia was not ruled out because bone marrow
biopsy and other examinations were not conducted. Throm-
botic microangiopathy (TMA) is frequently associated with
LA-positive SLE patients (10-12) and slightly elevated levels
of FDP are observed. However, the levels of fibrinogen and AT
III are usually observed within the normal range or are slightly
elevated in patients with TMA. Therefore, we diagnosed that
she had DIC based on the fact that her clinical manifestations
and laboratory findings fulfilled the criteria for DIC.

Hematological abnormalities in SLE may be due to
autoimmune manifestations, such as circulating anticoagu-
ulants, CICs or vasculitis (1, 13-15). Although the develop-
ment of DIC in SLE is an unusual clinical event, it has been suggested
that an activation of the coagulation system to some degree
occurs in the majority of the patients with active SLE (16).
Evidence supporting this includes an increase in fibrinogen
turnover (13) and FDP (1), elevated levels of fibrinopeptide A
(13) and thrombomodulin (TM) which is released due to the
injury of vascular endothelial cells as is observed in patients
with SLE as well as DIC (9). Only 11 cases of SLE associated
with DIC without any complications which usually induce DIC,
have been reported to date (6, 17–23). In these reports, vascular
involvement was found in most cases, and the patients had
severe clinical manifestations (Table 1). Among these 11 cases,
3 out of 6 cases were positive for circulating anticoagulants; one
case was positive for aCL (6) and the type of circulating anti-
coagulants was not described for the remaining 2 cases (18, 21).
Although there has been no report of patients with LA develop-
ing DIC, it may be possible that the circulating anticoagulants
including LA and/or aCL may induce DIC.

Cerebral infarction or cerebral ischemic attack often occurs
in patients with "antiphospholipid syndrome" (24). However, the loss of consciousness in this patient is unlikely due to
transient ischemic attack or lacunar stroke which was induced
by LA, DIC or both since the immunoglobulin indices in CSF
were markedly elevated at the onset of loss of consciousness.
It has been reported that an increase in the level of immunoglobulin
indices in CSF is more frequently detected in patients with
neuropsychiatric manifestation than in patients with cere-
brovascular accidents (25). Moreover, additional new low
density spots were not detected on the brain CT scan examined
during the 3rd week after the episode. Although vasculitis
associated with exacerbation of SLE could not be completely
ruled out, the levels of protein and cells of CSF are usually
elevated in vasculitis. This evidence strongly suggests that the
loss of consciousness was not due to cerebral thrombosis but
due to the so called "CNS lupus" (neuropsychiatric lupus) in
which polyclonal B cell activation occurred in the central
nervous system and the neuron-reactive antibodies in CNS
might have been involved (25, 26).

Due to the fact that the present patient had a recurrence of
"CNS lupus" immediately prior to the development of DIC and
showed no evidence of bacterial infection or other complica-
tions which may cause DIC, we considered that the occurrence
of DIC was possibly related to the exacerbation of SLE in this
case.

The pathogenesis of DIC in SLE patients is not fully un-
derstood. Vasculitis has been considered to be involved in the
### Table 1. Cases of SLE Associated with DIC

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>Clinical findings</th>
<th>Platelet</th>
<th>ESR</th>
<th>Fibrinogen</th>
<th>FDP</th>
<th>AT III</th>
<th>Circulating anti-coagulant</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mckay DG(23)</td>
<td>1965</td>
<td>38 y.o. SLE</td>
<td>Microscopic thrombi in small vessels</td>
<td>60×10⁴/mm³</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>Whitaker AN(18)</td>
<td>1972</td>
<td>26 y.o. male SLE</td>
<td>Pulmonary microembolism</td>
<td>60×10⁴/mm³</td>
<td>11 mm/h</td>
<td>200/100 ml (180-400)</td>
<td>34 µg/ml (0-8)</td>
<td>50% (75-125)</td>
<td>Positive</td>
</tr>
<tr>
<td>Beall CL(19)</td>
<td>1975</td>
<td>19 y.o. female SLE</td>
<td>Thrombocytopenia digital vascular thromboses microangiopathy</td>
<td>3.5×10⁴/mm³</td>
<td>32 mm/h</td>
<td>89 mg/100 ml (150-350)</td>
<td>&gt;80 ng/ml</td>
<td>N.D.</td>
<td></td>
</tr>
<tr>
<td>Shinmyozu K(20)</td>
<td>1983</td>
<td>49 y.o. female SLE</td>
<td>Macrohematuria Gl tract bleeding purpura</td>
<td>38×10⁴/mm³</td>
<td>3 mm/h</td>
<td>120 mg/100 ml (180-300)</td>
<td>160 µg/ml</td>
<td>50% (77-123)</td>
<td>N.D.</td>
</tr>
<tr>
<td>Chellingsworth M(17)</td>
<td>1985</td>
<td>40 y.o. female SLE (MCTD?)</td>
<td>Interstitial pneumonitis systemic thromboses</td>
<td>24×10⁴/mm³</td>
<td>34 mm/h</td>
<td>57 mg/100 ml (150-900)</td>
<td>240 mg/l</td>
<td>N.D.</td>
<td></td>
</tr>
<tr>
<td>Riddell SR(22)</td>
<td>1986</td>
<td>48 y.o. male SLE</td>
<td>Ecchymoses</td>
<td>82×10⁴/mm³</td>
<td>N.D.</td>
<td>80 mg/100 ml (170-400)</td>
<td>166.4 µg/ml</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>Bird AG(9)</td>
<td>1987</td>
<td>52 y.o. female SLE</td>
<td>Gangrene pancreatitis</td>
<td>80×10⁴/mm³</td>
<td>N.D.</td>
<td>700 mg/100 ml (2,000-4,000)</td>
<td>&gt;500 µg/l</td>
<td>N.D.</td>
<td>Positive (anti-CL)</td>
</tr>
<tr>
<td>Kerr LD(21)</td>
<td>1987</td>
<td>57 y.o. female SLE</td>
<td>Confusion vasculitic skin lesions</td>
<td>42×10⁴/mm³</td>
<td>55 mm/h</td>
<td>50 mg/100 ml</td>
<td>&gt;40 µg/ml</td>
<td>N.D.</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23 y.o. female SLE</td>
<td>Pleuroparicarditis seizure pancreatitis vasculitis</td>
<td>100×10⁴/mm³</td>
<td>1 mm/h</td>
<td>75 mg/100 ml</td>
<td>10-40 µg/ml</td>
<td>N.D.</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 y.o. female SLE</td>
<td>Bilateral occipital lobe infarctions vasculitic skin lesions</td>
<td>80×10⁴/mm³</td>
<td>43 mm/h</td>
<td>330 mg/100 ml</td>
<td>&gt;40 µg/ml</td>
<td>N.D.</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33 y.o. female SLE</td>
<td>Deep venous thrombosis</td>
<td>57×10⁴/mm³</td>
<td>3 mm/h</td>
<td>380 mg/100 ml</td>
<td>&lt;10 µg/ml</td>
<td>N.D.</td>
<td>Negative</td>
</tr>
<tr>
<td>Tanaka M</td>
<td>19 y.o. female SLE</td>
<td>Consciousness disturbance purpura</td>
<td>31×10⁴/mm³</td>
<td>3 mm/h</td>
<td>130 mg/100 ml (200-400)</td>
<td>30 µg/ml</td>
<td>59% (80-120)</td>
<td>Positive (LA)</td>
<td>Heparin 10,000 u/day bethamethasone 10 mg/day</td>
</tr>
</tbody>
</table>

N.D.: not described.
DIC in patients with SLE (21). CIC activates complements that may injure the vascular endothelial cells resulting in the release of tissue thromboplastin-like substances (27). Complement and platelet activation have been postulated as explanations for coagulation system activation in the setting of vasculitis (27-29). LA and aCL are responsible for the local intravascular coagulation. Although circulating anticoagulant has been demonstrated in only a few cases of SLE associated with DIC, our hypothetical view of this case is that LA may have been involved, in one way or another, in the occurrence of DIC due to the fact that a markedly prolonged APTT was detected prior to the onset of DIC without an increase of CIC. Massive production of LA during the exacerbation of SLE may have led to extensive and systemic injury of endothelial cells which might have triggered the development of DIC.

Despite the presence of vasculitis and FDP, DIC is not frequently mentioned in the extensive analysis of SLE. A higher index of suspicion may reveal the true incidence and pathogenesis of DIC in patients with SLE.

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References