CASE REPORT

HELLP Syndrome, Multiple Liver Infarctions, and Intrauterine Fetal Death in a Patient with Systemic Lupus Erythematosus and Antiphospholipid Syndrome

Yoko Wada¹, Yuichi Sakamaki¹, Daisuke Kobayashi¹, Junya Ajiro¹, Hiroshi Moro³, Shuichi Murakami¹, Izumi Ooki⁴, Akira Kikuchi⁷, Koichi Takakuwa⁷, Kenichi Tanaka⁴, Takehiro Sato⁵, Masaaki Nakano⁶ and Ichiei Narita¹

Abstract

We report a case of HELLP syndrome, multiple liver infarctions, and intrauterine fetal death in a woman in the 17th week of pregnancy with SLE and APS who had been in remission on a regimen of low-dose prednisolone and aspirin. An increase in the dosage of corticosteroid together with intravenous heparin infusion led to improvement of the clinical symptoms, laboratory parameters, and multifocal low-density liver lesions detected by computed tomography. Early onset and signs of severe organ involvement are the characteristic features of HELLP syndrome associated with APS, and patients that are at risk should be followed up carefully.

Key words: HELLP syndrome, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), multiple liver infarction, catastrophic antiphospholipid syndrome (CAPS)

(Inter Med 48: 1555-1558, 2009)
(DOI: 10.2169/internalmedicine.48.2284)

Introduction

The syndrome of hemolysis, elevated liver enzyme levels and low platelet count (HELLP) is a multisystemic thrombotic microangiopathy that complicates pregnancy. It is associated with a high maternal death rate and perinatal mortality, and is considered to be a severe form of pre-eclampsia (1-4). HELLP is estimated to occur in 0.17-0.85% of the general population, and is diagnosed antepartum in 70% and postpartum in 30% of cases. Among cases diagnosed antepartum, 90% are in the third trimester, and the syndrome rarely occurs before 27 weeks of gestation (2). Although the pathogenetic mechanism is not fully understood, it is thought to occur as a result of aberrant placental function, impaired placental vascular perfusion, and ischemia-producing oxidative stress, which stimulate the release of factors that injure the vascular endothelium via activation of platelets, vasoconstrictors, and loss of normal vascular relaxation in pregnancy (3, 4).

Antiphospholipid syndrome (APS) is known to be a major cause of fetal loss due to a thrombotic tendency leading to placental infarction during pregnancy (5, 6), and there is a growing body of evidence that APS may be one of the possible risk factors of HELLP syndrome (7-12).

Here we report a case of HELLP syndrome associated with systemic lupus erythematosus (SLE) and APS in the early second trimester, which was treated successfully with corticosteroid and heparin administration.

¹Clinical Nephrology and Rheumatology, Department of Medicine II, Niigata University Graduate School of Medical and Dental Sciences, Niigata, ²Department of Internal Medicine, Niigata-prefectural Central Hospital, Joetsu, ³Respiratory Medicine, Department of Medicine II, Niigata University Graduate School of Medical and Dental Sciences, Niigata, ⁴Department of Obstetrics and Gynecology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, ⁵Kitashiro Clinic of Family Practice, Joetsu and ⁶Department of Medical Technology, School of Health Sciences, Faculty of Medicine, Niigata University, Niigata

Received for publication March 19, 2009; Accepted for publication May 28, 2009
Correspondence to Dr. Yoko Wada, yoko.wada@gmail.com
Table 1. Laboratory Data on Admission to Our Hospital

<table>
<thead>
<tr>
<th>Blood count</th>
<th>Serum chemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>ALT 1049 IU/L</td>
</tr>
<tr>
<td>RBC 343 ×10⁴/µL</td>
<td>AST 1218 IU/L</td>
</tr>
<tr>
<td>Hb 10.4 g/dL</td>
<td>LDH 1292 IU/L</td>
</tr>
<tr>
<td>Ht 29.1 %</td>
<td>γGTP 209 IU/L</td>
</tr>
<tr>
<td>Plt 5.6 ×10⁴ /µL</td>
<td>ALP 442 IU/L</td>
</tr>
<tr>
<td></td>
<td>TB 1.4 mg/dL</td>
</tr>
<tr>
<td></td>
<td>DB 0.3 mg/dL</td>
</tr>
<tr>
<td></td>
<td>IB 1.1 mg/dL</td>
</tr>
<tr>
<td></td>
<td>ChE 136 IU/L</td>
</tr>
<tr>
<td></td>
<td>Amy 34 IU/L</td>
</tr>
<tr>
<td></td>
<td>BUN 9 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Cr 0.33 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Ferritin 5018 ng/mL</td>
</tr>
</tbody>
</table>

Coagulation tests
- APTT 51.1 sec (control 26.2)
- HPT 88 %
- Fbg 472 mg/dL
- FDP 91.2 µg/mL
- D-dimer 40.5 mg/dL
- ATIII 60 %
- Direct Coombs test (-)
- Indirect Coombs test (-)

Immunological Findings
- CRP 17.62 mg/dL
- IgG 1111 mg/dL
- IgM 131 mg/dL
- IgA 67 mg/dL
- C3 48.4 mg/dL
- C4 5.4 mg/dL
- CH50 20 U/mL
- ANA 66.9 index
- dsDNA 9 IU/mL
- LAC 2.33 (+)
- aCL/β2GPI <1.2 U/mL
- aCL-IgG <8 U/mL

Case Report

A 26-year-old woman in the 17th week of pregnancy was transferred to our hospital because of progressive severe liver dysfunction, thrombocytopenia, and elevated levels of acute inflammatory markers. She had a 12-year history of systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS), which had been in remission for more than 3 years under a treatment of 9 mg prednisolone daily and low-dose aspirin. She had become pregnant in July 2008, and at 17 weeks of pregnancy had developed acute epigastralgia and vomiting. Laboratory examinations had shown no significant abnormality, and famotidine had been prescribed for her symptoms. However, she visited the clinic again because of worsening of her symptoms one week after onset. At that time, severe thrombocytopenia together with liver dysfunction and an elevated level of C-reactive protein were observed, and she was therefore admitted to the emergency ward.

Laboratory examinations showed severe liver dysfunction, and data from coagulation studies met the diagnostic criteria for disseminated intravascular coagulation (DIC). Continuous intravenous infusion of nafamostat methylate together with antibiotics, gamma-globulin, and platelet transfusion did not improve the clinical symptoms or laboratory abnormalities.

When transferred to our hospital, the patient had a fever and persistent severe epigastralgia. Her blood pressure was normal and pulse was 154 min. Blood examination revealed leukocytosis and thrombocytopenia with severe liver dysfunction. Fragmented red blood cells were not observed. Urinalysis showed macroscopic hematuria without proteinuria. Ultrasound examination revealed intrauterine fetal death after transfer to our hospital, and induction of delivery was performed with platelet transfusion. Histopathological examination confirmed multiple placental infarctions with small-vessel thrombosis. Abdominal computed tomography (CT) scan after the delivery showed multiple low-density areas in the patient’s liver, suggesting multiple liver infarctions (Fig. 1).

Immediately after the delivery, the dosage of prednisolone was increased to 1 mg/kg body weight, together with continuous intravenous heparin infusion, and the clinical symptoms and laboratory data gradually improved (Table 2). Follow-up abdominal CT scan at 4 weeks demonstrated improvement of the multiple low-density liver lesions (Fig. 2).

Discussion

APS is a well known condition that has a close relationship with pregnancy-related complications (5, 6). Although the most characteristic complication is recurrent spontaneous abortion, recent studies have also indicated APS as a possible risk factor for the onset of HELLP syndrome (7, 8). HELLP syndrome associated with APS has been reported to have some characteristic features. In a retrospective study, Thuong et al reported that 16 pregnancies (10.6%) with APS

1556
Figure 1. Computed tomography scan of the upper abdomen, showing multifocal hypodense lesions in the liver and right pleural effusion.

Table 2. Clinical Course and Laboratory Findings in This Patient

<table>
<thead>
<tr>
<th>Day</th>
<th>8 Sep</th>
<th>12 Sep</th>
<th>14 Sep</th>
<th>22 Sep</th>
<th>14 Oct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>epigastralgia</td>
<td>fever</td>
<td>epigastralgia</td>
<td>fever resolved</td>
<td>no symptoms</td>
</tr>
<tr>
<td>Events</td>
<td>hospitalization</td>
<td>emergency</td>
<td>transfer to our hospital</td>
<td>induction of delivery</td>
<td>CT findings improved</td>
</tr>
<tr>
<td>Treatment</td>
<td>PSL 9mg, aspirin, nafamostat methilate, platelet transfusion</td>
<td>PSL 9mg, aspirin, nafamostat methilate, platelet transfusion</td>
<td>PSL 50mg, aspirin, nafamostat methilate, heparin</td>
<td>CT findings improved</td>
<td></td>
</tr>
<tr>
<td>WBC (×10⁴/µL)</td>
<td>14900</td>
<td>23860</td>
<td>24310</td>
<td>8830</td>
<td>9130</td>
</tr>
<tr>
<td>Platelet (×10⁴/µL)</td>
<td>5.1</td>
<td>5.6</td>
<td>1.9</td>
<td>19.7</td>
<td>19.9</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>280</td>
<td>1049</td>
<td>385</td>
<td>51</td>
<td>17</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>250</td>
<td>1218</td>
<td>892</td>
<td>135</td>
<td>19</td>
</tr>
<tr>
<td>CH50 (U/mL)</td>
<td>-</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>17.1</td>
<td>17.62</td>
<td>-</td>
<td>0.14</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

IUFD: intrauterine fetal death, PSL: prednisolone, LDAs: low density areas.

were accompanied by HELLP syndrome (7). Although the syndrome usually occurs in the third trimester or postpartum, they found that it occurred earlier and was more severe in APS-associated pregnancies than in the general population. Pauzner et al reported the relationship between liver infarction in HELLP syndrome and APS, and described that hepatic infarction during pregnancy was almost always associated with APS (13). Several other case reports have also indicated that patients with HELLP syndrome associated with APS are sometimes refractory to fetal delivery and require further intensive therapy such as corticosteroid administration or plasmapheresis, suggesting the severity of HELLP syndrome associated with APS (9-12).

Another focus of interest has been the similarities between some cases of HELLP syndrome and catastrophic APS (CAPS) during pregnancy (10, 14-17). CAPS is a very rare and life-threatening variant of APS characterized by multiple microvascular thromboses over a short period of time, leading to multiple organ failure and a high mortality rate. Around 50% of cases are thought to have a trigger event before the onset of CAPS, including infections, surgery, malignancy, lupus flares, and pregnancy (15-17). Gomez-Puerta et al reported 15 episodes of CAPS among 255 pregnancies associated with APS. Among these 15 cases, 8 showed overlap with HELLP syndrome, and the authors indicated that a severe form of HELLP syndrome was a major feature of CAPS, based on their own study and other case reports (14). Indeed, in some severe cases of HELLP syndrome, several organs are affected simultaneously, and the features can include liver infarction, acute renal failure, or acute respiratory distress syndrome, which could also meet the preliminary criteria for CAPS. In addition, aggressive immunosuppressive therapies such as high-dose steroid administration, intravenous immunoglobulin, and plasmapheresis appear to have a beneficial effect on both of these disorders (15-17). This might be attributable to the presence of severe systemic inflammatory response syndrome (SIRS) in both conditions (15, 16).
In the present case, hypocomplementemia during pregnancy might indicate lupus flare. Furthermore, HELLP syndrome involved at least two organs [the liver and hematologic system (DIC)], and met the preliminary criteria for probable CAPS (15). Thus, it was a reasonable decision to increase the dosage of prednisolone in the present case. The treatment was effective for both the clinical symptoms and laboratory abnormalities.

General recommendations for the management of APS in pregnancy and the puerperium have been proposed (5), but the establishment of prophylaxis against HELLP syndrome in patients with APS still remains a controversial issue. Further studies and accumulation of data will be needed in order to clarify the underlying pathogenesis of APS associated with pregnancy leading to a high rate of association with HELLP syndrome.

References