Kobe J. Med. Sci., Vol. 70, No. 1, pp. E22-E25, 2024

HELLP Syndrome at 20 Gestational Weeks Managed Using the Mississippi Protocol: A Case Report

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Received January 10, 2024/Accepted February 5, 2024

Keywords: Dexamethasone, HELLP Syndrome, Hypertensive Disorders of Pregnancy, Mississippi Protocol

Hemolysis, elevated liver enzyme levels, and low platelet count (HELLP) syndrome is one of the most severe complications of hypertensive disorders of pregnancy. HELLP syndrome occurring before 22 gestational weeks (GWs) is extremely rare, and patients prevalently exhibit underlying maternal diseases or fetal abnormalities. Here, we report the case of a pregnant woman who had HELLP syndrome at 20 GWs without any obvious underlying maternal diseases or fetal abnormalities. A 38-year-old pregnant woman was referred to Kobe University Hospital from another hospital at 19 + 5/7 GWs for hypertension, proteinuria, generalized edema, and fetal growth restriction. She was diagnosed with partial HELLP syndrome according to the Mississippi classification at 20 + 2/7 GWs. The patient was managed following the Mississippi protocol, including intravenous dexamethasone, magnesium sulfate, and antihypertensive drugs. She received intensive blood pressure and laboratory data monitoring using an arterial line and additional treatments, including platelet transfusion, intravenous haptoglobin infusion, and human atrial natriuretic peptide. The pregnancy ended in an induced delivery at 20 + 3/7 GWs, and she was discharged without complications 10 days postnatal. We performed laboratory tests for diagnosing underlying diseases but identified no obvious underlying diseases. This report indicates that early and intensive treatment of patients with HELLP syndrome occurring before 22 GWs according to the Mississippi protocol may enable clinicians to complete pregnancy termination without maternal complications and provide useful information to clinical practitioners in perinatal medicine.

Hemolysis, elevated liver enzyme levels, and low platelet count (HELLP) syndrome are some of the most severe complications of hypertensive disorders of pregnancy (HDP). The syndrome is associated with an increased risk of maternal morbidity, including eclampsia, placental abruption, disseminated intravascular coagulation, acute renal failure, pulmonary edema, hepatic rupture, and even mortality (1–3). HELLP syndrome occurs in 0.5%–0.9% of all pregnancies and mainly during the third trimester. The Mississippi protocol, including intravenous administration of dexamethasone (DEXA), magnesium sulfate ($MgSO_4$), and antihypertensive drugs, can be considered for managing HELLP syndrome (4).

HELLP syndrome occurring before 22 gestational weeks (GWs) is extremely rare, and such patients prominently demonstrated underlying maternal diseases or fetal abnormalities (e.g., maternal antiphospholipid syndrome [APS] or fetal triploidy) (5–8) in previous case reports.

Hereby, we report the case of a pregnant woman who had HELLP syndrome at 20 GWs without any obvious underlying maternal diseases or fetal abnormalities and was safely managed according to the Mississippi protocol.

CASE REPORT

This case report followed the principles of the Declaration of Helsinki. The patient signed written informed consent, and patient anonymity was maintained. The authors declare no potential conflicts of interest.

A 38-year-old pregnant woman, gravida 3, para 1, whose pregnancy was conceived through intracytoplasmic sperm injection, was referred to Kobe University Hospital from another hospital at 19 + 5/7 GWs for hypertension, proteinuria, generalized edema, and fetal growth restriction (FGR). She had neither a medical history nor HDP during her previous pregnancy. At the first visit, she demonstrated mild hypertension (blood pressure [BP]: 142/89 mmHg), 2+ proteinuria, and pitting edema. A fetal ultrasound examination revealed FGR (estimated fetal body weight: 186 g [−2.2SD]). She was admitted to the university hospital for HDP and FGR. The following were the

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laboratory results at admission: red blood cell counts: 367 × 10^4/μL; hemoglobin (Hb) concentration: 12.3 g/dL; platelet (PLT) counts: 10.7 × 10^4/μL; serum levels of alanine aminotransferase (ALT): 11 U/L; aspartate aminotransferase (AST): 20 U/L; lactate dehydrogenase (LDH): 197 U/L; total bilirubin (T-Bil): 0.9 mg/dL; indirect bilirubin (ID-Bil): 0.8 mg/dL; creatinine (Cre): 0.52 mg/dL; and blood urea nitrogen (BUN): 6.6 mg/dL.

The patient had acute upper abdominal pain and severe hypertension (BP: 176/100 mmHg) at 20 + 1/7 GWs. The laboratory test revealed moderate thrombocytopenia (PLT counts: 8.9 × 10^4/μL) and slight elevations in serum LDH (346 U/L), AST (89 U/L), and ALT levels (52 U/L), although with normal serum Cre (0.55 mg/dL) and BUN levels (7.5 mg/dL). She was diagnosed with partial HELLP syndrome according to the Mississippi classification; however, she had refractory severe upper abdominal pain. Therefore, she received an intravenous infusion of $MgSO_4$ and calcium channel blocker (CCB), together with an intravenous bolus injection of DEXA (10 mg) every 12 h following the Mississippi protocol (4).

She had controlled BP at 140–155/65–85 mmHg and worsened proteinuria (3+) at 20 + 2/7 GWs. Laboratory tests revealed severe thrombocytopenia (PLT counts: 3.6 × 10^4/μL), markedly increased serum LDH (1045 U/L), AST (310 U/L), and ALT (124 U/L) levels, slightly elevated serum Cre (0.7 mg/dL) and BUN levels (13.8 mg/dL), and a marked decreased serum haptoglobin level (<2 mg/dL) (Figure 1). She was diagnosed with class 1 HELLP syndrome according to the Mississippi classification. We inserted an arterial line for intensive laboratory data and BP monitoring. She received PLT transfusion (10 U), intravenous haptoglobin injection (4000 U), and intravenous human atrial natriuretic peptide (hANP) against oliguria, in addition to treatments according to the Mississippi protocol. The continuation of her pregnancy was thought to even cause maternal mortality; therefore, she and her spouse opted for termination of pregnancy (TOP) with informed consent.

Her BP was controlled at 125–155/70–80 mmHg at 20 + 3/7 GWs, but she required oxygenation because of dyspnea caused by pulmonary edema. She had persistent severe thrombocytopenia (PLT counts: 3.1 × 10^4/μL), elevated serum Cre (0.81 mg/dL) and BUN levels (21.6 mg/dL), and haptoglobin deficiency (<2 mg/dL). Conversely, serum LDH (660 U/L), AST (81 U/L), and ALT (57 U/L) levels were decreased (Figure 1). Additional PLT transfusion (20 U) and intravenous haptoglobin (4000 U) were administered. The pregnancy ended in induced delivery using gemeprost pessary, and the female stillborn weighed 170 g with an estimated blood loss of 76 mL postnatal.

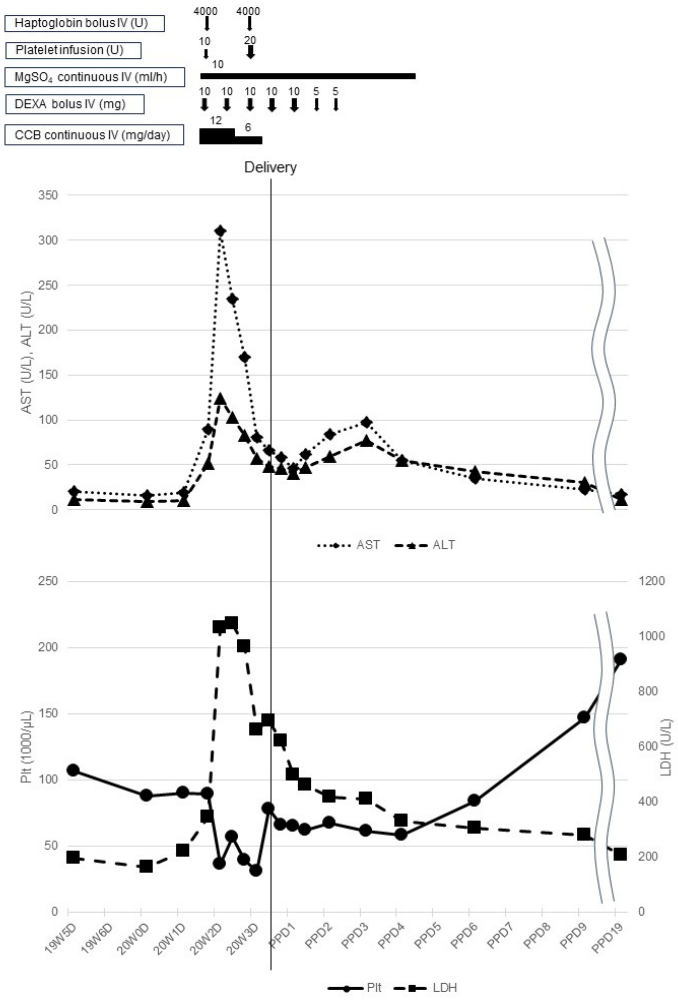

Figure 1. Clinical course of the patient
In the upper chart, (◆) and (▲) indicate the serum levels of aspartate aminotransferase (AST, U/L) and alanine aminotransferase (ALT, U/L) respectively. In the lower chart, (●) and (■) indicate the serum levels of platelet (Plt, /μL) and lactate dehydrogenase (LDH, U/L), respectively.
IV, intravenous injection; U, unit; $MgSO_4$, magnesium sulfate; DEXA, dexamethasone; CCB, calcium channel blocker; W, week; D, day; PPD, postpartum day.

She received intravenous administration of DEXA of 10 mg at 0 and 12 h and 5 mg of DEXA at 24 and 36 h postnatal according to the Mississippi protocol. Intravenous $MgSO_4$ administration was continued for 96 h postnatal. Her BP was controlled with oral CCB and angiotensin receptor blocker. Pulmonary edema improved and oxygenation was no longer required, as urine output increased. Serum Cre and BUN levels recovered to the normal range 1 day postnatal (0.49 mg/dL and 14.8 mg/dL, respectively). Proteinuria disappeared 4 days postnatal, and she was discharged without complications 10 days postnatal. PLT counts ($19.1 \times 10^4/\mu L$) and serum LDH (206 U/L), AST (17 U/L), and ALT (11 U/L) levels recovered to the normal range at 20 days postnatal (Figure 1). Hypertension resolved without medication at 47 days postnatal. We performed laboratory tests for diagnosing underlying diseases, including autoimmune diseases (e.g., APS, systemic lupus erythematosus, Graves' disease, and others), inherited thrombophilia (e.g., congenital deficiency of protein C, protein S, antithrombin, and factor XII), and acute hepatitis at both 19 + 5/7 GWs and 4 months postnatal but identified no obvious underlying diseases.

DISCUSSION

HELLP syndrome is a life-threatening condition that causes severe maternal and fetal complications. It mainly occurs during the third trimester, with a maternal mortality rate of 2%–24% (3). Conversely, HELLP syndrome that occurs before 22 GWs is extremely rare, and patients with the syndrome before 22 GWs commonly had severe underlying medical conditions or fetal abnormalities, such as APS or fetal triploidy (5–8), in previous case reports.

Clinical guidelines recommend that the pregnancies should be terminated as soon as possible if pregnant women are diagnosed with HELLP syndrome after 34 GWs (3, 9). In contrast, antenatal corticosteroid administration to pregnant women for promoting fetal lung maturation followed by TOP can be considered if the syndrome is diagnosed before 34 GWs (3, 9). Additionally, studies reported that treatment with intravenous DEXA combined with both $MgSO_4$ and antihypertensive drugs (the so-called Mississippi protocol) was effective for increasing PLT counts, decreasing serum LDH, AST, and ALT levels, and shortening intensive care unit admission duration (10, 11).

A previous systematic review of HELLP syndrome reported that 23% of patients with HELLP syndrome before 23 GWs developed hepatic complications, including hepatic rupture, which was the most common life-threatening maternal complication of this syndrome (12). Some case reports presented pregnant women without APS or fetal triploidy who had HELLP syndrome complicated by hepatic rupture at 22 GWs despite treatment according to the Mississippi protocol (13, 14). Conversely, a case report presented a pregnant woman who had HELLP syndrome before 22 GWs but did not demonstrate any underlying medical condition and was treated with $MgSO_4$ and antihypertensive drugs but without DEXA (15). Herein, the patient's general condition and laboratory data improved postnatal, although she developed eclampsia and posterior reversible encephalopathy syndrome.

We initiated treatments according to the Mississippi protocol in our case when the patient was diagnosed with partial HELLP syndrome accompanied by refractory severe upper abdominal pain. Additionally, our patient underwent intensive laboratory data and BP monitoring using an arterial line and received PLT transfusion for severe thrombocytopenia, intravenous haptoglobin administration for hemolysis, and intravenous hANP administration for oliguria in addition to the Mississippi protocol. The early initiation of treatments according to the Mississippi protocol and intensive management may have provided sufficient time to perform cervical dilation and enable clinicians to complete TOP without maternal complications in our case. Furthermore, the patient demonstrated no adverse events postnatal.

However, the Mississippi protocol has been indicated to not significantly improve the maternal and neonatal outcomes of pregnant women with HELLP syndrome (10, 16, 17). Therefore, more case series are required to prove the efficacy of the Mississippi protocol.

This case report on a pregnant woman with HELLP syndrome occurring at 20 GWs but without any obvious maternal underlying diseases and fetal abnormalities that were safely treated according to the Mississippi protocol could provide useful information for future similar cases to clinical practitioners in perinatal medicine.

ACKNOWLEDGMENTS

We acknowledge and thank all the members of the multidisciplinary teams at Kobe University Hospital, particularly Dr. Kazumichi Fujioka (Department of Pediatrics), Dr. Tomomi Kita, and Dr. Kenta Obata (Department Obstetrics and Gynecology).

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