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중증 전자간증 산모의 HELLP 증후군과 동반된 급성 신부전, 급성 폐부종, 매우 높은 간효소치의 급성 허혈성 간염, 혈관내 응고장애 1예

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A Case Report of Severe Preeclampsia with HELLP Syndrome in Preterm Pregnancy Complicated by Acute Pulmonary Edema, Acute Renal Failure, Highly Elevated Liver Enzymes Suggesting Ischemic Hepatitis and Coagulopathy

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HELLP syndrome represents a severe form of pre-eclampsia/eclampsia characterized by hemolysis, elevated liver enzymes, and low platelets. The mortality of HELLP syndrome is 1-30% and the morbidity is as high as 40%. Especially liver rupture and infarction with HELLP syndrome is very rare. We report a severe preeclampsia case with the HELLP syndrome of pregnant woman complicated by acute pulmonary edema, coagulopathy, acute renal failure, and ischemic hepatitis in postpartum period with a brief review of literature.

Key words: Preeclampsia, HELLP syndrome, Iischemic hepatitis

Hypertensive complications of pregnancy unfavorably impact on obstetric practice worldwide.[1,2] Since the HELLP syndrome was first decrypted by Weinstein,[2] authors from all over the world have report various cases of HELLP syndromes. Hemolysis (H), elevated liveremzyme (EL), thrombocytopenia (Low platelet count: LP) syndrome, also known as HELLP syndrome, is a multisystemic disorder with poor prognosis. 4-20% of pregnant women with hypertensive complication develop HELLP syndrome. The incidence of HELLP syndrome is reported as high as 0.2-1% of all pregnancies[2,3] with 1-30% of maternal mortality rate and approximately 40% of maternal morbidity rate.[4,5] Despite tremendous efforts so far, the pathogenesis of HELLP syndrome is still unclear and the clinical presentation of HELLP syndrome is not well characterized.

Here we report a case with severe epigastric pain and fulfilled criteria of HELLP syndrome, and morbidities involving multiple organs were developed.

CASE REPORT

A 29-year-old primigravida was transferred to CHA University, CHA Gangnam Medical Center, Seoul, Korea at 30 weeks and 6 days of gestation. The patient had severe epigastric pain of squeezing

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nature and dyspnea developed abruptly during management of preterm labor with tocolytics for 3 days at a local obstetric clinic. During the treatment, she did not complain of headache or visual disturbance. Pitting edema was noted but her blood pressure was within normal range and proteinuria was not checked in the local obstetrics. When admitted to intensive care unit at delivery room, she had elevated blood pressure (189/120) and proteinuria (+++). Laboratory investigations upon admission revealed normal renal function with a serum creatinine (sCr) of 0.7 mg/dL, but low platelet count of 99,000/uL, elevated serum aspartate transaminase (AST, 1,360 IU/L), alanine transaminase (ALT, 972 IU/L), lactate dehydrogenase (LDH, 4,494 U/L), and total bilirubin (T. Bil, 2.3 mg/dL). Because of dyspnea, she was put on SaO2 level to be 89-93% under room air. Hemoglobin level was 12.4 mg/dL and Whole Blood Count (WBC) was 19,870/uL with 89% of segment. Prothrombin time (PT) was prolonged to 14.2 sec (INR; 1.28). Except that B type natriuretic peptide (BNP) was elevated to 199 pg/mL, other cardiac enzyme studies were within normal range. Chest X-ray revealed left pleural effusion and mild cardiomegaly (Fig. 1). Normal sinus rhythm was noted on electrocardiography (EKG). On echocardiography, her ejection fraction was 66%, mild MR, TR and trivial AR was noted.

Based on the blood chemistry data above, we suspected HELLP syndrome and ruled out the risk of myocardiac infarction. Therefore, we checked abdomen sonography to detect any signs of lethal hepatic complications, which revealed diffuse and coarse echogenicity of liver without subcapsular hematoma or rupture (Fig. 2). Because her cervix neither was unripen nor dilated, she underwent an emergency cesarean section with the impression of HELLP syndrome and was treated with hydralazine for BP control, and oxygen inhalation with 8 L/min via mask for hypoxia.

During the operation, the patient lost approximately 800 mL of blood, which was more than usual. This was because of 10 cm sized myoma located on the anterior lower wall of uterus and hypotonicity of uterus as well as cogulopathy. Uterotonic agents were used and fresh frozen plasma (FFP) was started. To check the intraperitoneal bleeding, the drain was inserted. Intraoperative input/output was 1860/780 cc including urine output 80 cc for 2hour's operation. At the end of the operation, a followed up chest X-ray showed pulmonary edema and hemoglobin level was decreased to be 9.0 mg/dL, platelet count was 72,000/uL. Protein/albumin was measured to be 4.7/2.7 mg/dL, AST/ALT was 1,348/731 IU/L, which was slightly decreased from the begining. However, the patient became oliguric with urine output of 20 mL/hr.

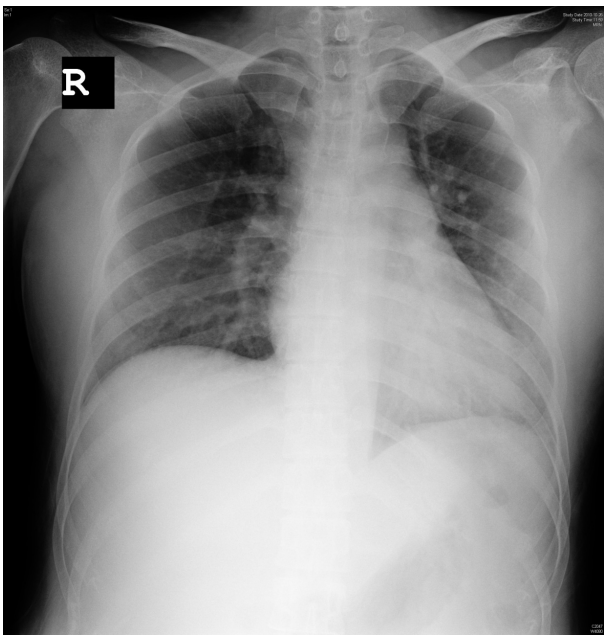

Fig. 1. Chest AP X-ray showed pleural effusion and mild cardiomegaly.

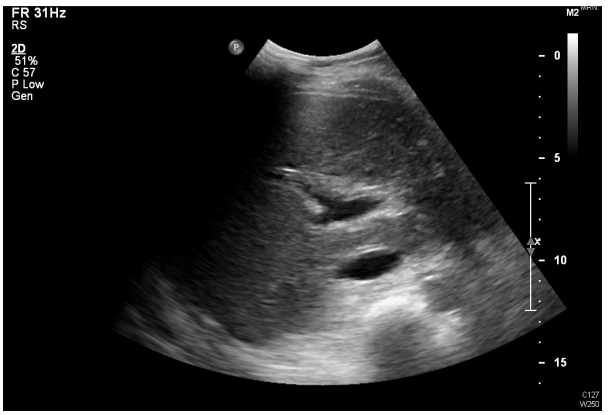

Fig. 2. Abdominal ultrasound showed coarse echogenicity of liver suggesting diffuse liver disease without subcapsular hematoma or rupture.

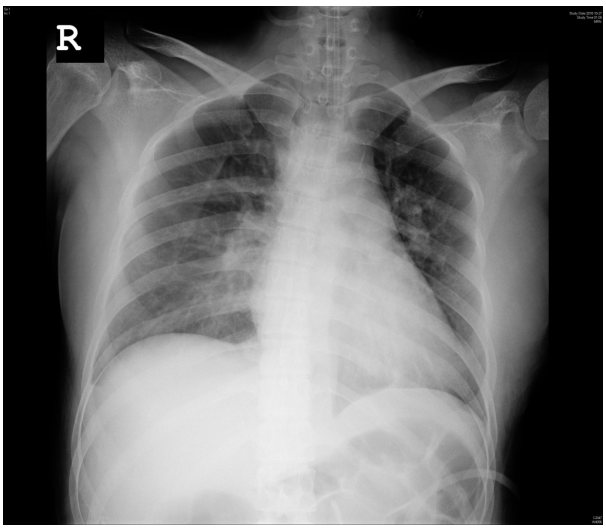

Fig. 3. Chest AP X-ray showed pulmonary edema.

Because of the newly developed pulmonary edema, the patient was sent to ICU with oxygen inhalation via venturi mask. Oliguria continued for the next hour. Hemoglobin level was decreased to be 7.1 mg/dL, platelet count was 46,000/uL, PT prolongation became worse up to 16 sec (INR; 1.44), fibrin degrade product (FDP) was increased by over 80 ug/mL, D-dimer was high up to 15667.49 ng/mL, while bleeding time (BT) and fibrinogen were within normal range. The patient received transfusion of the FFP, platelet concentrates and packed red blood cell to treat thrombocytopenia, bleeding tendency and anemia. Concomitantly augmentation of urination with diuretics intending relief of pulmonary edema was needed. Albumin was infused to relieve the pulmonary edema. The patient was kept intubated with oxygen inhalation via venturi mask (FiO_2; 3.5). She was in alert mental status during that night and her vital signs were stable.

On the first postoperative day the patient did not complain any symptoms except abdominal discomfort around the cesarean section wound. Based on her improved chest X-ray findings, extubation was performed and oxygen supplied through nasal cannula was tapered to 2 L/min until the second postoperative day. Her chest X-ray recovered to be normal on the third postoperative day (Fig. 3). Some of her laboratory findings, however, were out of normal ranges; AST/ALT aggravated up to 3,724/2,628 IU/L, T.Bil was 2.4 mg/dL, and sCr began to elevate up to 1.2 mg/dL. Therefore, we discontinued the blood transfusion and administered hepatotonic agents. The follow up of AST/ALT was checked to decrease on the same day (2,880/2,520 IU/L) and continued to decrease until the level of AST/ALT 33/178 IU/L on the ninth postoperative day on which she was discharged from the hospital. Following two weeks after discharge, AST/ALT decreased down to 30/36 IU/L. The sCr was normalized on the third postoperative day. According to the 24 hour urinary study (from arrival to postoperative day), creatinine clearance was 56.46 mL/min/1.73 m^2, fractional excretion of sodium was 0.64. Therefore, we could assume the cause of acute renal failure (ARF) to be prerenal origin; the depletion of intravascular volume was resolved with cautious hydration, replacement of oncotic pressure with albumin administration and cautious balancing of input/output. Proteinuria was relieved on the second postoperative day. Because her blood pressuere continued to be elevated, she was prescribed calcium channel blocker, Norvasc® 5 mg qd during the two week discharge period. Her blood pressure was normal at the two week follow-up.

A female baby weighing 1,170 g was delivered at 30 weeks 6 days of gestation with the APGAR score 2/7/8 (1 min/5 min/10 min) in footling presentation. The baby was kept in ICU for ventilatory care for now.

DISCUSSION

The development of HELLP syndrome imposes pregnant women with significant risk for morbidity and mortality.[3-5] Morbidity is categorized by which organ system affected and is stratified by the extent of disease using the classification systems.[6,7]

The Mississippi and tennesse classifications systems have been mostly commonly used since 1980s to identify patients at risk of significant maternal morbidity and outcomes (Table 1).[7-10] Mortality associated with only HELLP was reported in a recent review article[11]; cerebral Hemorrhage (27%), acute respiratory distress syndrome (22%) ,liver rupture (17%) and multi-organ failure (MOF, 12%) with decreasing frequency (Table 2). In case of concurrent

Table 1. Classification systems of HELLP syndrome

HELLP class	Mississippi classification[16,17,24]	Tennesse classifaction[18,19]
1	Platelet count≤50,000/uL AST or ALT≥70 IU/L LDH≥600 IU/L	Platelet count≤100,000u/L AST≥70 IU/L LDH≥600 IU/L
2	50,000/uL≤platelet≤100,000/uL AST or ALT≥70 IU/L LDH≥600 IU/L	
3	100,000/uL≤platelet≤150,000/uL AST or ALT≥40IU/L LDH≥600 IU/L	N/A
Partial HELLP/Incomplete HELLP	N/A	Severe preeclampsia+one of the following: ELLP, EK, LP

Table 2. Maternal causes of deaths by groups (Vigil et al. 2009)

Cause of mortality	Eclampsia (n=70, 70%)	HELLP/Eclampsia (n=47, 40.2%)	HELLP syndrome (n=60, 60.9%)
First	Cerebral hemorrhage (43%)	Cerebral hemorrhage (44%)	Cerebral hemorrhage (27%)
Second	Renal failure (26%)	ARDS (13%)	ARDS (22%)
Third	DIC (11%)	Cerebral edema (10%)	Liver rupture (17%)
Fourth	Cerebral edema (4%)	MOF (10%)	MOF (12%)

HELLP/eclampsia, cerebral hemorrhage (44%) was more common cause of death. Contrary to the causes of eclampsia or HELLP/eclampsia, liver rupture or MOF were the common cause of death in HELLP without seizure.[11]

Patients with non-eclamptic class 1 or 2 HELLP syndrome are 3.5 times more likely to develop significant central nervous system (CNS) complications compared to class 3 or non-HELLP severe preeclampsia.[6] The clinical presentations of CNS complications are generally stroke, mental status alterations. Visual complications are relatively rare (1.4% in class 1, 2) in regard to the severity of disease.[6] These CNS or visual complications are usually transient with full recovery within 1-6 months, except cerebral hemorrhage.[12-14] Even though our case was a class 1 HELLP case, the patient maintained alert mental status and did not develop CNS or visual complications.

The catastrophic hepatic complications are relatively uncommon and the clinical presentations are variable. Therefore, the diagnosis of subcapsular hematoma is often delayed.[7] When hepatic involvement is suspected, physicians should consider doing a hepatic imaging with transabdominal ultrasound (TAUS), computed tomography (CT) or magnetic resonance imaging (MRI). This patient had a markedly elevated level of AST liver enzyme (above 3,500 IU/L), but fortunately the TAUS showed diffuse and coarse echogenicity suggesting hepatic venous congestion without subcapsular hematoma, rupture or infarction. These findings indicate ischemic hepatitis as a pathophysiology in this patient. The most commonly accepted definition of ischemic hepatitis is an acute reversible elevation in either the serum alanine or aspartate aminotransferase level of at least 20 times the upper limit of normal, excluding known causes of acute hepatitis or hepatocellular injury, in an appropriate clinical setting.[15] The combination of hepatic congestion and insufficient systemic circulation is considered as a pathophysiologic mechanism of ischemic hepatitis. The prognosis of ischemic hepatitis depends on the effective treatment of underlying morbidity.[15]

Mortality was reported as high as 58.6% and which was not due in any of the cases to the hepatitis but rather the underlying causes.[16] After delivery our patient did not show any signs of lethal hepatic complications; epigastric or right upper quadrant pain, nausea and vomiting. We did not do a follow-up hepatic imaging since the liver lesions looked normal. Instead, we checked the levels of liver enzymes regularly after delivery.

In addition to the severe hepatocellular injury, multiple-organ insufficiency was noted in this patient: acute pulmonary edema and postoperative acute renal failure, the cautious management was needed in this case.

The risk of developing cardiopulmonary problem, particularly pulmonary edema, is more than two-fold for patients with class 1 HELLP syndrome (22%) compared to non-HELLP severe preeclampsia (10%).[6] In our case, previous tocolytics infusion and rapid blood transfusion might augment to the pathophysiologic condition of pulmonary edema in HELLP syndrome. The conservative management and prevention of ARDS are only possible treatment except prompt delivery.

Renal complications also increases as disease severity worsens in general,[6] and are strongly associated with obstetric complications such as abruptio placentae, fetal death, DIC, shock or sepsis.[17] The risk of developing renal complications was reported to be approximately 3% in class 1 or 2 HELLP.[3,18] Unlike most reported cases in which ARF was caused by acute tubular necrosis with generally good prognosis, the cause of ARF of this case was suggested with prerenal according to the urinary study; hypoperfusion aggravated by acute hemorrhage and hemolytic anemia could have the role. But the management of ARF in this case should be modulated because of accompanying acute pulmonary edema. We have to emphasize the prompt diagnosis and delivery as the ultimate treatment for prevention of irreversible organ damage or mortality.

Another complication in this case was disseminated intravascular coagulation (DIC). Prevalence of DIC increases from 0.5% with severe preeclampsia to 17.4% with class 1 HELLP syndrome.[6] Clinically significant bleeding requiring transfusion and wound hematoma appear to be increased with worsening disease.[3,6,9] In our case, PT was prolonged and FDP and D-dimer levels were increased but fibrinogen was within normal range. Normal fibrinogen level should be cautiously interpreted because in normal pregnancy the fibrionogen levels can double from nonpregnant state.[19]

Another possible complication of HELLP syndrome is infection and sepsis. Patients with HELLP syndrome often have more infectious morbidity than those with non-HELLP severe preeclampsia (43% vs. 20%).[20] Cesarean delivery could double the risk of infectious complications from 19% to 41%.[6] Cesarean delivery is performed more often for patients with class 1 HELLP syndrome (61%) than class 2 (57%), class 3 (53%), or non-HELLP severe preeclampsia (48%).[6] Mode of delivery is decided by gestational age, maternal-fetal status, and class of disease. Cesarean delivery is associated with doubling of maternal morbidities (cardiopulmonary, hematologic-coagulation and infectious complications).[7] In obstetrical perspective, the risk of placental abruption, placenta previa, eclampsia, and episiotomy breakdown is increased compared to non-HELLP pregnancies.[21,22]

To manage the patients with HELLP syndrome, delivery has been regarded as the ultimate treatment to prevent maternal morbidities and mortality. Stabilizing the maternal condition before delivery using antihypertensive agents might be beneficial when blood pressure is above systolic 160 mmHg or diastolic 105 mmHg. If hydralazine does not adequately lower blood pressure or maternal side effects, such as tachycardia or headaches, developed another drug such as labetalol or nifedipine, can be used. Maternal and fetal conditions should be assessed. MgSo4 was not used for prophylaxis and corticosteroid was not used either in this case. The use of steroids in order to stabilize platelet values and facilitate recovery and mature the preterm fetal lung has been suggested by some investigators.[7] However, a recent randomized controlled trial does not the use of steroids for this indication.[23] In deciding the time for delivery of the preterm viable fetus and HELLP syndrome, physicians should consider the maternal-fetal status, gestational age, presence of labor, cervical Bishop score, obstetrical history, and the usefulness of aggressive corticosteroid administration.[6] The

case of above 34 weeks gestation, a prompt delivery should be performed. But for below 34 weeks gestation, only if there were complications; fetal distress, maternal distress, eclampsia, DIC, renal failure, abruptio placenta, respiratory distress and suspected liver hematoma, a prompt delivery should be performed.[10] For the cases of below 34 weeks gestation without complications, the usefulness 24-48 hrs latency for steroid administration was proposed by some authors [refs]. There are still, however, debates about the efficacy and risk of prolonging the pregnancy duration.[7,10]

In our case, the patient with HELLP syndrome was complicated with multiple morbidities; especially highly elevated liver enzymes suggesting severe hepatocellular injury due to the ischemic hepatitis was the problem. Fortunately, hepatic hematoma and resulting rupture did not occur. The etiology of ischemic hepatitis; pregnancy with HELLP syndrome was removed before the complications progressed to irreversible organ failure. Moreover, the patient was experiencing other complications including pulmonary edema, acute renal failure, severe hemolytic, hemorrhagic anemia and coagulopathy. However, early diagnosis and prompt delivery, which is important treatment point of HELLP syndrome, might make this patient recover without sequelaes.

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「국문초록」

HELLP 증후군은 전자간증의 중증 형태로, 용혈, 간 효소 수치 상승과 저혈소판혈증을 특징으로 한다. HELLP 증후군의 사망률은 1~30%로 보고되며, 합병증은 40%까지 높게 보고 되었다. 이중 HELLP 증후군에 이환 된 산모에서 간 파열이나 간 괴사가 합병되는 경우는 매우 드물게 보고 되고 있다. 본 증례에서는 HELLP증후군에 이환 되었던 중증 전자간증 산모에게서 산후에 급성 폐 부종, 혈관 내 응고 장애, 급성 신부전과 더불어 매우 높은 간효소치를 보인 급성 허혈성 간염이 발생하였다가 보존적 치료로 회복된 경우로 간단한 문헌 고찰과 함께 보고하는 바이다.

중심 단어: 전자간증, HELLP증후군, 급성 허혈성 간염