

COVID-19: A Cause of HELLP Syndrome? A Case Report

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Purpose: There are still many unexplained points about how COVID-19 affects pregnant women and what kind of clinical and laboratory findings it reveals. These findings can become clinical conundrums when there is significant overlap with known and serious syndromes in pregnancy. The aim of this study is to report a case with a laboratory-proven diagnosis of COVID-19 and HELLP syndrome hypothesis.

Case Presentation: A 30-year-old multigravida (g3p2, repeated cesarean section) 32-week pregnant patient reported to the emergency service with complaints of chills, cough and shortness of breath that started 6 days ago. Following comprehensive screening tests for the differential diagnosis of lymphopenia, high liver enzymes, low platelets, abnormal coagulation panel, high D-dimer, high total bilirubin, high LDH and HELLP syndrome in the laboratory examinations of the patient, the patient's laboratory findings were evaluated as compatible with HELLP syndrome. Emergency cesarean section was performed on the patient because of maternal hypoxemia. The finalization of the microbiological diagnosis of COVID-19 resulted to start conventional COVID-19 treatment. The fetus was also confirmed to be positive for COVID-19, and the newborn died on the 5th postnatal day. Unfortunately, our mother patient died on the 10th day of her hospitalization.

Conclusion: This report describes a case of multigravida, 30 years old, who presented with respiratory tract infection symptoms and hypothesized HELLP syndrome, who later tested positive for the novel coronavirus. The distinction between these two etiologies and onset times is extremely difficult. However, given the sequence of events in this case, it is reasonable to consider that COVID-19 may be an etiological factor associated with the pathophysiology of HELLP, despite the lack of conclusive evidence.

Keywords: COVID-19, pregnancy complication, HELLP, overlapping clinics, preeclampsia

Introduction

The coronavirus (CoV) pandemic still maintains a state of global urgency, and COVID-19 continues to remain a mystery with many still unknown features.¹ There are reports of infectious diseases that mimicking hemolysis, elevated liver enzymes, and low platelet syndrome (HELLP) in pregnant patients.^{2,3} In this context, studies examining the effects of COVID-19 on pregnant women have also begun to be published.⁴ However, there are still many unexplained points about how COVID-19 affects pregnant women and what kind of clinical and laboratory findings it produces⁵. Furthermore, these findings can become clinical conundrums when they overlap significantly with known and serious syndromes in pregnancy. In this respect, sharing country experiences is of vital importance in learning lessons from mistakes, creating evidence and guides, and managing the process correctly.

HELLP syndrome occurs in 0.5–0.9% of all pregnancies, mostly in the last trimester (70%) and in multiparous women.^{6,7} It may present with nonspecific respiratory tract infection symptoms such as malaise, nausea, vomiting, abdominal pain and headache, as well as common pregnancy findings such as edema, proteinuria and hypertension. Although there is a close relationship between HELLP Syndrome and preeclampsia, hypertension may be mild in 16% of this syndrome and absent in 15%.⁸ In addition, in advanced cases, clinical manifestations such as impaired renal function, intracranial hemorrhage, intrahepatic hemorrhage, coagulopathy, and disseminated intravascular coagulation (DIC) may occur.⁹ Diagnostic criteria in the Tennessee classification are signs of microangiopathic hemolysis (abnormal peripheral

smear, increased bilirubin level $>1.2\text{mg/dl}$, high LDH $>600\text{ IU/L}$, elevated liver enzymes (AST $>70\text{ IU/L}$), and low platelet count ($<100\text{k/dl}$). It is defined as mm^3 .¹⁰

Common laboratory abnormalities in COVID-19 patients include lymphopenia, elevated liver enzymes, and elevated C-reactive protein (CRP).^{11,12} In addition, studies in patients with severe disease showed laboratory abnormalities consistent with DIC and coagulopathy including thrombocytopenia,¹³ increased activated partial thromboplastin time (aPTT), prothrombin time (PT), D-dimer, interleukin-6 (IL-6), fibrin degradation products, and evidence of microangiopathic hemolytic anemia.^{11,14–20} It is possible that the pathology causing this clinical picture, defined as COVID-19-associated coagulopathy,¹⁶ may be the same and/or origin as the microangiopathy causing HELLP syndrome. For this reason, we would like to present a pregnant patient who has a positive new coronavirus test and has laboratory findings that match exactly with HELLP, and we want to create projections for further research in this direction.

Case Presentation

A 30-year-old multigravida (g3p2, repeated cesarean section) 32-weeks pregnant patient reported to the emergency service at 10 PM with complaints of chills, cough and shortness of breath that started 6 days ago. She had no medical history and her previous pregnancies had normal processes. There has never been a COVID-19 vaccine. Her respiratory rate was 26/min, blood pressure was 110/75 mm Hg, oxygen-free saturation was 84%, and body temperature was 38.8 °C. There was no uterine activity.

Initial laboratory examinations of the patient in the emergency room revealed lymphopenia, elevated liver enzymes, low platelets, increased Prothrombin Time (PT/INR) and activated Partial Thromboplastin Time (aPTT), high D-dimer, high total bilirubin, and high LDH; hemoglobin and kidney function tests were normal. The patient's laboratory findings were evaluated as compatible with HELLP syndrome (Table 1). Gynecological examination by obstetrician (no uterine tenderness, no foul-smelling discharge, no amniotic discharge in speculum examination and ponding test), Ultrasound findings (head presentation, fetal heart rate: 145/min, amniotic fluid volume normal, biparietal diameter normal, placenta anterior) and NST findings (no reactive contraction) were normal. With these findings, the patient was admitted to the 3rd level intensive care unit reserved for COVID-19 patients, with preliminary diagnoses of COVID-19, sepsis and HELLP syndrome.

In the intensive care follow-up, the patient accepted the tomography recommendation, and bilateral diffuse ground glass areas, diffuse peripheral interstitial thickening and bilateral mild pleural effusion were found in the thorax CT examination, and these findings were reported to be compatible with viral pneumonia (COVID-19) (Figure 1). Immediately after this, the oropharyngeal swab sample obtained for the COVID-19 polymerase chain reaction (PCR) test was positive. Also, hepatitis markers studied and HIV test were negative. There was no growth in the blood and urine cultures taken on the first day. Serum electrolytes (Na, K, Cl, Ca, P, Mg) and cardiac markers (Troponin I, CKMB) were normal. Anti-Covid treatment (Lopinavir/Ritonavir, Hydroxychloroquine) was started upon the recommendation of the infection specialist, after obtaining the patient's written consent.

The patient became hypertensive (blood pressure value $\geq 185/120$ in consecutive measurements) at the end of the second day of hospitalization. Pregnant patient's oxygen-free saturation dropped below 80% and a change in consciousness level developed. The patient was intubated in this condition. Obstetrician was consulted again to evaluate the possibility of termination of pregnancy, but they decided to operate the patient if hemodynamic stabilization was achieved. Our pregnant patient did not have risk factors for preeclampsia such as twin pregnancy and first pregnancy. However, hypertension developed. Therefore, the patient was started on antihypertensive treatment (sodium nitropruside) and magnesium sulfate for seizure prophylaxis upon the recommendation of the obstetricians.

Haptoglobin studied on the 2nd day of hospitalization was 21 mg/dl, Reticulocyte Count was 98,109/L, Corrected Reticulocyte Percentage (Ret% $\times\text{HCT} /45$) was 2.93 and direct COOMBS test was negative. Abdominal USG was evaluated as normal (liver size, parenchyma echo was normal) and there was no acute fatty liver of pregnancy. In addition, Anti Ds DNA studied for differential diagnosis of HELLP Syndrome, IFT (5.88 IU/mL), Lupus anticoagulant/confirmation test (31.6 sec), Anti-nuclear Antibody (FANA) (IFA), Anti Cardiolipin IgG (5.6 GPL-U/ mL) was found to be negative on the 3rd day of hospitalization. In addition to these, thyroid function tests, vit-B, folic acid levels, Brucella Agglutination (Rose Bengal), lipase, urine microscopy and culture were also normal.

Table I Laboratory Findings of the Patient

	HD 0	HD 1*	HD 3**	HD 5 (PPD 2)	HD 7	HD 9 ‡	Reference Range
White-cell count (10 ³ /μL)	5.79	6.92	11.9	17.35	20.86	13.56	4.4–10.9
Lymphocyte count (10 ³ /μL)	0.80	0.61	0.67	0.82	0.86	1.68	1.1–4.2
Neutrophil count, (10 ³ /μL)	4.64	5.49	10.73	16.15	19.1	11.6	1.8–7.8
Red-cell count (10 ⁶ /μL)	3.87	3.12	3.02	3.31	3.17	3.38	3.8–5.3
Platelet count (10 ³ /μL)	59	32→[†]96	41→^{††}114	137	124	109	145–400
Hemoglobin (g/dL)	11.7	9.7	8.7→ ^{††} 10.9	10.4	10.2	10.7	11.7–15.8
Hematocrit (%)	32.4	29.2	28→^{††}33.7	32.1	34	32.3	35–48
Serum electrolytes: Na/K/Cl (mmol/L)	130/3.6/101	125/3.4/98	135/3.1/101	129/5.7/87	122/5.6/89	119/6.1/92	136–145/ 3.5–5.1/ 98–109
Erythrocyte sedimentation rate (mm/h)	70	68	62	58	-	-	4–57 (in pregnant)
C-reactive protein (mg/L)	214.7	273.0	279.7	119.4	82.7	93.6	0–5
Creatinine (mg/dL)	0.79	1.15	1.94	2.00	2.4	4.8	0.56–0.85
Blood urea nitrogen (mg/dL)	9.6	26.0	65.8	79.5	27.8	67.5	7–18.7
Bilirubin Total/ Direct (mg/dL)	2.54/0.7	2.90/0.9	4.24/1.01	1.96/0.63	2.16/0.91	3.8/2.12	0.2–1.2/ 0–0.5
Aspartate aminotransferase (U/L)	146	164	486	74	86	101	11–25
Alanine aminotransferase (U/L)	102	116	187	51	49	62	7–28
Lactate dehydrogenase (mg/dL)	697	898	1074	210	245	198	125–243
Prothrombin time (INR)/partial thromboplastin time (sn)	1.26/37	1.49/40.7	2.52/44.4	0.97/18.3	2.04/44.3	3.45/49.5	0.8–1.2/ 21–36
D-Dimer (mg/L)	35.2	38.4	34.83	7.31	5.27	5.62	0–0.55
Fibrinogen (mg/dL)	467.3	596.4	747.6	265.6	-	-	170–420
Urinalysis	+1 protein (dipstick test)	+3 protein (dipstick test)	530 mg/24 h	285 mg/24 h	-	-	Trace amount (in pregnant)
Procalcitonin (ng/mL)	1.71	1.85	8.48	4.25	-	-	< 0.5
Troponin I (pg/mL)	-	11.8	637.5	421.4	837.2	742.8	0–15.6
COVID-19 RT-PCR test	Positive		Positive	Positive			
Peripheral smear	Schistocytes (2%), polychromasia and occasional spherocytes (HD 1)						
Placenta Pathology Findings	Perivillous fibrin deposition (DIC) representing severe placental bleeding consistent with chronic villitis, intervillitis and disseminated intravascular coagulation (HD 3)						

Notes: Bold/coloured values indicate values outside the reference range. *The patient was transferred to the COVID-19 intensive care unit. **Cesarean section performed. ‡ Last day before death. †After 2 unit of single donor platelet transfusion. ††Pre-operative, after 2 units of erythrocyte suspension, 5 units of platelet, 2 units fresh frozen plasma transfusion.

Abbreviations: HD, hospital day; PPD, postpartum day; RT-PCR, reverse transcription polymerase chain reaction.

However, in the echocardiography performed on the 3rd day of the intensive care follow-up, segmental wall motion defects were detected and myocarditis was considered in the forefront by the cardiologist in the patient who developed concurrent troponin and CRP elevations. For the patient who was consulted again with the obstetrics and gynecology department on the same day (day three) (due to a progressive deterioration in maternal oxygen saturation, progressive

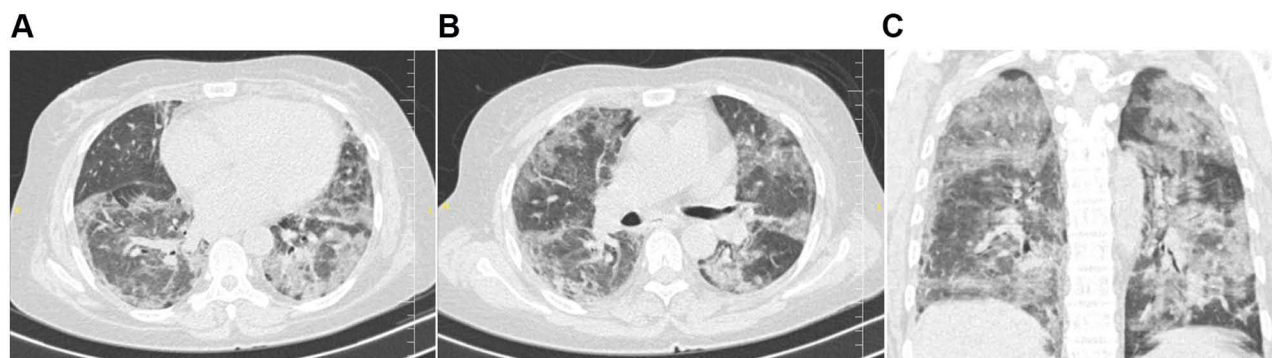


Figure 1 Chest tomography showing diffuse pulmonary involvement (hospital day 1). (A) Axial section. (B) Axial section. (C) Coronal section.

deterioration in the blood picture despite platelet, FFP, fibrinogen replacement, a deterioration parallel to the pregnant's baseline low in the NST follow-up of the fetus and in order to protect the fetus from hypoxic damage as much as possible), cesarean delivery was recommended. Thereupon, the patient was given preoperative two units of erythrocyte suspension, five units of platelet, two units of fresh frozen plasma transfusion with the recommendation of internal medicine physicians, and a singleton live baby boy via CS with Apgar scores of two and six was delivered on the third day of her hospitalization. Following delivery, the general condition and vital signs of the newborn deteriorated rapidly and he was intubated. Chest X-ray was normal, but the fetus was confirmed to be positive for COVID-19. Pancytopenia and renal failure developed on the 2nd day of intensive care hospitalization. The newborn died on the 5th postnatal day.

During the intensive care treatment, fluid, electrolyte, blood and blood products resuscitation, antihypertensive treatment, magnesium sulfate, antibiotherapy, hemodialysis due to anuria continued to be applied, however, the general condition of the patient gradually deteriorated. Brain MRI examination performed on the 9th day of her hospitalization revealed normal brain MRI findings. However, many attempts to extubate the patient were unsuccessful, and unfortunately the mother patient died on the 10th day of her hospitalization. This case belongs to a research proposal with ethical approval code of Mogadishu Somalia Recep Tayyip Erdogan Training and Research Hospital institutional Medical Ethics Committee (MSTH/8135).

Discussion

While the patient's initial symptoms and clinical picture were suggestive of a respiratory infection, the diagnosis of HELLP syndrome seemed reasonable considering the laboratory findings. In the face of the mixed clinical picture at the beginning, the consultation reports of the relevant branches were only recommendations. The finalization of the microbiological diagnosis of COVID-19 caused us to start traditional COVID-19 treatment. In addition, we considered HELLP Syndrome as a highly probable diagnosis, as a result of microangiopathic hemolytic anemia characterized by schistocytes in peripheral smear and other findings supporting hemolysis, low platelet count and abnormal liver function tests, and extensive screening tests for differential diagnosis and exclusion of HELLP syndrome. Emergency cesarean section was applied to the patient due to the maternal hypoxemia and preeclampsia. On the 2nd day after cesarean section, liver enzymes decreased, platelet count increased, and this provided us with further evidence for the diagnosis of HELLP Syndrome, although not conclusive. This case is different from the cases previously presented in the literature.^{5,21,22} Because both diseases (COVID-19, HELLP) have a typical clinical course proven by laboratory findings and it is a case in which differential diagnostic diseases are ruled out with comprehensive screening.

The pathology of COVID-19 appears to be multifactorial, including thrombocytopenia, activation by aggregation and thrombosis, impaired bone marrow and megakaryocyte activity, and endothelial damage. In addition, it may cause platelet defragmentation due to changes in pulmonary capillary bed morphology.^{23,24} It is now a known fact that endothelial damage, platelet activation and thrombosis are also present in the physiopathology of HELLP syndrome and Preeclampsia.⁶⁻⁹ Despite the uncertainties based on this case, the synergism of these pathophysiological mechanisms

(ie, causing HELLP syndrome in the most severe form of COVID-19, which is already a cause of thrombocytopenia) may have played an important role in reducing our patient's already low platelet counts.

As in this case, there are already reports of elevated liver enzymes, thrombocytopenia, DIC, cardiomyopathy, acute renal failure, and ARDS in the general population infected with COVID-19.²⁵⁻²⁹ Pregnant patients infected with COVID-19 are likely to present with similar signs and symptoms, and most, if not all, of the same laboratory abnormalities, as in the general population.^{30,31} While the similarities between COVID-19 and HELLP are clear, it is essential to focus on some clinical criteria that can help the emergency physician or obstetrician differentiate between the two. The first is the presence or absence of high blood pressure. Depending on the severity of the disease, the elevated blood pressure seen in HELLP cases (seen in 20%) will be evident when compared to COVID-19 patients with normal or low blood pressure. The presence of proteinuria with hypertension will favor the diagnosis of HELLP syndrome, but normotensive and atypical HELLP syndrome cases without proteinuria should not be overlooked.³² Presence of fever, leukocytosis, respiratory distress and hypoxia will increase the suspicion of COVID-19. D-dimer is widely used as an initial screening parameter for COVID-19, but its sensitivity is known to be low in pregnancy.¹² On the other hand, a chest X-ray or CT is helpful. Because the presence of "ground glass appearance" or "irregular infiltrates" can help differentiate COVID-19.^{33,34} Early chest imaging may also guide treatment in the acute phase when the COVID-19 PCR test may be negative. Also, early documentation of the respiratory infectious process can help avoid confusion when changes indicative of HELLP occur. On the other hand, while HELLP will begin to resolve 24 to 72 hours postpartum, it is likely that COVID-19 has nothing to do with timing of birth.

As a result, the distinction between these two etiologies and times of onset will be extremely difficult, as both diseases may cause similar laboratory findings and clinical presentations.⁵ In this respect, considering the current scenario in our case, the time of onset for respiratory infection symptoms and the sequence of events in this case, although there is no conclusive evidence, suggest that COVID-19 may be an etiological factor associated with HELLP physiopathology (hemolysis and thrombocytopenia) and it is reasonable to assume that it is a high risk for serious problems. However, the final clue will appear after microbiological diagnosis. In this context, our case report supports the early documentation of a positive COVID-19 test regardless of the severity of the disease and the early testing of pregnant women in centers where rapid viral tests are possible. Furthermore, it may help to encourage emergency physicians and obstetricians to gain insight into pregnant patients presenting to the clinic with findings similar to those presented in this case report, and to collaborate with a multidisciplinary team for the need for intensive care follow-up and possible preterm delivery.

Conclusion

This report describes a case of multigravida, 30 years old, who presented with respiratory tract infection symptoms and hypothesized HELLP syndrome, who later tested positive for the novel coronavirus. The distinction between these two etiologies and onset times is extremely difficult. However, given the sequence of events in this case and the extensive screening tests we performed for differential diagnosis of HELLP syndrome, it is reasonable to consider that COVID-19 may be an etiological factor associated with the pathophysiology of HELLP, despite the lack of conclusive evidence. However, the hypothesis that we have established in line with the clinical course of this case needs to be supported and proven by further studies to be conducted in this direction.

In this sense, we hypothesize that early documentation of a positive COVID-19 test when caring for pregnant women during the COVID-19 pandemic can help clinicians to avoid delays in early treatment and related complications of HELLP and COVID-19.

Institutional Review Board Statement

The ethics approval form was received from the ethics committee of Mogadishu Somali Turkey, Recep Tayyip Erdogan Training and Research Hospital (approval number MSTH-8135).

Data Sharing Statement

Data are included in the manuscript.

Consent to Participate

Written informed consent has been obtained from the patient (the relatives of the patient) to publish this paper.

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Disclosure

The author declares no conflicts of interest associated with this publication.

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