

 Case Report

Elevated D-Dimer, the Only Clue for COVID-19 Hepatitis: A Case Report

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Abstract

Background: The World Health Organization named the severe acute respiratory syndrome with the new coronavirus disease (COVID-19), which originated in Wuhan, China, in 2019 and rapidly spread around the world. COVID-19 is a mysterious infectious disease that leads to respiratory illness and organ failure. In addition to typical symptoms of shortness of breath, fever, cough, and dyspnea, gastrointestinal symptoms are increasingly recognized among patients with COVID-19.

Case Presentation: This case study reports a 42-year-old woman presented with fever, weakness, and anorexia for three days in Urmia Imam Khomeini Hospital in March 2020. Initially, acute hepatitis A was detected in the patient, and then she was diagnosed with COVID-19 based on her computed tomography scan findings.

Conclusion: Significantly increased D-dimer can be a diagnostic clue for hepatitis caused by COVID-19 infection. D-dimer may significantly increase in mild diseases.

Keywords: COVID-19, Hepatitis A, D-Dimer

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Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for coronavirus disease 2019 (COVID-19), first originated in Wuhan, China, in late 2019 and quickly spread worldwide, resulting in over 30 000 deaths to date (1). On March 11, 2020, the World Health Organization declared it a pandemic after infecting more than 114 countries (1), and most patients were reported with mild COVID-19. However, some patients may experience pneumonia, acute respiratory distress syndrome, and possibly death due to the condition (2). This case report concerns a 42-year-old woman who presented with fever, weakness, and anorexia without respiratory symptoms for three days. Initially, the patient was labeled with acute hepatitis A and finally diagnosed with COVID-19.

Case Presentation

A 48-year-old Iranian woman presented with fever, weakness, nausea, and anorexia for three days in Urmia Imam Khomeini Hospital in March 2020. She denied other complaints, such as cough, sore throat, shortness of breath, diarrhea, vomiting, or abdominal pain. The patient had no known individual or family history of liver disease. She had not visited a primary care physician in the last few years. Her outpatient medications included multivitamins, omega-3, and vitamin E. There was no abnormality with recent outpatient liver chemistries.

An examination of her physical condition revealed that she was fully conscious, with a blood pressure of 110/70 mmHg, a pulse rate of 82 beats per minute, a temperature of 39°C, a respiratory rate of 16, and a peripheral oxygen saturation of 96% on room air. There was no sign of jaundice, right upper quadrant tenderness, hepatomegaly, or splenomegaly in her pathology examination. Three days after the onset of the fever, the patient had a chest computed tomography (CT) scan, which displayed no pathologic lesions. However, following the start of respiratory symptoms on the eighth day of the disease, the patient's CT confirmed the presence of COVID-19 (Figure 1).

According to further evaluation, laboratory tests demonstrated increased D-dimer, C-reactive protein, lactic acid dehydrogenase (LDH), aspartate aminotransferase, and alanine transaminase with weakly positive hepatitis A virus antibody immunoglobulin M (IgM). Abdominal ultrasonography revealed a normal-sized liver and spleen. The color Doppler sonography of the portomesenteric system showed no pathologic lesions. Nasopharyngeal samples taken for the SARS-CoV polymerase chain reaction (PCR) test were negative on the second day of symptom occurrence. The following serological tests were performed and represented cytomegalovirus antibody immunoglobulin G (IgG) and Epstein-Barr virus antibody IgG were positive, but the IgM of these viruses was negative. Hepatitis B Ab

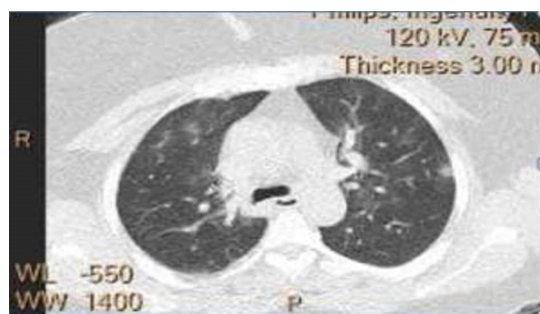


Figure 1. Chest Computed Tomography Scan

due to previous vaccination was positive, while blood cultures and screening for autoimmune markers were negative. D-dimer and LDH markedly elevated. Due to the patient's severe anxiety, SARS-CoV Ab and HAV Ab were measured three times in different laboratories. SARS-CoV Ab was negative three times, but HAV Ab was borderline two times and normal one time. Due to the appearance of COVID-19 symptoms in her husband, the patient had to take an antibody test 40 days after the disease onset. Hematologic laboratory results of the patient are summarized in Table 1. The patient was quarantined at home for 14 days and underwent symptomatic treatment. All symptoms, except fatigue, were resolved. After 24 days, the husband revealed fever and myalgia, and nasopharyngeal samples taken for the SARS-CoV PCR test were positive. This study was approved by the Ethics Committee of Urmia University of Medical Sciences, and written informed consent was obtained from the patient before participation in the study.

Discussion

The major physiopathology of impaired liver enzymes is viral infection and autoimmune liver disease. Fever, sore throat, cough, shortness of breath, decreased appetite, and myalgia are typical symptoms of COVID-19 infection. The first case of COVID-19 infection presented as acute nonicteric hepatitis was reported by Wander et al in China (3). In this case study, the patient had nonicteric hepatitis with bilateral interstitial opacities. She had no lung involvement in a spiral chest CT three days after initiating symptoms. However, following the onset of respiratory symptoms on the eighth day of the disease, the patient's CT confirmed the presence of COVID-19. The sensitivity of chest CT on the asymptomatic or mild disease, especially without respiratory symptoms, was low (4-6). To the best of our knowledge, this is the first case of COVID-19 infection presenting as acute hepatitis without respiratory symptoms in the early stages of the disease. Our patient demonstrated very mild signs of COVID-19 infection and was tested only due to her alertness and sensitivity to the disease. Other possible liver abnormality causes were eliminated; therefore, acute hepatitis was directly caused by COVID-19.

One of the most widely used diagnostic tools, especially during the pandemic, is the reverse transcription (RT)-PCR. This test uses a person's respiratory sample to diagnose viral particles and determine if the person may have been infected with a virus. According to the findings published on May 13, 2020, in the *Journal of Annals of Internal Medicine*, the researchers discovered that the probability of a false-negative result decreased from 100% on day 1 of being infected to 67% on day 4. The false-negative rate decreased to 20% on day 8 (three days after a person began experiencing symptoms). They also discovered that when a person began to experience actual symptoms of illness, the average false-negative rate was 38%. Furthermore, the false-negative rate increased from 21% on day 9 to 66% on day 21 (7). In the present case, RT-PCR was performed three days after the fever, which was negative. We thought this was a false negative. This case demonstrates that the absence of respiratory symptoms in patients with an exposure history cannot rule out COVID-19. In this case study, RNA tests were negative for the first time.

The researchers discovered that the sensitivity of antibody testing (the percentage of the patients infected with COVID-19 that the test can detect) is closely related to the testing time. The IgG and IgM antibody tests were identified only in 70% of patients with COVID-19 14 days after the onset of symptoms. However, when the researchers examined data, reported between 15 days and 35 days following the first symptoms onset, antibody tests correctly identified over 90% of COVID-19 patients. The COVID-19 antibody was checked four times in this case study, which was negative three times and tested positive the last time.

According to the study by SL et al D-dimer levels increased in cirrhotic patients, and there was a significant difference between chronic hepatitis and cirrhotic hepatic (8). No increased D-dimer in acute hepatitis has been reported so far. One of the most common laboratory findings noted in patients with COVID-19 that requires hospitalization is the elevated D-dimer level, which is identified as one of the predictors of mortality (9).

According to studies conducted on 1,099 patients with laboratory-confirmed COVID-19 in China, 560 patients were hospitalized, and D-dimer ≥ 0.5 mg/L was noted in 260 (46.4%) cases; among them, 43% had a non-severe disease, and 60% had a severe disease (10). In our case, significantly increased D-dimer levels were observed without any signs and symptoms of the severity of the disease.

Conclusion

Significantly increased D-dimer levels might be considered the only clue of COVID-19 infection, and D-dimer could be increased dramatically in mild disease. COVID-19 might be presented only with acute self-

Table 1. Laboratory Finding of the Patient

	Day 3	Day 6	Day 9	Day 17
White blood cell count	3800	5180		5210
• Neutrophil	28%	59.9%	-	50.3%
• Lymphocyte	15%	34.6%		39.6%
Platelets	150000	235000	-	340000
ESR	17	12	-	-
CRP	12.4 (Neg < 6 mg/dL)	11	5.15	2
Ferritin	380 (NL 5-204 ng/mL)	368.9	243	-
D-dimer	5973 (NL up to 500 ng/mL)	2028	2345	743
SARS CoV Ab (IgM)	0.35 (Neg < 0.9)	-	-	0.19
SARS CoV Ab (IgG)	0.43 (Neg < 0.9)	-	-	0.28
LDH	1476 (NL < 480)	422	344	-
CMV Ab (IgM)	10.4 (Neg < 18)	-	-	-
CMV Ab (IgG)	68.2 (Neg < 12)	-	-	-
HSV Ab (IgM)	0.4 (Neg < 0.9)	-	-	-
HSV Ab (IgG)	0.2 (Neg < 0.8)	-	-	-
EBV Ab (IgM)	0.7 (Neg < 0.8)	-	-	-
EBV Ab (IgG)	10.2 (Neg < 0.8)	-	-	-
	Day 3	Day 6	Day 9	Day 17
HBsAb	678 (Neg < 0.8)	9.05	-	-
HAV Ab (IgM)	1.3 (Neg < 0.9)	0.77	0.94	1.01
HAV Ab (IgG)	6.73 (Neg < 1)	9.05	8.05	3.03
HCV Ab	0.060 (Neg < 1)	-	-	-
AST	1170 (NL up to 33 U/L)	266	96	31
ALT	1493 (NL up to 33 U/L)	803	462	104
ALK.P	659	418	354	230
T-Bil	1.24	0.77	-	-
INR	1	1	-	-
Albumin	4.5	-	-	-
25 OH Vit D	38	-	-	-
ANA	1/20 (Neg < 1/100)	-	-	-
ASMA	0.01	-	-	-
Anti LKM1	0.01 (Neg < 15)	-	-	-
IgG	8	-	-	-
HBsAg	0.7 (Neg < 0.8)	0.77	-	-

Note. SARS: Severe acute respiratory syndrome coronavirus 2; COVID: Coronavirus disease; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; SARS CoV Ab (IgG): SARS COVID antibody (immunoglobulin G); LDH: Lactate dehydrogenase; CMV Ab (IgM): Cytomegalovirus antibody (immunoglobulin M); HSV Ab (IgM): Herpes simplex virus antibody (immunoglobulin M); EBV Ab (IgM): Epstein-Barr virus antibody (immunoglobulin M); HBsAb: Hepatitis B surface antigen antibody; HAV Ab (IgM): Hepatitis A virus antibodies (immunoglobulin M); HCV Ab: Hepatitis C virus antibody; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALK.P: Alkaline phosphatase; T-Bil: Total bilirubin; INR: International normalized ratio; 25 OH Vit D: 25 hydroxy vitamin D; ANA: Antinuclear antibody; ASMA: Anti-smooth muscle antibody; Anti-LKM1: Liver kidney microsome type 1 antibody; HBsAg: Hepatitis B surface antigen.

limited hepatitis.

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Ethical Approval

This case study was approved by the Ethics Committee of Urmia University of Medical Sciences (code IR.UMSU.HIMAM.REC.1401.038).

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