

Case Report

COVID-19 with acute hepatitis A virus co-infection in a fully-vaccinated individual: a case report

Masra Lena Siregar^{1,2*}, Rabid Yahya Putradasa¹, Arini Nisaul¹, Suheir Muzakkir²

¹Regional Public Hospital of Sawah Besar, Central Jakarta, Indonesia; ²Division of Tropical Medicine and Infectious Disease, Department of Internal Medicine, Faculty of Medicine, Universitas Syiah Kuala, Indonesia.

*Correspondence:

Masra Lena Siregar
Medical Research Unit,
School of Medicine,
Universitas Syiah Kuala;
Division of Tropical
Medicine and Infectious
Disease, Department of
Internal Medicine,
Faculty of Medicine,
Universitas Syiah Kuala,
Indonesia.

E-mail address:
masra.lena@unsyiah.ac.id

Abstract

In a developing country with varying degree of public hygiene and sanitation, prevalent infectious diseases such as hepatitis A (HAV) could add to the burden of infection during coronavirus disease 2019 (COVID-19) pandemic and complicate its gastrointestinal and hepatic manifestation. Here we present a case COVID-19 with acute hepatitis A virus co-infection in a young female with fever, joint pain, non-productive cough, loss of smell, abdominal discomfort, darkened urine, and pale loose stool before admission. The significant finding was slightly icteric sclera, hepatomegaly with tenderness in the epigastrium and right upper quadrant, increase in aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, C-reactive protein and, D-dimer. A naso-oropharyngeal swab examination for SARS-CoV-2 infection was positive, and IgM anti-HAV was reactive with a total anti-HAV titer >60 mIU/mL. Subsequently, she was hospitalized for 14 days, successfully recovered; her symptoms resolved and her level of liver enzymes back to normal, and she was discharged for self-isolation at home. RT-PCR for SARS-CoV-2 infection came back negative 7 days later. In light of the pandemic, physicians need to raise suspicion of co-infection of COVID-19 with other hepatitis viruses in cases with gastrointestinal and hepatic manifestation. A marked increase in liver enzyme may warrant further testing for hepatitis viruses where such infection should be suspected.

Keywords: COVID-19, SARS-CoV-2, acute hepatitis, HAV; co-infection

Introduction

Coronavirus disease 2019 (COVID-19) outbreaks have reached a global pandemic and public health crisis. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a causative pathogen in this infection. The most common presentation of COVID-19 is respiratory symptoms (WHO., 2020). Co-infection diseases in COVID-19 patients is variable. The prevalence of abnormal liver tests presenting in COVID-19 patients is still undetermined. Data from the American College of Gastroenterology, more than 20-30% of patients with COVID-19 have abnormal level of liver enzymes (Wander et al., 2020). Here, we would like to present the case of COVID-19 patients with acute hepatitis A co-infection.

Case report

A 28-year-old woman came to the hospital with the complaint of loss of smell three days before admission. The previous seven days, she had been having a fever, joint pain, and dry cough. She also felt discomfort in the stomach, particularly in the middle and upper right quadrant, had nausea and vomiting, decreased appetite, and bitter taste for the last two days. There were no complaints of shortness of breath, sore throat, and painful during swallowing. Her urine was dark-colored. There was no dysuria and the frequency of her urination was normal. She had a history of diarrhea three days before admission. However, it had stopped when she came to the hospital and since one day before admission, her stool color was pale. The contact history with confirmed COVID-19 survivors was unknown. There was no history of diabetes mellitus, hypertension, hepatitis, or other diseases. The patient works as a laboratory worker in

Article Information
Received : 27 Aug 2021
Accepted : 28 Aug 2021
Published : 1 Sep 2021

the hospital and has received two doses of COVID-19 vaccine (Coronavac). She was last vaccinated 6 weeks before admission.

On the physical examination, the general condition appeared moderately ill and alert, blood pressure 100/66 mmHg, pulse rate 78 times per min, breathing 20 times per min, temperature 36.7°C, oxygen saturation 98% on room air, her weight was 63 kg and her height was 165 cm. Her eyes conjunctiva were not anemic and her sclera was slightly icteric. Cardiac and pulmonary examinations were within normal limits. In the abdominal examination, hepatomegaly with tenderness in the epigastrium and right upper quadrant (RUQ) was found. There was no edema and no icterus in her extremities.

The laboratory investigations showed hemoglobin 12.1 g/dL, hematocrit 38%, leukocyte $4.6 \times 10^3/\mu\text{L}$, platelets $318 \times 10^3/\mu\text{L}$, neutrophil lymphocyte ratio (NLR) 5.6. Kidney function was in normal limits (urea 14 mg/dL, creatinine 0.76 mg/dL), electrolytes were normal limits (sodium 135 mmol/L, potassium 4.3 mmol/L, chloride 106 mmol/L). There was an increase in aspartate aminotransferase (AST) 1172 IU/L, alanine aminotransferase (ALT) 1440 IU/L, alkaline phosphatase 218 IU/L, hyperbilirubinemia with total bilirubin 4.3 mg/dL and direct bilirubin 3.9 mg/dL. Investigations for hepatitis marker revealed non-reactive HBsAg, non-reactive anti-HCV, reactive IgM anti-hepatitis A virus (HAV), and reactive total anti-HAV (>60 mIU/mL). Reverse transcriptase-PCR (RT-PCR) for SARS-CoV-2 was positive, C-reactive protein 3.1 mg/dL [normal ranges <0.5 mg/dL], and D-dimer 1030 ng/mL [normal ranges: 0.0-500.0 ng/mL]. Chest X-ray revealed no abnormalities in the heart and lungs and abdominal ultrasonography was essentially normal.

The patient was diagnosed with COVID-19 moderate co-infection with acute hepatitis A and hypercoagulation. The initial management of the patient was treated supportively and symptomatically with Ringer's Lactate infusion, Neurobion®, anti-emetic drugs, and proton pump inhibitor. She was also given roborantia, hepatoprotector, vitamin D3, vitamin E, and Zinc. The patient was given a nasal wash with normal saline two times a day and she was given azithromycin and favipiravir for COVID-19 therapy.

During treatment, the patient still complained of continuous nausea and intermittent vomiting. She also complained of pain in the RUQ of the abdomen and the pit of epigastrium. Her sclera looked icteric and the frequency of diarrhea was three times per day. The infusion was still given with a low fiber diet and anti-diarrhea medicine. The patient also received drip N-Acetylcysteine and Stronger Neo-Minophagen C (SNMC) for 3 days.

At 7 days later, the patient still complained of nausea but was no longer vomiting, her appetite had increased and there was no more diarrhea. Other complaints such as cough and shortness of breath were absent. The second RT-PCR for SARS-CoV-2 examination was done and still came back positive. Evaluation of the transaminase enzyme examination showed a significant decrease. The results of the recapitulation of the trend of decreased liver function (Figure 1). Since the complaints of nausea, vomiting, and abdominal discomfort had disappeared, on the 14th day of treatment, the patient was discharged even though the RT-PCR of SARS-CoV-2 result was still positive and she was advised to continue with self-isolation at her home. One week after treatment, the patient returned to undergo RT-PCR of SARS-CoV-2 examination for evaluation, and the result was negative.

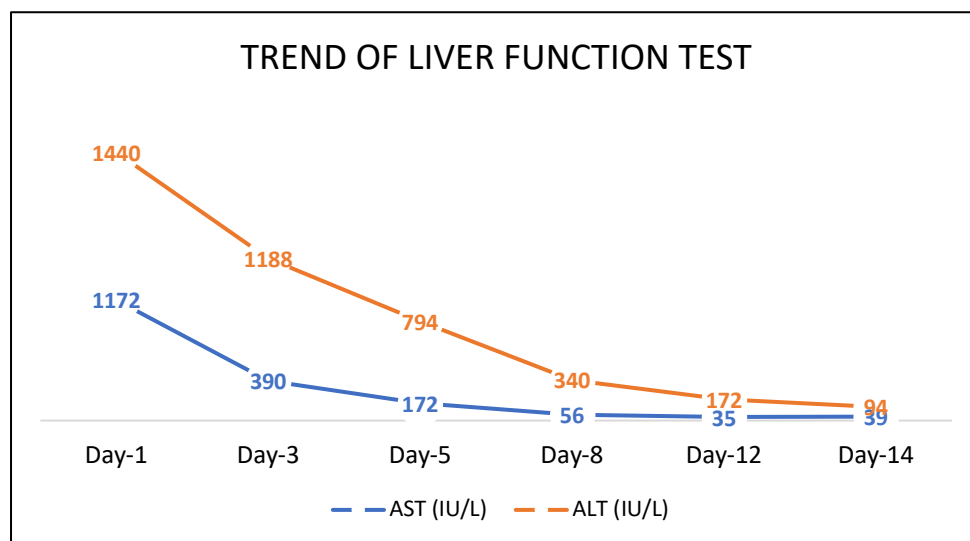


Figure 1. The progress of the liver function test

Discussion

COVID-19 pandemic has become a global health disaster especially in a populous, highly diverse, and developing country like Indonesia, with more than 1.9 million confirmed cases and more than 54,000 deaths by June 2021 (WHO., 2021). This presents a major public health concern in a developing country such as Indonesia (Fahriani et al., 2021). Indonesia have faced a big burden of infectious diseases even before the pandemic started, such as hepatitis A infection. Around 2.9 million of Indonesian population are infected with hepatitis A in 2014 (Ministry of Health., 2014). Indonesian population has high prevalence of anti-HAV, with prevalence in small towns being much higher than in the big cities (Mulyanto., 2016). Interestingly, hepatitis A susceptibility in the population is thought to be correlated with COVID-19 mortality in one study; individuals with immunity against hepatitis A probably have cross-immunity against SARS-CoV-2 which happens to be RNA virus-like HAV, hence can protect individuals from developing more severe cases of COVID-19 (Sarialioglu et al., 2021).

HAV is transmitted via fecal-oral route, through person-to-person contact and ingestion of food or water contaminated with feces of an infected person (WHO., 2020). While SARS-CoV-2 as the causative agent for COVID-19 is transmitted via respiratory droplets and contact with contaminated surface, hence warrants prevention measures for droplets and contact transmission; gastrointestinal manifestation of COVID-19 and detectable COVID-19 viral RNA fragments in the fecal matter of COVID-19 patients suggest intestinal infection by SARS-CoV-2 (WHO., 2020; Xiao et al., 2020). Although there have been no reports of fecal-oral transmission of SARS-CoV-2, safe water management and sanitation service with good hygiene practice will provide co-benefits in also preventing other infectious diseases such as hepatitis A infection, hence basic hygiene practice should always be enforced during the COVID-19 pandemic (WHO., 2020). Proper and hand hygiene practice is one of the most pivotal methods to prevent both COVID-19 and HAV infection (WHO., 2020; Xiao et al., 2020; Ntouva et al., 2019).

We reported the case of COVID-19 and HAV co-infection. The patient presented with a chief complaint of loss of sense of smell, along with dry cough and constitutional symptoms. These are typical manifestations of COVID-19 infection (WHO., 2020). The patient also had gastrointestinal complaints, such as stomach discomfort, nausea, vomiting, decreased appetite, and history of liquid defecation. One meta-analysis

shows that 15 percent of COVID-19 patients had digestive symptoms (Mao et al., 2020). The patient had had two doses of Coronavac vaccination, but RT-PCR for SARS-CoV-2 test was positive, confirming the diagnosis of COVID-19 in this patient.

The finding of clinical icterus as shown in the sclera, the stomach discomfort at right upper quadrant, hepatomegaly with tenderness in epigastrium, and darkened urine suggests involvement of the liver. Liver abnormalities might occur in 19% of COVID-19 patients as stated by one meta-analysis, and acute hepatitis as the manifestation of COVID-19 has been reported (Mao et al., 2020; Wander et al., 2020). The clinical manifestation of hepatitis along with elevated levels of aspartate aminotransferase and alanine aminotransferase increased bilirubin with predominant direct bilirubinemia, and elevated level of alkaline phosphatase necessitates further investigation for other possible etiology. Our patient tested negative for HBsAg and anti-HCV, excluding the diagnosis of hepatitis B and C. The reactive anti-HAV with high titer confirmed our suspicion that our patient also contracted HAV by the time her COVID-19 diagnosis was made (Jeong & Lee., 2010; CDC., 2020).

Mild to moderate liver abnormalities are commonly observed in COVID-19 patients, but they are found more in severe cases than in mild cases of COVID-19 (Licata et al., 2021; Zhang et al., 2020; Yang et al., 2020). Some possible pathophysiological bases that might help explain liver dysfunction in COVID-19 patients, including direct SARS-CoV-2 infection of liver cells, drug hepatotoxicity, and immune-mediated inflammation involving cytokine storm and pneumonia-associated hypoxia (Zhang et al., 2020; Yang et al., 2020). Epithelium of bile ducts plays an important role in liver regeneration and modulation of immune response (Licata et al., 2021). The increase in alkaline phosphatase in our patient suggests the damage of cholangiocytes. Cholangiocytes express angiotensin-converting enzyme-2 (ACE-2) receptor on its surface that facilitates entry for SARS-CoV-2, suggesting viral infection in the cholangiocytes, hence plays role in dysregulation of liver and bile duct function in COVID-19 patients (Yang et al., 2020; Chai et al., 2020).

The level of liver enzymes in our patients was quite high, probably resulted from two ongoing infections by SARS-CoV-2 and HAV in the hepatocytes, resulting in more marked inflammation and destruction of hepatocytes. Both SARS-CoV-2 and HAV are RNA viruses with tropism for hepatocytes (Jeong & Lee., 2010; Wang et al., 2020). Direct infection of SARS-CoV-2 in hepatocytes might not be the main cause of liver abnormalities in COVID-19 patients, but rather by multiple pathophysiologies (Yang et al., 2020). When faced with a significant level of liver abnormalities in COVID-19 patients, physicians should pay extra awareness not only to the likelihood of co-infection of COVID-19 with other hepatitis viruses but also the prognosis of the patient. Although rare, hepatitis A alone can result in fulminant hepatitis, and we think it might be prone to happen in COVID-19 patients with already ongoing liver injury (Jeong & Lee., 2010; Zhang et al., 2020; Wander et al., 2020). Meticulous evaluation should be done in COVID-19 patients that undergo significant liver damage to identify any comorbidities or pre-existing liver disease, exposure to hepatotoxins (alcohols, drugs, chemicals), hypoxia, and circulatory problems (Yang et al., 2020).

Liver damage in mild cases of COVID-19 is usually temporary with liver enzymes returning to normal levels without specific treatment, however severe liver damage might necessitate liver protective drug as a treatment (Zhang et al., 2020; Yang et al., 2020). In our case, we treated our patient supportively for HAV infection, and also used favipiravir as the antiviral of COVID-19 and curcuma as a standard hepatoprotector, then later added with N-Acetylcysteine and Stronger Neo Minophagen C (SNMC) to help treating the liver injury. We could see improvement of clinical symptoms and subsequent decrease in levels of ALT and AST. Other means of treatment might be used in different clinical situations depending on the

pathophysiology: improving oxygenation and circulation in hypoxic hepatitis; continuous renal replacement therapy in cytokine storm phase; dose reduction or even discontinuation of hepatotoxic drugs; and treatment with L-ornithine-L-aspartate in hepatic encephalopathy. Prebiotics and probiotics could also be considered to support the growth of normal flora and preventing secondary intestinal bacterial infection. (Yang et al., 2020).

There were several reports of COVID-19 infection presenting as non-icteric hepatitis and COVID-19 infections inducing flares of pre-existing hepatitis B and hepatitis C infection, but co-infection with HAV as an acute viral illness in COVID-19 remain unreported to date (Akarele et al., 2021; Yigit et al., 2021; Aldhaleei et al., 2020). Co-infection of COVID-19 with multiple pathogens primarily infecting the respiratory tracts has also been reported, including various bacteria, viruses, and fungi (Lai et al., 2020). Our report added HAV to the long list of pathogens that might co-infect patients with COVID-19.

Conclusion

We have reported this case to highlight the importance of the index of suspicion in COVID-19 patients with significant liver injury for possible co-existing acute or acute on chronic hepatitis viral infections. Our case of SARS-CoV-2 and HAV co-infection was treated and recovered successfully. Moreover, this case also adds knowledge about another coinfection in COVID-19 patients.

Author contributions

Conceptualization: MLS, RYP, AN and SM; Data Curation: MLS, RYP, AN and SM; Investigation: MLS, RYP, AN and SM; Supervision: MLS; Validation: MLS, RYP, AN and SM; Writing – Original Draft Preparation: MLS, RYP, AN and SM; Writing – Review & Editing: MLS, RYP, AN and SM

Consent for publication

Informed written consent was given by the patient to publish this case report and related data.

Acknowledgments

We are grateful to the patient for consent to publish this case and the medical team in the Regional Public Hospital of Sawah Besar for their cooperation in providing the data for research.

Conflict of interests

No conflict of interest is declared.

Funding

This study received no funding.

References

- Akerele IO, et al. Coronavirus disease (COVID-19) and acute nonicteric hepatitis: A case report from Asokoro, Nigeria. *J Fam Community Med* 2021; 28(1): 59-62.
- Aldhaleei WA, et al. COVID-19 induced hepatitis B virus reactivation: a novel case from the United Arab Emirates. *Cureus* 2020; 12(6): e8645.
- CDC. Hepatitis A questions and answers for health professionals. 2020; Available

- from: <https://www.cdc.gov/hepatitis/hav/havfaq.htm#travel>. Accessed on Jun 21, 2021.
- Chai X, et al. Specific ACE-2 expression in cholangiocytes may cause liver damage after 2019-nCoV Infection. *bioRxiv* 2020.
- Fahriani M, Anwar S, Yufika A, Bakhtiar B, et al. Disruption of childhood vaccination during the COVID-19 pandemic in Indonesia. *Narra J* 2021;1(1): e7.
- Jeong S, et al. Hepatitis A: Clinical manifestations and management. *Intervirology* 2010; 53(1): 15-19.
- Lai C, et al. Co-infections among patients with COVID-19: The need for combination therapy with non-anti-SARS-CoV-2 agents?. *J Microbiol Immunol Infect* 2020; 53(4): 505-512.
- Licata A, et al. Liver injury, SARS-CoV-2 infection and COVID-19 - What physicians should really know? *GastroHep* 2021; 3(3): 121-30.
- Mao R, et al. manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; 5(7): 667-678.
- Ministry of Health. Prevalensi hepatitis. 2014; Available from: <http://www.pusdatin.kemkes.go.id/article/view/15073000001/w-a-s-p-a-d-a-2-9-juta-lebih-penduduk-indonesia-mengidap-hepatitis.html>. Accessed on Jun 19, 2021.
- Mulyanto. Viral hepatitis in indonesia: past, present, and future. *Euroasian J Hepatogastroenterol* 2016; 6(1): 65-69.
- Ntouva A, et al. Hepatitis A in primary care: working in partnership for diagnosis, management, and prevention of outbreaks. *Br J Gen Pract* 2019; 69(687): 521-522.
- Sarialioğlu F, et al. Hepatitis A susceptibility parallels high COVID-19 mortality. *Turkish J Med Sci* 2021; 51: 382-384.
- Wander P, et al. COVID-19 presenting as acute hepatitis. *Am J Gastroenterol* 2020; 115(6): 941-942.
- Wang Y, et al. SARS-CoV-2 Infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol* 2020; 73(4): 807-816.
- WHO. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: Interim guidance. 2020; Available from: <https://apps.who.int/iris/bitstream/handle/10665/330893/WHO-nCoV-Clinical-2020.3-eng.pdf?sequence=1&isAllowed=y>. p 1-10. Accessed on 20 Jun 2021.
- WHO. Hepatitis A. 2020; Available from: <https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-a>. Accessed on 19 Jun 2021.
- WHO. Update on coronavirus disease in Indonesia. 2021; Available from: <https://www.who.int/indonesia/news/novel-coronavirus>. Accessed on Jun 19, 2021.
- WHO. Water, sanitation, hygiene and waste management for the COVID-19 virus. 2020; Available from: <https://apps.who.int/iris/rest/bitstreams/1271257/retrieve>. Accessed on 19 Jun 2021.
- Xiao F, et al. Evidence for gastrointestinal infection of SARS-CoV-2. *Gastroenterology* 2020; 158(6): 1831-1833. <https://doi.org/10.1053/j.gastro.2020.02.055>.
- Yang R, et al. Etiology and management of liver injury in patients with COVID-19. *World J Gastroenterol* 2020; 26(32): 4753-4762.
- Yigit Y, et al. Can COVID-19 cause flare-ups of acute hepatitis B? an atypical presentation of COVID-19 with acute hepatitis B. *Case Rep Infect Dis* 2021; 8818678.
- Zhang C, et al. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020; 5(5): 428-430.