Volume 10, Issue 06, June 2024,
Publish Date: 015-06-2024
Doi https://doi.org/10.55640/ijmsdh-10-06-02

International Journal of Medical Science and Dental Health (Open Access)

PROTRACTED SEVERE ACUTE HEPATITIS B ON A PATIENT WITH HYPERTHYROIDISM

MICHAEL JOHAN[1], HANDRY PANGESTU[2]

[1]General Physician, Mitra Keluarga Kemayoran Hospital, Jakarta-Indonesia
[2]Internal Medicine Physician, Mitra Keluarga Kemayoran Hospital, Jakarta-Indonesia

ABSTRACT

Acute hepatitis B is a self-limiting infection, but severe cases resulting in liver failure and death have been reported in 1% of acute hepatitis B cases. Severe acute hepatitis B is diagnosed when one of the following criteria is present: international normalized ratio (INR) >1.5, severe jaundice (total bilirubin >3 mg/dL), or encephalopathy. Severe acute hepatitis B is considered prolonged if it lasts >4 weeks. Hyperthyroidism may lead to liver cell disruption or cholestasis injury. Severe acute hepatitis B associated hyperthyroidism is a case that is very rare.

We report a 37-year-old woman with severe acute hepatitis B with protracted jaundice and thyrotoxicosis. Total bilirubin levels persisted >20 mg/dL during eight weeks of treatment despite liver enzymes falling after two weeks of treatment. The patient also had a relapse of hyperthyroidism which had been on remission phase for ten years. The patient was treated with antiviral combination of tenofovir and entecavir to prevent deterioration to liver failure. Methimazole and propranolol were given to manage the patient's hyperthyroid symptoms.

The association of hepatitis B with thyrotoxicosis and persistent jaundice is debatable, as is the extrahepatic manifestation of hepatitis B which trigger the relapse of hyperthyroidism. Combination management of two antivirals should be considered in protracted severe acute hepatitis to prevent liver failure.

Keywords: Antivirus, Acute Hepatitis B, Hyperthyroidism.

INTRODUCTION

Acute hepatitis B is generally a self-limiting infection, although severe cases resulting in liver failure, liver transplantation, and death have been reported.[1] National data shows that 7.1% of the population is HBsAg(+), but data on acute hepatitis B is not available.[2] Rimšelienė et al. noted that the incidence of acute hepatitis B cases in Norway was 1.2/100,000 population in 2009, compared to the incidence of chronic hepatitis B at 17.4/100,000 population in the same year.[3] One percent of acute hepatitis B

cases can lead to liver failure.[4] A person is considered to have severe acute hepatitis B if any of the following criteria are present: INR >1.5, severe jaundice (total bilirubin >3 mg/dL), or encephalopathy. Severe acute hepatitis B is considered protracted when it has occurred for more than four weeks. [5,6]

Thyrotoxicosis is the clinical manifestation of increased thyroid hormone activity in tissues due to an increase in thyroid hormone from the thyroid gland or other organs such as the pituitary gland. The state of thyrotoxicosis due to an increase in thyroid hormone from the thyroid gland is called hyperthyroidism. [7] Thyroid hormone is an important hormone in the regulation of the basal metabolic rate of all body tissues, including liver cells. Thyrotoxicosis is known to cause damage to liver cells or cholestasis. [8]

Although cases of hyperthyroidism have been reported, severe acute hepatitis B with thyrotoxicosis is rare. [9] This case report serves as a lesson to clinicians for early diagnosis and prompt treatment of acute hepatitis B with comorbid thyrotoxicosis to avoid serious complications and prolonged disease course.

Case Illustration

We report an adult patient named Mrs F, 37 years old, who presented to our hospital with complaints of vomiting with yellowish skin for 10 days. The patient also complained of frequent diarrhoea and fatigue for the last 10 days. The patient is known to have a history of hyperthyroidism for 10 years and has never sought treatment as she was told she was cured. The patient has a history of drinking about 1-2 glasses of alcohol per week. The patient is afebrile, icteric all over the body, hepatomegaly and there is tenderness in the right upper quadrant of the abdomen.

Initial laboratory exam revealed haemoglobin 10.8 g/dL, leukocytes 8220/µL, basophils 0%, eosinophils 2%, rod neutrophils 0%, segmental neutrophils 55%, lymphocytes 30%, monocytes 13%, hematocrit 35%, platelets 233000/µL, indirect bilirubin 1.93 mg/dL, direct bilirubin 14.81 mg/dL, total bilirubin 16. 74 mg/dL, serum glutamic oxaloacetic transaminase (SGOT) 1290 U/L, serum glutamic pyruvic transaminase (SGPT) 1538 U/L, gamma glutamyl transferase (GGT) 126 U/L, alkaline phosphatase (AP) 180 U/L, urea 16 mg/dL, serum creatinine 0. 22 mg/dL, blood glucose 89 mg/dL, lipase 21 U/L, amylase 12 U/L, C-reactive protein (CRP) 4.9 mg/L, sodium 138 mEq/L, potassium 4.2 mEq/L, albumin 3.5 g/dL, prothrombin time 20.3 (16.2) and INR 1.48.

The preliminary working diagnosis was hepatitis, so the patient was tested for hepatitis markers. Hepatitis marker testing revealed non-reactive hepatitis A virus IgM, reactive HbsAg with a serum/cut-off ratio (S/CO) of 3473.3, and non-reactive anti-HCV. The examination was then continued for further evaluation of which phase of hepatitis B had occurred with reactive anti-HBc IgM, HBeAg 461.52 S/CO, negative anti-HBe, negative anti-HBs describing acute hepatitis B. Abdominal CT scan results in the patient suggestive of acute hepatitis with gallbladder wall oedema, no signs of obstruction or hyperdense stones intraluminal biliary tract.

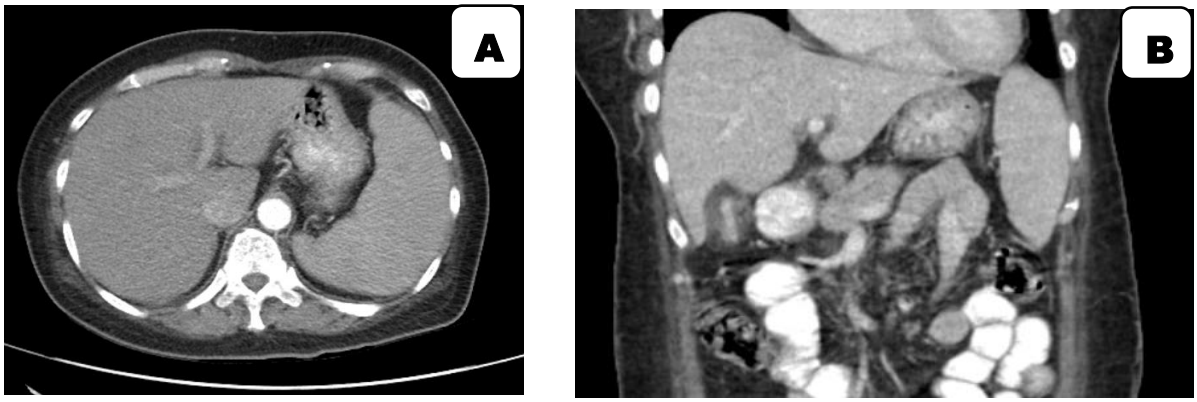

Figure 1. *(**Abdominal CT-Scan imaging of a patient with acute hepatitis B. A:** Axial Abdominal CT-Scan; B: Coronal Abdominal CT-Scan.)*

After five days of treatment with supportive care including a proton pump inhibitor (PPI), anti-nausea, antipyretic and liver support supplements, the patient was still nauseous and jaundice. The patient's SGOT and SGPT decreased, but total bilirubin increased. The patient was then started on tenofovir 300 mg one tablet per day and ursodeoxycholic acid 250 mg every eight hours.

On the 10th day of treatment, SGOT and SGPT levels decreased, but bilirubin levels remained high. Examination of the patient also revealed fine tremor and diffuse enlargement of the thyroid gland, so thyroid hormone testing was performed. The patient's thyroid-stimulating hormone (TSHs) was <0.01 µIU/mL and free thyroxine (FT4) was >5 ng/dL, indicating hyperthyroidism. The patient's hyperthyroidism was then treated with methimazole 15 mg, twice daily, and propranolol 10 mg, one tablet every eight hours.

On the 15th day of treatment, the patient's SGOT and SGPT levels decreased but the bilirubin level was still high, so the patient was tested for HBV DNA and the result was 245 IU/mL. The patient was also tested for antinuclear antibodies (ANA) to rule out the possibility of autoimmune hepatitis, but this was negative. The patient was then considered for additional antiviral combination therapy with entecavir 0.5 mg once daily for persistent severe acute hepatitis B. On day 25 of treatment, the patient was no longer nauseous and her SGOT/SGPT had decreased to near the upper normal limit, but her bilirubin level was still high at 24.29 mg/dL. Due to the clinical improvement, the patient was discharged for outpatient care.

On the 30th day after the first treatment, the patient was readmitted because of nausea, vomiting and jaundice. Laboratory investigations revealed the following results: albumin 2.8 g/dL, indirect bilirubin 5.1 mg/dL, direct bilirubin 19.3 mg/dL, total bilirubin 24.4 mg/dL, SGOT 111 U/L, SGPT 65 U/L, GGT 71 U/L, FA 248 U/L, prothrombin time 16.5 (14), INR 1.18, FT4 3.58 ng/dL, and TSH <0.01 µIU/mL. Patient received supportive care, which improved her clinically after one week of treatment, and was discharged to outpatient care.

On the 45th day after initial admission, the patient was readmitted because of nausea and vomiting accompanied by jaundice. Laboratory investigations revealed the following result: SGOT 164 U/L, SGPT 110 U/L, independent bilirubin 3.32 mg/dL, rec bilirubin 16.79 mg/dL, total bilirubin 20.11 mg/dL, GGT 65 U/L, FA 282 U/L, CRP 81.6 mg/dL, FT4 4.77 ng/dL and TSHS <0.01 µIU/mL. These results showed severe jaundice with unresolved thyrotoxicosis. The patient was put on supportive care,

tenofovir and entecavir were continued, but the dose of the antithyroid drugs was increased to 20 mg twice daily, as there was no drug-induced liver injury (DILI) due to methimazole. After the patient was treated for 6 days, there was improvement, with SGOT values dropping to 81 U/L, SGPT dropping to 76 U/L, total bilirubin to 10.92 mg/dL, and FT4 to 2.71 ng/dL. The patient was subsequently discharged to outpatient care.

On the 75th day since the initial admission, the patient was much improved, with total bilirubin of 1.72 mg/dL and FT4 of 0.91 ng/dL. One month later her total bilirubin had dropped to 0.74 mg/dL, FT4 of 0.98 ng/dL, and HBsAg of 1.26 S/CO. Because of her clinical improvement, entecavir was discontinued and the patient continued to receive tenofovir one tablet daily.

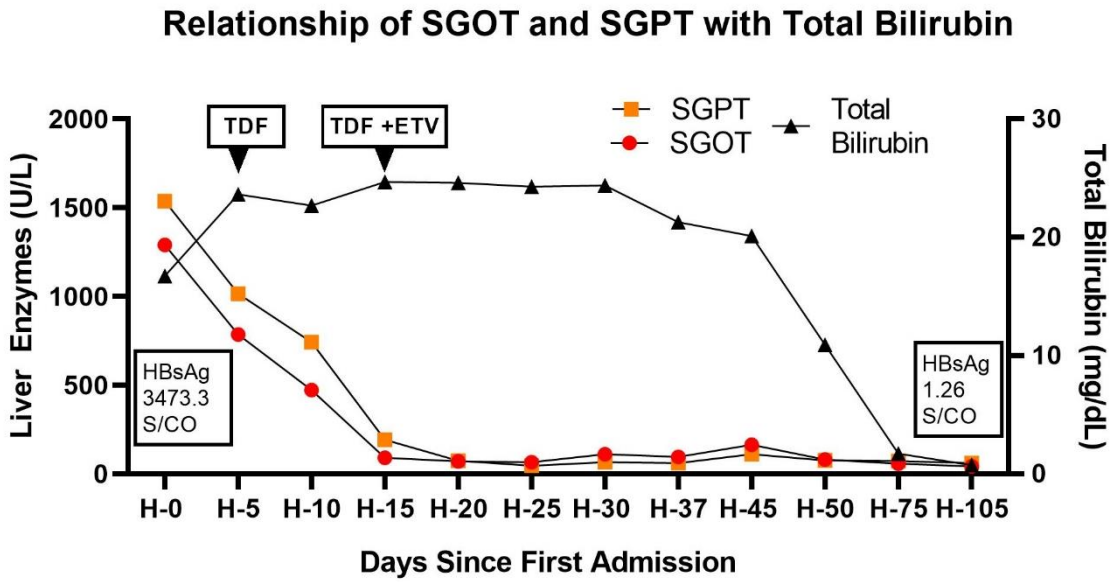

Figure 2. (Relationship of the SGOT and SGPT with total bilirubin. *The figure shows that the decrease in SGOT/SGPT in the first week was not accompanied by a decrease in bilirubin levels. H-0: day the patient was admitted for the first time; H-30: Day of second hospitalization; H-45: Day of third hospitalization; H-75: Outpatient visit to the polyclinic; TDF: Tenofovir disoproxil fumarate; ETV: Entecavir; S/CO: Serum/cut-off ratio.)*

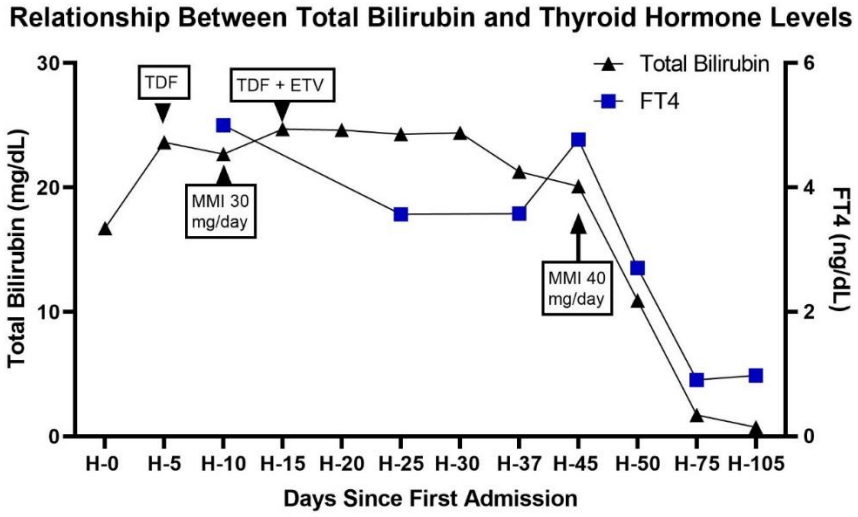

Figure 3. (Relationship Between Total Bilirubin Levels and Thyroxine Hormone (FT4). *The figure shows a decrease in FT4 levels accompanied by a decrease in total bilirubin. H-0: Day the patient was admitted for the first time; H-30: Day of second hospitalization; H-45: Day of third hospitalization; H-75: Outpatient visit to the polyclinic. TDF: Tenofovir disoproxil fumarate; ETV: Entecavir; MMI: Methimazole.)*

DISCUSSION

Acute hepatitis B can generally recover on its own without the need for antiviral in a short period of time, but the case of acute hepatitis B detailed above has a long disease course characterized by persistent jaundice. [10] This jaundice persisted even after the SGOT and SGPT improved.

Generally, international guidelines such as AASLD, EASL, and APASL recommended the administration of antiviral on severe acute hepatitis B characterized by bilirubin total >3 mg/dL, INR >1.5, or encephalopaty.[5,11,12] Antiviral therapy is known to delay HBsAg sero-clearance, but antiviral therapy in severe acute hepatitis B is beneficial as it can significantly reduce mortality in patients with severe acute hepatitis B.[10] Historically, treatment of acute hepatitis B with early-generation antivirals such as lamivudine and adefovir has been unsatisfactory. However, treatment with second-generation, high-barrier antivirals such as tenofovir and entecavir has shown satisfactory results. [13] In patients with severe acute hepatitis B, the AASLD also recommends the use of entecavir and tenofovir DF/AF. [5] In cases where it is not possible to distinguish between a new episode of acute hepatitis B or spontaneous reactivation of chronic hepatitis B, antiviral treatment is still recommended. [12]

The patient was initially treated with tenofovir alone, but because the patient tended to become increasingly jaundiced after 10 days of treatment, tenofovir was combined with entecavir. The goal of combination antiviral therapy is to prevent severe acute hepatitis B from worsening into acute liver failure. A report by Maya et al. supports the use of combination antiviral therapy in severe acute hepatitis B. 30-day survival in the group of patients receiving tenofovir and entecavir was significantly better than in the group not receiving therapy. [14]

The patient's jaundice persisted despite a dramatic decrease in SGOT and SGPT after treatment with a combination of antivirals, as shown in Figure 2. This finding contradicts the description of a case of severe acute hepatitis B by Bockmann et al. in which bilirubin had decreased significantly after two weeks of therapy, along with the decrease in SGOT and SGPT. [15] Observation of thyroid hormone and bilirubin levels revealed that both remained high despite antiviral therapy and antithyroid drugs. Based on the above findings, it is possible that the persistent jaundice in this patient is related to the patient's thyrotoxicosis. This can be seen from the improvement in the bilirubin level as the patient's thyroid hormone level decreased in Figure 3. This decrease in thyroid hormone may be due to the increased dose of antithyroid drugs. However, this relationship is still controversial and further research is needed to find a correlation between bilirubin levels and thyrotoxicosis in acute hepatitis B patients.

Liver injury caused by thyrotoxicosis is common and is classified as hepatic or cholestatic. Hepatic type liver injury appears to result from relative hypoxia in the perivenular region causing an increase in hepatic oxygen demand that is not compensated by increased blood flow to the liver. The hepatic type of injury is characterized by elevated SGOT and SGPT, whereas the cholestatic type of liver injury is contributed by centrilobular intrahepatocyte cholestasis characterized by elevated serum alkaline phosphatase and GGT. [8]

Methimazole (MMI), a first-line antithyroid drug used in hyperthyroid patients, is known to induce hepatotoxicity, although the mechanism remains unclear. [16] After 10 days of methimazole therapy, patients were evaluated for drug-induced liver injury (DILI) using the Roussel-Uclaf Causality Assessment Method (RUCAM) score. [17] The patient's RUCAM score was 1 (unlikely). Therefore, it was decided to continue the methimazole therapy.

Although rare, some immune-mediated extrahepatic manifestations may occur may occur after acute or chronic hepatitis B infection. Extrahepatic manifestations are not specific to hepatitis B, but some conditions are quite common as extrahepatic manifestations, such as serum sickness-like syndrome, glomerulonephritis, polyarthritis, skin disorders, vascular disorders, and neurological disorders.[18] Yoffe et al. identified the distribution of extrahepatic hepatitis B virus nucleic acids in lymph nodes, spleen, kidney, and thyroid tissues by Southern blot hybridization analysis.[19] Cui et al. reported a patient who developed hyperthyroid Graves' disease triggered by acute hepatitis B in a patient with no history of thyroid disease.[9] Antigen mimicry, epitope modification, T-cell activation, or direct invasion of hepatitis viruses are thought to be the mechanisms that induce hepatitis-associated Graves' disease.[20] This relationship is still controversial as there are not many reports on the association between autoimmune thyroid disease as an extrahepatic manifestation of hepatitis B. However, it is possible that severe acute hepatitis B can trigger a relapse of autoimmune thyroid disease, in this case Graves' disease.

CONCLUSION

Patients with acute hepatitis B who have comorbid hyperthyroidism require more rapid and aggressive therapy to prevent progression of acute hepatitis B. The association of hepatitis B with thyrotoxicosis and persistent jaundice is controversial, as is the extrahepatic manifestation of hepatitis B causing relapse of Graves' hyperthyroidism. Dual antiviral therapy should be considered in severe acute hepatitis to prevent acute liver failure.

REFERENCE

1. Wang CY, Zhao P, Liu WW. Acute liver failure caused by severe acute hepatitis B: a case series from a multi-center investigation. Annals of clinical microbiology and antimicrobials. 2014 Jun; 13:23.
2. H Muljono D. Epidemiology of Hepatitis B and C in Republic of Indonesia. Euroasian journal of hepato-gastroenterology. 2017;7(1):55–9.
3. Rimšelienė G, Nilsen Ø, Kløvstad H, Blystad H, Aavitsland P. Epidemiology of acute and chronic hepatitis B virus infection in Norway, 1992-2009. BMC infectious diseases. 2011 May; 11:153.
4. Hyun Kim B, Ray Kim W. Epidemiology of Hepatitis B Virus Infection in the United States. Clinical liver disease. 2018 Jul;12(1):1–4.
5. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology (Baltimore, Md). 2018 Apr;67(4):1560–99.
6. Yim HJ, Kim JH, Park JY, Yoon EL, Park H, Kwon JH, et al. KASL clinical practice guidelines for management of chronic hepatitis B. Clinical and molecular hepatology. 2019 Jun;25(2):93–159.

7. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016;26(10):1343–421.
8. Malik R, Hodgson H. The relationship between the thyroid gland and the liver. QJM: monthly journal of the Association of Physicians. 2002 Sep;95(9):559–69.
9. Cui W, Deng B, Wang W, Liu P. Graves' hyperthyroidism accompanied with acute hepatitis B virus infection: an extrahepatic manifestation? Virology journal. 2016 May; 13:80.
10. Yim HJ, Kim JH, Park JY, Yoon EL, Park H, Kwon JH, et al. Comparison of clinical practice guidelines for the management of chronic hepatitis B: When to start, when to change, and when to stop. Clinical and molecular hepatology. 2020 Oct;26(4):411–29.
11. Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA, Papatheodoridis G, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. Journal of hepatology. 2017 Aug;67(2):370–98.
12. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HLY, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatology international. 2016 Jan;10(1):1–98.
13. Menzo S, Minosse C, Vincenti D, Vincenzi L, Iacomi F, Zaccaro P, et al. Long-Term Follow-Up of Acute Hepatitis B: New Insights in Its Natural History and Implications for Antiviral Treatment. Genes. 2018 Jun;9(6).
14. Maya P, Augustine P, Mathew PG, Francis J V, Chettupuzha AP, Mukkada RJ, et al. Entecavir + tenofovir combination improved survivial in acute severe hepatitis B. Journal of Clinical and Experimental Hepatology. 2013 Mar 1;3(1): S56.
15. Bockmann JH, Dandri M, Lüth S, Pannicke N, Lohse AW. Combined glucocorticoid and antiviral therapy of hepatitis B virus-related liver failure. World journal of gastroenterology. 2015 Feb;21(7):2214–9.
16. Li X, Yang J, Jin S, Dai Y, Fan Y, Fan X, et al. Mechanistic examination of methimazole-induced hepatotoxicity in patients with Grave's disease: a metabolomic approach. Archives of toxicology. 2020 Jan;94(1):231–44.
17. Teschke R, Zhu Y, Jing J. Herb-induced Liver Injury in Asia and Current Role of RUCAM for Causality Assessment in 11,160 Published Cases. Journal of clinical and translational hepatology. 2020 Jun;8(2):200–14.
18. Kappus MR, Sterling RK. Extrahepatic manifestations of acute hepatitis B virus infection. Gastroenterology & hepatology. 2013 Feb;9(2):123–6.
19. Yoffe B, Burns DK, Bhatt HS, Combes B. Extrahepatic hepatitis B virus DNA sequences in patients with acute hepatitis B infection. Hepatology (Baltimore, Md). 1990 Aug;12(2):187–92.
20. Pastore F, Martocchia A, Stefanelli M, Prunas P, Giordano S, Toussan L, et al. Hepatitis C virus infection and thyroid autoimmune disorders: A model of interactions between the host and the environment. World journal of hepatology. 2016 Jan;8(2):83–91.