CASE REPORT

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Coinfection of typhoid fever and hepatitis B: a case report

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ABSTRACT

Background: Enteric fever (or more commonly known as typhoid fever) is an infectious disease characterized by systemic manifestations such as fever with a step-ladder pattern and abdominal pain. This disease is mainly caused by gram-negative bacteria *Salmonella enterica serovar Typhi (S. typhi)* and other *Salmonella enterica serovars* such as *S. paratyphi A, S. paratyphi B* and *S. paratyphi C*. Although there have been great advances in public health and hygiene in developing countries, enteric fever is still endemic in some of these countries with the case fatality rate of enteric fever reaching 2.49%. This study aims to further discuss the coinfection of typhoid fever with acute hepatitis B.

Case: A 40-year-old female patient who presented with the chief complaint of fever at night, nausea, vomiting and abdominal pain. Widal serological examination showed an increase in antibody titers of S. typhi and *paratyphi*. The results of laboratory tests showed increased levels of SGPT and SGOT. Follow-up immunoserology examination for HBsAg showed a reactive result. During hospitalization, the patient was given antibiotik therapy for typhoid infection and supportive therapy for acute hepatitis B. The occurrence of worsening symptoms, complications and manifestations of hepatitis (such as jaundice) was not observed in this patient.

Conclusion: It can be concluded that the manifestation of viral hepatitis coinfection in enteric fever varies from asymptomatic to fulminant hepatitis. The therapeutic strategy for co-infection of typhoid fever with viral hepatitis follows the therapeutic guidelines for each disease in addition to close monitoring of liver function.

Keywords: acute hepatitis B, coinfection, typhoid fever

INTRODUCTION

Despite major advances in health and hygiene in developing countries, enteric fever (also known as typhoid fever) is still endemic in these countries. Typhoid fever is mainly caused by gram-negative bacteria *Salmonella enterica serovar Typhi (S. typhi*), but can also be caused by *S. paratyphi A, S. paratyphi B (Schotmulleri)* and *S. paratyphi C (Hirschfeldii)* with milder manifestations.[1] Transmission occurs through water or other substances contaminated by human feces. Thus, areas with poor sanitation and difficult access to clean water will increase the risk of transmission.[2] Epidemiological data from the Global Burden of Disease Study in 2017 shows that approximately 14 million people experience enteric fever each year with a mortality rate of 136,000 cases, especially in low to middle income countries. Enteric fever is observed to be more common in South Asian countries (incidence of > 500 per 100,000 population), followed by Southeast Asia, sub-Saharan Africa, Oceania and Latin America.[3]

Enteric fever is more common in children or young adults. Clinical symptoms occur 7-14 days after exposure (within 3-60 days). Patients generally present with a chief complaint of fever characterized by gradual onset of fever and temperature may increase to a plateau value of 39-40^{o} C at the end of the week. This slow increase in temperature is different from the high fever that is intermittent with rigor in malaria.[4] Patients with enteric fever will have predominant abdominal symptoms, such as diarrhea, nausea, vomiting and abdominal tenderness. Abdominal tenderness is diffuse and difficult to localize, but more intense in the right iliac fossa area, thus it resembles abdominal pain observed in appendicitis. Other accompanying clinical symptoms such as headache, cough and malaise may be observed.[5]

Diagnosis is commonly confirmed through clinical examination. Additional investigations may include complete blood counts and blood cultures. The presence of leukocytosis suggests intestinal perforation or other differential diagnosis such as pyogenic infection or leptospirosis. C-reactive protein (CRP) is also generally elevated in enteric fever.[6] Confirmation of the diagnosis is usually done through blood cultures to isolate microorganisms and tests for antimicrobial sensitivity. Serological tests, such as the Widal test or other rapid diagnostic tests, are not sufficient to confirm the acute phase of the disease.[7] Complications due to typhoid fever like encephalopathy, gastrointestinal bleeding, nephritis and hepatitis generally begin to occur in the 2nd week.[8] The case fatality rate in enteric fever reaches 2.49% so that early treatment such as the provision of adequate antimicrobial therapy, hydration and other symptomatic

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treatment will help to shorten the duration of the disease and reduce mortality rates.[9]

Coinfection of typhoid fever with other infectious diseases may occur and often requires more complex and comprehensive treatment to prevent the risk of complications. In several case studies, co-infection of enteric fever with other enteric hepatitis was reported, especially hepatitis A and E.[10] Another study by Nurtjahyani and Handajani isolated Hepatitis B virus from 9 patients with typhoid fever at R. Kusma Hospital. This study aims to report a case of coinfection of typhoid fever with acute hepatitis B at Kasih Ibu Hospital, Kedonganan.[11]

CASE REPORT

A 40-year-old female patient came to the ER of Kasih Ibu Kedonganan Hospital with the chief complaint of fever since 2 days before admitted. The fever was said to commonly appear at night. Body temperature was never measured. The patient also complained of weakness accompanied by nausea and vomiting since 2 days ago. Vomiting was said to happen every time the patient ate and drank. She also complained of epigastric pain that had been felt since last night and penetrated to the back. The patient passed 4 episodes of loose stools since yesterday. Appearance of mucus and blood in stools was denied. Patient had decreased appetite due to nausea. Other symptoms such as coughing, runny nose, shortness of breath, loss of sense of smell and taste, bloody vomit were denied. The patient had taken antacids and vomiting medicine (but the patient did not remember the name of the medicine), however symptoms still did not improve.

A history of other systemic diseases was denied. There was no family member who had the same complaint as the patient (fever, nausea and vomiting, loose stools). The patient was a private employee and unmarried. History of smoking, drinking alcohol and using illegal drugs was denied.

On physical examination, the patient was well conscious. The patient looked moderately ill with blood pressure of 120/70 mmHg, pulse of 88x/minute regular, respiratory rate of 20x/minute, temperature of 37.6º C and oxygen saturation 98% of room air. Eye examination showed non-anemic eyes but icteric sclera and minimal sunken eyes. The lip mucosa was also dry. On cardiac examination, JVP PR was + 0 cmH_2O, non-visible and non-palpable ictus cordis, right heart border on right parasternal line and left border on anterior axillary IC IV with single I and II heart sound on auscultation, regular beat without murmur. On lung examination, inspection showed symmetrical static and dynamic chest movement, negative focal fremitus, resonant percussion in both lung fields, vesicular breath sounds and no additional breath sounds were found. On abdominal examination, there was no visible distention or collateral veins, increased bowel sounds of 10x/minute, meteorism (+), epigastric tenderness, liver and spleen were not palpable, and no shifting dullness was found. The patient's extremities were warm without pitting edema.

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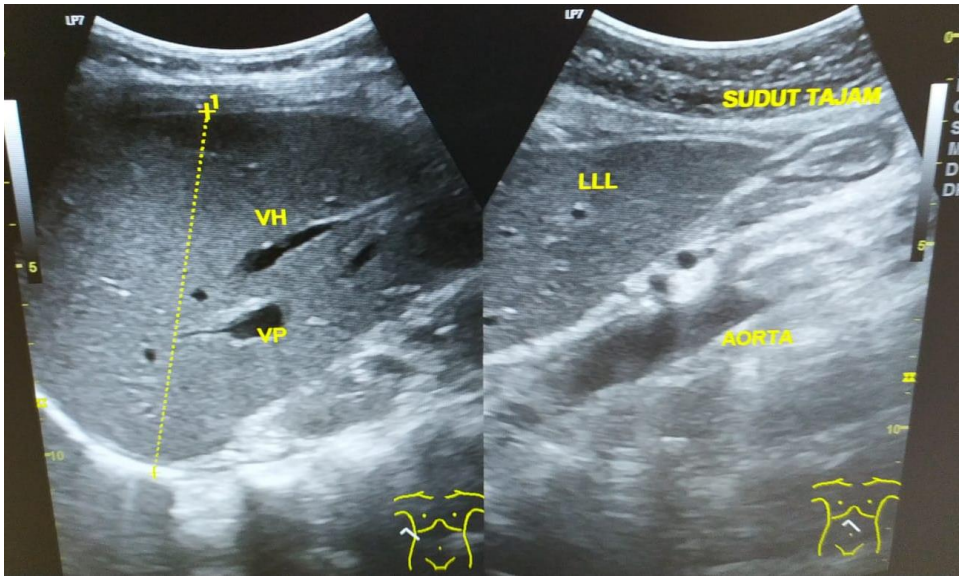

Figure 1. Abdominal ultrasonography of the patient

The patient was planned to undergo an initial laboratory examination, which showed increased monocyte levels of 1.05 x 10^3/µL, while the total leukocyte, platelet and hemoglobin values were within normal limits. On clinical chemistry examination, there was an increase in liver function tests with ALT of 689 U/L and AST of 798 U/L. Electrolyte examination was within normal limits. Widal serological examination showed the titre of S. typhi O was 1/160, S. paratyphi of OC 1/320 and S. typhi H of 1/160. The SARS-CoV-2 antigen test was negative. Thorax AP examination on September 13, 2021, showed normal heart size, CTR of 55%, sharp left and right pleural sinuses, no consolidation in the lung area. The patient refused to undergo further

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investigations such as anti-HAV IgM, HBsAg, HBeAg and anti-HCV.

According to the clinical symptoms, physical examination and initial supporting examination, the patient was diagnosed with typhoid fever accompanied by mild to moderate dehydration caused by low intake, transaminitis et causa viral suspicion with a differential diagnosis of typhoid related. The patient was planned to do fluid therapy with IVFD RL 300 cc loading followed by intravenous fluid administration 30 drops per minute, injection of pantoprazole 40 mg every 24 hours, injection of paracetamol 500 mg every 8 hours, injection of ondansetron 8 mg every 12 hours, injection of levofloxacin 500 mg (initial skin test was done) and the patient was also advised to consume a soft diet.

During hospitalization on the 1st and 2nd days, the patient still complained of weakness, nausea and vomiting and heartburn, however the fever had decreased. On the last day of hospitalization (3rd day) the patient said that the weakness had decreased, nausea and vomiting were no longer felt, heartburn had disappeared, body temperature was normal and vital signs were stable. The patient was then allowed to be discharged and the intravenous administration of drugs was substituted with oral administration of drugs, which were pantoprazole 40 mg every 24 hours, ondansetron 4 mg every 12 hours and levofloxacine 500 mg every 24 hours.

Within 5 days after the patient was discharged, she was scheduled for a follow up consultation to the Internal Medicine Polyclinic. Upon follow up consultation, the patient said that the condition had improved and there were no current complaints. Physical examination showed stable vital signs and examination of the liver and spleen were within normal limits. The result of laboratory investigations revealed reactive HBsAg immunoserology. On abdominal ultrasound, there was no abnormality found in the liver and splenomegaly was not observed. The patient was diagnosed with acute hepatitis B and was given supportive oral therapy with Curcuma 2 tablets every 8 hours. Patient was also planned for repeated liver function tests, HBeAg and HBV DNA after 3 months.

DISCUSSION

Enteric fever (or more commonly known as typhoid fever) is a bacterial infection caused by gram-negative bacteria Salmonella enterica serovar typhi (S. Typhi) or Salmonella enterica serovar Paratyphi (S. Paratyphi) A, B or C. Enteric fever still causes significant morbidity and mortality worldwide, with current estimates of 13.5 – 26.9 million new cases of S. typhi and S. paratyphi A each year.[3] In endemic areas, these infections are caused by food or drinks contaminated with pathogens. Thus, the risk factors of being infected with typhoid fever include drinking water that is not boiled or the result of consuming food that is not prepared properly.[12] From the anamnesis result, the patient recalled that she always consumed packaged or boiled drinks, consumed food that was cooked by herself or bought food from places she regularly visited. Although direct contact with pathogenic organisms is the main source of transmission of enteric fever, the study by Harris et al. showed that in 80% cases of enteric fever, the source of infection is not clearly known.[13]

Enteric fever is associated with a wide spectrum of clinical symptoms, ranging from asymptomatic to symptoms such as fever, weakness, headache, nausea and vomiting, abdominal pain, bloating, anorexia and diarrhea (in 66% of cases).[14] The incubation period of typhoid fever ranges from 7 to 14 days (with a range of 3 to 60 days).[15] The pattern of fever in Salmonella infection follows a "step ladder" pattern, in which the fever increases slowly in the late afternoon until late at night and will decrease during the day. The fever will get higher (reaching 39-40o Celsius) and persist in the second week. Patients will experience symptoms of enterocolitis approximately 12 to 48 hours after inoculation. These symptoms of enterocolitis last for several days and are self-limiting so any medical intervention is not necessary.[16] In this patient, fever occurred 2 days before admission, usually appeared at night, but she had never measured the body temperature during fever. Fever was also accompanied by weakness in all body areas. The fever lasted for 4 days in this patient. According to a research conducted by Mustofa et al., enteric fever generally occurs for 6-8 days.[17] Symptoms of enterocolitis observed in patients include 4 episodes of loose stools accompanied by nausea, vomiting and decreased appetite.

The physical examination in patients with enteric fever is non-specific. In the first week, the patient may complain of fever accompanied by decreased pulse. In the second week, the dominant physical examination result was abdominal distension. Red spots (rose-colored erythematous macular lesions) on the abdomen may indicate infection of the gram-negative bacteria *Salmonella enterica*, but these symptoms are rarely observed. Patients may appear dehydrated such as paleness, sunked eyes, dry mucous membranes and lethargy especially if persistent nausea and vomiting or profuse diarrhea are present.[18] Some patients may appear icteric with yellowish skin and sclera, pale colored stools, dark colored urine and enlargement of the reticuloendothelial system if any pathology of the biliary system is observed. If the diagnosis of enteric fever is missed until the 3rd week, complications may have occured causing the patient to look toxic, anorexic, weight loss and peritonitis are observed due to intestinal perforation. Neurological complications such as delirium, psychosis, insomnia, confusion and apathy may also occur.[5,19] The patient in this case report presented with a less specific physical examination. The patient had fever with temperature of 37.6^{o} C without bradycardia. The patient appeared to be mildly dehydrated which was seen through minimal sunken eye and dry mucosal lips. Abnormalities on abdominal examination presented in the form of tenderness of the epigastrium area, however liver and spleen are not palpable. Due to the widespread use of antibiotics nowadays, the classic symptoms of typhoid fever such as slow onset fever with a “step-ladder” pattern and systemic toxicity are rarely observed.[2]

Diagnosis confirmation of typhoid fever can be done through various supporting examinations such as peripheral blood examination, serological examination and culture examination, which is the gold standard to

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establish the diagnosis of typhoid fever. Isolation of S. typhi or S. paratyphi from blood is the gold standard to confirm typhoid infection.[2] Widal test is a serological test to detect agglutinating antibodies against O and H antigens. This test is widely used because it is easy and cheaper, but the sensitivity of this test is still low and operator dependent. Accurate interpretation of antibody tests requires repeated examinations within 10-14 days to obtain an adequate rise in antibody titers in order to diagnose Salmonella infection. Typhoid rapid antibody test (Typhidot®) detects IgM and IgG antibodies within 2 minutes thus antibiotics can be started as early as possible.[20,21]

The results of the Widal serological examination in this patient showed antibody titre of S. typhi O 1/160, S. paratyphi OC 1/320 and S. typhi H 1/160. The interpretation of the Widal serological examination is seen through the levels of both O and H agglutinins.[20] The Widal serological test requires two specimen collections, one in the acute period and another specimen from the convalescent period with an interval of 10-14 days. The diagnosis is confirmed with an increase in antibody titers of more than or equal to 4 times the acute titer.[22] High agglutinin titer in a single specimen can not distinguish whether the infection is a new or old infection. Based on the instructions from the kit, the positive result is met if the O antibody titer is > 1/160 and H antibody titer is > 1/160. In endemic areas such as Indonesia, where Salmonella typhi infection is more common, it is better to set a positive result at a larger dilution (>1/160) to prevent overdiagnosis of Salmonella typhi infection.[20,23]

In endemic areas, around 60 to 90% of cases of typhoid fever can be treated with oral antibiotics. Hospitalization is only necessary in complicated cases. Currently, the fluoroquinolone (ciprofloxacin and ofloxacin) is the antibiotics of choice for typhoid fever. The fluoroquinolone has a relatively short duration of therapy (3-7 days) and has cure rate of 96%.[2] The cephalosporin antibiotics (such as ceftriaxone and cefixime) and azithromycin are good alternatives for Salmonella bacteria that are not sensitive to fluoroquinolones.[24,25] In this case, the antibiotic therapy given to the patient was levofloxacine at a dose of 500 mg every 24 hours. After administration of antibiotics, improvement of symptoms was observed on the first day until the third day. In addition to antibiotic therapy, nutrition and fluid intake are also important for typhoid fever patients. Patients are also advised to rest for 7 days after fever subsides.

Coinfection of enteric fever with other infectious diseases such as malaria, tuberculosis, hepatitis and others may occur.[10,26,27] Coinfection of enteric fever requires complex management strategies and may worsen the patient's prognosis. Hepatitis is more often described as a manifestation of typhoid fever rather than a complication and generally occurs in the 2nd to 3rd week in 60-100% of cases. The pathogenesis of hepatitis in typhoid fever is multifactorial, including bacterial endotoxin and host immune reactions accompanied by hyperplasia of the reticuloendothelial system, portal gap infiltration and decreased microcirculation leading to necrosis. The manifestations of patients with typhoid hepatitis are generally divided into two forms, (1) patients with evidence of liver enlargement or abnormal liver function tests and (2) patients with dominant hepatic manifestations. Jaundice is a clinical manifestation that is rarely found in cases of typhoid hepatitis, thus in patients who present with jaundice, other diagnoses such as viral hepatitis need to be considered due to similar enteric transmission of some hepatitis viruses.[28]

Clinically, it is difficult to differentiate salmonella hepatitis from viral hepatitis. However, from biochemical examination, aminotransferase levels are found to be more elevated in viral hepatitis compared to salmonella hepatitis. The calculation of the ALT/LDH ratio is a good discriminator to differentiate between the two diagnoses, whereas a ratio < 4 indicates salmonella hepatitis while a ratio of > 4 indicates viral hepatitis. Immune responses evoked by viruses and bacteria are different, but an overlap in the innate or non-specific immune responses is common. Normally, in the infection process there will be a balanced reaction between pro- and anti-inflammatory production, however in synergistic infections there will be a decrease in pathogen elimination process and amplification of the inflammatory process. Proteases produced by bacterial infection also have the potential to increase the levels of glycoproteins which serve as the medium for viral replication thus increasing viral loads.[29]

In several case studies that reported co-infection of typhoid fever with hepatitis A, the diagnosis of viral hepatitis was confirmed thorugh laboratory examinaton of IgM antibody to HAV or by blood culture. Patients with typhoid fever and hepatitis A coinfection have varied manifestations, ranging from hepatomegaly with elevated liver function tests, fulminant hepatitis with elevated liver function tests, prolonged coagulation studies and liver abscess.(28) Case study by Suda et al. reported coinfection of *Salmonella typhi* with hepatitis E virus that caused biphasic acute hepatitis. Salmonella typhi coinfection with HAV and HEV is common due to the similar sources of infection and transmission processes. Salmonella typhi coinfection with HBV is rarely reported.[29] Experimental study by Nurtjahyani et al. conducted in Tuban, Indonesia found positive PCR results for HBV1 and HBV2 viruses in 9 patients with typhoid fever who were treated at R. Kusma Hospital.(11) Hepatitis B infection is a life-threatening liver infections with the main transmission through body fluids such as blood, semen and vaginal secretions. Clinical manifestations of HBV infection may vary, in the acute phase, patients generally experience subclinical or anicteric hepatitis, icteric hepatitis or fulminant hepatitis (very rare). In the chronic phase, liver damage such as cirrhosis or hepatocellular carcinoma begins to occur.[30]

The patient in this case report was diagnosed with hepatitis B from immunoserological test for HBsAg which showed a reactive result. Acute hepatitis B can be confirmed by further advanced testing such as IgM anti-HBc. In this patient, no symptoms of jaundice, enlargement of the liver and spleen were observed. After 4 days of treatment, the patient remained asymptomatic and did not show any clinical worsening of hepatitis. The weakness, nausea and vomiting and abdominal tenderness observed in this patient may be due to HBV infection, but this possibility was ruled out considering that these symptoms improved after administration of specific

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antibiotics for typhoid fever. Acute hepatitis B infection is self-limiting in 95% of adult cases. Management of acute HBV infection is only supportive, however patients who present with bilirubin levels of > 10 mg/dl, INR of > 1.6 and hepatic encephalopathy require antiviral therapy.[30] The therapy given to the patient in this case report is supportive with Curcuma supplementation which act as hepatoprotectant taken 2 tablets every 8 hours.

CONCLUSION

This case report is the first study to report typhoid fever coinfection with HBV. In patients diagnosed with typhoid fever accompanied by increased liver function, it is necessary to take complete history, physical examination and additional investigations (anti-HAV IgM, HBsAg, anti-HBS, anti-HCV, anti-HEV and calculation of the ALT/LDH ratio) to determine the presence of viral hepatitis coinfection. Manifestations of viral hepatitis may vary from asymptomatic to fulminant hepatitis. The therapeutic strategy for coinfection of typhoid fever and viral hepatitis follows the guidelines for each disease in addition to close monitoring of liver function and symptoms of fulminant hepatitis or liver failure.

LIMITATIONS

This study still has limitation as longer term of follow up is necessary. Further research is expected to have longer follow up periods in order to observe any repeated episodes or complications that occur due to the coinfection.

CONFLICT OF INTEREST

The research was carried out independently without involving the interests of other parties in this research.

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