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A Patient with Typhoid Hepatitis

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ABSTRACT

Typhoid hepatitis is typhoid fever accompanied by symptoms of jaundice, hepatomegaly and abnormal liver function tests. The incidence varies between 0.4 -26% of typhoid fever patients. We report a case of a 34-year-old male, presented with fever, epistaxis, gastrointestinal symptoms, thrombocytopenia and elevated AST/ALT, thus the patient was first diagnosed as dengue hemorrhagic fever grade II. On day 9th the signs and symptoms were persisted, Ig M and Ig G Dengue was negative. Then we evaluated the virus marker for hepatitis and blood culture. The results were negative for HBsAg, anti HCV and Ig M anti HAV, but Salmonella typhi detected on blood culture. The patient was treated with ceftriaxone 1000mg bid iv and get better then discharged from hospital.

Keywords: *Typhoid hepatitis, salmonella hepatitis, typhoid fever, demam enterik, Salmonella typhi*

ABSTRAK

Hepatitis tifosa adalah demam tifoid yang disertai gejala-gejala ikterus, hepatomegaly dan kelainan tes fungsi hati. Insidennya bervariasi antara 0,4-26% dari pasien demam tifoid. Kami sajikan kasus seorang laki-laki, usia 34 tahun, datang dengan demam, epistaksis, gejala gastrointestinal, trombositopenia dan peningkatan AST/ALT, sehingga pada awalnya pasien didiagnosis dengan demam berdarah dengue stadium II. Pada hari ke-9, keluhan dan gejala menetap, dengan Ig M dan Ig M Dengue negatif. Kami periksa penanda virus hepatitis dan kultur darah. HBsAg, anti HCV dan Ig M anti HAV negatif, tetapi didapatkan pertumbuhan kuman Salmonella typhi pada kultur darah. Pasien diterapi dengan seftriakson iv tiap 12 jam dan sembuh serta dipulangkan.

Kata kunci: *epatitis tifosa, salmonella hepatitis, demam tifoid, enteric fever, Salmonella typhi*

INTRODUCTION

Typhoid fever is a common infectious disease in developing countries, associated with high morbidity and mortality, thus becoming a global health problem. In 2000, it was estimated that more than 2.16 million cases of typhoid fever worldwide, resulted in 216,000 deaths, and more than 90% of these morbidity and mortality occurred in Asia [1,2].

In Indonesia, the incidence of typhoid fever averages 900,000 cases per year with more than 20,000 deaths. The largest population is aged 3-19 years which constitutes 91% of cases of typhoid fever and positive blood culture for typhoid fever is 1026 per 100,000 per year [3]. In Indonesia, there is no data on the incidence of typhoid hepatitis.

The clinical features of typhoid fever vary widely

with increasing atypical symptoms. Typhoid hepatitis is typhoid fever accompanied by symptoms of jaundice, hepatomegaly and abnormal liver function tests.[4] It is one of the atypical clinical features of typhoid fever and should be considered in patients with fever and features of liver involvement, especially in endemic areas, because it can mimic other diseases that occur in this area, such as acute viral hepatitis, amoebic hepatitis or malaria.[5] We report a case of a patient with typhoid hepatitis.

CASE ILLUSTRATION

A 34-year-old male, Surabaya, Javanese, single, private employee, from Surabaya, admitted to infectious ward of Dr. Soetomo General Hospital with chief complaint of fever. The patient had fever since 5 days before admission. The temperature was immediately high and went normal if taking paracetamol. The patient also complains of nausea, vomiting, and diarrhea. The diarrhea was about 5 times per day, the amount of ± 1 tablespoon each, yellow color, no blood and mucus. The stomach feels bloated, but no abdominal pain. No changed on urinate. The patient had nosebleed once, but no gums bleeding and red spots on body parts. The history of flooding, traveling to eastern Indonesia, having dengue fever in the home or work environment is denied. Patients often eat at the street food stall.

From physical examination found that the general condition was weak, GCS 456, blood pressure 130/80, pulse rate 90x/minute, regular and adequate pulse, respiratory rate 20x/minute, axillary temperature 39.8°C. On head and neck examination, there were no anemia, jaundice, cyanosis, conjunctival suffusion, typhoid tongue, enlarged lymph nodes and increased jugular venous pressure. On examination of the heart, there was no abnormality, there was no lung abnormality. Abdominal examination shows distension, increased bowel sounds and meteorism. The liver and spleen were not palpable, there was no metallic sound, shifting dullness. In the superior and inferior extremities, there is no ptekie, edema.

Laboratory examination on addimision day were haemoglobin (hb) 11.2g/dL, hematocrit (hct) 33%, leukocytes 4,400/µL, platelets 77,000/µL, granulocytes 78.5%, partial thromboplastin time (PTT) 11.7 seconds/control 10.9 seconds, activated-partial thromboplastin time (aPTT) 25.2sec/control 26secs, random blood glucose (RBG) 96mg/dL, aspartate transaminase (AST) 454U/L, alanine transaminase (ALT) 222U/L, albumin 3,4g/dL, blood urea nitrogen (BUN) 16mg/dL, creatinine serum(CrS)1.25mg/dL, sodium 127mmol/L, potassium 3,2mmol/L, chloride 94mmol/L, calcium 8.3mg/dL, widal slide: typhi O (-), typhi H 1/320, paratyphi A (-), paratyphi B (-). Chest x-ray was normal.

Based on anamnesis, physical, laboratory and radiology examination, we diagnosed the patient as dengue hemorrhagic fever (DHF) grade II + Acute Kidney Injury (AKI) dd Acute on Chronic Kidney Disease (ACKD) + elevated transaminase pro evaluation + Hypovolemic hypotonic hyponatremia + Hypokalemia. Planning for this patient management were high-calorie high protein diet 2000 kcal/day with extra fruit, vegetable, broth, Asering Ringer infusion 1500mL/24h, ranitidine 50 mg/24h iv, paracetamol 500mg+n-acethyl sistein 200mg 1tab/8h prn, KSR 600mg/day, serial CBC, serum electrolyte, AST & ALT, BUN &CrS, Ig M & Ig G Anti Dengue, HBsAg, Anti HCV, IgM anti HAV.

On 4th day of admission, the patient still had fever (day 9th), diarrhea, nausea, vomiting and bloating, but there are no epistaxis and gum bleeding. The patient has no history of drugs user, free sex, tattoo, typhoid fever before. From physical examination we found that general condition was still weak, GCS 456, blood pressure 120/70, pulse rate 80x/minute, regular and adequate, respiratory rate 20x/minute, axillary temperature 38.8°C, the palpebral conjungtiva looked jaundice, the abdomen was still distended, increased bowel sounds and meteorism. The laboratory finding: hb 11,1g/dL, hematocrit 31.6%, leukocytes 4400/µL, platelets 43,300/µL, granulocytes 71.9%, AST 656U/L, ALT 288U/L, BUN 13mg/dL, CrS 0.62mg/dL, sodium 129mmol/L, potassium 3,5mmol/L, chloride 91mmol/L, Ig M & Ig G anti Dengue, HbsAg, Anti HCV, Ig M anti HAV were all negative. Based on that data we dignosed the patient as suspected typhoid hepatitis + Acute Kidney Injury (AKI) improved + Euvolumic hyponatremia + Corrected hypokalemia, with diagnostic and therapeutic planning: CBC &peripheral blood smear, direct bilirubin, total bilirubin, AST & ALT, stool analysist, Ig M Salmonella, stool and blood culture, plain abdominal radiograph, HIV 3 methods serology test, abdominal ultrasonography, bed rest, diet high calories high protein 2000 kcal/day low fiber, NaCl 0.9% 1500mL/24h iv, ceftriaxone 1g/12h iv, ranitidine 50mg/24h iv, paracetamol 500mg+n-acethyl sistein 200mg 1tab/8h prn.

On day 6th the signs and symptoms are getting better and the laboratory results are Hb 11.7g/dL, leukocytes

5600/µL, platelets 56,700/µL, AST 353U/L, ALT 269U/L, bilirubin direct 1.11mg/dL, bilirubin total 1.73mg/dL, LDH 765U/L, ratio ALT/LDH 0.35, Ig M Salmonella positive, HIV 3 methods serology test negative. We diagnosed the patient as typhoid hepatitis + Acute Kidney Injury + Euvolumic hyponatremia + post hypokalemia.All theraphies were continued.

On day 8th the patient was better, with laboratory results were sodium 129mmol/L, potassium 3,5mmol/L, chloride 91mmol/L, blood culture: Salmonella typhisensitive toaztreonam, amoxicillin-clavulanic acid, ampicillin, ampicillin-sulbactam, pepiracillintazobactam, ceftazidime, cefotaxime, cefoperazone-sulbactam, cotrimoxasol, tetracyclines, chloramphenicol, fosfomycin, imipenem, meropenem; resistant to amikacin, tobramycin, gentamicin, cefazolin. The diagnosis and treatment were persist. The patient was getting better clinically and laboratory and discharged after 10 days of hospitalization.

DISCUSSION

Typhoid fever is caused by *S typhi* or *S paratyphi*, spread through the ingestion infectious doses of bacteria from contaminated water or food which is affected by poor sanitation.[6] After passing the gastric, the bacteria reach the small intestine and invade the intestinal epithelium through M cells contained in Peyer's plaque which are then phagocytes by macrophages, then through the mesenteric lymph ducts and thoracic ducts enter the systemic blood circulation (bacteremia I) and reach the reticuloendothelial cells in the liver, spleen and bone marrow. *S.typhi* or *S.paratyphi* replicates in phagocytes, which are then recognized by the human immune system, thereby stimulating the release of proinflammatory cytokines, antibodies and the release of endotoxins. Bacteria and endotoxins then enter the gallbladder and systemic blood circulation again (bacteremia II) which causes symptoms of typhoid fever.[7]

The clinical symptoms of typhoid fever are not specific, include fever (100%), headache (80%), chills (35-45%), cough (30%), sweating (20-25%), myalgia (20%), malaise (10%),arthralgia (2-4%). Common gastrointestinal symptoms include anorexia 55%, abdominal pain (30-40%), nausea (18-24%), vomiting (18%), diarrhea (22-28%), constipation (13-16%). On clinical examination, can be found typhoid tongue (51-56%), relative epistaxis and bradycardia (<50%), rose spots (30%), abdominal tenderness (4-5%), hepatosplenomegaly (3-5%).[7,10]

The definitive diagnosis of typhoid fever requires isolation of *S.typhi* or *S.paratyphi* from blood, bone marrow, other sterile sites, feces or gastrointestinal secretions. Blood culture sensitivity is only 40-80%, probably due to antibiotic use and only small amounts of *S.typhi* are present in the blood (usually <15 organisms / mL). Bone marrow culture has a sensitivity of 55-90%, and unlike blood cultures, the results can remain positive after 5 days of antibiotic use [7].

This patient had 10 days of fever, nausea, vomiting, diarrhea, relative bradycardia, hepatomegaly with positive S.typhi blood culture results so that it was confirmed typhoid fever.

Hematogenous spreading of organisms or toxins from salmonella can cause systemic involvement that affects all major organs [8]. Liver involvement in typhoid fever was first reported by William Osler in 1899 [8,9]. The pathogenesis of typhoid hepatitis is not completely clear, it is thought to be multifactorial, including direct hepatic damage by invading bacteria, endotoxin, or inflammatory processes and or secondary damage due to host immune mechanisms.[5,11]

In typhoid hepatitis, the frequent clinical features are hepatomegaly and an increase in transaminases that occur in 23-60% of typhoid fever patients [9,11]. Diagnosis of typhoid hepatitis is a probable case or confirmed case of typhoid fever with meets 3 or more criterias: (a) hepatomegaly, (b) jaundice, (c) biochemical abnormalities, or (d) liver histopathology .[8,12]

This patient was confirmed typhoid fever, as well as jaundice, hepatomegaly, increased bilirubin, AST and ALT that met the diagnostic criteria for typhoid hepatitis.

The clinical symptoms of typhoid hepatitis are difficult to distinguish from other causes of fever and jaundice, especially in the first 5 days of the disease course. In most areas, acute viral hepatitis and non-infectious causes of hepatitis (eg, drug-induced liver injury, toxic or alcoholic hepatitis), are the main differential diagnosis of typhoid hepatitis. In developing countries, typhoid hepatitis is similar to other infectious diseases such as leptospirosis, malaria, amoebic liver abscess, dengue fever.[5]

The patient was initially diagnosed with DHF grade II, but the fever persisted on 9th days, with intestinal complaints (nausea, vomiting, diarrhea, bloating), relative bradycardia, jaundice, positive Salmonella IgM, positive *S typhi* blood culture, elevated serum transaminase, increased bilirubin, abdominal ultrasound: non-specific hepatomegaly, negative dengue Ig M,

Table 1. Recommended Antibiotic Treatment for Typhoid Fever[6,7,14].

Susceptibility	Optimal Treatment			Alternative Effective Treatment		
	Antibiotics	Dose mg/kg	Course Day	Antibiotics	Dose mg/kg	Course Day
			Uncomplicated disease			
Sensitive	Fluoroquinolone	15	5-7	Chloramphenicol	50-75	14-21
				Amoxycillin	75-100	14
				TMP-SMX	8-40	14
MDR	Fluoroquinolone	15	7-14	Azithromycin	8-10	7
	Cefixime	15-20	7-14	Cefixime	15-20	7-14
Quinolone	Azithromycin	8-10	7	Cefixime	20	7-14
Resistance	Ceftriaxone	75	10-14			
Severe disease						
Sensitive	Ciprofloxacin orOfloxacin	15	10-14	Chloramphenicol	100	14-21
				Amoxycillin	100	14
				TMP-SMX	8-40	14
MDR	Fluoroquinolone	15	10-14	Ceftriaxone	75	10-14
	Cefixime	15-20	10-14	Cefotaxime	80	10-14
Quinolone	Ceftriaxone	75	10-14	Fluoroquinolone	20	7-14
resistance	Cefotaxime	80	10-14			
	Azithromycin	8-10	10-14			

MDR: multi drugs resistant; TMP-SMX: trimethoprim-sulfametoxazole

negative anti-HAV IgM, negative HBsAg, negative HBC negative, 3 methods HIV serology negative, so then diagnosed as typhoid hepatitis.

Severe typhoid fever (occurs 10-15%) is influenced by host factors (immunosuppression, therapy that reduces stomach acid, previous exposure, vaccination) and germ virulence, the choice of antibiotic therapy. Complications can include gastrointestinal bleeding (10-20%), intestinal perforation (1-3%), neurological manifestations (2-40%) including meningitis, Guillain-Barré syndrome, neuritis and neuropsychiatric symptoms.[7]

The general principles of management of typhoid hepatitis are the same as typhoid fever, which are rapid diagnosis and proper administration of antibiotics, adequate rest, hydration and correction of electrolyte imbalance, administration of anti-pyretics if needed, adequate diet (soft diet, easy to digest unless there is abdominal distension or ileus) , hand washing and limiting contact with susceptible individuals during acute phase infection, follow-up and monitoring of complications and recurrences[6]. The choice of antibiotics is based on local resistance patterns and antibiotic sensitivity. [13]

The patient had no symptoms and signs of severe typhoid fever and received bed rest therapy, high-calorie diet high protein 1800 kcal/day low fiber, 0.9% 14tpm NaCl infusion, 2x1g iv ceftriaxone injection for 7 days, ranitidine injection 1x50 mg iv . Antibiotic therapy was continued with cefixime 2x100mg po.

The prognosis for typhoid hepatitis is generally good because it responds well to antibiotics. However, the mortality can reach 20% in conditions of malnutrition, anemia and/or late receiving appropriate and adequate therapy. Diagnosis and therapy with appropriate antimicrobial agents are very important to reduce mortality.[15]

The patient improved clinically and laboratory after receiving antibiotic therapy and was discharged after 10 days of treatment.

Typhous hepatitis is very difficult to distinguish from acute viral hepatitis, amoebic hepatitis, malaria, dengue hemorrhagic fever or leptospira. Typhous hepatitis must always be considered in patients with fever and impaired hepatic function, especially in endemic areas, because prompt diagnosis and appropriate antibiotic therapy will reduce mortality.

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