Prolonged Cholestatic as a Typical Manifestation of Hepatitis A Infection: Diagnosis and Management

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ABSTRACT

Hepatitis A virus (HAV), a positive-strand RNA virus, is stable at moderate temperature and low pH level. These characteristics allow the virus to survive in the environment and be transmitted through fecal-oral route.

Twenty-year-old male came with jaundice and itchy skin since one month before admission. He was diagnosed as hepatitis A cholestasis type according to his history taking, physical examination, and laboratory result. Blood test showed elevated total bilirubin 27.4 g/dL, direct bilirubin 21.2 g/dL, indirect bilirubin 6.2 g/dL, alanin aminotransferase (ALT) 95 U/L, aspartate transaminase (AST) 134 U/L, alkaline phosphatase (ALP) 221 U/L, and gamma-glutamyltransferase (gGT) 17 U/L. His ultrasound results showed mild, non-specific hepatomegaly without common bile duct dilatation. The patient got symptomatic therapy with ursodeoxycholic acid (UDCA) 300 mg twice daily for his itchy skin and steroid therapy 0.5-1 mg/kg per day on the tenth day. He did not vomit or feel nausea anymore. After five days of steroid therapy, his total bilirubin level became 10.83 g/dL. He was discharged home with steroid therapy and steroid was tapered off during follow-up in the clinic.

Prolonged cholestasis is one of atypical manifestation of hepatitis A which is rarely found. Cholestasis increases morbidity and prolongs hospitalization. Steroid therapy decreased bilirubin level and gave clinical improvement to the patient.

Keywords: *hepatitis A, prolonged cholestasis, steroid therapy*

ABSTRAK

Hepatitis A merupakan virus RNA yang mempunyai sifat stabil dalam temperatur sedang dan pH rendah. Karakteristik ini memungkinkan virus mampu bertahan hidup dalam lingkungan dan ditransmisikan melalui oro-fekal.

Seorang laki-laki usia 20 tahun datang dengan keluhan tubuh kuning dan gatal sejak lima minggu sebelum masuk rumah sakit. Dari hasil anamnesis, pemeriksaan fisik dan laboratorium, pasien didiagnosa hepatitis A tipe kolestatik. Pada hasil pemeriksaan laboratorium ditemukan peningkatan bilirubin total 27,4 g/dL, bilirubin direk 21,2 g/dL dan indirek 6,2 g/dL, ALT 95 U/L, AST 134 U/L, ALP 221 U/L, dan gamma GT 17 U/L. Pada pemeriksaan ultrasonografi menunjukkan gambaran hepatomegali ringan non spesifik tanpa pelebaran duktus kanalikuli maupun pelebaran duktus bilier komunis. Pasien mendapatkan terapi simtomatik asam ursdeoksikolik 300 mg dua kali sehari untuk mengatasi gatal dan diberi steroid 0.5-1 mg/kg berat badan. Setelah 5 hari pemberian kadar bilirubin total menurun menjadi 10,83 g/dL, keluhan mual dan muntah tidak ditemukan lagi. Pasien dipulangkan dengan terapi steroid dan dilakukan penurunan dosis steroid secara bertahap selama masa rawat jalan.

Kolestasis hepatitis A merupakan salah satu manifestasi atipikal yang jarang ditemukan. Kolestasis meningkatkan morbiditas dan masa rawat di rumah sakit. Pemberian kortikosteroid dapat menurunkan bilirubin, mempercepat penyembuhan, dan perbaikan gejala klinis pada pasien.

Kata kunci: *hepatitis A, kolestasis, terapi steroid*

INTRODUCTION

Hepatitis A virus (HAV), a positive-strand RNA virus, is stable at moderate temperature and low pH.These characteristics allow the virus to survive in the environment and be transmitted through fecal-oral route. HAV is still an important etiology of acute viral hepatitis worldwide. Poor sanitation, contaminated food, and poor personal hygiene contributes to the transmission.[1] This viral can be inactivated by boiling for one minute, use of formaldehyde, chlorine and ultraviolet radiation. Clinical manifestation of hepatitis A depend on the age of the host; less than 30% of infected young children showed symptomatic hepatitis, while about 80% of infected adults manifests as severe acute hepatitis.with remarkably elevated serum amino transferase.[2]

Clinical spectrums of HAV infection range from asymptomatic infection to fulminant hepatitis. Its replication is limited to the liver, but the virus is present in the liver, bile, stools, and blood during the late incubation period and acute pre-icteric phase of illness. Despite persistence of virus in the liver, viral shedding in feces, viremia, and infectivity diminish rapidly once jaundice becomes apparent. Typical manifestation of HAV infection starts with incubation period for about 2-7 week, including fever, malaise, nausea, vomiting, abdominal discomfort, dark urine and jaundice. Jaundice could be seen in infected adult with concentration of bilirubin below 10 mg/dL, and begin to recover in two weeks.[3]

Clinical illness and laboratory abnormalities recover within two months from the onset of disease. No evidence of chronic infection seen in HAV infection but some cases continue to prolonged cholestatic form or relapsing disease lasting up to six months. There have been reports on atypical manifestation of HAV, including prolonged cholestasis, acute kidney injury, recurrent hepatitis, hemolytic anemia, or other extra-hepatic manifestation.

In this case report we will discuss about diagnosis and management of patient with prolonged cholestatis HAV. From the literature,itis reported that this manifestation occurs rare only at a rate of 0.4-0.8%.[3] Effective and efficient treatment is needed in order to reduce morbidity, but no differences in mortality.

CASE ILLUSTRATION

Twenty-year-old male came with jaundice and itchy skin since one month before admission. He had nausea and vomit followed with fever and fatigue since five weeks ago. He felt fever all day long, gradually increased every day, but no chills. Then, he realized that he had jaundice and dark urine. He did not have either pale or black stool and felt itchy skin. He also complained of continuous, dull right upper abdominal pain. The laboratory result diagnose as hepatitis. After several follow up in the clinic, he felt less nausea and vomit and no fever. But he still complained of jaundice and itchy skin. His blood test showed elevated bilirubin level.

On physical examination, patient had normal vital signs, icteric sclera, but no anemic conjunctiva. There was no spider nevi. Heart and lung sounds were clear. He had hepatomegaly, one finger below costal arch with blunt edge, elastic in consistency, smooth surface and tenderness. There was no ascites and splenomegaly. He did not have clubbing finger and leg swelling. His extremity was warm.

Laboratory result showed hemoglobin 16.5 g/dL, leukocytes 7,800/µL and platelet 254,000/µL, total bilirubin 8.8 g/dL, direct bilirubin 7.1 g/dL, indirect bilirubin 1.5 g/dL, alanin-aminotransferase (ALT) 64 U/L, and aspartate transaminase (AST) 180 U/L. Six days later because of his worsen jaundice, the laboratory result showed elevated total bilirubin 27.4 g/dL, direct bilirubin 21.2 g/dL, indirect bilirubin 6.2 g/dL, ALT 95 U/L, AST 134 U/L, alkaline phosphatase (ALP) 221 U/L, and gamma GT 17 U/L. His hepatitis serology showed reactive IgM anti HAV with index 7.85, and non reactive to HbsAg, anti-Hbc and anti-HCV. The laboratory result revealed high bilirubin level with minimally elevated AST and ALT. His ultrasound showed mild, non-specific hepatomegaly without canaliculi and common bile duct dilatation.

He was diagnosed as hepatitis A cholestasis type according to his anamnesis, physical examination, laboratory result, and ultrasound. He never had hepatitis before, no history of sexual multi-partner, intravenous drug-abuse, and herbal medicine consumption. He did not lose weight and appetite. There is no history of malignancy in the family.

He got symptomatic therapy with ursodeoxycholic acid (UDCA) 300 mg twice daily for his itchy skin. He did not vomit or feel nausea anymore. His bilirubin test showed total bilirubin was decreased from 29.93 g/dL to 25.4 mg/dL and 19.44 g/dL in the fifth day of treatment. Therefore, steroid therapy was not added to his treatment. However, his laboratory result then showed elevated total bilirubin level on the seventh and tenth day, respectively 21.55 g/dL and 23.83 g/dL. He got steroid therapy 0.5-1 mg/kg per day on the tenth day. After five days of steroid therapy, his total

bilirubin level became 10.83 g/dL. He was discharged with steroid therapy and steroid was tappered off during follow-up in the clinic. Patient did not check laboratory tests as adviced but from follow up 4 weeks later, he did not complain any jaundice.

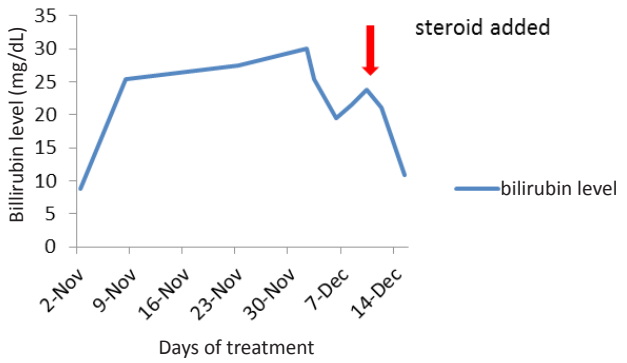

Figure 1. Patient's bilirubin level

DISCUSSION

Prolonged cholestasis is one of atypical manifestations of hepatitis A infection. Appropriate diagnosis and treatment is needed because this manifestation will increase morbidity and medical cost.

Prolonged cholestasis is defined as elevated total bilirubin > 5 mg/dL more than 4 weeks after diagnosis.[4] Previous definition of acute cholestatic hepatitis A was based on the following criteria: clinically jaundice for at least 12 weeks, with a peak serum bilirubin greater than 10 mg/dL at a time when the serum aspartate aminotransferase level was rapidly declining.[3] But we can not wait until 12 weeks because it will increase morbidity, so if any patient has a hepatitis A infection and jaundice more than four weeks we should start to think about prolonged cholestatis. Signs and symptoms of prolonged cholestasis are pruritic skin, fatigue, loose stool and weight lost.[2] HAV RNA could be detectable until 20 days after infection.[2] These symptoms were similar to our patient who admitted to hospital with chief complaint of jaundice for four weeks. The patient felt nausea and vomit followed by jaundice. He was diagnosed as hepatitis A in the clinic. The laboratory result showed elevated total bilirubin level 8.8 g/dL, elevated liver transaminase and reactive IgM HAV. His bilirubin level was still elevated after 4 weeks with the highest level was 29.93 g/dL. Antibodies to HAV can be detected during acute illness when serum aminotransferase activity is elevated and fecal HAV shedding is still occurring. Thus early antibody response is predominantly of the IgM class and persists for several months, rarely for 6–12 months. During the convalescence, however, anti HAV of the igG class becomes the predominant antibody.Therefore the diagnosis of hepatitis A is made during acute illness by demonstrating anti HAV of the IgM class.[1]

Classic and atypical hepatitis usually begins with prodromal symptoms, followed with jaundice and elevated liver enzyme. It happened to this patient. He started to feel nausea and vomit followed with jaundice and dark urine. A study conducted by Tong et al revealed that the most common symptoms of patient with hepatitis A are dark urine (81%), fatigue (80%), gastrointestinal upset and fever (58%). The most common signs are hepatomegaly (78%) and jaundice (71%).[5] This patient had all this signs and symptoms. But during follow up at the ward, the only signs and symptoms found were jaundice and hepatomegaly.

The patient's bilirubin level showed elevation and fluctuation since the initial treatment, but the transaminase level decreased to normal level on the discharge day. Transaminase serum level never elevated up to three times as high as the normal limit than normal while patient was hospitalized. Patient with cholestasis can have diarrhea, weight lost, and pruritic skin. But he only complained of pruritic skin without diarrhea. Pruritic skin is caused by the bile deposition in the skin.

Incidence of intrahepatic cholestasis in hepatitis A is 0.4-0.8%. Another study in Korea showed higher incidence which was 4.7%, even previous study showed 7% incidence of prolonged cholestasis due to hepatitis A infection with bilirubin level 8-38 mg/dL (average is 20) with time duration 12-16 weeks after onset.[5] In patient with classic manifestation of hepatitis A, bilirubin levels returned to nearly normal levelby mean of 5.3 weeks.

A prospective study in Korea found out that risk factors for prolonged cholestasis were older patients (35 vs 30 year old), hepatitis B carrier, higher level bilirubin (15.7 mg/dL vs. 6.4 mg/dL) and in patients with low albumin level (3.5 g/dL vs. 3.7 g/dL). Time duration from admission to cure and improvement liver function in prolonged cholestasis can be up to 70 days compared to patients without cholestasis which is 36 days ($p < 0.01$). Chronic hepatitis B infection, prolonged prothrombine time/INR (1.6 vs. 1.2) and higher bilirubin level are associated with prolonged cholestasis. Eventhough cholestasis increase morbidity but patient can betotally cured.[4] During the illness, the peak bilirubin level of this patient was 29.93 mg/dL. This finding was in concordance to the study in

Korea, that revealed patient significantly predispose to complicate to prolonged cholestasis.

In this case abdominal ultrasonography (USG) showed mild hepatomegaly without dilatation of intra- and extrahepatic bile ducts. With this USG, we could be sure that there was no extrahepatic obstruction. No further evaluation was needed because it was considered time-consuming, costly and involved potential risk.[3]

Cholestasis happens because of some mechanism, including decreased bilirubin uptake, conjugation dysfunction, bilirubin excretion dysfunction and biliary obstruction. In hepatitis A, cholestasis happens because of inflammatory process. Endotoxin and pro inflammatory cytokines are released from liver and also as systemic response. TNF alfa and IL-1 inhibit mrp2 (multidrug-resistance associated protein 2), one of the proteins that has role in bilirubin excretion.[6]

Prolonged cholestasis is also caused by host factor or severe destruction in liver cells in the beginning of infection. It is true because there is also prolonged prothrombin time and elevated bilirubin in patient with prolonged cholestasis. It can be also caused by the virus itself that inhibits bile salt transport eventhough the mechanism is unknown yet. In patients with prolonged cholestasis due to hepatitis A, the duration of HAV viremia was longer than the classic one, so it makes probably direct effect on the transporters related to cholestatis.[6]

UDCA is the main therapy for chronic cholestasis such as in patient with primary billiary cirrhosis (PBC). UDCA has protective effect on bile salt by increasing hydrophilic fraction so it becomes more water-soluble and has role in membrane stability. A randomized-study wasconducted in 79 patients treated with UDCA and placebo in 3 weeks. Patients who got UDCA had earlier decreased bilirubin, gamma GT, alkaline phospatase and transaminase level than placebo. But statistically not significant for transaminase level.[7]

The patient received ursodeoxy cholic acid 300 mg twice daily in the tenth day of hospitalization because he complained of pruritic skin and elevated bilirubin level. The rationale for this treatment was based on the studies that showed beneficial effects on serum biochemistries. This agent also relieves pruritus in some patients and is well tolerated with insignificant side effects, apart from diarrhea, which occurs in less than 2% of patients. It is well known that UDCA administration may prevent or reduce damage to liver cells and may also reduce cholestasis induced by high concentration of hydrophobic bile acids. In this case the bilirubin level was slightly decreased but increased again with slight clinical improvement.

There was an elevated bilirubin level in the tenth day of therapy but no biliary obstruction was found, so then steroid therapy was initiated in this patient. Some case reports and randomized-placebo control trial showed steroid could help to improve cholestasis A case-report from India, a child with jaundice for six weeks and also with pruritic skin in the last two weeks showed elevated bilirubin level in a serial laboratory test. Serology test showed hepatitis A infection. The patient was diagnosed hepatitis A with prolonged cholestasis because there was no improvement in jaundice. The patient was given steroid therapy with prednisolone 60 mg. After three days of steroid therapy, there was clinical improvement with decreased bilirubin level. After two weeks of steroid, the dosage was tapered into 30 mg/day and gradually tapered off in two weeks. After 4 weeks of steroid therapy, bilirubin level decreased to 2.6 mg/dL.[8] In this case corticosteroid could improve clinical manifestation and relieve pruritus. No adverse reaction was reported.

Three case reports from Korea stated about steroid therapy as management of prolonged cholestasis in hepatitis A. The first case was about 40 year-old-male diagnosed ashepatitis A, with jaundice until 4 weeks after diagnosis. Bilirubin level was increased as high as 23.5 mg/dL. The patient got prednisolone 30 mg/day. After 13 days of steroid therapy, total bilirubin was

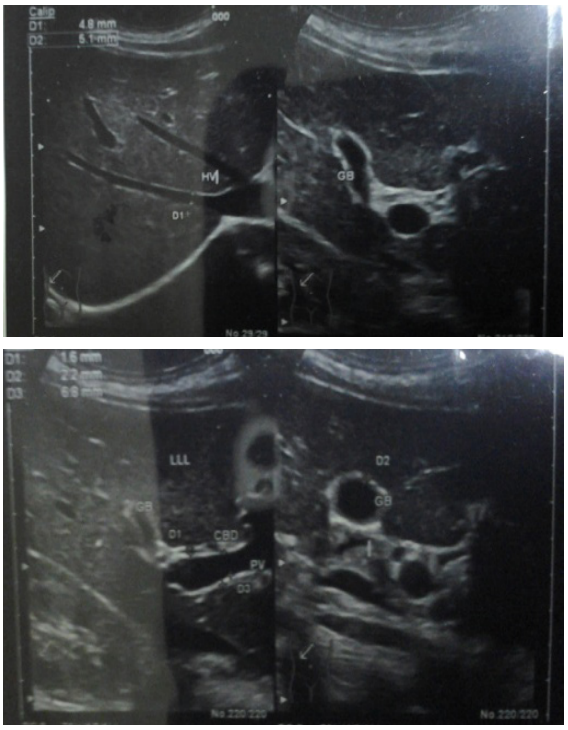

Figure 2. Ultrasound showed no dilated ducts

decreased to 11.3 mg/dL. After 4 weeks of prednisolone therapy, the dose was tapered gradually to 10 mg every two weeks. Bilirubin level in the eighth week was 1.7 mg/dL. Second case was about 35 year-old-male with the same symptoms. His serial bilirubin tests showed increased bilirubin level as high as 31.79 mg/dL. After 4 weeks of conventional treatment without improvement, the patient got prednisolone 30 mg/day. On the 23rd day following administration of steroid, total bilirubin declined to 13.2 mg/dL. They stopped prednisolone in the twelfth week after gradual tapering since fourth week. Bilirubin level decreased to 1.09 mg/dL in the twelfth week. The third case was about 42 year-old male. He was referred after 4 weeks of in-hospital treatment with highest bilirubin level was 31.5 mg/dL and also be given the same dosage of prednisolone. He got steroid therapy for nine weeks and his bilirubin level decreased to 0.32 mg/dL. Serial bilirubin level tests after steroid therapy showed clinical significance. Bilirubin level was half than maximum level in the 13th, 23rd and 8th day in every case.[6] These case reports were similar to our patient, which had jaundice for 4 weeks before admission and started conventional therapy for the next ten days, because no or less clinical improvement, the patient was given steroid and in the fifth day bilirubin level was decreased to half. From this case, we knew that corticosteroid could be given to patients with prolonged jaundice which showed no improvement with conventional therapy.

A randomized study was held to evaluate efficacy of steroid therapy as management of prolonged cholestasis in hepatitis A. This study compared UDCA and prednisolone (group A) with UDCA and placebo (grup B). From 84 patients with hepatitis A, 21 of them were diagnosed as prolonged cholestasis. Eleven patients were given UDCA and prednisolone and 10 patients were given UDCA and placebo.[9]

Average bilirubin level in group A was 29.4 mg/dL with no significant difference compared to group B which was 28.6 mg/dL. Bilirubin level was checked in day 3, 7, 14, 21, 28, 35, 42, and 49. The decrease in bilirubin in group A (cumulative mean) at day 3, 7, 14, 21, 28, 35, 42, 49 was 20.1%, 45.6%, 58.6%, 64.6%, 71.7%, 76.1%, 80.5% and 86.4%, respectively. The mean time for bilirubin normalization was 44 days (range 28–84 days). In group B who got UDCA and placebo, bilirubin level was 2.1%, 5.9%, 11.9%, 25.1%, 29.3%, 33.3%, and 38.5%, in average 91 days (74-138 days), with $p < 0.05$. Pruritic skin got better in day 5 (4-8) in group A compared to group B in day 24 (18-45). There was no side effects of steroid found in this study.[9] The use of corticosteroid could improve clinical manifestations significantly including decreased bilirubin level and relieved pruritus.

Study in Korea about the clinical manifestations of acute cholestatic hepatitis was presented recently. From 21 patients,mean value of total bilirubin was 17.2 mg/dL and the mean time for bilirubin to be normalized was 93 days. So it was suggested that severe cholestasis would take longer duration to be cured by supportive treatment only.[10]

TNF alfa and IL-1 have important role in pathogenesis of prolonged cholestasis in hepatitis A. It is therefore conceivable that cholestasis associated with this inflammatory process can be improved by the administration of steroids.[5] A study on steroid showed that dexamethasone inhibited TNF alfa and IL-1 synthesis, so dexamethasone could prevent impairment in the function of mrp2 in the canaliculi of endotoxemic rats. Dexamethasone has the capability in induction of expression mrp2 twice compared to normal liver cells and facilitates bilirubin metabolism.[6]

Actually the presence of persistent cholestasis can still be managed symptomatically, but this frequently lengthens hospital stay and causes higher medical expenses and social economic loss. Therefore, it is imperative that methods are developed to improve clinical courses more promptly in patients with acute viral hepatitis A complicated by persistent uncontrolled cholestasis. The use of corticosteroids has not been shown to influence the ultimately favorable outcome of patients with cholestatic viral hepatitis. Nevertheless, a salutary role for steroids in the treatment of some forms of cholestatic hepatitis has been previously recognized. The decision to begin steroids was based on the often debilitating symptoms associated prolonged cholestasis. Prednisone or corticosteroid generally resulted in symptomatic relief and rapid initial drop in serum bilirubin levels.[3]

Therefore, there are still controversies on the efficacy of steroid therapy. It was reported that cholestasis spontaneously resolves although corticosteroids may hasten the resolution, but it may predispose the patient to develop a relapse of the hepatitis.

This patient has no contraindicated for steroid therapy like prolonged, so this patient got steroid therapy according to literature above. The patient had total 4-5 week jaundice before admitted to our hospital, and despite additional 10 days of conservative therapy, the total bilirubin was still elevated up to 23.83 mg/dL. Methyl prednisolone was initiated at 32 mg in divided dose. Steroid improves edema caused

by inflammation in liver cells which caused biliary obstruction. Five days after steroid therapy, bilirubin level decreased from 23.83 g/day to 10.83 mg/dL with clinical improvement. Total bilirubin decreased to 50% before steroid therapy. The patient did not complain of itchy skin, nausea and vomit anymore. He was discharged in day 16.

Prolonged cholestasis is one of atypical manifestation of hepatitis A which is rarely found. Cholestasis increases morbidity and prolonged hospitalization. Steroid therapy decreased bilirubin level and gave clinical improvement to the patient.

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