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Case Report

Cholestasis as Primary Manifestation of Cytomegalovirus Infection: A Case Report

Dyah Suci Handayani[1], Muzal Kadim[2]

[1]Department of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

[2]Gastrohepatology Division, Department of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

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Corresponding author:
Muzal Kadim
muzalk@yahoo.com

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Abstract:

Background: Jaundice, marked by yellow discoloration of the sclera, skin, and mucous membranes due to bilirubin accumulation, can be physiological in neonates but may also signal pathological conditions like cholestasis. Cholestasis is commonly associated with biliary atresia; however, it can arise from various causes such as cytomegalovirus (CMV) infection. Thus, this study aims to discuss the diagnostic approach on neonatal cholestasis as the main manifestation in CMV infection.

***Case*:** A 2-years-old boy referred to the hospital with chief complaint of jaundice in both eyes and skin since 4 days of age and persisted until the age of 40 days old. Abdominal ultrasound in prior hospital revealed obstruction of bile duct which indicative for biliary atresia. However, subsequent abdominal and ARFI ultrasound showed no showed results inconsistent with biliary atresia. Furthermore, other examinations indicating infection, which were confirmed as CMV infection through serological and PCR test. Patient was then treated using valganciclovir treatment.

***Discussion*:** The diagnostic approach for cholestasis includes comprehensive anamnesis and physical examination, laboratory tests including complete blood count, bilirubin levels, liver function analysis, and coagulation factors, as well as ultrasound. CMV infection should be considered a potential cause of neonatal cholestasis, even in the absence of specific manifestations beyond jaundice and gastrointestinal symptoms.

Conclusion: CMV infection can present solely with cholestasis and gastrointestinal symptoms, without other typical CMV manifestations. Thus, comprehensive evaluation, CMV screening, and careful assessment of the patient's condition are essential for accurate management.

Keywords: cholestasis, cytomegalovirus, diagnostic approach, infection

Introduction

Jaundice is a condition characterized by yellow discoloration of skin, sclera, and mucosal membrane, caused by the accumulation of bilirubin beyond normal level (hyperbilirubinemia).[1, 2] Jaundice commonly manifest during the first two weeks of life and is one of the most frequent causes of readmission for neonates after discharge from the hospital.[1] Around 60-80% of neonates, regardless of gestational age, experience jaundice during their first week of life, with most of them being mild, transient, and resolving spontaneously. This condition is referred as physiologic jaundice. However, in certain cases, jaundice may indicate an underlying pathological condition and is termed pathological jaundice. Physiological jaundice typically manifests 24 hours after birth and resolves before 14 days of age in term infant.).[1, 2] In contrast, pathological jaundice is defined as jaundice that appears before 24-hours of age, with total bilirubin exceed 95th percentile according to age, increase total bilirubin over 5 mg/dL/day or 0.2 mg/dL/hours, and persistent jaundice surpassing 14 days of age.[1] Evaluation of the underlying pathological cause of jaundice should be excluded first before establishing the diagnosis of physiological jaundice.

The primary cause of jaundice is cholestasis, which is defined as the stagnation or reduction in bile acid secretion and flow, due to obstruction or functional defect of the hepatocytes. The accumulation of bile duct, which contains bilirubin, may lead to the development of jaundice in cholestatic patient. In the neonatal period, the main cause of identified cholestasis is biliary atresia. Without proper management, 50% of patients with biliary atresia require a liver transplant before reaching the age of 2 years.[1, 3, 4] Other etiology of cholestasis in newly born infant is cytomegalovirus infection (CMV). Cytomegalovirus is a double-chain DNA virus from *Herpesviridae* family and transmitted from human to human without exhibiting any significant manifestation.[5] However, in vulnerable population such as immunodeficient patients, CMV infection caused high morbidity and mortality rates.[5, 6] In neonates, CMV infection is a congenital viral infection with highest prevalence and among the diseases with highest mortality and morbidity. The prevalence of CMV infection is slightly higher in the developing countries (0.6-6.1%) compared to the developed countries (0.2-6%).[5] Moreover, congenital CMV infection should be a concern as it is the main cause of sensorineural hearing loss not associated with genetic abnormalities and neurological developmental disabilities.[5, 6]

Biliary atresia and CMV infection are the main etiologies of cholestasis in neonates. However, the management and treatment approaches for these conditions differ significantly. Additionally, differentiating between the two conditions is quite challenging, as the result of physical examination, laboratory findings, and other supporting examinations often fail to establish the diagnosis. Thus, this study aims to

discuss the clinical approach of cholestasis in newly born infant with jaundice manifestation, particularly on the management of patient with CMV infection.

Case

A 2-years-old boy came to the hospital with a chief complain of yellow discoloration on both eyes, first noticed at 4 days old. The patient was born at term through caesarian section without any complications during and after birth. On the fourth days of age, patient's mother observed yellow discoloration of the sclera with normal skin color. She also noted a clay-colored stools without episodes of tea-colored urine. There is no complains of fever, vomiting, and lethargy. Patient was breastfeeding well and appeared active. Patient were then taken to a midwife, who recommended sunbathing in the morning. However, no improvement was observed.

At 40 days of age, patient's mother reported yellow discoloration on the skin with persistent prior manifestation. Patient were then taken to the hospital and ultrasound examination was performed, revealing a bile duct obstruction. Patient was referred to Cipto Mangunkusumo Hospital (RSCM), a tertiary, national referral, teaching hospital in Indonesia for further management. Prior to the arrival, patient was given amikacin 90 mg/24 hours IV for 5 days and ursodeoxycholic acid 50 mg per 3 hours (30 mg/kg/day), which was discontinued after the patient arrive in our hospital.

Patient is the fourth child of four siblings. Patient was born at a local hospital through caesarean section with birth weight of 3300 gram and a length of 51 cm. During pregnancy, patient's mother had no medical problem, never consumed any medication other than prenatal vitamins provided by the community health center, regularly attended check-ups with midwifes and had an ultrasound by obstetrician, which revealed normal pregnancy and fetus. Patient had no history of breastfeeding problem and had normal growth and development for his age. Patient only received one immunization in the right thigh after birth and never received further immunization due to jaundice.

Initial examination in our center demonstrated jaundice in the eyes and skin, with no complaint of fever, abdominal distention, lethargy, or seizures. Patient was given formula milk 90 ml per 3 hours to ensure adequate nutrient intake as the mother reported reduction of breast milk production. Patient was able to finish the milk provided, in addition to direct breastfeeding. During physical examination, the patient appeared moderately ill. Blood pressure was 81/40 mmHg (50th-90th percentile), pulse rate 130 beats/minute (regular, strong, and adequately filled), respiratory rate 32 breaths/minute, temperature 36.4°C, and oxygen saturation 98% on room air. The patient weighed 5.39 kg and measured 56.9 in height, with normal nutritional status based on the 2006 WHO Child Growth Standards curve. Eye examination revealed

pale conjunctiva and icteric sclera. Skin inspection revealed jaundice from the face to the arms and lower legs (Kramer scale IV). Other physical examinations were within normal limits.

Laboratory findings obtained six days prior admission to our hospital showed hemoglobin (Hb) 8.7 g/dL, hematocrit (Ht) 27%, leukocytes 16,700/µL, and platelets 548,000/µL. Total bilirubin was measured at 17.1 mg/dL, with direct bilirubin 12.8 mg/dL, and indirect bilirubin 4.2 mg/dL. Hepatitis B screening was reported as non-reactive. Upon admission to our center, the laboratory results revealed similar findings. Patient was anemic (Hb 8.7 g/dL) with a mean corpuscular volume (MCV) of 82.2 fl, mean corpuscular hemoglobin (MCH) of 29.2 pg, and mean corpuscular hemoglobin concentration (MCHC) of 35.5 g/dL, indicating a microcytic hypochromic anemia. Leukocytosis was identified, with leukocytes and thrombocytes counts of 20,620/µL and 594,000/µL, respectively. Electrolyte analysis showed sodium at 133 mEq/L, potassium at 5.6 mEq/L, and chloride at 106.3 mEq/L, indicating hyperkalemia. Bilirubin levels were reported as 17.91 mg/dL for total bilirubin, 12.15 mg/dL for direct bilirubin, and 5.76 mg/dL for indirect bilirubin. High level of liver function tests were also observed, with Serum Glutamic Oxaloacetic Transaminase (SGOT) at 534 U/L, Serum Glutamic Pyruvic Transaminase (SGPT) at 197 U/L, gamma-glutamyl transpeptidase (GGT) at 77 IU/L, and alkaline phosphatase at 405 IU/L. Coagulation profiles showed a prothrombin time (PT) and activated partial thromboplastin time (aPTT) of 1x and 1.4x, respectively. Urinalysis, random blood glucose were within normal limits. Overall, the findings indicated microcytic hypochromic anemia, leukocytosis, cholestasis, hyperkalemia, liver dysfunction, and bilirubinuria. Patient was then diagnosed with extrahepatic cholestasis suspected to be caused by biliary atresia and hyperkalemia, with differential diagnosis for cholestasis included CMV infection.

Patient were then given extensively hydrolyzed protein formula containing medium-chain triglycerides (90 ml every 3 hours, equivalent to 480 kcal/day), empirical antibiotics (intravenous ceftriaxone 300 mg per 24 hours), ursodeoxycholic acid (80 mg per 8 hours, 50 mg/kgBW/day, per oral), management of hyperkalemia using salbutamol inhalation (2.5 mg every 8 hours), and supplementation of multivitamins, particularly fat-soluble vitamins. Patient was also referred to pediatric surgeon for further evaluation and management of suspected biliary atresia.

Subsequent examination and follow-up showed consistent clay-colored stools from three phase stool analysis. Abdominal and ARFI ultrasound showed results inconsistent with biliary atresia. Meanwhile, TORCH serology revealed reactive Cytomegalovirus (CMV) IgG and IgM, prompting quantitative blood CMV Polymerase Chain Reaction (PCR), which confirmed CMV infection (viral load:

$7.8x10^2$ IU/ml). Patient was then referred to ophthalmologist and otorhinolaryngology specialist for evaluation of chorioretinitis and hearing impairment due to CMV infection, which revealed normal results. A head ultrasound to check for CMV-related abnormalities revealed a right choroid plexus cyst, considered a normal variant.

Patient's final diagnosis were then established as intrahepatic cholestasis due to CMV infection and planned for valganciclovir treatment. During hospitalization, patient remained jaundice with no signs of progression. Stools remained clay-colored with normal bowel movement frequency and stool consistency. Repeat blood tests indicated decreased of leukocyte to 12,090/μL, leading to the discontinuation of antibiotics. On the ninth day of hospitalization, the patient was discharged for outpatient care due to clinical improvement and stable condition. Oral valganciclovir treatment was continued for six weeks.

Discussion

The diagnostic approach to jaundice in infants involves a comprehensive history taking, physical examination, and additional investigation. Detail information regarding the characteristic of the jaundice, including onset of the symptoms, progression, and associated symptoms, are crucial during the history taking.[7] The patient presented with jaundice at four days of age. Physiological jaundice remains a possible consideration, however, the presence of acholic stools and dark urine in this case suggest pathological jaundice, which required further investigation.

A comprehensive review of the maternal and neonatal history is essential to assess the possibility of congenital infections. This includes history of abortion, maternal liver dysfunction, infectious exposures indicated by fever or rash, and medication use during pregnancy. Additionally, it is important to evaluate neonatal screening result and the administration of vitamin K. This patient showed no significant maternal and neonatal history.[7]

Nutritional intake should also be investigated, including the type of milk, frequency of feeding, and volume consumed. Tolerance of enteral feeding, such as the timing of the first meconium passage, frequency of defecation, and stool's characteristic should also be assessed. In addition, it is important to inquire about any history of long-term parenteral nutrition.[7] In this case, breastfeeding jaundice was excluded, due to the adequate breastfeeding. There was no history of parenteral nutrition in this patient.

Apart from liver and biliary system dysfunction, hemolysis, congenital heart disease, and vascular abnormalities need to be considered as an etiology of cholestasis jaundice. In this case, the patient's condition from birth appears normal. The presence of

jaundice accompanied by acholic stools and dark urine and the absence of other abnormalities since birth is commonly seen in infants with biliary atresia.[7]

On physical examination, aside from inspection of the skin, sclera, and mucous membranes for jaundice, palpation of the liver and spleen should be performed. Hepatomegaly is a common finding in patients with biliary atresia, while splenomegaly is more likely to occur after the neonatal period. Splenomegaly in the 2-4 week of age is typically associated with hematological and storage disorders.[7] In this patients, hepatomegaly and splenomegaly were not present. However, their absence does not completely rule out biliary atresia. Other physical examination was unremarkable, which aligns with the potential diagnoses of biliary atresia or infection as the underlying cause of jaundice. Additional evaluations were then conducted, including laboratory test, imaging, histopathology, and an intraoperative cholangiogram.[7, 8]

Jaundice becomes apparent in infants only when serum total bilirubin levels exceed 2.5-3.0 mg/dL. While visual examination can be used to estimate bilirubin levels, the result is subjective and prone to error, even when performed by experienced clinicians. Therefore, laboratory measurement of serum total and conjugated bilirubin is essential for accurate diagnosis.[1, 8] Liver function test should also be evaluated to assess the severity of liver dysfunction. These tests include ALT, AST, alkaline phosphatase, gamma-glutamyl transferase (GGT), prothrombin time (PT), international normalized ratio (INR), and albumin. Elevated AST, with normal level of ALT and albumin levels, suggest a musculoskeletal or hematologic disorder than a hepatologic condition.[7, 8]

Laboratory findings in this patient revealed increased total bilirubin with direct bilirubin >1 mg/dL, accounting for more than 20% of the total bilirubin. These findings strongly support a diagnosis of cholestasis. This patient also exhibited elevated liver function test both AST and ALT suggesting a hepatocellular injury. The GGT level in this patient was at 77 IU/L, which is relatively low compared to the values typically observed in cases of biliary atresia, in which GGT levels usually exceed 250 IU/L.[7, 8] Therefore, the GGT findings in this patient were less consistent with a diagnosis of biliary atresia.

Imaging studies commonly used in the diagnosis of cholestasis include a 2-phase abdominal ultrasound, performed while the patient is fasting and after consumed fluids. This ultrasound can identify obstruction in biliary system and detect cyst. Moreover, this 2-phase abdominal ultrasound can assess parenchymal abnormalities, the hepatic vascular system, and spleen abnormalities. In this patient, the liver, spleen, and biliary system morphology appeared normal. There was no evidence of stenosis, and the gallbladder contraction was adequate. This ultrasound findings did not support the diagnosis of biliary atresia.[7, 8]

If infection is suspected, microbiological investigations, including blood and urine culture, as well as serological or PCR testing, should be performed. In this patient, TORCH serology result was reactive for both IgG and IgM CMV antibodies, prompting further CMV PCR testing to confirm the diagnosis of CMV infection.[7, 8] Cytomegalovirus (CMV) is the most common congenital viral infection. In infants with CMV infection, the infection can be either congenital or acquired after birth.4-6 [5, 6, 9]

To differentiate between congenital and acquired CMV infection, a PCR test on body fluids should be performed before the infant reaches 3 weeks of age. The detection of CMV DNA after 3 weeks of age could be due to either congenital or acquired infection, making it challenging to determine the precise source of infection.[9-11]

Viral DNA PCR testing is recommended using urine or saliva samples, as these specimens offer high sensitivity. A positive CMV PCR result on saliva should be confirmed with a PCR test on a urine sample, which has a sensitivity of 93-100%. While CMV serology can be used as a screening tool, it cannot be relied upon as the sole diagnostic test for CMV infection due to its limitations in sensitivity and specificity.[9-11]

In this 2-moths-3-week-old patient, a CMV PCR test using serum was chosen because PCR testing of saliva and urine samples had become less reliable at this stage. The positive CMV PCR result confirmed our diagnosis of CMV infection. However, as the patient was older than 3 weeks at the time of testing, it was not possible to determine whether the infection was congenital or acquired. Therefore, additional tests, such as liver function tests, hearing tests, and head ultrasound, are necessary to assess the severity of the infection and guide appropriate management.

Symptomatic congenital CMV infection typically presents with more severe manifestations and permanent abnormalities. In contrast, acquired CMV infection usually causes milder symptoms, although severe infections can occur, especially in premature infants.[9]

Previous study have stated that gastrointestinal symptoms had been frequently observed and indicative for CMV infection.[12] However, the occurrence of CMV infection commonly observed with other signs and symptoms. Congenital CMV infection is often associated with permanent sensorineural hearing loss, while acquired CMV infection is less likely to cause this type of hearing impairment. Furthermore, other potential manifestations of congenital CMV infection include petechiae, purpura, a blueberry muffin rash, hepatomegaly, splenomegaly, neurological

abnormalities (such as lethargy, hypotonia, seizures, and poor sucking reflex), ventriculomegaly, anemia, thrombocytopenia, leukopenia, elevated transaminase enzymes, direct hyperbilirubinemia, retinal hemorrhage, optic atrophy, strabismus, and cataracts.[5-7, 9]

Interestingly, this patient only presented with the manifestation of gastrointestinal problem. Based on the examination, there was no evidence of CMV chorioretinitis in both eyes. Hearing function tests, including OAE and BERA, also revealed no impairments. Head ultrasound also showed a normal variant, a right choroid plexus cyst, which is not a typical finding in CMV infection. This further emphasize the importance of CMV screening in patient with cholestasis.

The severity of CMV infection can be classified into mild, moderate, or severe. Mild CMV infection is characterized by subtle symptoms such as petechiae, mild hepatosplenomegaly, and slightly abnormal laboratory findings, including mild thrombocytopenia, anemia, leukopenia, elevated transaminases, and direct hyperbilirubinemia. Low birth weight may also be present, but without microcephaly or significant abnormalities on virologic tests. Furthermore, moderate CMV infection is associated with persistent laboratory abnormalities for more than two weeks and at least two persistent clinical manifestations.[9]

Severe CMV infection can be further categorized into three types: CMV disease, life-threatening CMV infection, and isolated hearing impairment. CMV disease is characterized by microcephaly, central nervous system calcifications, chorioretinitis, and white matter changes in the brain parenchyma. Life-threatening CMV infection involves severe involvement of one or more organs, but without significant central nervous system involvement.[9]

Generally, mild CMV infections do not require antiviral therapy. Antiviral therapy, such as ganciclovir or valganciclovir, is recommended for moderate and severe CMV infections. For moderate infections, therapy may be considered for 6 weeks to 6 months, in consultation with an infectious disease specialist. For severe and life-threatening infections, antiviral therapy should be initiated promptly and continued for approximately 6 months.[9, 11]

It is important to note that antiviral therapy is primarily recommended for infants younger than 4 weeks of age, as there is limited evidence from randomized controlled trials to support its use in older infants. However, therapy may still be considered for infants older than 4 weeks, depending on the individual patient's condition and in consultation with an infectious disease specialist.[9, 11]

In our case, after consultation with tropical disease and infectious disease specialists, antiviral therapy (valganciclovir) was initiated. The therapy is planned to last for 6 weeks, with close monitoring of the patient's clinical response and laboratory parameters, including for potential complications of CMV infection and side effects of the therapy.

Common short-term side effects of antiviral therapy include neutropenia and transient hepatotoxicity, which usually resolve upon discontinuation of the medication. While long-term side effects of ganciclovir and valganciclovir in humans have not been definitively established, animal studies have suggested potential carcinogenic and gonadotoxic effects. In addition to monitoring for side effects of therapy, it's important to monitor for symptoms of CMV infection. Hearing function tests should be performed every 3-6 months during the first year, every 6 months until the age of 3 years, and annually until the age of 6 years.[9]

The patient's outpatient follow-up showed improvement in symptoms, including stool color and weight gain. While the patient still exhibited jaundice, his clinical condition had improved. After four weeks of antiviral therapy, a serum PCR CMV test was performed to assess the treatment response. The negative result indicated a good therapeutic response, and therefore, antiviral therapy (valganciclovir) was discontinued.

Conclusion

Cholestasis is one of liver disease with clinical manifestation of yellow discoloration in the eyes and skin. Cholestasis occurs due to functional defect in hepatocytes or obstruction in bile duct which leads to the accumulation of bilirubin. CMV infection is one of the diseases which could cause cholestasis. Our study reported that CMV infection can present solely with cholestasis and gastrointestinal symptoms, without other typical CMV manifestations. Therefore, comprehensive evaluation, CMV screening, and careful assessment of the patient's condition are essential for accurate management.

Conflict of Interest

None declared

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