

Case Report

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Biliary Atresia with Cytomegalovirus Infection, Congenital Heart Disease and Pneumonia: A Case Report

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ABSTRACT

Biliary atresia (BA) is a condition of biliary obstruction. Kasai portoenterostomy (KPE) is a treatment option. The aim to determine the success rate of kasai procedure and prognosis in BA patients with other underlying diseases. This is a descriptive case study research. We report a boy, 2 months and 11 days with jaundice all over his body since one week old; putty stool, and dark urine. Old man's face, icteric, rib xylophone, subcostal retraction, rales, continuous heart murmur, and wasting. Total and direct bilirubin, SGOT, SGPT, and gamma GT are increased. A Kasai surgical procedure was carried out, but did not significantly improve his condition because the operation was performed at the age of 4 months and 8 days with liver cirrhosis, sepsis, pneumonia, and malnutrition. Cytomegalovirus (CMV) infection and acyanotic congenital heart disease also worsened his preoperative condition. Kasai portoenterostomy is a method of managing biliary atresia, but our patient was diagnosed with biliary atresia accompanied by CMV infection, congenital heart disease, or pneumonia, so the procedures not enough for this condition, and mortality rate is higher than biliary atresia alone. Age at surgery time also influences the prognosis.

Keywords: Biliary atresia; jaundice; congenital heart disease



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Introduction

The intrahepatic and extrahepatic bile ducts are involved in the obstructive cholangiopathy known as biliary atresia.¹ About 25 to 30 percent of patients and long-term survivors have biliary atresia. The incidence of BA worldwide varies from 1 in 8,000 to 18,000 live births.² The reported incidence of BA varies by geography, with larger occurrences found in the Asia and Pacific region. About 1 in 5000 live births in Taiwan, 1 in 10,000 in Japan, 1 in 17,000–19,000 in the UK and France, 1 in 19,000 in the Netherlands, and 1 in 15,000 in the United States have the condition.³ There are no clear reports regarding the incidence of biliary atresia in Indonesia.

Putty stools, hepatomegaly, and prolonged jaundice are the newborn signs of biliary atresia.¹ At the time of diagnosis, biliary atresia in newborns and babies is linked to cytomegalovirus (CMV) infection. It is hypothesized that CMV infection triggers an immunological response that damages the liver and biliary tree, leading to biliary atresia.⁷ Infants with biliary atresia frequently have congenital structural abnormalities. The incidence rate varies between 13.4% and 20.3%. One of the most prevalent congenital malformations is congenital heart disease (CHD) that coexist with biliary atresia, occurring in 6.3% to 15% of infants. Therefore, it is believed that newborns with CHD are at a significant risk of developing biliary atresia.⁴ 69% of all CHD fatalities in 2017 were in newborns under the age of one year. Meanwhile, respiratory infections (i.e., pneumonia) are the leading cause of death in children globally. Infants with hemodynamically severe CHD are at high risk of developing acute respiratory failure (ARF), the majority of which is caused by pneumonia (70% of cases).⁵

The biliary atresia must be recognized early in these patients. It is lethal if untreated, with a reported 3-year survival rate of fewer than 10%.¹ In cases of cholestasis due to biliary atresia, the success rate of Kasai procedure is highest when performed before the baby is 30-45 days old.⁶ Meanwhile, if accompanied by CMV infection, congenital heart disease, or pneumonia, it will further worsen the prognosis. This report aims to determine the success rate of Kasai procedure performed on BA patients with CMV, congenital heart disease and pneumonia aged > 45 days and the prognosis. Therefore we report on a male infant who was diagnosed with biliary atresia, accompanied by CMV infection, congenital heart disease and pneumonia.

Methods

This research design is a descriptive case study, which is a research method used to create a picture of the problem that occurred, which aims to describe what happened when the research was carried out. The subject in this case report is a boy aged 2 months 11 days who was diagnosed with biliary atresia with CMV, congenital heart disease and pneumonia and was treated at Wahidin Sudirohusodo General

Hospital, Makassar. This research uses secondary data. We selected data on patients with biliary atresia with CMV, congenital heart disease and pneumonia who were treated at Wahidin Sudirohusodo General Hospital, Makassar based on medical records. This study did not use informed consent because data was taken secondary (medical records). This case report keeps the patient's personal data confidential.

Case

A boy, 2 months 11-days of age came to the hospital with the chief complaint 2 months of jaundice all over his body. There was putty stool and dark urine from the age of 1 week. The patient had shortness of breath since birth. The patient was also diagnosed with acyanotic congenital heart disease. The patient had undergone phototherapy for 2 days.

On physical examination, there was an old man's face, scleral icteric, jaundice, xylophone ribs, and wasting. There was subcostal retraction, rales, and continuous heart murmur. Based on physical examination of the abdomen, hepatomegaly was found.

Laboratory values revealed altered liver function test direct bilirubin (17.14 mg/dL) and total bilirubin (20.35 mg/dL). There was elevated, increased SGOT (420 U/L) and SGPT (388 U/L), increased Gamma GT (430 U/L), hyponatremia (124 mmol/L) and hypoalbuminemia (3.3 gr/dL), On investigation there was anemia (8.4 gr/dL), ferritin >1200 ng/ml, leukocytosis (16,500/ μ L), reactive thrombocytosis (513,000/L), Anti-Toxoplasma IgG reactive (titer 10), and anti-CMV IgG reactive (titer 11).

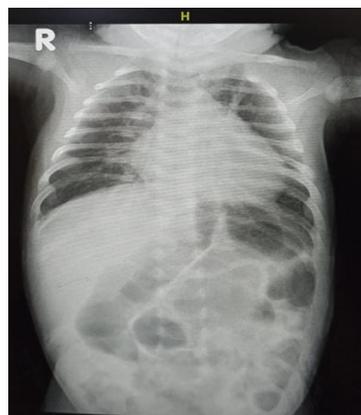


Figure 1. Thorax Imaging

The peripheral blood smear is examined, and the result is normocytic normochromic anemia, a presumed chronic disease source, together with leukocytes displaying indications of infection. Procalcitonin was 0.81 ng/dL. Routine urine examination results showed bilirubin 2+.

The chest X-ray showed an L to R shunt (Figure 1). Echocardiography showed a small atrial septal defect + ventricular septal defect PMO + small hemodynamic significant patent ductus arteriosus. The results of a 2-phase ultrasound examination showed an uncontracted gallbladder (CI: 13.95 % (Normal

CI: 86% +/- 18%) (Figure 2)

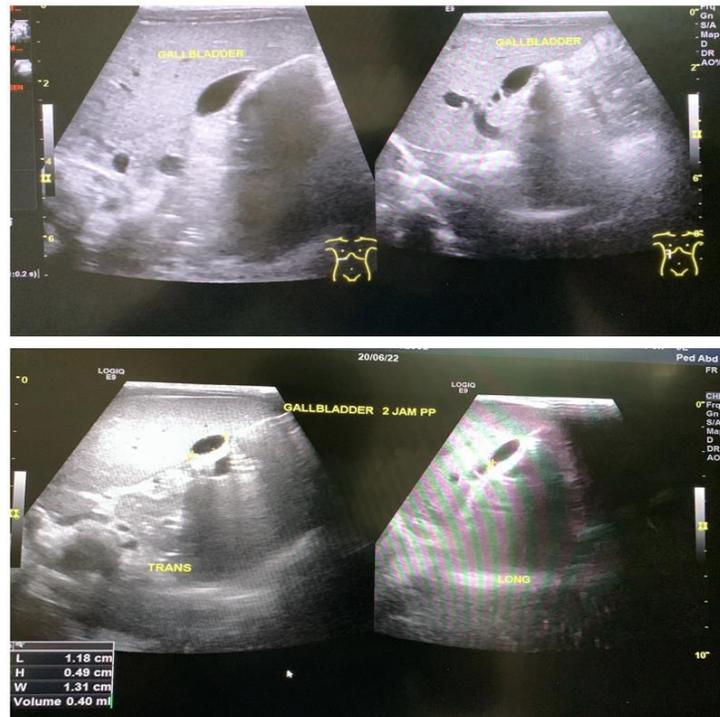


Figure 2. 2-phase ultrasonography. a) during fasting, b) post-prandial)

The results of MR cholangiopancreatography (MRCP) showed the structure of the cystic duct, common bile duct, and no connection between the right and left intrahepatic hepatic ducts according to type IIa biliary atresia (Figure 3).

On the 25th day of treatment, the cascading procedure was performed (Figure 4). A black liver was found and there was a gallbladder, not dilated, no left and right hepatic ducts, and no common bile duct. The common hepatic and left and right hepatic ducts and the common bile duct were fibrotic tissue, a remnant appearance.



Figure 3. MR Cholangiopancreatography

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Figure 4. Kasai procedure

This patient was diagnosed with septic shock, extrahepatic cholestasis et causa biliary atresia type III, intrahepatic cholestasis et causa cytomegalovirus infection, acyanotic congenital heart disease et causa ASD+VSD+PDS, community-acquired pneumonia, hypoalbuminemia, elevated transaminase enzymes, malnutrition-marasmus type, and electrolyte imbalance.

On Treatment, the patient received ampicillin 85 mg/6 hour/intravenously, gentamicin 8,5 mg/12 hours/intravenously, then changed into ceftriaxone 340 mg/24 hours/intravenously to meropenem 115 mg/8hours/intravenously to ceftazidime 170 mg/12 jam/intravenously, amikacin 85 mg/24 hours/intravenously, valganciclovir 60 mg/12 hours/oral, ursodeoxycholic acid 35 mg/8 hours/sonde, cholestyramine 0.85 gram/24 hours/sonde, spironolactone 3.5 mg/12 hours/sonde, furosemide 2 mg/24 hours/sonde. However, on the 56th day of treatment, the patient was passed away.

Discussion

Biliary atresia (BA) is an idiopathic cholangiopathy, which is a disease that progressively damages the extrahepatic bile ducts due to obliterative fibrosclerotic lesions. This is the most common cause of liver cirrhosis and liver failure and death if not treated.⁷ Biliary atresia's underlying etiology is unknown. According to many views, the aberrant embryogenesis or ductal inflammation, damage, and necrosis that results in progressive fibrosis of the intrahepatic and/or extrahepatic bile ducts are caused by a complex etiology. Between 3% and 20% of kids with BA have a congenital disorder or related condition.⁸

Our patient had a positive anti-CMV IgG result. Perhaps the presence of CMV can trigger biliary atresia. Several viruses such as cytomegalovirus (CMV), reovirus, human herpes virus, human papillomavirus, adenovirus, Epstein-Barr virus, hepatitis B virus, parvovirus B19 and rotavirus (RV) may play a role as etiology. Poisoning as well as genetic and immunological factors are also suspected as the cause of biliary atresia.^{3,8} Intrahepatic cholestasis initially had a higher prevalence of cytomegalovirus infection (without BA). However, several investigations have demonstrated that extrahepatic cholestasis can be a site of CMV infection (BA). According to the study, viruses like CMV might function as catalysts for immune system dysregulation due to genetic effects, which can ultimately result in BA. Hepatocytes and cholangiocytes can both become infected with cytomegalovirus and grow the virus. The virus can directly harm the liver and bile duct system as well as the immune system of infected cells, which causes inclusion bodies to develop in hepatocytes and epithelial vascular cells, particularly when they are combined with bile duct epithelial cells.^{3,9,10} As Zhao's study (2021) showed that biliary atresia patients who were also infected with CMV had a poorer prognosis, concerning jaundice clearance.¹¹

Antiviral medications have been a feasible therapy option during the past three decades. Several preliminary investigations in kids with symptomatic CMV treated for 6 weeks with intravenous ganciclovir show encouraging clinical improvement. Ganciclovir has been superseded by the antiviral medication valganciclovir, which is taken orally. It is used to treat CMV symptoms. 16 mg/kg/dose is administered twice a day for six months. Valganciclovir was administered orally every 12 hours to our patient.¹²

Clinically, Biliary atresia comes in two different kinds: perinatal and embryonic. In the early postpartum weeks, there is jaundice in the perinatal kind, which is (acquired, or non-syndromic), asymptomatic, and. The embryonic form, on the other hand, lacks a jaundice-free interval and has one or more congenital anomalies, including intestinal malrotation, site anomaly, bronchial anomaly, polysplenia or asplenia, discontinuity of the inferior vena cava's suprarenal section with azygote continuation, and preduodenal portal vein. Thus, the biliary tree's aberrant growth appears to be the cause of embryo formation, which includes children with biliary atresia splenic malformation syndrome

(BASM).¹³

Jaundice, which occurs when the liver does not eliminate bilirubin, is the initial sign of biliary atresia. Jaundice is brought on by bilirubin accumulation in the blood due to bile duct obstruction.¹⁴ It can be challenging to spot jaundice. Due to an underdeveloped liver, many healthy newborns experience moderate jaundice during their first one to two weeks of life. Unlike biliary atresia jaundice, which worsens over time, this kind of jaundice goes away 2 to 3 weeks after birth.³ Gray or white stools indicate a lack of bilirubin reaching the intestines, as do poor weight gain and growth. Dark urine indicates excessive levels of bilirubin in the blood leaking into the urine.¹⁴ Our patient complained of hepatomegaly, white stools, black urine, and persistent icterus more than two weeks after birth. It is crucial to know what color this chalky/putty stool is. Three separate (8-hour) stools are referred to as stool three servings. The three servings of feces collected in biliary atresia will typically be pale white (putty).

The infant appears healthy and shows no symptoms of failure to thrive in the early stages. At a more advanced stage, however, there will be obvious clinical symptoms, such as gastrointestinal and cerebral bleeding caused by portal hypertension or reduced vitamin K absorption, ascites and splenomegaly, which are signs of portal hypertension.^{4,12} Patients may also experience malnutrition and malabsorption brought on by chronic liver disease, gallbladder removal, and cholestasis. Our patient has been malnourished. In BA patients, the patient's daily caloric needs will increase, and it must be ensured that the patient maintains an intake of 125-150 percent of the recommended caloric intake. Due to its capacity to be absorbed directly through the portal vein, medium chain triglycerides (MCTs) should be included in enteral nutrition when it is necessary. A feeding tube should be available if required. To avoid developing a deficit in fat-soluble vitamins, vitamins A, D, E, and K should also be administered. The suggested doses of vitamin A are 5000–25000 IU/day, vitamin E is 25 IU/kg/day, vitamin D is 1200–4000 IU/day, and vitamin K is 2.5 mg three times per week. Prothrombin time and vitamin levels should be frequently checked. Our patient received 0.5 ml/24 hours/sonde vitamin drop and 12x50ml infant milk via sonde.¹⁵

Diagnosing biliary atresia is a challenge. The particular cause of intrahepatic cholestasis can be determined using diagnostic investigations that are guided by the history and physical examination.¹⁶ One study in Taiwan reported that clay excreta had high sensitivity (76.5%) but low specificity (99.9%) in predicting biliary atresia.¹⁷ Since time is an important factor in the prognosis of biliary atresia, a broad investigative approach is recommended. Ruling out other possible etiologies serology of congenital infection (TORCH; Toxoplasmosis, Rubella, CMV, Herpes simplex virus) is indicated.¹⁸ High serum Gamma GT (GGT) levels are usually found. Alkaline phosphatase is produced by bile duct epithelial cells and serum levels are elevated in cases of extrahepatic obstruction, cholangitis, and intrahepatic

cholestasis. Because alkaline phosphatase is also produced in bone, associated bone conditions may cause difficulties in interpreting the results. In cases of high alkaline phosphatase levels and GGT above 600 U/L, biliary atresia, or other obstructive ductal lesions, or even alpha-1 antitrypsin deficiency would be prime diagnostic candidates. GGT has been reported as a BA discriminatory tool and at a cutoff value of 250.5 U/L it has a sensitivity of 86.7% and a specificity of 65%.¹⁹

We performed an MRCP examination on our patients. An accurate non-invasive imaging method for the diagnosis of biliary atresia is functional MRCP. To prevent needless surgery in newborns with cholestatic jaundice, preoperative MRCP is highly advised. A tiny gall bladder on an MRCP has been said to be strongly indicative of biliary atresia.²⁰ Because MRCP does not directly demonstrate bile flow like hepatobiliary scintigraphy or ERCP does, this is one of its weaknesses.¹³ We diagnosed our patient with biliary atresia because it was clinically consistent with biliary atresia. The patient had icterus, puffy stools, and dark urine, as well as hepatomegaly. An investigation also lead to biliary atresia, which indicates an underdeveloped gallbladder.

To identify the existence and location of obstruction, every patient with suspected biliary atresia should have an exploratory laparotomy and direct cholangiography. Patients with lesions that can be repaired can receive direct drainage. In the absence of a correctable lesion, biliary epithelium can be identified and the size and patency of the remnant bile duct can be assessed using a frozen section taken from the transected porta hepatis.²⁰ Even though 80% of people with biliary atresia will eventually need a liver transplant, the Kasai procedure is still the preferred initial treatment. The Roux-en-Y branch, which is anastomosed to the porta hepatis following biliary resection, is used in the Kasai procedure to reestablish biliary flow between the liver and the gut. At the start of surgery, the liver and biliary tract are examined to make the diagnosis of biliary atresia. If the Kasai procedure is carried out before the baby is eight weeks old, the success rate for restoring normal bile flow is substantially higher (90%) than otherwise. Therefore, it's crucial to report infants with suspected biliary atresia early and evaluate them right away.²¹ Likewise, research by Verkade, et al (2016) concluded that kasai surgery must be carried out immediately before the age of 35 days to get a better prognosis.²²

In general, the diagnosis can be made if there is a fibrotic gallbladder and a cholestatic or even fibrotic liver. Cholangiography should be done if the gallbladder is patent or if there is a cyst near the liver's hilum. The color of the cyst or gallbladder's contents (yellow-green vs. translucent) should be noted since it can be used to determine the kind of biliary atresia and alter the surgical strategy. By using conventional techniques, jaundice can be lost in 50 - 60% of cases.⁷ In this patient, Kasai surgery was performed with the identification of the liver when opening the peritoneum, the impression was black and the gallbladder was present, not dilated. There were no left and right hepatic ducts, and no common bile ducts were found.

Common hepatic and left and right hepatic duct and common bile duct are only fibrotic tissue, remnant impression. Based on the anatomy of biliary atresia it is classified according to the degree of obstruction according to Japanese and Anglo-Saxon classification which consists of 3 main types, namely: Atresia of type 1 affects just the common bile duct, gallbladder, and patent hepatic duct (distal biliary atresia). The hepatic duct is affected by type II atresia, although the proximal intrahepatic duct is patent (proximal biliary atresia). Type IIa, gallbladder and patent common bile duct (sometimes with hilum cysts) (cystic atresia). Obliteration of the gallbladder, cystic duct, and common bile duct in type IIb. Type III: bilateral intrahepatic hepatic duct discontinuity as well as the entire tract extrahepatic biliary obstruction (complete biliary atresia).⁷ Based on the findings during the Kasai procedure, our patient was diagnosed with type III biliary atresia.

Effective postoperative management includes prevention and treatment of complications such as cholangitis and effective nutrition and family support. Although solid data supporting their utility is lacking, prophylactic antibiotics (to avoid cholangitis) and choleric drugs are sometimes administered.¹³ In addition, in severe cholestasis, ursodeoxycholic acid (UDCA) 20 mg/kg/day, rifampicin 5-10 mg/kg/day and phenobarbitone (5-10 mg/kg/day) can be given. Our patient received ursodeoxycholic acid 35 mg/8 hours/sonde and cholestyramine 0.85 gram/24 hours/sonde. In addition, our patient also received meropenem 115mg/8hours/iv and amikacin 85mg/24hours/intravenously.²³ This is in accordance with the results of the stool culture examination of this patient that the bacteria are sensitive to meropenem and amikacin.

In a study conducted by Mahmud et al, it was found that more than 2,000 extrahepatic cases died and only 6% of cases improved. But among intrahepatic cases 72.9% improved, 12.5% worsened and 14.6% died.²⁴ Complications of cholestasis can be avoided if intervention is done early. The success rate in making bile flow depends on the age of the baby at the time of surgery as well as the experience of the surgeon. The success rate can reach 80% if the operation is performed at the age of less than 30 to 45 days.¹³ The patient's prognosis is not good because the patient underwent Kasai surgery at the age of 4 months 8 days.

Our patient also has acyanotic congenital heart disease which may worsen the prognosis. The combination of BA and congenital heart abnormalities is linked with an especially high mortality risk and is one of the leading causes of death in BA. Mortality in the first year of life was found to be 20% in a recent analysis of the UK National Cohort of Children with Serious Congenital Heart Defects.²⁵ Shunt lesions were more prevalent than other types of lesions, such as pulmonary stenosis (7.7%), including patent ductus arteriosus (PDA), atrial septal defect (ASD), and ventricular septal defect (VSD) (23%). The most frequent congenital cardiac abnormality among patients with biliary atresia is patent ductus arteriosus.²⁶ ASD, VSD, and PDA all affect our patient. Some researchers assumed that BA was caused

by an inflammatory process involving the extrahepatic bile ducts in the late intrauterine or early neonatal period, despite the fact that the exact cause of BA is still unclear. Therefore, faulty organogenesis during the early embryonic phase may be a contributing factor in the pathogenesis of BA with structural malformations. Beginning as early as day 10 of pregnancy, the cardiovascular system develops, and by the end of the seventh week, the heart is virtually fully formed.²⁶ Digitalis and diuretics have long been the cornerstones of pharmacological therapy for heart failure in kids with big left-to-right shunts. Furosemide and spironolactone are two of the diuretics that are commonly used to treat CHF in newborns and young children due to their efficacy and lack of adverse effects. Optimizing diet, maintaining proper hemoglobin levels, and managing the accompanying respiratory symptoms are all part of the overall therapy.²⁷ According to our patients who underwent spironolactone medication at a dosage of 3.5 mg every 12 hours and furosemide at a dosage of 2 mg every 24 hours. However, our patient's electrolyte balance deteriorated after taking diuretics. As in the case of our patient, furosemide may cause clinically severe disturbances in fluid and electrolyte balance, including hypovolemia, hyponatremia, hypochloremia, hypokalemia, and alkalosis.²⁷

Our patient also had complaints of shortness of breath, and on physical examination, there are crackles. Our patient was diagnosed with community-acquired pneumonia. Acute lower respiratory tract infections are made worse by congenital heart disease, which is a significant risk factor. Pneumonia is the most typical acute lower respiratory tract illness. Pneumonia can be caused by a number of circumstances, including severe starvation.²⁸ There is pulmonary overcirculation and pulmonary oedema in CHD, such as acyanotic CHD, due to a left to right shunting of blood via a septal defect or the artery duct. The lower respiratory tract infection spreads to the pulmonary oedema, which results in congestive heart failure. Children who have cyanotic CHDs such as VSD, PDA, or atrioventricular septal defect (AVSD) are more likely to develop bronchopneumonia.⁵ In hospitalized cases, neonates with respiratory compromise should always be assumed to have bacterial pneumonia until proven otherwise. Administration of the antibiotic's ampicillin and gentamicin with or without cefotaxime should be started as soon as possible. Ampicillin is also the first-line antibiotic given to children aged > 3 months who have been immunized with uncomplicated pneumonia. For children with severe infections (those in the ICU), those who are not immunized, or in areas with high levels of penicillin-resistant pneumococci, a third-generation cephalosporin antibiotic (ceftriaxone or cefotaxime) should be given. If there is suspicion of an atypical pathogen or if the patient does not improve with this regimen, then a macrolide class can be added.²⁹

On the 56th day of treatment, the patient experienced decreased consciousness, shortness of breath and fever. The patient was diagnosed with septic shock. That same day, the patient was passed away. The poor prognosis of these patients is worsening by congenital heart disease, pneumonia, electrolyte

disturbances, malnutrition, and septic shock. The incidence of cardiac anomalies in biliary atresia was reported to be 8%-16% in a North American multicenter review. Congenital heart disease is associated with a very high risk of death and is one of the leading causes of death in biliary atresia overall.²⁵

Conclusion

Biliary atresia is a rare disease, and has a poor prognosis. Appropriate management should be given immediately to promote a more favorable prognosis. Pneumonia, sepsis, and congenital heart disease may further worsen the prognosis in patients with biliary atresia. The earlier treatment is given, the better the prognosis.

Conflict of Interest

There is no conflict of interest

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