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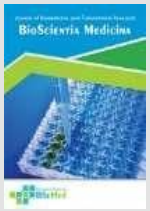

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Successful Steroid Treatment of Extrahepatic Cholestasis: A Case Report

Bagus Setyoboedi[1*], Rendi Aji Prihaningtyas[1], Muhammad Irawan[2], Syania Mega Octariyandra[1], Sjamsul Arief[1]

[1]Department of Child Health, Dr. Soetomo General Academic Hospital/Universitas Airlangga, Surabaya, Indonesia

[2]Department of Child Health, Saiful Anwar General Academic Hospital, Malang, Indonesia

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***Corresponding author:**
Bagus Setyoboedi

E-mail address:
bagus.setyoboedi@fk.unair.ac.id

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A B S T R A C T

Background: Biliary atresia is the most common cause of cholestasis. However, not all healthcare facilities are capable of performing Kasai surgery and liver transplantation. The involvement of inflammatory processes in the bile ducts triggered by viral infections has been suggested in several theories of pathogenesis. This case report describes the successful steroid treatment of an infant with extrahepatic cholestasis. **Case presentation:** A girl aged 2 months and 20 days presented with complaints of jaundice since the age of 2 weeks, with no improvement and worsening of the jaundice, with the color of the stools becoming paler than before. The nutritional status is normal. The physical examination revealed icteric sclera, hepatomegaly, and splenomegaly. There was cholestasis (total bilirubin 7.30 mg/dL and direct bilirubin 5.75 mg/dL), as well as elevated levels of AST (249 U/L), ALT (251 U/L), GGT (995.7 U/L) and increased to 1529.6 U/L, CMV reactive IgG 28.9, and Rubella reactive IgG 6.90. A two-phase ultrasound of the abdomen showed a thickening of the gallbladder wall. A liver biopsy showed mild portal fibrosis (F1). Steroids at a dose of 2 mg/kg/day in combination with ursodeoxycholic acid were administered. At follow-up one month later, the jaundice had improved. Stools were yellow-brown, and liver function tests and bilirubin were normal. **Conclusion:** Adjunctive steroid therapy to suppress the inflammatory process in biliary obstruction may be beneficial in the early phase of the disease, especially in limited surgical and transplant settings.

1. Introduction

Cholestasis is the stagnation or impairment of bile flow. Cholestasis can result from hepatocyte dysfunction in bile secretion and/or obstruction of the intrahepatic or extrahepatic ducts.[1] Cholestasis affects approximately one out of every 2,500 full-term infants. Biliary atresia is the most common cause of cholestatic jaundice during the first few months of life.[2] Biliary atresia (BA) is a fibroinflammatory disease that damages the extrahepatic and intrahepatic bile ducts. Biliary atresia is the most common cause of liver transplantation in children.[3] Failure to transport bile salts causes accumulation in the liver, resulting in membrane injury and decreased membrane function. Hepatotoxicity can also result from retained bile.[1] Although Kasai surgery has been performed to resolve extrahepatic bile obstruction, the stimulation of many biological mechanisms and the origin of biliary atresia remain unknown, contributing to liver inflammation and biliary cirrhosis.[3] Recently, several theories of disease pathogenesis have emerged, including increasing evidence for an inflammatory process in the bile ducts triggered by perinatal viral infection. Alternative therapies are still needed to benefit pediatric patients with biliary atresia. This case report aims to describe the successful treatment of an infant with extrahepatic cholestasis. Steroid therapy

may be of benefit in extrahepatic cholestasis which can be a sign of biliary atresia.

2. Case presentation

A 2-month-old and 20-day-old girl presented to Dr. Soetomo General Academic Hospital Surabaya with a primary complaint of jaundice. The complaint started with history of jaundice since two weeks old, accompanied by greenish-yellow feces, but the jaundice became more apparent, and the stool color paler than before (Figure 1). There was no fever, vomiting, or bloating, the baby drank well, and the weight gain was appropriate for her age. The patient had previously visited a pediatrician and received ursodeoxycholic acid therapy, but the baby remained jaundiced, so she was referred. There was no history of similar illness in the family. There was no previous illness. The patient was referred with a presumptive diagnosis of biliary atresia.

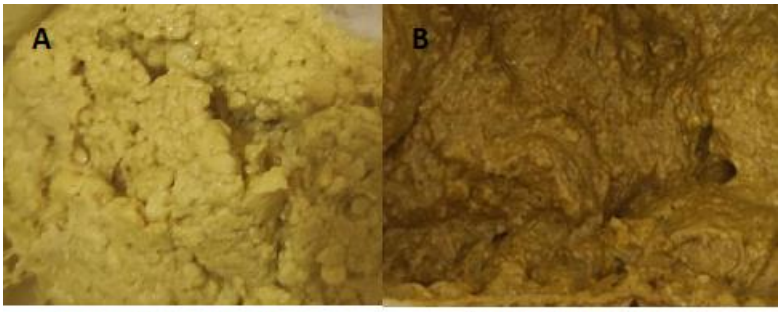

Figure 1. Acholic stool improvement after therapy.

The patient was the third of three children born by cesarean section at 40 weeks gestation due to failure to dilate following induction. She cried immediately and showed no signs of cyanosis. There were family members with similar complaints. The first child was jaundiced from the age of one month, was diagnosed with cholestasis, and died at 13 months old. The patient's current developmental milestone is smiling, but not yet able to lift the head. The patient has received HepB, Polio and BCG immunizations. The patient was breastfed until 3 weeks of age only, and continued with formula milk. The general clinical condition of the patient was good with a body weight of 5300 grams, body length 61 cm, head circumference 41 cm, abdomen circumference 38cm, upper arm circumference 13 cm. Nutritional status was normal. The vital signs were also normal. The physical examination revealed an icteric sclera, a hepatomegaly measuring 5 cm x 5 cm x 3 cm with a spongy consistency, sharp edges, a flat surface, and splenomegaly S1H1.

Liver function tests revealed elevated levels of AST (249 U/L), ALT (251 U/L), GGT (995.7 U/L), bilirubin (total 7.30 mg/dL, direct 5.75 mg/dL), and albumin (4.60 g/dL). Hb 13.5 g/dL, Hct 40.1, Wbc 7.15 x10^3/µL, Plt 607 x10^3/µL, ALP 447 U/L, PPT 10.3 sec, aPTT 33.9 sec, CRP <0.1 mg/dL, HbsAg non-reactive, Thyroid hormone was normal (FT4 0.98, and TSH 1.262). TORCH analysis revealed reactive CMV IgG 28.9 and reactive Rubella IgG 6.90. Two weeks later, liver function test levels were evaluated, including: AST 191 U/L, ALT 385 U/L, GGT increased to 1529.6 U/L, and ALP 184 U/L (Figure 2 & 3).

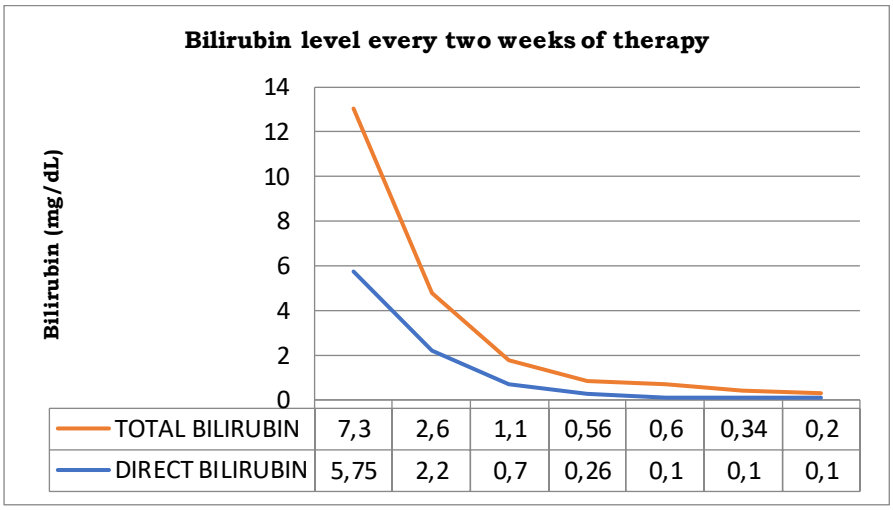

Figure 2. Bilirubin level of the patient.

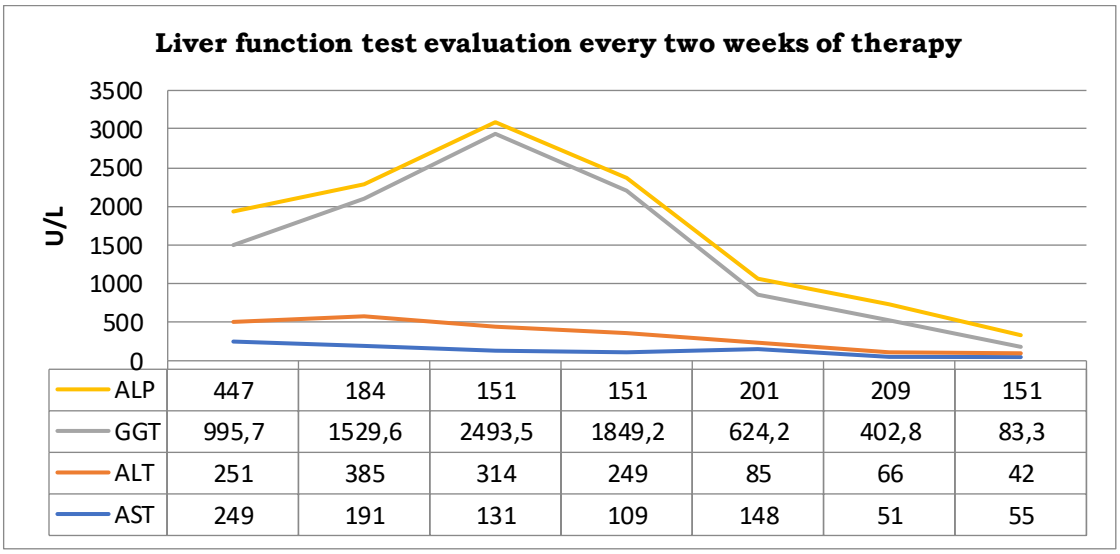

Figure 3. Liver function test measurement of the patient.

Echocardiography showed normal results. Eye and ENT screening were normal. Two-phase abdominal ultrasound showed gallbladder wall thickening, fasting volume +/- 0.06 cc, non-fasting +/- 0.04 cc, contractility index +/- 33% (CI N: 68-104%), with triangular cord sign supporting biliary atresia (Figure 4). Percutaneous liver biopsy showed inflammatory cell infiltration of neutrophils and lymphocytes concentrated in the portal tract. The hepatic lobules were composed of polygonal hepatocytes with partially turbid degeneration and hydrophic degeneration. MT/RC staining showed mild fibrosis in the portal tract (F1). The patient refused Kasai surgery and received a steroid dose of 2 mg/kg/day combined with ursodeoxycholic acid. Complaints of jaundice and pale stools were evaluated every subsequent day by parents who had been educated on stool color cards. Laboratory tests were evaluated every 2 weeks, showing decreased bilirubin levels, followed by decreased SGOT, SGPT, GGT, and ALP levels. At the time of evaluation after one month later, the jaundice had improved, the stools were

yellow-brown, the abdominal circumference had reduced, and developmentally, the patient was able to lift her head and lie on her stomach at 3 months of age.

3. Discussion

Cholestasis is always a pathological condition and an indication of hepatobiliary dysfunction, however, it is rarely recognized by health care professionals and is often dismissed as physiological jaundice.[2] Biliary atresia is the leading cause of cholestasis in the first month of life. It is still a health problem although it has been discovered in 1817 by Dr. John Burns.[4] Delays in diagnosis are still a common problem, especially in Indonesia. The disease is life threatening and survival rate of less than 10% at 3 years of age in untreated.[4]

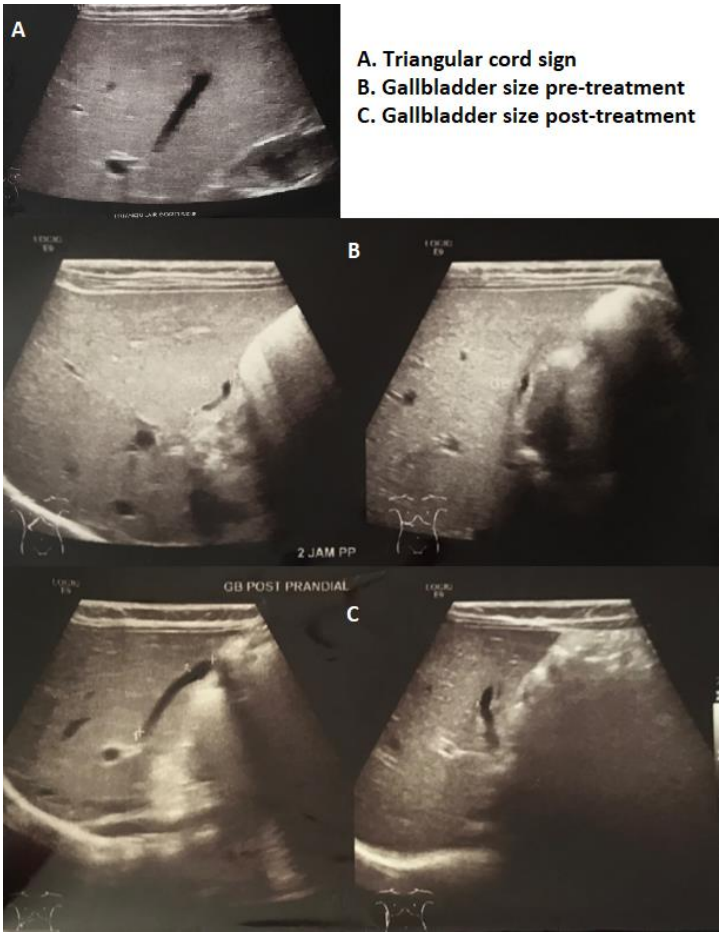

Figure 4. Two-phase abdominal ultrasound follow up after therapy.

Biliary atresia presents with persistent jaundice, clay-colored stools and hepatomegaly.[4,5] Studies in Indonesia suggest that acholic stool and elevated ALT and AST are associated with extrahepatic cholestasis compared to intrahepatic cholestasis.[6] Acholic stool has a sensitivity and specificity of 87% (95% CI; 82-91%) and 78% (95% CI; 74-82%) in establishing the diagnosis of biliary atresia.[7] Another study stated that in establishing the diagnosis of biliary atresia, clinical evaluation, hepatomegaly, stool color, and serum gamma-glutamyl transpeptidase (GGT) levels had an accuracy of 76.0%, 51.8%, 84.3%,

70.0%, %, specificity 70.2%, 77.5%, 74.8%, sensitivity of 83.1%, 87.6%, 96.1%, positive predictive value 69.0%, 72.6%, 75.7%, 64.6%, and negative predictive value 83.6%, 8.5%, 95.9%, 75.7%.[8] The sensitivity and specificity of MRCP for the detection of biliary atresia were 96 % (95% CI; 92-98%) and 58% (95% CI; 51-65%), liver function tests were 84 % (95% CI; 78-89 %) and 97% (95%; CI 97-98 %), and percutaneous liver biopsy was 98 % (95% CI; 96-99%) and 93% (95 % CI 89-95 %), respectively.[7]

Therefore, percutaneous liver biopsy has the highest sensitivity and specificity for diagnosing biliary atresia.[7] More than 80% of biliary atresia cases are identified by the presence of acholic stools and direct bilirubin levels >2 mg/dl in all cases, supported by liver biopsy results.[9] GGT levels greater than 524 U/L (8.7 times the upper limit of normal) have a sensitivity and specificity of 81.7% and 72.9%, respectively, suggesting biliary atresia.[10] The patient was found to be jaundice, pale stool, hepatosplenomegaly and cholestatic with a direct bilirubin level >20% of the total bilirubin level (total bilirubin of 7.30 mg/dL and direct bilirubin of 5.75 mg/dL), with elevated levels of AST (249 U/L), ALT (251 U/L) and GGT (995.7 U/L). The presence of cholestasis with a high GGT elevation was suggestive of biliary atresia.

Elevated serum direct bilirubin levels (direct bilirubin levels >1.0 mg/dL or >17 µmol/L) should be considered timely for evaluation and referral to a hepatologist,[2] although not all health workers and parents understand that infants who develop jaundice after 2 weeks of age should be evaluated for cholestasis by measuring total serum bilirubin and direct bilirubin. Previous study shows high sensitivity and specificity for identifying patients with chronic liver disease using a DB cutoff of 0.6 mg/dL.[11] Meanwhile, the success of Kasai surgery depends on patient age, and not all centers in Indonesia can perform Kasai surgery. The rate of delayed treatment is still quite high and varies from region to region. It is not always possible to provide optimal treatment. Therefore, alternative therapies to suppress biliary inflammation are very beneficial for patients.

This patient refused Kasai surgery. Therefore, steroids were administered as adjuvant therapy to suppress the inflammatory process in the bile ducts that progressively occurs in biliary atresia. A role for the immune system in the pathogenesis of epithelial injury and ductal obstruction has been supported by several patient-based studies. Studies have identified the involvement of CD8+ T lymphocytes, CD4+ cells, and pro-inflammatory cytokines such as interferon-gamma (IFNγ), interleukin-2, and tumor necrosis factor-alpha (TNFα) in the process of bile duct epithelial injury and obstruction.[5] Methylprednisolone was administered at a dose of 2 mg/kg/day, and ursodeoxycholic acid was added, followed by tapering of the steroid dose. Patients were routinely evaluated every 2 weeks assessing jaundice, stool color, bilirubin levels, and liver function. Following steroid administration, jaundice resolved and stools became more colored. Levels of bilirubin, AST, ALT, GGT, and ALP gradually decreased to normal levels. The patient was reported jaundice-free and is being monitored for growth.

4. Conclusion

Currently early detection and management of cholestasis remains a challenge. Extrahepatic biliary obstruction, most commonly due to biliary atresia, remains a health problem, especially in limited healthcare settings. Steroid administration as adjuvant therapy to suppress the inflammatory process of biliary obstruction may be beneficial in the early phase, especially in limited surgical and liver transplant facilities.

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