The Use of Steroid Therapy in Cholestasis: A Case Report

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Abstract

Background: Biliary atresia is defined by progressive fibroinflammatory obliteration of the extrahepatic and intrahepatic bile ducts, almost always resulting in cholestasis, portal fibrosis, and biliary cirrhosis. Almost all patients with biliary atresia present with hepatomegaly, acholic stools, and chronic jaundice. Surgery is the main treatment for biliary atresia, but not all centres can perform surgery. In patients with cholestasis that is suggestive of biliary atresia, treatment with steroids may be a beneficial alternative to initial therapy in the setting of limited health capacity for the prevention of liver fibrosis. **Case presentation:** A 2-month-old, 4-day-old boy presented to the hospital with a chief complaint of jaundice. The patient had jaundice since the week after birth and underwent phototherapy for one week, but the condition persisted. Yellow-brown urine and pale or acholic stools were also reported along with the complaints. Laboratory findings included elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), reactive IgG and IgM cytomegalovirus (CMV), and elevated direct bilirubin (cholestasis). A two-phase abdominal ultrasound showed a pre-prandial GB volume of +/- 0.295 cc and a post-prandial volume of +/- 0.166 cc with a contractility index of 12.9%. The patient was given ursodeoxycholic acid at a dose of 2 mg/kg BW/day in addition to steroid treatment. Laboratory tests were monitored every two weeks. After 8 weeks of therapy, clinical manifestations, and laboratory results were within normal limits. **Conclusion:** In infants with cholestasis suspected of biliary atresia, steroid therapy may be a useful alternative initial therapy in limited healthcare facilities to help suppress the progress of inflammation leading to bile duct fibrosis.

Keywords: Biliary Atresia; Cholestasis; Infant; Steroid; Jaundice

1. Introduction

A complex pathological state called cholestasis is characterized by decreased bile flow, which leads to the buildup of bile acids and other harmful compounds in the liver and causes liver injury.[1] Conjugated hyperbilirubinemia may be a symptom of neonatal cholestasis (NC), defined as decreased bile production or flow with retention of bile contents in the liver.[2] With an incidence of 1 case per 2,500 live births, neonatal cholestatic liver disease is the most common liver disease of the neonate. Neonatal cholestasis and destructive inflammatory obliterative cholangiopathy are often the result of biliary atresia, which can subsequently affect the intra- and extrahepatic bile ducts.[3]

Biliary atresia (BA) is defined by progressive fibroinflammatory obliteration of extra- and

intrahepatic bile ducts, almost always resulting in cholestasis, portal fibrosis, and cirrhosis. Asia has the highest incidence, while Europe and North America have the lowest. [4] Although Kasai portoenterostomy (KPE) is the standard surgical treatment for BA, liver transplantation is still recommended to prevent the consequences of further liver damage. Most patients with BA will eventually require liver transplantation due to the progression of cirrhosis and liver failure after KPE. As not all hospitals in Indonesia are equipped to perform liver transplantation, adjuvant therapies are urgently needed. Treatment with steroids is one of the therapeutic approaches that is under investigation.[5,6]

2. Case Presentation

A 2-month-old, 4-day-old boy presented to the hospital with a chief complaint of jaundice. The patient had been jaundiced since the week after birth and was treated with phototherapy for one week, but the jaundice persisted. The patient's jaundice continued to worsen until one month of age, at which time it was followed by an enlarged abdomen with visible blood vessels. Along with these complaints, yellow-brown urine and pale or acholic stools were reported. There were no additional complaints such as fever, vomiting, or bleeding. The patient had been treated with ursodeoxycholic acid in the past, but the distended abdomen and the elevated bilirubin level were still present. There was no history of prior illness or surgery. There is no history of similar diseases in the family.

Biliary atresia is suspected. Laboratory, radiographic, and liver biopsy were performed. Laboratory tests indicating elevated liver function included aspartate aminotransferase (AST) 130 U/L, alanine aminotransferase (ALT) 152 U/L, gamma-glutamyl transferase (GGT) 353.3 U/L, alkaline phosphatase (ALP) 404 U/L, and direct and total bilirubin (11.20 mg/dL and 15.00 mg/dL). FT4 1.17 ng/dL, TSH 1.1130 µU/mL, HbsAg non-reactive, APTT 38.0 sec, PPT 11.4 sec, and CRP 0.10 mg/dL were additional laboratory findings. TORCH serologies showed CMV IgG reactive at 23.7 IU/mL (<6) and CMV IgM reactive at 6.46 IU/mL (<0.85). After a routine blood test was performed, the following results were obtained: Haemoglobin 11.8 g/dL, Hct 35.3%, white blood cells 6.27 x103/µL, and platelets 20.5 x103/µL.

On two-phase abdominal ultrasound obtained liver measuring +/- 6.55 cm, sharp angles, flat edges, echo intensity parenchyma appears normal homogeneous, no visible dilation of IHBD/EHBD, v. porta caliber +/- 0.61 cm, a. hepatica caliber +/- 0.17 cm (ratio HAD/PV: 0.27), v. hepatica looks normal, triangular cord sign (-), no visible subcapsular hepatic flow, no visible nodules/cysts/masses. Gallbladder (GB) with pre-prandial size +/- 0.54 x 1.13 x 0.93

cm, no wall thickening, no stones/nodules/sludge, postprandial size +/- 0.46 x 1.07 x 0.65 cm with GB contractility index +/- 12.9% no abnormal hypo/ hyperechoic lesions. Spleen with longitudinal length +/- 5.28 cm, parenchyma echo intensity appeared normal, and no mass/cysts were seen. A two-phase abdominal ultrasound showed pre-prandial GB volume +/- 0.295 cc and post-prandial +/- 0.166 cc with a contractility index of 12.9%. Percutaneous liver biopsy showed infiltration of lymphocyte inflammatory cells and a few PMN in the portal tract. There is no bile duct proliferation. In the portal tract, the lobules consist of hepatocyte cells, some of which have undergone cloudy degeneration, the cytoplasm contains pigmented bile, the mebelar contains pigmented bile, and several multinucleated giant cell hepatocytes are visible. There are also foci of inflammatory lymphocyte cells between the hepatocyte lobules. On MT/RC staining: No fibrosis was found.

In addition to receiving ursodeoxycholic acid, the patient also received 2 mg/kgBW/day of steroids. Parents who had also received education regarding stool color cards assessed complaints of jaundice and acholic stools daily. Laboratory tests were monitored every two weeks. The patient had weekly tapered off of steroid therapy. The jaundice symptoms have improved, and the acholic stools have darkened (Figure 1). Following steroid medication, a reassessment of liver function showed total bilirubin 0.50 mg/dL, direct bilirubin 0.40 mg/dL, AST 69 U/L, ALT 61 U/L, and GGT 65.1 U/L. According to the findings of the laboratory examination, during the eighth week of treatment, there was a drop in the levels of AST, ALT, GGT, and bilirubin, with total bilirubin reaching 0.50 mg/dL and direct bilirubin reaching 0.40 mg/dL (Figure 2).

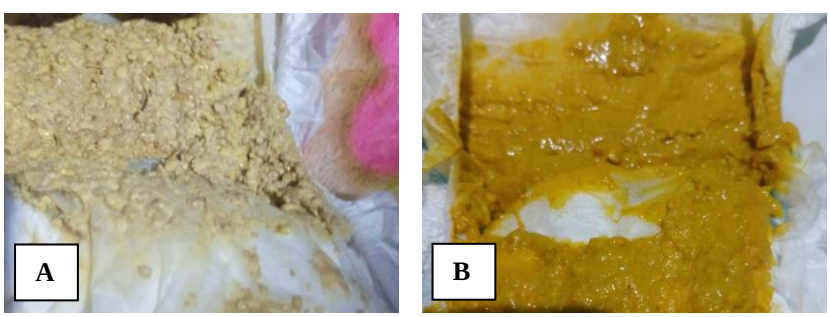

Fig. 1. Stool color evaluation (A. Before treatment; B. After treatment)

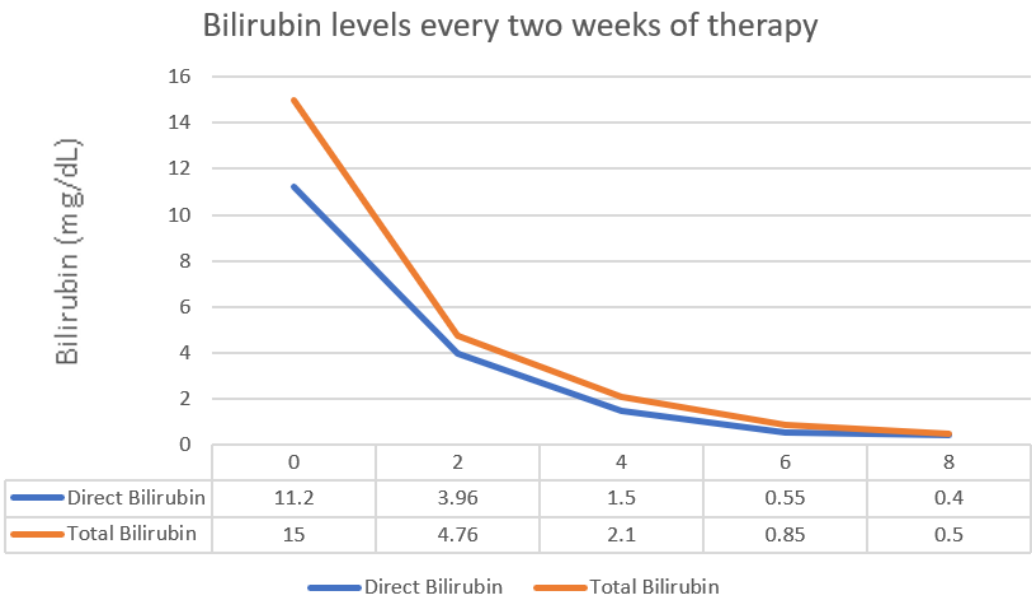

Fig. 2. Serum bilirubin level elevation every two weeks during treatment

3. Discussion

Clinical features in this patient, including hepatomegaly, acholic stools, and chronic jaundice, were suggestive of biliary atresia.[7] An increase in direct bilirubin of 11.2 mg/dL, or more than 20% of total bilirubin, in this patient was suggestive of cholestasis, supporting the diagnosis of biliary atresia (BA).[8] On a 2-phase abdominal ultrasound examination, a gallbladder index < 25% was obtained suggesting biliary atresia. Gallbladder is defined as abnormal if it is absent or its length is <1.9 cm or contractility index is <60%.[9] Since 1981, serum gamma-glutamyl transferase (GGT) activity has been used for the diagnosis of BA. As a result, various cut-off levels of serum GGT have been proposed to increase the accuracy of the diagnosis of BA. A cut-off value of >250 U/L with a sensitivity of 83.3% (95% CI 55.2-95.3%) and a specificity of 70.6% (95% CI 46.9-86.7%) was found to have the highest diagnostic performance for the identification of BA.[10]

Several circumstances may cause bile flow disorders. Antigenic stimuli, exotoxins, endotoxins, xenobiotics, and microbes can all stimulate cholangiocyte responses that can lead to cholestatic states. However, most of the environmental triggers are still unknown. Another risk factor is obstruction of the biliary tract. Both extrahepatic and intrahepatic obstruction can result from extrinsic benign compression (cystic disease) and malignant mass impact (cholangiocarcinoma), as well as from cholelithiasis production or

migration across the biliary network. [11]

Numerous potential pathomechanisms have been hypothesized as an etiopathogenesis of biliary atresia. These are divided into several categories, including toxins, genetic variations, immunogenic abnormalities or autoimmune illnesses, vascular problems, microchimerism in mothers, viral infections, and morphogenesis anomalies. A viral infection that causes an initial lesion to the bile ducts could trigger an immune-mediated fibro obliterative process that progresses and eventually destroys the bile ducts. Benjamin Landing originally postulated in 1974 that biliary atresia and other infantile obstructive cholangiopathies are caused by a viral infection of the liver and hepatobiliary tree. It has been suggested that several viruses, such as rotavirus (RV), cytomegalovirus (CMV), reovirus, human herpes virus, human papillomavirus, adenovirus, Epstein-Barr virus, hepatitis B virus, and parvovirus B19, may be involved in these circumstances. Extensive study has been conducted on reovirus, CMV, and RV.[12] Inflammatory factor overexpression is a hallmark of biliary atresia, a progressive fibro-inflammatory disease. Solvable inflammatory adhesion molecules and cytokines are more prevalent in the liver and bloodstream of biliary atresia patients. These molecules may be used to predict the survival of the native liver following Kasai portoenterostomy treatments. However, despite the Kasai portoenterostomy, there may still be persistent inflammation in the native liver, which may eventually lead to cirrhosis of the liver.[13,14]

Cytomegalovirus

The DNA virus known as CMV is a member of the Herpesviridae family. It is responsible for a widespread, unrecognized infection in children and adults that affects 60 percent to 90 percent of the people in the world. It can be fatal in newborns. The disease can be asymptomatic viremia, tissue-invasive CMV disease, or CMV syndrome with organ involvement (pneumonitis, colitis, hepatitis). Infections during pregnancy and congenital conditions can also lead to liver involvement. Liver involvement can range from mild, resulting in hepatomegaly or elevated transaminases, to moderate to severe, including cirrhosis, cholestatic liver disease, and hepatitis, although the latter is uncommon.[15]

Viruses can directly destroy cholangiocytes, but can also trigger an autoimmune proinflammatory process that damages liver tissue even after primary infection is treated. CMV is one of the infectious agents that has been found in 10% to 38% of infants diagnosed with BA. It has been suggested that the inflammatory obstruction of the extrahepatic and intrahepatic bile ducts in BA is mediated by the immunological response induced by CMV.[14] Viral infection, as a result of tolerance failure or impaired immune regulation, has been shown to activate the immature immune system and trigger an autoimmune pattern. It is characterized by an imbalance in Th1/Th2 cell development and abnormalities in regulatory T cell quantity and function, resulting

in epithelial and ductal cell damage, fibrosis, and cirrhosis.[15]

There are two types of adaptive immune responses: humoral immunity, which is mediated by B cells that produce antibodies, and cellular immunity, which is mediated by T cells that produce cytokines. Cellular immunity's role in bile duct damage in BA has been studied extensively over this past decade. Many studies have shown that in the portal tract infiltrates surrounding the bile ducts, both CD4+ and CD8+ T lymphocytes are present. These lymphocytes have been found to invade the spaces between the bile duct epithelia and cause intrahepatic bile duct degeneration. The proliferative cell surface marker CD71 and the activation markers CD25 and LFA-1 indicate that the T cells are highly activated. The T cells in the BA liver and extrahepatic bile duct remnants were found to be oligoclonal with a restricted repertoire for TCR Vβ, indicating that the T cells are proliferating in response to a specific antigen(s). When other immune cells are stimulated, activated effector T cells can produce cytokines that directly or indirectly damage epithelial cells. In individuals with BA, the Th1 cellular cytokines IFN-γ, IL-2, and TNF-α are secreted by T cells in the liver; this feature is specific to BA and not present in other neonatal cholestatic diseases.. [16]

Upon recognition of antigens, B cells initiate the humoral immune response by secreting antibodies specific to the antigen during the effector phase. The recognition of protein antigens by CD4+ T cells, which in turn activate B cells to produce antibody responses, may indicate a synergistic relationship between humoral and cellular immunity. The possible involvement of humoral immunity in the pathophysiology of BA is poorly understood. Immunoglobulin deposition in the biliary remains of BA was reported more than thirty years ago by Hadchouel et al. Twenty-five specimens were found to be depleted of immunoglobulin (Ig)M, while 19 of the 128 remaining examined were found to contain both IgM and IgG.[16]

To determine if steroid medication is appropriate for BA, one must consider both the drug's potential side effects and efficacy. This allows for a fair risk-benefit analysis. However, there has been no prospective evaluation of the safety of steroid treatment in infants with BA. Because data collection has been retrospective, it is not surprising that very few, if any, adverse events have been documented in the numerous publications. Five complications—wound dehiscence, gastrointestinal bleeding and perforation, anastomotic failure, and candida infection—were noted in the Japanese national study. It is impossible to determine causality with accuracy in this report because it does not have a sufficient control group.[17] There were no side effects of steroid administration in this case.

Winahyu AK et al. showed that steroid use might benefit biliary atresia therapy. According to the case report, the infant had increased GGT levels, persistent jaundice, cholestasis, and acholic feces. The liver biopsy results also suggested extrahepatic cholestasis. Methylprednisolone was administered as a steroid at a dose of 2 mg/kg/day, with weekly tapering off. Every two weeks, therapeutic evaluations including laboratory

and clinical testing were carried out. Following medication, there was an improvement in the cholestasis-related clinical and laboratory outcomes. There may be a new potential target therapy to prevent fibrosis in BA with the use of steroids, but more extensive research is needed to demonstrate the early benefit of steroids in preventing the progression of cholestasis to BA.[18]

Setyoboedi B. et al. also showed that using steroids can be beneficial in patients with BA. A 2-month-old and a 20-day-old girl had previously shown jaundice and acholic stools since they were two weeks old. An analysis of liver function tests showed that bilirubin (total 7.30 mg/dL, direct 5.75 mg/dL), AST (249 U/L), ALT (251 U/L), and GGT (995.7 U/L) were all increased. Reactive IgG for CMV (28.9) and Rubella (6.90) was found by TORCH serology analysis. The following results of the liver function tests were evaluated two weeks later: ALP was 184 U/L, ALT was 385 U/L, GGT had increased to 1529.6 U/L, and AST was 191 U/L. This patient refused Kasai surgery. Therefore, steroids were administered as adjuvant therapy to reduce the inflammatory process in the bile ducts that progressively develop in biliary atresia. The steroid dosage was tapered after adding ursodeoxycholic acid and methylprednisolone at a dose of 2 mg/kgBW/day. Patients were routinely evaluated every two weeks. Liver function, bilirubin levels, stool color, and jaundice were assessed. Following steroid treatment, jaundice resolved and stool color improved. The levels of bilirubin, AST, ALT, GGT, and ALP have all gradually returned to the normal range. The patient is being monitored for growth and has been reported to be free of jaundice. [5]

Methylprednisolone was started at 2 mg/kg BW/day and tapered weekly as part of the patient's steroid therapy. The patient was then evaluated every two weeks. The patient showed clinical improvement with less pale stools and jaundice. There was also a decrease in bilirubin, AST and ALT levels. The patient is currently in the 8th week of treatment and will still be under observation for growth and development.

4. Conclusion

Biliary atresia remains a difficult diagnosis and the disease tends to get worse over time. Biliary atresia is not always easily diagnosed in the medical setting and requires immediate surgical intervention. In infants with cholestasis who are suspected of having biliary atresia, steroid medications may be a useful alternative initial therapy in limited healthcare settings to help prevent progression to biliary fibrosis.

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