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A CASE REPORT OF SUCCESSFUL STEROID TREATMENT IN INFANT WITH EXTRAHEPATIC CHOLESTASIS

LAPORAN KASUS KEBERHASILAN PENGOBATAN STEROID PADA BAYI DENGAN KOLESTASIS EKSTRAHEPATIK

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Case Study
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A B S T R A C T

Background: *Cholestatic jaundice in infants is a significant healthcare challenge, particularly in regions where access to surgical intervention and liver transplantation is limited. An immunologic mechanism underlies the pathogenesis of biliary atresia leading to fibro-obliteration of the bile ducts. However, the successful management of biliary atresia is often difficult because treatment typically occurs at an advanced stage. Therefore, alternative therapies that can suppress bile duct inflammation are urgently needed. Administering anti-inflammatory drugs such as methylprednisolone to infants in the early stages of cholestasis may provide opportunities to improve outcomes in the limited capacity to perform Kasai surgery and liver transplantation.* ***Purpose:*** *This case report describes the clinical improvement of extrahepatic cholestasis following steroid administration.* ***Case analysis:*** *We report a case of a 24-day-old male infant presenting with clinical symptoms of jaundice and pale stool. Liver biopsy revealed features consistent with extrahepatic obstructive cholestasis characteristic of biliary atresia. The patient was treated with methylprednisolone (a corticosteroid) and ursodeoxycholic acid without surgical intervention.* ***Result:*** *The combination of methylprednisolone and ursodeoxycholic acid normalized liver function tests and led to significant clinical improvement. Both jaundice and pale stools completely resolved within two months of treatment.* ***Conclusion:*** *Steroid therapy may provide clinical benefits for infants with extrahepatic cholestasis, particularly in settings with limited healthcare resources. Steroid administration may play a role in the suppression of the inflammatory process that causes fibrosis and bile duct obliteration in the early stages of the disease.*

A R T I C L E I N F O

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A B S T R A K

Latar belakang: Penyakit kuning kolestatik pada bayi merupakan tantangan kesehatan yang signifikan, terutama di negara dengan akses terhadap pembedahan dan transplantasi hati terbatas. Mekanisme imunologis mendasari patogenesis atresia bilier yang menyebabkan fibro-obliterasi saluran empedu. Namun, keberhasilan penanganan atresia bilier bervariasi karena sering kali ditangani pada stadium lanjut. Oleh karena itu, terapi alternatif yang dapat menekan peradangan saluran empedu sangat dibutuhkan. Pemberian obat anti-inflamasi seperti metilprednosolon pada bayi pada tahap awal kolestasis mungkin dapat memberikan peluang untuk meningkatkan luaran pada fasilitas kesehatan yang terbatas dalam melakukan operasi Kasai dan transplantasi hati. **Tujuan:** Laporan kasus ini menjelaskan perbaikan kolestasis ekstrahepatik setelah pemberian steroid. **Analisis kasus:** Kami menyajikan sebuah kasus bayi laki-laki berusia 24 hari yang datang dengan gejala klinis ikterus dan feses berwarna pucat. Kolestasis obstruktif ekstrahepatik yang merupakan karakteristik atresia bilier, ditemukan pada biopsi hati. *Metilprednisolone* (kortikosteroid) dan asam ursodeoksikolat diberikan tanpa tindakan operasi. **Hasil:** Kombinasi metilprednisolon dan asam ursodeoksikolat, memberikan perbaikan fungsi hati. Penyakit kuning dan feses pucat membaik dalam waktu dua bulan pengobatan. **Kesimpulan:** Terapi steroid bermanfaat bagi penyembuhan bayi dengan kolestasis ekstrahepatik, terutama digunakan di fasilitas kesehatan yang terbatas. Berdasarkan pemahaman tentang mekanisme autoimun yang mendasari atresia bilier, pemberian steroid dapat berperan dalam menekan proses inflamasi yang menyebabkan fibrosis dan pembuntuan saluran empedu pada tahap awal penyakit.

Kata kunci:
Kolestasis, Kolestasis ekstrahepatik, Penyakit kuning, Kedokteran Steroid

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INTRODUCTION

Cholestatic jaundice in infants remains a challenging health problem. It is often misdiagnosed as physiological jaundice (Maisels *et al*., 2014; Setyoboedi *et al*., 2022). Biliary atresia can cause elevated direct bilirubin shortly after birth (Harpavat *et al*., 2011). Cholestatic jaundice needs to be treated immediately because of the risk of liver damage (Patel, 2023). Therefore, any prolonged jaundice that occurs in an infant for more than 2 weeks after birth should be evaluated for cholestatic jaundice because of the risk of progressive liver damage (Götze *et al*., 2015; Hodgson *et al*., 2018).

In confirmed cases of cholestasis, evaluation and specific therapy for suppression of liver fibrosis due to bile flow obstruction should be initiated immediately. Measuring direct and total bilirubin fractions is highly recommended for prolonged jaundice in infants (Fawaz *et al*., 2017). Cholestasis is typically diagnosed when direct bilirubin exceeds 1.0 mg/dL with total bilirubin below 5.0 mg/dL, or when direct bilirubin constitutes more than 20% of total bilirubin if the total level exceeds 5.0 mg/dL. Direct bilirubin levels ≥1.0 mg/dL have been shown to be more sensitive for detecting biliary atresia than the direct: total bilirubin ratio in infants aged 3 to 60 days (Liao *et al*., 2022). In addition to an elevated serum direct bilirubin level, cholestasis has been associated with depigmented stools or cholestatic feces. These findings suggest an extrahepatic obstructive process. Early identification of infants with biliary atresia—a leading cause of cholestasis—is essential for timely intervention and improved outcomes (Götze *et al*., 2015). However, a significant clinical limitation is that not all healthcare facilities are equipped to perform a Kasai to achieve optimal surgical outcomes. The purpose of this case report is to describe the improvement of extrahepatic cholestasis after administration of steroids.

CASE STUDY

A 24-day-old infant boy presented to the outpatient clinic for pediatric hepatology with the primary complaint of jaundice since birth, accompanied by acholic stools. Physical examination revealed that he had icteric sclerae, hepatomegaly, with no evidence of splenomegaly. He was born via normal delivery with a birth weight of 2700 grams. He was admitted to the NICU at the age of 3 days due to a lung infection. His laboratory results were aspartate aminotransferase (AST) 397 U/L, Alanine aminotransferase (ALT) 257 U/L, direct bilirubin 23.29 mg/dl, total bilirubin 33.25 mg/dl, albumin 3.15 g/dl, Gamma-glutamyl transferase (GGT) 65 U/L, and alkaline phosphatase (ALP) 275 U/L. A 2-phase abdominal ultrasound showed pre-prandial gallbladder with the size of 1.57 x 0.8 cm and postprandial gallbladder with the -+size of 0.79 x 0.23cm.

The liver biopsy revealed a dilated portal tract with proliferation of bile ducts, several bile ducts containing bile pigment, accompanied by inflammatory cells, lymphocytes, and neutrophils. Hepatocytes showed ballooning degeneration and cloudy swelling, with some containing dilated intracanalicular bile pigment. Multinucleated giant cell hepatocytes were also observed, and foci of lymphocytes inflammation were present between the hepatocytes. The MT and RC staining showed fibrosis of the portal vein (F1). The conclusion was an extrahepatic obstructive cholestasis, which can be obtained in biliary atresia. The patient was subsequently started on methylprednisolone 2 mg/kg/dose in divided doses, followed by tapering and ursodeoxycholic acid 10 mg/kg/dose 3 times a day. Parents refused the Kasai surgery.

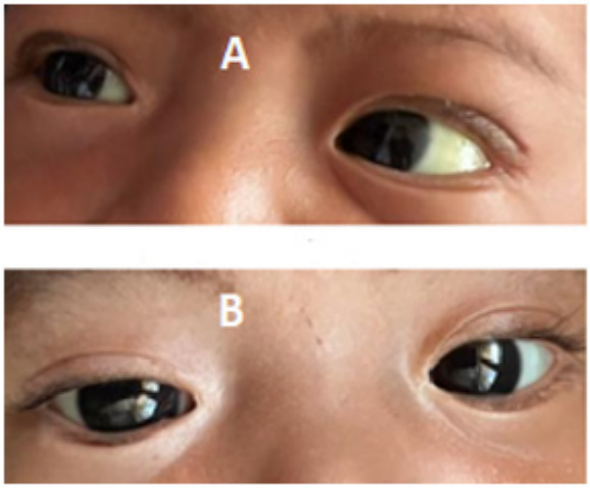


Figure 1. Clinical jaundice of the patient (A. Before therapy and B. After therapy)

Two months after initiating treatment, the patient showed no jaundice, the stool was yellow and the laboratory results were AST 56 U/L, ALT 82 U/L, Gamma GT 244 U/L, direct bilirubin 0.8 mg/dl, total bilirubin 1.3 mg/dl (Figure 1 and Figure 2). No recurrence jaundice was observed post-steroid treatment. The stool color was darker than before, followed by an improvement in laboratory values (Figure 3). The second phase 2 abdominal ultrasound evaluation showed gallbladder measurements of preprandial ± 1.4 x 3.19 x 1.4 cm (volume ± 3.2 cc), postprandial ± 0.95 x 2, 97 x 1.28 cm (volume ± 1.87 cc) with a contractility index of 43% (Figure 4).

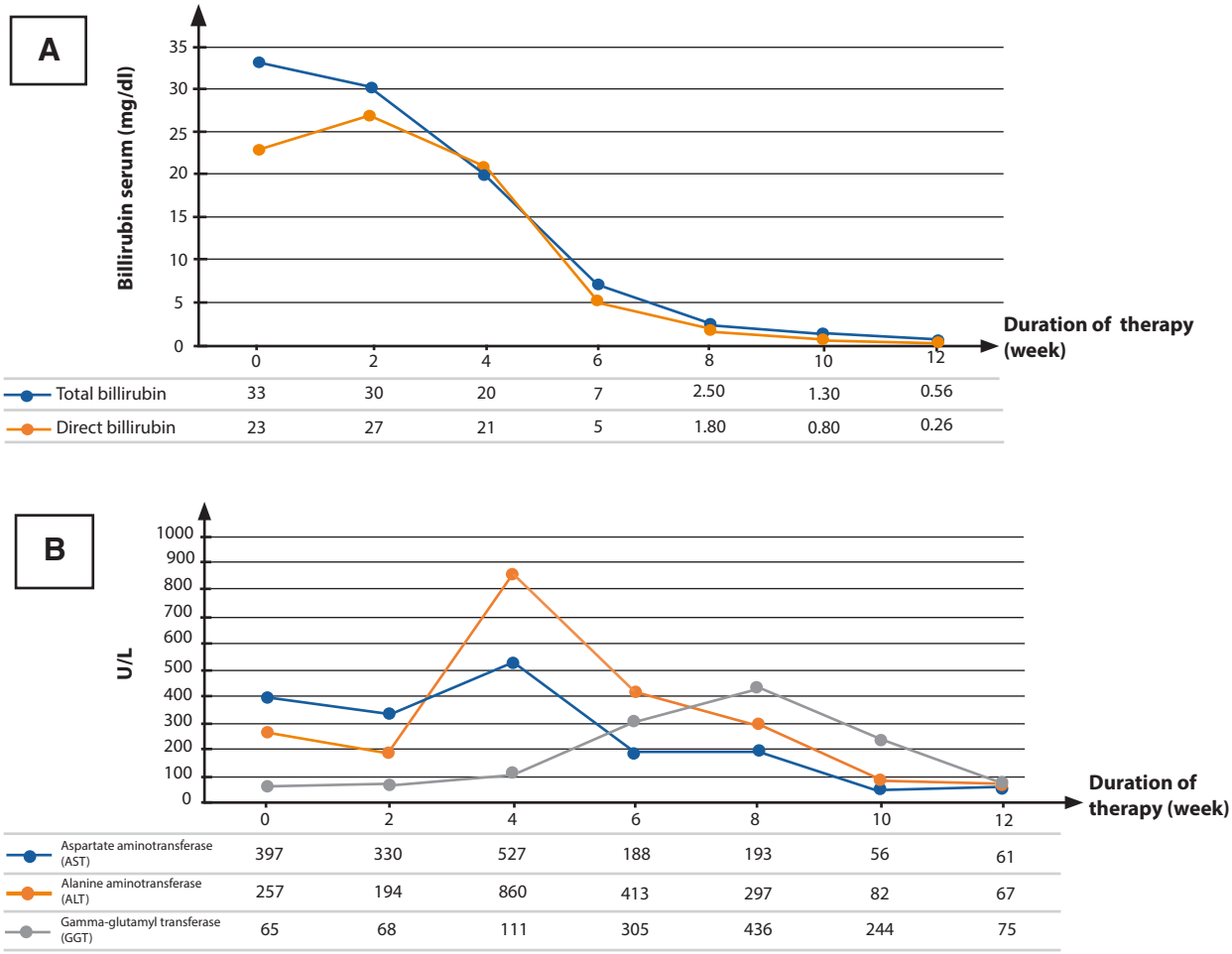
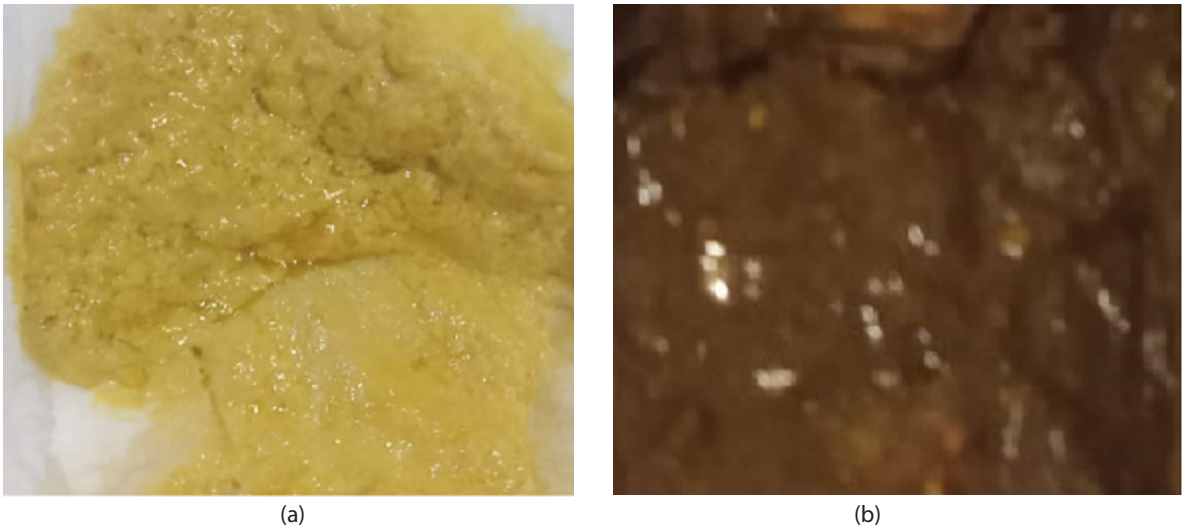


Figure 2. Improvement of laboratory parameters of the patient every two weeks evaluation (A. Bilirubin serum level and B. Liver function test)



(a) (b)

Figure 3. Acholic stool improved after therapy. (a) Before therapy and (b) After therapy

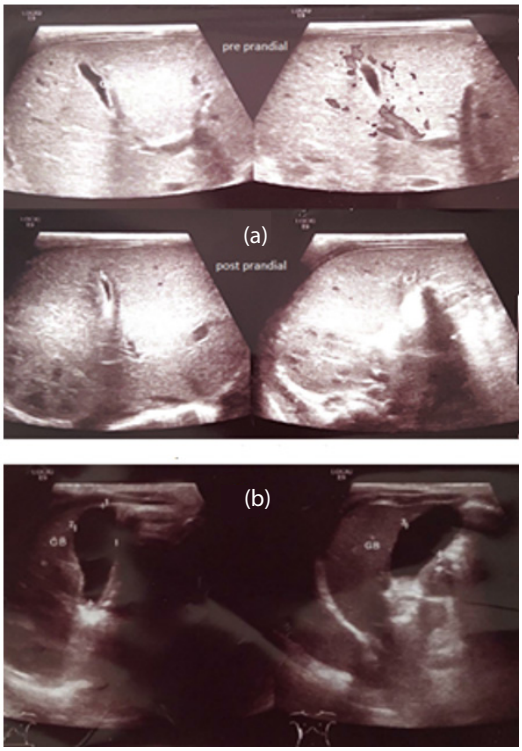


Figure 4. Abdominal ultrasonography of the patient. (a) Before therapy and (b) After therapy

RESULT

Direct and total bilirubin measurements are needed to rule out cholestasis in infants with prolonged jaundice. Cholestasis is established if the serum direct bilirubin level exceeds 1 mg/dl (17.1 µmol/L) when the total serum bilirubin level is less than 5 mg/dl (85.5 µmol/L), or if the serum direct bilirubin level is more than 20% when the total serum bilirubin level is greater than 5 mg/dl (85.5 µmol/L). Cholestasis can be the first sign of severe hepatobiliary impairment (Feldman and Sokol, 2021). If cholestasis is confirmed by serum bilirubin measurements, a two-phase ultrasound and biopsy of the liver may be performed. An intraoperative cholangiogram or ERCP may be performed if the results of this examination are inconclusive (Götze *et al*., 2015). Neonatal cholestasis is often caused by biliary atresia, which occurs when the bile ducts become blocked within the first 3 months of life. This condition is quite common, affecting approximately 1 in every 6.000 to 12.000 live births worldwide (Fawaz *et al*., 2017). Occasionally, other congenital abnormalities, such as malformations at birth, may manifest (Davenport *et al*., 2006).

Clinically, distinguishing cholestatic jaundice from physiological jaundice in infants can be challenging. Current guidelines include conducting bilirubin tests in newborns who continue to have jaundice after reaching 2 weeks of age. Furthermore, it is recommended to refer these children to a hepatologist if their direct serum bilirubin levels exceed 1.0 mg/dL or 17 mmol/l (Fawaz *et al*., 2017). Cholestasis is usually associated with elevated levels of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, but does not always indicate a specific cause. However, elevated γ-glutamyl transpeptidase (GGT) levels (>150 - 200 U/L) are often found in biliary atresia (Fawaz *et al*., 2017; Feldman and Sokol, 2021).

Biliary atresia may present with cholestasis, elevated liver transaminase levels, increased GGT levels, and pale stools. Variable hepatosplenomegaly may be seen in biliary atresia, in addition to acholic stools and dark urine (Vij and Rela, 2020). An abdominal ultrasound is performed to rule out other causes of biliary atresia, such as choledochal cysts, gallstones, or bile casts. The presence of a tiny gallbladder or its complete absence is suggestive of biliary atresia (Götze *et al*., 2015). In this case, the infant was jaundiced from birth, with persistent jaundice for more than 2 weeks of life, followed by pale stools. Laboratory results showed cholestasis, abdominal ultrasound showed impaired gallbladder and liver biopsy suggested extrahepatic cholestasis. All these findings support biliary atresia.

DISCUSSION

Early diagnosis of biliary atresia remains a significant clinical challenge. In most cases, the condition is characterized by jaundice accompanied by acholic stool (Okajima *et al*., 2016). Laboratory examination shows cholestasis and is supported by abdominal ultrasound and liver biopsy. Among patients diagnosed with biliary atresia, 73% exhibit a so-called

pseudo gallbladder, whereas 27% show no gallbladder or gallbladder-like features as discovered by abdominal ultrasonography (Aziz *et al*., 2011).

Percutaneous liver biopsy is essential when identifying neonatal cholestasis. Percutaneous liver biopsy for biliary atresia is performed before surgery in most cases. Studies have shown that the accuracy of diagnosing biliary atresia using liver biopsy ranges from 85% to 95%. In a recent study, it was found that needle biopsy has an accuracy rate of approximately 90.1%. The sensitivity and specificity for detecting biliary atresia were determined to be 88.4% and 92.7% respectively. Furthermore, liver biopsy is a valuable tool for eliminating other potential causes of neonatal cholestasis, including viral infection, neonatal sclerosing cholangitis, Progressive Familial Intrahepatic Cholestasis (PFIC), Idiopathic Neonatal Hepatitis (INH), Alpha-1 antitrypsin (A1AT) deficiency, Alagille syndrome (ALGS), and metabolic liver disease (Feldman and Sokol, 2021; Russo *et al*., 2016).

Performing a percutaneous liver biopsy followed by an intraoperative cholangiogram is considered the gold standard for diagnosing biliary atresia. This procedure is typically done when the liver biopsy results are inconclusive. The biopsy examination has an accuracy rate of 79 - 98% of cases, which is described by the presence of inflammatory cell infiltrates around the bile ducts, fibrosis of the portal tract, biliary obstruction due to accumulation of bile, followed by proliferation of the bile ducts. Biliary atresia is currently treated with Kasai surgery, but the success rate is variable and multifactorial (McKiernan *et al*., 2009). At present, late diagnosis still occurs, affecting surgical success (Butler *et al*., 2016; Götze *et al*., 2015).

Environmental, infectious, and genetic factors are believed to contribute to the development of biliary atresia (Siddiqui and Koirala, 2024). However, it has been discovered that autoimmunity may play a role in the development of biliary atresia. Acquired or perinatal form accounts for more than 70 - 80% of biliary atresia cases (Lykavieris *et al*., 2005). Acquired or perinatal biliary atresia is mediated by an autoimmune process that causes biliary inflammation, resulting in biliary injury leading to fibrosis and blockage of the ducts (Feldman and Sokol, 2021; Lakshminarayanan and Davenport, 2016). Although Kasai surgery was commonly performed, there is still a risk of persistent intrahepatic bile duct injury and the development of liver cirrhosis. Biliary atresia is an important factor in the need for liver transplantation in children, accounting for more than half of the cases (Davenport *et al*., 2006; Lykavieris *et al*., 2005).

The onset of biliary injury in biliary atresia is believed to occur before birth. The development of biliary atresia is understood to be caused by damage to the bile ducts, triggered by a viral infection, which then leads to an excessive inflammatory or autoimmune reaction that specifically affects the bile duct epithelium (Feldman and Sokol, 2021). There is evidence of increased expression of TLR8 and IFN-γ mRNA in biliary atresia, indicating the involvement of innate immune responses in biliary injury (Dong *et al*., 2011; Saito *et al*., 2011). IL-18 and IFN-gamma were found to be elevated, suggesting that the adaptive immune system plays a role in developing biliary atresia (Vejchapipat *et al*., 2012). Corticosteroids exert anti-inflammatory effects through multiple pathways. The steroid binds to the glucocorticoid receptor across the cell membrane to form the receptor-glucocorticoid complex. The glucocorticoid-receptor complex translocates to the nucleus and modulates transcription factors that regulate the production of proinflammatory mediators. The production of various inflammatory mediators is suppressed. Glucocorticoids have the effect of suppressing the initial processes in the inflammatory response and triggering the resolution of the inflammation (Coutinho and Chapman, 2011; Williams, 2018). The production of various inflammatory mediators has been reported in several studies in biliary atresia, which seemed to be suppressed by steroid administration. This prevents the progression of inflammation that leads to biliary injury and fibrosis, thus avoiding the bile duct obstruction in biliary atresia.

CONCLUSION

This case report highlights the use of steroids as a therapeutic option for treating extrahepatic cholestasis in infants with clinical features suggestive of biliary atresia. Steroid administration was associated with marked improvement in both clinical symptoms and laboratory parameters. These findings suggest that corticosteroids may play an important role in suppressing the inflammatory processes that lead to fibrosis and bile duct obliteration during the early stages of the diseases.

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AUTHOR CONTRIBUTION

R. A. P. and M. N. A. A. analyzed and interpreted the patient data regarding the disease. R. A. P., M. N. A. A., and B. S. conceived and designed the study, contributed to data generation and analysis. B. S. and S. A. supervised the study and reviewed the manuscript critically for important intellectual content. All authors discussed the results, contributed to the manuscript preparation, and approved the final version.

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Not applicable.

DATA AVAILABILITY

Not applicable.

CONFLICT OF INTEREST

The authors state there is no conflict of interest with the parties involved in this study.

ETHICAL APPROVAL

This study does not require ethical approval because it does not use experimental animals and/or humans.

INFORMED CONSENT

The authors confirm that written informed consent for publication of the clinical details and accompanying images in this case report was obtained from the patient's parent. The consent form is held by the authors and is available for review by the journal's editorial office upon request.

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