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Novel Technique for Management of Post-Transplant Refractory Diarrhea in Children with PFIC-1

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Abstract

Methods: Retrospective observational case series study of 3 patients with PFIC type 1 who underwent LT (Liver Transplant) with one of them had biliary diversion (BD) after LT while all of them had their Roux loop marked during the transplantation procedure. The patient who underwent BD had a novel technique of external drainage of bile performed by the interventional radiology owing to the previous marking of the Roux loop facilitating the access to the biliary diversion without the need for major surgical intervention.

Results: Biliary diversion post liver transplantation for Case 1 resulted in moderate clinical and histopathological improvements. Specifically, that the patient experienced a reduction in bowel movements, diarrhea, and itching. Additionally, the severity of hepatic steatosis decreased from severe to moderate, and there was no progression of fibrosis. Marking the Roux loop during the transplantation procedure facilitated less invasive intervention in the early postoperative period.

Conclusion: Marking the Roux loop during the transplantation procedure for PFIC 1 is a novel and straightforward technique. It can be easily implemented when needed to address post-liver transplant complications such as diarrhea or steatosis. This approach should be considered as a preemptive measure to avoid more invasive surgical interventions in the future, facilitating easier and more accessible interventional radiology.

Keywords: Liver Transplantation, Biliary Diversion, Refractory Diarrhea, Roux-en-Y Loop Marking, Pediatric Gastroenterology, Steatosis, External Biliary Drainage

Introduction

Progressive familial intrahepatic cholestasis (PFIC) type 1, also known as Byler disease, is a rare, inherited disorder that affects bile flow through the liver, predominantly in children [1]. This autosomal recessive condition arises from mutations in the ATP8B1 gene, leading to a deficiency of the familial intrahepatic cholestasis 1 (FIC1) protein [2]. FIC1 is a transporter protein located on the canalicular membrane of hepatocytes, crucial for the movement of specific phospholipids across the cell membrane [3]. A deficiency in FIC1 disrupts bile salt secretion, leading to cholestasis, resulting in progressive liver damage and ultimately end-stage liver disease [1, 2].

While liver transplantation (LT) offers a curative treatment for

PFIC1, it is not without its own set of complications. Post-LT, PFIC1 patients frequently experience a worsening of extrahepatic manifestations, particularly chronic watery diarrhea and continued growth failure [4]. These complications often manifest as a result of the increased bile acid load delivered to the small intestine, which is already compromised due to the systemic nature of FIC1 deficiency. This heightened bile acid exposure can lead to significant osmotic diarrhea, negatively impacting quality of life and potentially contributing to graft steatosis and fibrosis [5, 6].

The management of these post-transplant complications presents a significant challenge for clinicians. While medical therapies such as bile acid resins and ursodeoxycholic acid (UDCA) may provide some relief, they are often insufficient to fully address the persistent diarrhea and steatohepatitis [5, 6]. This underscores the need for novel approaches to effectively manage post-LT complications in PFIC1 patients.

To address the anticipated post-transplant complications in PFIC 1, we developed a novel approach for facilitating biliary diversion if clinically indicated. This technique involves marking the Roux loop during the liver transplant procedure with a radiopaque marker. This allows for future biliary diversion to be performed through interventional radiology, potentially minimizing the need for major surgery. We have successfully implemented this strategy in three PFIC 1 patients, one of whom required partial external biliary diversion while the remaining two have not yet required biliary diversion. This case series will present a detailed description of the first patient who underwent this novel approach. We will discuss the benefits and drawbacks of the procedure, emphasizing the pre- and post-procedure alterations in the clinical presentation, liver histopathology, and biochemical parameters. For the other 2 cases we will describe the procedure only as they did not have biliary diversion post-transplant.

Case 1:

1st born child to a 1st cousin consanguineous marriage presented with worsening jaundice, and pale colour stools at around 2 months of age. He had a history of febrile illness at 6 weeks of age. He had failure to thrive and developmental delay. Antenatal period was uneventful. No family history of liver disease. He underwent liver biopsy which was suggestive of PFIC-1 with bile duct paucity. He underwent partial external biliary diversion with biliary cutaneous jejunal loop at 6 months of age to relieve reactive pruritis [7]. Following biliary diversion his pruritis and delayed development improved temporarily. Later he started developing recurrent cholangitis and his liver function deteriorated. He was listed for transplant by 2 years of age. During his transplant waiting list period he had worsening jaundice and protracted diarrhea. He was also diagnosed with rickets and started treatment.

He received a cadaveric whole liver transplant at 2.5 years of age. His explant showed micronodular cirrhosis secondary to bile duct paucity. 1 month after the transplant he started developing diarrhea. He had extensive evaluation for identifying cause of diarrhea, including upper GI endoscopies and biopsies which didn't show any infective or inflammatory causes.

4 months after liver transplant he developed mild acute rejection with raised LFT. Liver biopsy during that time showed microvascular steatosis without cholestasis and with features of mild rejection. Diarrhoea showed good response to cholestyramine and loperamide until 2 years following transplant [8].

He persistently had protracted diarrhoea and was visiting the emergency department often. 2.5 years post-transplant he developed EBV infection which was managed conservatively. 6 months later he developed raised LFT and liver biopsy showed severe steatosis (micro and macro) and low-grade chronic hepatitis with mild fibrosis and inflammation in the liver allograft.

6 years after the transplant he was diagnosed to have hearing loss. Secondary to his chronic disease and immune suppression, he has also developed adrenal suppression, delayed puberty and short stature. Later he developed 2 episodes of pancreatitis and cholangitis. His Azathioprine was stopped and Cyclosporin was changed to tacrolimus. 1 year later he developed acute rejection proven with liver biopsy. His rejection episode was treated with steroid pulse therapy [9]. Following years, he started developing recurrent ascites, deteriorating LFT and decompensated liver disease along with worsening diarrhoea.

At 12.5 years of age (10 years following first liver transplant) he received a 2nd liver transplant. In view of his previous post-transplant diarrhoea, during surgery Roux-en-Y loop was marked using a radio-opaque material (?name of the material) and fixed to anterior abdominal wall which can be targeted by interventional radiology (IR) team for external biliary diversion later if needed. Unfortunately, he had to undergo relaparotomy for biliary leak and repair of biliary anastomosis was done [10].

7 months post-transplant he developed severe watery diarrhoea and underwent partial external biliary diversion with IR guidance (figure 1).

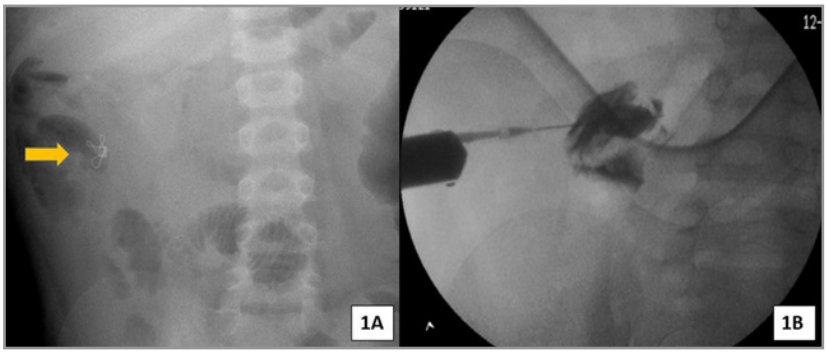

Figure 1(a): Radiopaque Material in The Roux Loop, **Figure 1**(b): Percutaneous Access to The Roux Loop

The patient underwent dilatation of the biliary stoma with reformation of the stoma 2 years later, however, his external drain was progressively stenotic without possible dilatation, so a partial Internal/External biliary diversion was performed 4.5 years after the second transplant. His Roux loop was identified, and a side-to-side anastomosis was created to the adjacent transverse colon (Jejuno-colonic anastomosis, Roux-en-Y to transverse colon). This anastomosis was proximal to his existing external stoma. Although he developed worsening diarrhea in the early post-operative period, he recovered well from the surgical procedure and was restarted on medications to control his pruritus and diarrhea (Cholestyramine, Codeine, Loperamide). His stool output and frequency gradually subsided towards the end of his stay. At the time of discharge, he had demonstrated good weight gain and was passing semi formed stool 2-3 times a day.

Following biliary diversion, the patient experienced a significant improvement in diarrhea, accompanied by reduced itching and serum bile acid levels [11]. Prior to the procedure, the patient had an average of 12-15 bowel movements per day, which decreased to 8-10 times daily post-diversion. This reduction in bowel frequency led to fewer hospital admissions related to dehydration. The patient's daily loperamide dosage also decreased from 10 mg four times a day before diversion to 4 mg four times a day one year after the procedure. Histopathological examination revealed a notable improvement in the degree of steatosis post-diversion. The liver biopsy before the procedure demonstrated steatohepatitis, while the post-diversion biopsy showed moderate steatosis without inflammation. Importantly, no progression of fibrosis was observed.

Table 1: Shows the Improvement in Degree of Steatosis Before and After Biliary Diversion with No Progression of Fibrosis.

Histopathology	Before BD	9 months post BD
Steatosis	• severe macrovesicular fatty change. There are scattered small foci of lobular inflammation, parts of these constituting small fat granulomas. • There is no definite hepatocellular ballooning and no Mallory's hyaline.	Moderate macrovesicular fatty change in a predominately perivenular distribution. There is no cholestasis and no ballooning. . Compared to the previous biopsy the steatosis has decreased.
Fibrosis	Mild portal fibrosis Mild perisinusoidal / pericellular fibrosis.	Very mild portal fibrosis with occasional periportal pericellular fibrosis. - no progression of fibrosis
Portal Inflammation	• Mild chronic inflammatory infiltrate. There is no significant interface inflammation. • Occasional small foci of neutrophils and chronic inflammatory cells are present within the parenchyma	• Only very minimal and patchy portal inflammation is seen. • There is no interface inflammation • A rare small focus of lobular inflammation is identified

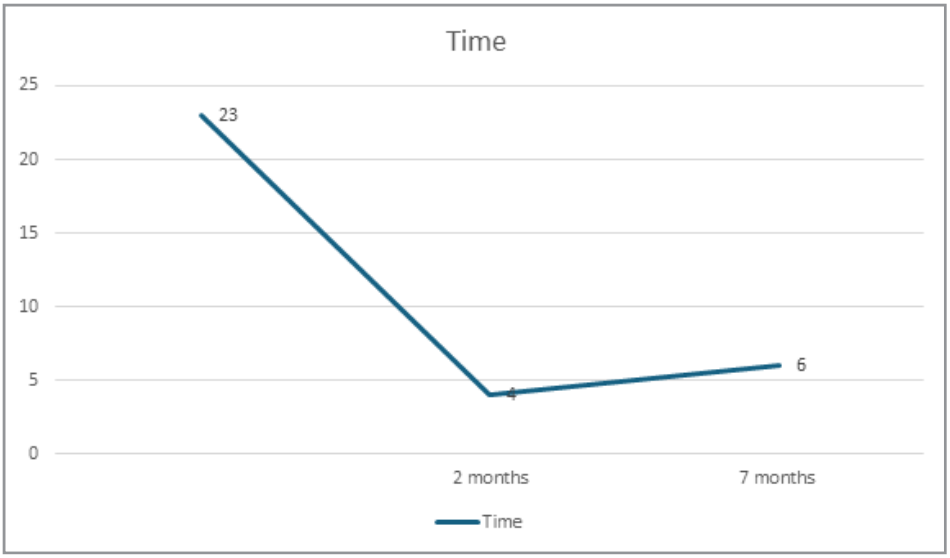

Figure 2: Shows the Decline in Bile Acid Level After Biliary Diversion and Hence Decrease of Itching in Case

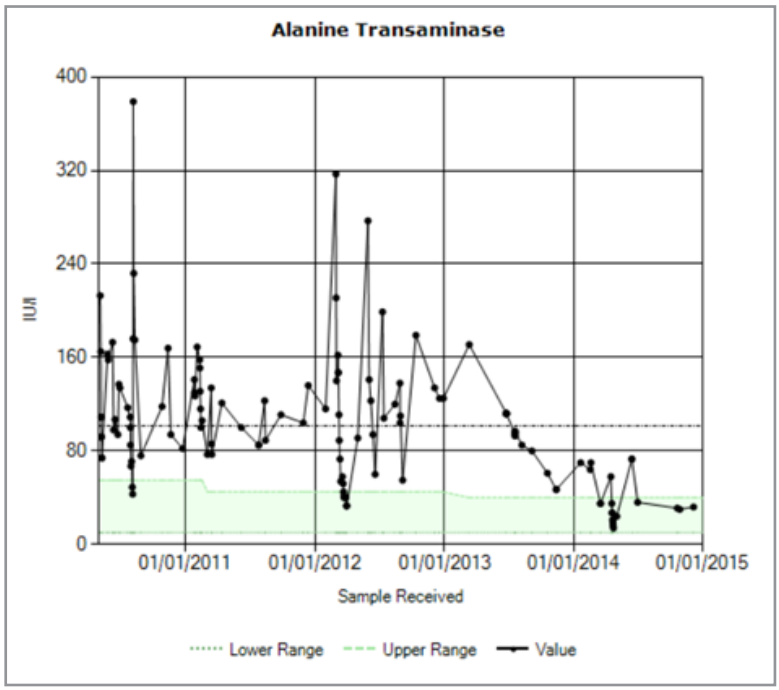

Figure 3

Figure 3 shows gradual decline in ALT post BD with periods of fluctuations post BD due to stomal stricture which then was dilated and reformed eventually with noticeable decline in ALT .Other liver biochemical markers (Bilirubin , GGT) were not significantly different before and after biliary diversion [12].

Interestingly, improvements in diarrhea post biliary diversion helped to increase absorption of vitamin D and normalization of its levels which was difficult to achieve before biliary diversion. Fig 3.

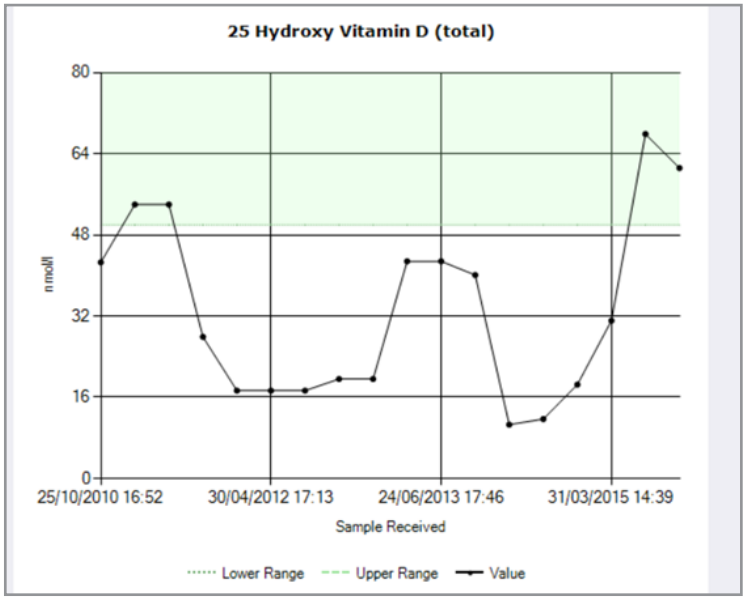

Figure 4

Unfortunately, due to severe genu valgum his weight and height centiles remained the same (<0.4th centile) before and after biliary diversion. However, the patient underwent orthopedic surgeries for correction of genu valgum and received testosterone injection to boost his growth and puberty.

Of note, the presence of external drain with bile excretion has been a source of distress and anxiety to the patient due to the excoriation of the skin surrounding the stoma site and physical stigmata. This contributed to many psychological discomforts to the child and eventually the external end of the internal/external diversion was closed to alleviate the patient anxiety and discomfort [13].

Case 2

Is an 11 year and 8 m old child who underwent liver transplantation at the age of 3 years and 7-month-old for PFIC type 1. His Roux loop was marked by a radio-opaque marker during the transplant operation. He also developed watery diarrhea post-transplant. Although his first liver biopsy at 1 year post

transplantation did not show steatosis, he had mild degree of steatosis at 5-year surveillance biopsy post transplantation [14].

Case 3

Is a 19-year-old boy with PFIC type 1 and has undergone LT at the age of 4.5 years with marking of the Roux loop during the transplant procedure to facilitate BD in the future. He had biliary diversion before transplant at 2 years of age to alleviate pruritis till transplant [15]. His liver histopathology showed minimal steatosis and occasional clusters of foamy macrophages at 1-year post LT, a finding that was persistent till 8 years post LT but not present in 10 years post-transplant histopathology.

Discussion

Biliary diversion, a surgical procedure to reroute bile flow, has emerged as a crucial therapeutic strategy for patients with PFIC type 1. While liver transplantation (LT) offers a definitive cure, the complexities surrounding PFIC1, particularly post-LT complications, have highlighted the importance of biliary diversion, both as a bridge to transplantation and as a post-LT intervention [16].

Biliary diversion for pruritis associated with cholestasis was first described in 1980s by Whitngton 1988. (1) Several surgical techniques exist for biliary diversion, each aiming to reroute bile flow and reduce its toxic effects in PFIC patients. Partial external biliary diversion (PEBD) is the most commonly employed approach [17]. In PEBD, a stoma is created by directly diverting the gallbladder to the skin or by interposing a segment of small bowel between the gallbladder and the skin.

Internal biliary diversion (IBD)or ileal bypass (IB), in contrast, reroutes bile from the gallbladder directly into the colon. This shortcut aims to drastically reduce the enterohepatic circulation of bile salts. Another technique involves bypassing the terminal ileum, the primary site of bile reabsorption, through an ileocecal anastomosis. This procedure excludes the final 100 cm of the distal ileum.

While IBD and ileocecal anastomosis offer potential benefits, they are often considered less effective than PEBD due to the possibility of adaptation by other parts of the small bowel, leading to a temporary relief of symptoms. PEBD generally remains the preferred surgical option for biliary diversion [18].

Has described a cohort of 24 children with PFIC types 1,2 and 3 who underwent biliary diversion with either partial external biliary diversion (PEBD)or ileal bypass (IB) for relief of cholestasis and pruritis before liver transplantation [19]. However, in his study there was no significant change in bile acid levels (BA) after conversion to IB, suggesting a lack of effectiveness for their patient population. A significant proportion (almost a third) of the study's patients converted from PEBD to IB, primarily female teenagers. This choice was often driven by personal preference rather than medical necessity.

Although liver Transplantation (LT) emerged as the only curative treatment for PFIC -1, patients often experience persistent extrahepatic symptoms, specifically diarrhoea. This is attributed to impaired intestinal FIC1 expression, leading to increased BA levels in the ileum and colon [20].

Had contrasting approaches to biliary diversion in PFIC1 patients, each with its own set of advantages and limitations. Used a preemptive total internal biliary diversion (TIBD) performed concurrently with LT. This novel technique aims to interrupt the enterohepatic circulation at the small intestinal level, theoretically preventing post-LT complications like diarrhoea and graft steatosis. In their single-case report, TIBD led to rapid resolution of jaundice and pruritus, with normalization of bilirubin and total bile acids [8]. Notably, the patient remained free of diarrhoea and demonstrated no progression of macrovesicular steatosis over a 9-month follow-up.

On the other hand, presented a case of a child who underwent TIBD five years after LT as a rescue therapy for refractory diarrhea, emaciation, and worsening liver function with steatohepatitis. This post-LT intervention yielded remarkable results with a complete resolution of steatosis and fibrosis, and significant weight and height gain [21].

Described a retrospective analysis of 40 children with PFIC, including 13 who underwent partial external biliary diversion (PEBD) (6 with PFIC 1 and 7 with PFIC 2). All were before liver transplantation in order to prolong the native liver survival and delay LT. The time to LT was significantly longer in PFIC-1 compared to PFIC-2, however, this should be personalized according to each case clinical condition.

In our case series, we adopted a novel preemptive approach by marking the Roux loop for facilitation of less invasive biliary diversion in the future once needed according to the clinical, laboratory and histopathological changes post liver transplantation for PFIC-1 patients. One of our cases had the biliary diversion done through an IR approach without invasive surgical intervention. There was improvement in his symptoms of diarrhea, itching and steatosis. However, due to stoma stricture and patient prefernece, the stoma was converted to internal biliary diversion.

Challenges and Considerations

Although biliary diversion was effective in improving post-transplant comlications in PFIC-1 patinets, it is a procedure that carries its own risk of complications. For example, colonic reflux particularly with PEBD and stoma complications e.g. leakage, strictures and subsequent need for conversion to internal drainage. In addition, high stoma output can also lead to electrolyte depletion and dehydration [21].

Alternative approaches, e.g. Pharmacological diversion using bile acid-adsorptive resins or IBATi (intestinal bile acid transporter inhibition), should be considered alongside surgical options.

While biliary diversion post liver transplantation for PFIC-1 has shown benefits to these population, further research is needed to understand the long-term effects of both TIBD and PEBD on hepatobiliary and digestive physiology, including potential complications like fat-soluble vitamin deficiency and colonic carcinogenesis.

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