A 107-day super-prolonged idiopathic cholestasis following endoscopic retrograde cholangiopancreatography

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Introduction

The effectiveness and safety of endoscopic retrograde cholangiopancreatography (ERCP) in removing stones from the common bile duct and relieving obstructive jaundice are widely recognized [1]. Prolonged cholestasis is an extremely rare complication of ERCP [2]. We presented a case wherein prolonged cholestatic development after a successful therapeutic ERCP, despite the absence of any retained stone, inadequate drainage of bile, or any other unrelated etiology of liver disease. The patient exhibited an unresponsive state to corticosteroid treatment, and although plasmapheresis was helped, the condition worsened immediately after stopping the treatment. We presented the patient’s clinical data and engaged in a comprehensive discussion of the potential mechanisms underlying prolonged cholestasis following ERCP, as well as its therapeutic considerations.

Case presentation

A male patient in his 60s was admitted to our hospital with abdominal distension and yellow urine persisting for 4 days. Laboratory tests showed elevated levels of total bilirubin at 137.5 μmol/L and direct bilirubin at 75.7 μmol/L. Tests for viral hepatitis-related antibodies and autoimmune liver disease antibodies were negative. Coagulation function and IgG4 levels were normal. Magnetic resonance cholangiopancreatography (MRCP) revealed common bile duct (CBD) stones with duct dilatation (Figure 1A). During the subsequent ERCP procedure (Figure 1B), cholangiography using 20 mL of iohexol showed a dilated CBD with a diameter of 14 mm and a filling defect in the CBD. A papillary sphincterotomy was performed and the stones were successfully removed. Post-ERCP, both alanine aminotransferase and aspartate aminotransferase levels steadily declined (Supplementary Figure 1). However, total bilirubin levels continued to rise (Figure 1E). Additional MRCP and nasal cholangiography ruled out obstructive jaundice from residual stones. Ursodeoxycholic acid (UDCA) and methylprednisolone were given orally, but total bilirubin levels kept increasing along with intense pruritus. Liver biopsy revealed ballooning and hyaline degeneration of liver tissue, with evident cholestasis (Figure 1C). Subsequently, intravenous methylprednisolone was started, along with two sessions of plasmapheresis. Skin pruritus substantially abated and total bilirubin had a temporary decrease. However, total bilirubin showed an upward trend after stopping plasmapheresis, even exceeding the pre-treatment levels, leading the patient to request to transfer to the Department of Liver Disease. Six plasmapheresis procedures were performed (Figure 1E), along with a 4-week regimen of methylprednisolone injections, which was discontinued due to the development of a secondary pulmonary fungal infection (Figure 1D). Despite the above treatment measures, the patient’s bilirubin levels continued to rise, peaking at 510.9 μmol/L on the 56th day. Until the 57th day following ERCP, the patient’s markers of cholestasis exhibited signs of improvement. Serum total bilirubin levels returned to within the normal range (24.4 μmol/L) on the 107th day post-ERCP.

Discussion

In this case, the patient developed hyperbilirubinemia after ERCP and his bilirubin levels continued to rise over an extended period. Possible contributing factors include residual stones, blood clots, biliary stent occlusion, nasobiliary drainage obstruction, retrograde cholangitis, or drug-induced cholestasis [3]. Further imaging and serological tests are needed for proper diagnosis. Prolonged idiopathic cholestasis following ERCP is considered a rare complication [2, 4], and its exact mechanism remains unclear [5]. In this particular case, viral, mechanical, and immune-related causes were ruled out, leading to consideration of whether drugs and the ERCP procedure itself contributed to...
the prolonged cholestasis. Drugs administered during hospitalization, such as antibiotics, proton pump inhibitors, and indomethacin, had been used previously without adverse events. Other potential drugs causing cholestasis after ERCP include pethidine, diazepam, and contrast agent, although specifics were not available. A "re-exposure test" could confirm this, but it was deemed unethical due to potential risks to the patient. In this case, the second nasal cholangiography unintentionally exposed the patient to a contrast agent again, after which total bilirubin levels continued to rise. The temporal relationship between contrast agent use and total bilirubin increase suggests possible toxicity. Therefore, the potential risk factor identified was idio-pathic cholestasis possibly caused by the contrast agent. It is worth attention that the results of liver biopsy indicate intrahepatic cholestasis without hepatocyte necrosis, while the histological features of drug-related intrahepatic cholestasis often present a mixed pattern of both hepatocellular and cholestatic liver injury [6].

There have been five documented cases [2, 3, 7, 8] of prolonged cholestasis associated with contrast agent use (Supplementary

Figure 1. Imaging examinations, pathology findings, and course of total bilirubin levels of this case. (A) Illustration showing dilation of the common bile duct and intrahepatic bile duct, with the lower segment of the common bile duct cut off (indicated by red arrow). (B) Intraoperative cholangiography using iohexol displaying common bile duct dilation with a maximum diameter of 14 mm and a filling defect in the lower segment of the common bile duct (indicated by red arrow). (C) Pathological results of liver biopsy showing ballooning and hyaline degeneration of liver tissue, along with significant cholestasis and some neutrophil infiltration (Haematoxylin and eosin staining). (D) Radiological imaging revealed multiple low-density patchy shadows with blurred boundaries in both lungs. (E) Course of total bilirubin levels in the patient.
remains to be further verified. Considering the potential for idiosyncratic adverse reaction resulting in selective damage to the biliary epithelium and subsequent intrahepatic cholestasis and jaundice [2, 9].

Currently, there is no established standard medical therapy for post-ERCP cholestasis. UDCA and glucocorticoids are commonly recommended medications for treatment [7]. Plasmapheresis should be considered for persistent pruritus and cholestasis refractory to drug therapies [10]. In this case, the patient received methylprednisolone for 43 days, which was discontinued due to a secondary pulmonary fungal infection, and UDCA orally for 48 days, plasmapheresis was performed eight times, pruritus was significantly improved, but the total bilirubin level persisted its upward trend. After medication withdrawal, the patient’s bilirubin gradually decreased from the peak to normal. Based on the total bilirubin changes in the other five patients, we speculate that idiosyncratic response may underlie the syndrome.

In summary, this case highlights that cholestasis may persist despite successful common bile duct stone removal through ERCP. Based on our experience and previous cases, we recommend initiating noninvasive imaging to exclude residual stone after the initial therapeutic ERCP. The prognosis of prolonged idiopathic cholestasis after ERCP seems favorable. UDCA, cholestyramine, and glucocorticoids may alleviate the patient’s symptoms, but whether they can shorten the course of cholestasis remains to be further verified. Considering the potential for spontaneous resolution, excessive medical interventions should be avoided to prevent secondary injury.

Supplementary Data
Supplementary data is available at Gastroenterology Report online.

Authors’ Contributions
Y.Z.B. drafted the manuscript. Y.S., L.M.Z., and S.J.Y. analyzed and interpreted the data. J.Z. edited and revised the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest
None declared.

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