CASE REPORT

A Rare Case of Benign Recurrent Intrahepatic Cholestasis Initially Diagnosed in Middle-age

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ABSTRACT

Background • Repeated episodes of jaundice and pruritus are common in a group of autosomal recessive liver diseases known as benign recurrent intrahepatic cholestasis. Benign recurrent intrahepatic cholestasis (BRIC) is divided into two types, type 1 and type 2, and is caused by mutations in the *ATP8B1* and *ABCB11* genes. Here, we report a rare case of BRIC type 2 mutation.

Case presentation • A 45-year-old Chinese man had three frequent episodes of jaundice marked by extensive excoriation and severe pruritis, although he had no prior history of jaundice. Laboratory investigations showed no evidence of liver damage caused by viral, autoimmune, or acquired metabolic etiologies. The CT scan revealed an enlarged gallbladder with numerous punctate high-density shadows, while no wall thickening was observed. Endoscopic ultrasonography showed no evidence of dilation of the intrahepatic and extrahepatic bile duct, as well as the absence of gallstone.

Diagnostic evaluation • Immunohistochemical examinations of liver biopsy samples showed cytokeratin-7 positive hepatocytes, suggesting chronic intrahepatic cholestasis. The reticulin fiberstaining demonstrated that the portions of the hepatic plate in the center of the lobule were asymmetrically organized,and somewhat enlarged, with collapsed areas indicating intralobular inflammation. Moreover, there were areas of collapse that indicated the presence of intralobular inflammation. Whole exome sequencing revealed mutations in the *ABCB11* gene; c.3084A>G, p.A1028A homozygous mutation (chr2-169789016), and c.2594C>T, p.A865V heterozygous mutation (chr2-169801131). Based on these findings, the final diagnosis of the patient was metabolism-related jaundice.

Treatment • Apart from receiving tapering dosage of prednisone to lower bilirubin levels, the patient received no extra care.

Conclusion • The comprehensive diagnosis of a middle-aged male patient with BRIC-2, which involved extensive radiological, hematological, and genetic investigations, informed a tailored tapering prednisone regimen, highlighting the importance of personalized medicine in managing atypical presentations of this rare cholestatic disorder. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Background

Benign recurrent intrahepatic cholestasis (BRIC) is a rare inherited bile salt transport disorder that is transmitted by an autosomal recessive mechanism. BRIC is regarded as a member of the larger familial intrahepatic cholestasis (FIC) family encompassing disorders such as BRIC-1 and -2 and progressive familial intrahepatic cholestasis (PFIC) 1, -2, and -3.[1,2] Hepatocytes in persons with PFIC have impairment in bile secretion, resulting in its accumulation, causing jaundice and itching.

Genectic basis of BRIC

Mutations in several genes are shared between BRIC and PFIC, including i) *ATP8B1* (ATPase phospholipid transporting 8B1) gene in chromosome 18q21–22 responsible for BRIC-1 and PFIC-1, ii) the *ABCB11* (ATP-binding cassette, subfamily B member 11) gene linked to BRIC-2 and PFIC-2, and iii) the *ABCB4* gene in chromosome 2q24 linked to PFIC-3.[1-3]

BRIC has BRIC-1 and BRIC-2 subtypes. In BRIC-1 patients, the *ATP8B1* gene, which encodes a P4-type ATPase (FIC1), is typically altered. Although the exact role of the

FIC-1 protein is still unknown, it is surmised that in *ATP8B1*-deficient animals, it functions as an amino-phospholipid translocase, transporting phospholipids from the outer leaflet (in contact with bile) of the bile canalicular membrane to the inner leaflet (in contact with the cytosol) of hepatocytes thereby maintaining the membrane asymmetry and fluidity.[4] On the other hand, BRIC-2 is associated with a mutation in the *ABCB11* gene that encodes the bile salt export pump (BSEP) protein. The primary function of BSEP is the transport of bile salt, particularly monovalent conjugated salt, across the canalicular membrane, which is the rate-limiting step for the movement of bile salt from hepatocytes to biliary canals.[5]

Clinical presentation and diagnosis

The clinical features of BRIC include recurrent episodes of jaundice, pruritus, and abdominal pain, and the diagnosis is typically confirmed by the presence of at least two episodes of jaundice separated by asymptomatic phases lasting anywhere from months to years. Confirmatory diagnosis include i) laboratory tests demonstrating intrahepatic cholestasis; ii) severe pruritus caused by cholestasis with normal intra- and extrahepatic bile ducts; iii) centrilobular cholestasis suggested by liver biopsy; and iv) absence of other cholestasis-causing factors.

Onset and triggers

BRIC can present at any age, but in approximately 80% of cases, it presents before the end of the second decade.[6] The causes of the first appearance of symptoms are unclear. In certain cases, upper respiratory tract infections may occur subsequent to episodes of jaundice. At the same time, in other instances, disturbances in the hormonal imbalance following pregnancy or oral contraceptive use may be present.[6,7]

Given the rarity of this disorder, the investigation of comprehensive case presentations through the use of n-of-1 trials has thus far constituted to establish a foundational understanding. N-of-1 trials are particularly useful in situations where traditional clinical trial designs may not be feasible due to the rarity of the disease or the heterogeneity of the patient population. Such trials provide a mechanism to gather valuable data on treatment effectiveness at an individual level, contributing to the field of personalized medicine and enhancing our understanding of rare diseases with BRIC as an example. Against this backdrop, we describe a case of BRIC that exhibits an atypical onset in middle age.

CASE REPORT

Patient history and presentation

A 45-year-old man experienced intermittent pain in his right upper quadrant and presented with pruritis. He had no history of jaundice; however, his mother and brother suffered from cholecystolithiasis and underwent cholecystectomy. When he first experienced the attack, he visited a couple of hospitals within a short span that suspected choledocholithiasis. Upon experiencing the initial episode, the patient sought medical attention at multiple hospitals within a brief period, where the healthcare providers suspected choledocholithiasis. Accordingly, liver parameters were determined and found to be elevated (Table 1 for all time points). Throughout this phase, which persisted for 2-3 weeks, the patient self-administered traditional Chinese medicine (TCM), including Xiaoyanlidan soft capsules (prepared from *Andrographis paniculata*, *Picrasmaquassioides* and *Isodon serra*) and anisodamine. However, none of these interventions yielded any relief, and the patient subsequently sought treatment at our hospital (C-JFH).

Table 1. Liver function parameters.

Date	TBIL mmol/L	DBIL mmol/L	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	GGT (IU/L)	ALB (g/L)	GLB (g/L)
First episode 23rd April, 2022	55.9	29.6	134.1	256.3	340	777.2	44	26
Second episode 14th May, 2022	226.3	129.6	90.5	41.9	207	140	42	24
Third episode (C-JFH) 3rd August, 2022	18.2	9.0	106	32	217	623	45	25

Abbreviations: TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferease, ALB, albumin; GLB, globulin. C-JFH, China-Japan Friendship Hospital, authors' hospital.

Table 2. Blood parameters.

Date	WBC (10^9/L)	N (%)	L (%)	M (%)	E (%)	B (%)	P (10^9/L)	RBC (10^{12}/L)	Hb (g/L)	Ht (L/L)
First episode 23rd April, 2022	11.97	72	20	6.8	1.0	0.3	343	4.64	136	40
Second episode 14th May, 2022	5.04	68.1	22.6	7.7	1.2	0.4	345	4.65	138	42
Third episode (C-JFH) 3rd August, 2022	5.31	54.8	38.6	4.7	1.5	0.4	233	3.86	117	34

Abbreviations: N, neutrophil; L, lymphocyte; M, monocyte; E, eosinophil; B, basophil; P, platelet count; Hb, hemoglobin; Ht, Hematocrit; C-JFH, China-Japan Friendship Hospital, authors' hospital.

Table 3. Coagulation parameters.

Date	PT	PT-INR	PTA%
Second episode 14th May, 2022	12.3	0.90	121
Third episode (C-JFH) 3rd August, 2022	12.1	0.88	127

Abbreviations: PT, prothrombin time in second; INR, international normalized ratio; PTA%, prothrombin activity; C-JFH, China-Japan Friendship Hospital, authors' hospital.

Diagnostic workup

On examination, he had jaundice, extensive excoriation, and severe pruritus. The abdomen was soft, without tenderness or rebound tenderness, the liver and spleen were not palpable, the Murphy's sign was negative, and there was no moving dullness. His hematologic and coagulation parameters were normal (Tables 2 & 3). He was negative for hepatitis (screened for A, B, C, and E), Epstein-Barr virus and cytomegalovirus antibody IgM. While checking for autoimmune liver disease, he was found negative for antinuclear antibody, and his IgG subtype was normal. He was also negative for antinuclear antibody and autoimmune liver antibody, and his IgG subtype was normal. The patient did not consume toxins, abuse alcohol, or have any metabolic disorders.

Radiological evaluation

CT scan showed that the surface of the liver was smooth, that there were no noticeable size or shape abnormalities, and that the right lobe of the liver had a dense shadow. The gallbladder was full, with moderate wall thickening and high-density shadowing. There was no sign of a neoplastic mass in the pancreas. The spleen was small and uniform. Endoscopic ultrasonography and magnetic resonance cholangiopancreatography showed no dilation of the intrahepatic and extrahepatic bile ducts and the absence of stones in the common bile duct (CBD), thus ruling out choledocholithiasis.

Histological evaluation

In an effort to diagnose the disease, a histologic evaluation of liver biopsy was performed. As shown in Figure 2, histology indicated normal lobular architecture with intralobular cholestasis and the presence of bile plugs in the canaliculi. The size of hepatic cell nuclei around the central vein was not very different, and the hepatic lobule shape was relatively distinct. Intraluminal bile plugs were extensively observed in zone 2, and a few hepatocytes with bullous steatosis (range <5%) were seen in zone 3. Periodic acid Schiff with Diastase (PASD) staining showed the activation and hyperplasia of Kupffer's cells that are required for removing injury-related debris from previously damaged areas. Reticulin staining for collagen type 3 showed that hepatic plates in the center of the lobule were irregularly arranged, slightly enlarged, and disrupted, suggesting the presence of intralobular inflammation. Cytokeratin-7 (CK-7), an intermediate filament, is expressed in bile ducts and hepatocyte progenitor cells.[8] Cholestasis is suspected when hepatocytes express the bile duct-specific protein CK-7.[9,10] We observed CK-7-positive hepatocytes in the perivenular areas, suggesting the occurrence of cholestasis. From the histologic studies, it appeared that the patient had moderate lobular hepatitis with severe intrahepatic cholestasis.

Genetic analysis

Given the presence of histologic features of cholestasis, the *ABCB11* gene, which encodes the bile salt export pump (BSEP), and whose mutation causes a spectrum of cholestatic diseases, we studied the mutation of this gene as the possible disease etiology. Whole exome sequencing showed the following mutations in the *ABCB11* gene:c.3084A>G, p. A1028A homozygous mutation (genomic location chr2-169789016), and c.2594C>T heterozygous mutation (genomic location chr2-169801131).

Treatment and response

The drug treatments received by the patient are given in Table 4. Suspecting unexplained gallbladder and biliary disorders, gallbladder puncture and a percutaneous cholecystostomy were performed. However, these procedures failed to lower the total bilirubin (TBIL) and direct bilirubin (DBIL), ruling out the presence of any such conditions. Since the patient self-administered TCM, a case of drug-induced liver injury was suspected. As a result, he was treated with prednisone (60 mg), which caused his TBIL and DBIL to decline. Over the course of the next 30 days, the prednisone dose was gradually decreased, and the patient's TBIL and DBIL values continued to decline even though they were still higher than their normal ranges (Figure 1).

Table 4. The treatments received by the patients during the attacks

Treatment	Anisodamine	Xiaoyanlidan	Prednisone	Ursodeoxycholic acid	Rifampicin
First episode 23rd April, 2022	No	Yes	No	No	No
Second episode 14th May, 2022	No	Yes	No	No	No
Third episode (C-JFH) 3rd August, 2022	No	No	Yes	No	No

Figure 1. Clinical course from April 23 to June 22 in 2022. Prednisone was given to the patient at the indicated doses.

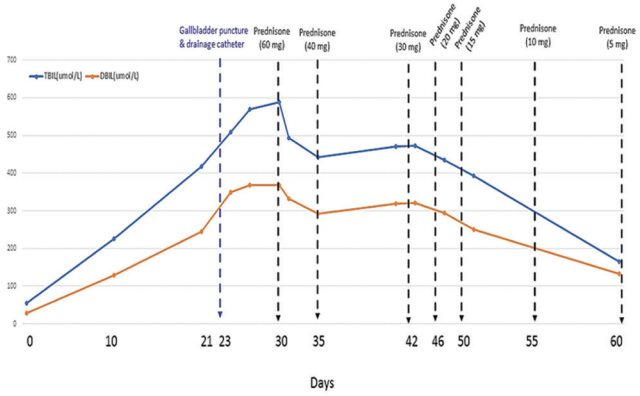
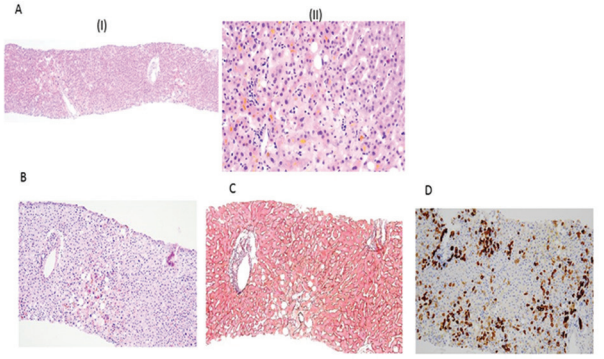


Figure 2. Histopathologic findings in the liver sections. (A) Liver tissue at lower scope showed normal lobular architecture and diffuse cholestasis in hepatic lobules by H&E staining; I - X40. Higher magnification (II, X200) allowed for clearer observation of extensive hepatocyte cholestasis and development of bile embolism in zones 2 and 3. (B) Kupffer's cells in zone 3 are visible by PASD staining as bright pink cells with ingested debris (X100). (C) Reticulin stain showing architecture of hepatic plates (X100). (D) CK7 positive hepatocytes were identified in the periportal regions although the intralobular bile duct arrangement was intact.



Conclusion

Based on an extensive study of the case history, clinical characteristics, examination, liver biopsy, and genetic analysis, it was concluded that the patient was suffering from severe intrahepatic cholestasis and was diagnosed with BRIC-2. The patient received tapering dosages of prednisone to manage excessive bilirubin. At this point, the patient was discharged, and no further therapy was prescribed.

DISCUSSION

The typical manifestation of BRIC occurs in the first two decades of life. However, we report an atypical case presented in middle age that introduces diagnostic complexities, as BRIC is often not considered in the differential diagnosis for cholestatic liver conditions in adults. The challenge lies in distinguishing it from other liver disorders, highlighting the need for tailored diagnostic approaches in cases that do not conform to conventional onset age. In this case, there was a gallstone in CBD with no structural abnormalities on liver imaging. A liver biopsy revealed severe cholestasis of hepatocytes in zone 3 after the common causes of liver damage, such as viral infections, autoimmune illnesses, alcoholic liver disease, and drug-induced liver disease, were ruled out. Combined with the results of the ABCB11 gene variant, he was ultimately diagnosed with BRIC-2, emphasizing the importance of genetic testing to identify mutations associated with BRIC.

BRIC may be triggered by various factors, the most common of which is infection (especially viral infections). Other potential factors include abrupt hormonal changes during pregnancy, the use of oral contraceptives, certain medical interventions and vaccines, and hyperthyroidism.[7] In the present case, none of these trigger factors appear to be present. However, the patient experienced episodes of jaundice and pruritis after consuming wine and taking TCM. As the symptoms were precipitated by the consumption of wine and TCM, it suggests a potential interplay between genetic predisposition and triggers. The liver's sensitivity to specific compounds in these substances, individual variability in drug metabolism, and the unique genetic makeup of the patients may collectively contribute to the onset of cholestatic symptoms. The patient was therefore advised to refrain from taking these, and the underlying cause of the subsequent occurrence of the incident was closely looked into.

The formation of gallstones in ABCB11 defects as an extrahepatic trigger for cholestasis is reported in BRIC-2 3,11 and could distinguish it from BRIC-1. Gallstone formation may have been more common because of the supersaturation of cholesterol induced by low bile salt concentrations in the bile of BRIC2 patients as a result of decreased BSEP activity.[12] Because not all BRIC-1 patients had extrahepatic symptoms, and not all BRIC-2 patients had cholelithiasis, distinguishing between BRIC-1 and BRIC-2 just based on clinical presentation is challenging. Moreover, we did not find stone in CBD. BRIC-2 is characterized by gallstone formation and mutations in the *ABCB11* gene, while BRIC-1 is not associated with gallstones and is linked to mutations in the *ATP8B1* gene. Understanding these distinctions is crucial for accurate diagnosis and tailored management of individuals with these subtypes of BRIC. Thus, to accurately distinguish between BRIC-1 and BRIC-2, genetic testing was required, and accordingly, we performed whole exome sequencing and observed mutations in *ABCB11* gene.

ABCB11 mutation is known to affect BSEP function, leading to decreased bile salt output, thus giving rise to BRIC-2 characteristics.[13] Mutations in *ABCB11* are also prevalent in PFIC2. Although mutations in the same gene cause both BRIC2 and PFIC2, the clinical features of PFIC2 and BRIC2 are different.[14] Contrary to benign traits of BRIC, PFIC is characterized by intrahepatic cholestasis with a severe phenotype and a poor prognosis since it frequently advances to end-stage liver disease.[2] Additionally, PFIC2 develops at neonatal stage.[14] Hence, the clinical profiles of this patient is different from PFIC2.

Similar to most other genetic and metabolic diseases, there are currently no known therapies for BRIC. Alleviating symptoms, curbing uncomfortable episodes, and limiting adverse consequences are the goals. Furthermore, there is currently no specific course of treatment based on BRIC subtypes. The literature describes various outcomes with the use of a variety of medicines or surgical techniques. Ursodeoxycholic acid is a commonly used drug for symptomatic relief. It acts through a variety of mechanisms, including (1) protecting damaged cholangiocytes from the toxic effects of bile acids, (2) promoting impaired biliary secretion, (3) augmenting bile acid detoxification, and (4) inhibiting hepatocyte apoptosis. As a result, serum transaminase levels are increased, leading to the mitigation of pruritis. Rifampicin, a potent activator of human pregnane X receptor, is also considered to be effective in treating pruritus and preventing a cholestatic episode in BRIC patients. However, caution should be exercised in view of the reported long-term use of rifampicin causing severe hepatotoxicity in patients with cholestatic liver disease.[15] Cholestyramine was successfully used to treat a patient with severe BRIC to prevent the recurrence of additional cholestatic episodes.[16] Corticosteroids, such as methylprednisolone resulted in symptomatic relief in a BRIC-2 patient.[17] Another corticosteroid, budesonide, resulted in significant symptom improvement along with stabilization of their liver enzymes and bile salt levels in 2 individuals with PFIC2, both compound heterozygotes for *ABCB11*.[18] The patient, in this case, represents a similar corticosteroid response and may underscore the need for further consideration of this class of therapy in the management of BSEP deficiencies. With the progress in understanding the genetic bases of this disease, it is possible to select right drugs for each BRIC subtype in future.

Besides medications, endoscopic nasociliarydrainage (NBD) is used in BRIC patients for the diversion of bile outside the body, which immediately improves jaundice and pruritus, albeit temporarily.[19-22] The Molecular Adsorbent

Recirculating System (MARS), an artificial system to remove albumin-bound bile acids and toxins, has been used as a treatment for intractable pruritis in BRIC-2 because this has been effectively used in achieving clinical remission in BRIC-1 patient.[23] However, in the case of MARS, special attention should be paid to patients with platelet counts below 50 000/ml or an international normalized ratio that is related to a prothrombin time >2.3. The use of plasmapheresis may not be recommended to reduce the length of symptoms as it yielded contradictory results.[11,24,25]

Notwithstanding the aforementioned treatment options for BRIC, it is recognize that each patient is unique and that treatments should be tailored to address symptoms rather than applying uniform treatment to all patients. For patients with varying degrees of symptom severity, a combination of pharmacologic (medication) and non-pharmacologic (NBD or MARS) treatments outlined earlier may be attempted for rapid and lasting alleviation of BRIC-2 symptoms. However, evaluation of the efficacy of various available treatment options in BRIC is challenging due to the rarity of this disease which prevents conducting multi-centric prospective trials with an intervention based on insight into the function of the proteins encoded by the causative genes. Therefore, utilizing n-of-1 trials, derived from case reports involving a single case can contribute to clinical management by objectively determining the optimum course of treatment.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

ETHICS STATEMENT

Our patient agreed and signed the informed consent for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XW and SD wrote the manuscript. SD supervised the study. FL, WL, and MZ participated in the acquisition of data and critical revision. ZS and XW performed a genetic analysis. All authors discussed the results and contributed to the final manuscript.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials. Further inquiries can be directed to the corresponding author.

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