CASE REPORT

A cholestatic diagnostic dilemma

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SUMMARY

A 28-year-old man with hereditary spherocytosis presented with abdominal pain and jaundice. He had severe, mainly conjugated (642 $\mu\text{mol/l}$), hyperbilirubinaemia (1033 $\mu\text{mol/l}$), with elevated liver enzymes: alkaline phosphatase (ALP) (163 IU/l), γ -glutamyltransferase (GGT) (277 IU/l) and aspartate transaminase (AST) (358 IU/l). Abdominal ultrasound and magnetic resonance cholangiopancreatography (MRCP) showed gallstones in the gallbladder but an absence of biliary duct dilation. Liver biopsy was consistent with cholestasis but showed no large duct obstruction. The cause of the cholestasis was unclear, was it a primary intrahepatic pathology or secondary to a posthepatic cause?

He presented with similar symptoms days later with gallstones in the bile duct (choledocholithiasis) and underwent endoscopic retrograde cholangiopancreatography (ERCP) and cholecystectomy. This report guides one through the assessment of jaundice and serves as an example whereby the diagnosis of a common cause of illness is blurred by an atypical clinical presentation and relevant comorbidities. A diagnosis of benign recurrent intrahepatic cholestasis (BRIC) is also considered.

BACKGROUND

Jaundice is a common presenting symptom or sign caused by hyperbilirubinaemia. Medical teams commonly encounter it during day-to-day practice. Hyperbilirubinaemia has numerous aetiologies and can be classified into the broad categories of prehepatic (unconjugated), hepatic (mixed) or posthepatic (conjugated) hyperbilirubinaemia.

We report a rare presentation of cholestatic jaundice in a young man. Over three different admissions, this gentleman presented with clinical features that fitted all three of the above anatomical classifications of jaundice. This case illustrates to readers how the diagnostic workup of this jaundiced patient was approached and some of the difficulties clinicians face in making a diagnosis.

CASE PRESENTATION

A 28-year-old Caucasian male presented to the emergency department with constant, non-colicky epigastric pain, vomiting, pruritus and jaundice. His abdominal pain was non-radiating and had gradually worsened over 1 week. Both the non-bilious vomiting and jaundice had been present for 2 days. He had pale stools and dark urine. He denied any fevers. He had never experienced similar symptoms in the past. He had known hereditary spherocytosis and reported previous episodes of mild jaundice following viral illness that faded after 24 h. He never had gallstones or any other medical history. He took no medications, herbal or over-the-counter

remedies. There was no family history of jaundice. He had no tattoos or history of illicit drug use; he reported no recent foreign travel. A sexual history did not reveal risk factors for hepatitis. He drank 20 units of alcohol weekly and was a non-smoker. On examination he was found afebrile and jaundiced. Abdominal examination revealed splenomegaly and no tenderness. All observations were within the normal range.

INVESTIGATIONS

On admission, his haemoglobin was 12.1 g/dl and platelets were 128 ($10^9/\text{l}$). Bilirubin was 1033 $\mu\text{mol/l}$, with a conjugated fraction of 642 $\mu\text{mol/l}$. ALT was 358 IU/l; ALP was 163 IU/l and GGT was 277 IU/l. Prothrombin time and albumin were both within the normal range, as was his white cell count and C reactive protein. Abdominal ultrasound demonstrated the presence of gallstones in the gallbladder (cholethiasis), but no duct dilation. MRCP confirmed the lack of duct dilatation. He had a negative liver serology screen, which included viral hepatitis and autoimmune conditions. We proceeded to liver biopsy, which showed evidence of cholestasis within the liver parenchyma, but no large duct obstruction.

DIFFERENTIAL DIAGNOSIS

The overarching diagnostic challenge was this gentleman had biochemistry results suggestive of a cholestatic aetiology (conjugated bilirubin fraction/raised ALP and GGT), yet ultrasound sonography and MRCP were grossly normal. Furthermore, the constant pain of 7 days was not suggestive of biliary colic or acute cholecystitis. Second, he had a colossal hyperbilirubinaemia that needed close monitoring. It is very rare to see bilirubin so markedly elevated. Sustained such high levels can lead to renal failure; fortunately the maturity of the blood-brain barrier in adults protects against kernicterus, that is seen in jaundiced neonates. To further complicate this diagnostic puzzle, haemolysis secondary to hereditary spherocytosis is likely to have contributed to the hyperbilirubinaemia, corroborated by the mild anaemia and mildly elevated reticulocyte count, a marker of haemolysis. The normal prothrombin time and albumin levels ruled out aetiologies that cause acute liver failure from our differential diagnosis.

The very high initial conjugated hyperbilirubinaemia is not solely explained by mild haemolysis and unobstructed bile ducts. Most likely, it was due to a non-overt hepatic or biliary infection (secondary to gallstone disease) superimposed on ongoing haemolysis. Other possibilities to consider are drug causes (including herbal remedies) or rarer intrahepatic aetiologies such as BRIC.

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BRIC is a rare genetic disorder characterised by recurring episodes of intense pruritus and jaundice. Diagnosis is through exclusion of other cholestatic aetiologies and liver biopsy. In this case, this diagnosis was considered due to the lack of obvious infective or obstructive evidence.

TREATMENT

He was treated with 5 days of ursodeoxycholic acid in an attempt to reduce itching and hepatic impairment. He was also started on high-dose prednisolone, but only for 5 days as there was no symptomatic improvement or change in his liver function tests. He continued to receive antihistamine medication for relief of pruritus.

OUTCOME AND FOLLOW-UP

The patient was discharged from the hospital feeling well with an outpatient gastroenterology appointment booked. However, he presented again the following week with similar symptoms, except the epigastric pain was more severe. An ultrasound scan this time revealed both intra hepatic and extra hepatic biliary dilation. CT confirmed duct dilatation, but no obvious biliary calculi. Bilirubin was 863 µmol/l; AST 201 IU/l; ALP 194 IU/l; gGT 175 IU/l. MRCP 5 days later showed that the biliary tree dilation had improved since the CT, suggesting the likely passage of a gallstone. Bilirubin levels fell to 277 µmol/l and the patient was discharged with a cholecystectomy booked for 2 weeks later.

However, 3 days later, he presented with a sudden onset, severe, unremitting epigastric pain and projective vomiting. Bilirubin was 309 µmol/l; AST 121 IU/l and ALP 209 IU/l. The team proceeded to ERCP, removing two gallstones from the common bile duct and also sphincterotomy, to prevent future occurrences. This was complicated by post-ERCP bleeding that was controlled with endoscopic treatment. A cholecystectomy was performed the following day. On discharge, bilirubin was 97 µmol/l; ALP was 65 IU/l and AST was 29 IU/l.

DISCUSSION

This patient's second presentation to the hospital highlights the importance of going back to the basics: ordering the ultrasound despite only recently being discharged from the hospital with similar symptoms. We were surprised to find duct dilation so acutely, in the absence of similar findings previously for what appeared to be an identical presentation. The short time frame between the first two seemingly identical admissions would suggest that the aetiology of the first admission was in fact related to gallstone pathology. In addition, patients with hereditary spherocytosis are at greater risk of forming gallstones, due to the formation of more bilirubin from increased red cell catabolism.

Three factors challenged a diagnosis of BRIC. First, 80% of BRIC cases present before the age of 20¹ and this patient had had no prior episodes of sustained jaundice. Second, abdominal pain is not associated with BRIC and this was his main symptom. Last, it is a recurring disease and this could not be ascertained due to the first presentation.

Liver biopsy can be a valuable tool in the workup of a patient with cholestatic jaundice who have a normal ultrasound/MRCP and negative autoimmune profiling and drug history.² However, it has its pitfalls along with its invasiveness and risk of bleeding. There are many potential anatomical sites where bile flow can be interrupted in the liver, impacting its sensitivity and also the morphological features seen under a microscope are relatively non-specific. We believe the liver biopsy was performed too early during our diagnostic workup. First, using hindsight, it did not change our management decisions and moreover, he did have gallstones present in the gallbladder on abdominal ultrasound. Perhaps a watch-and-wait approach would have been more suitable.

If the patient was to present again with similar symptoms we would reconsider the diagnosis of BRIC, which is caused by genetic mutations in canalicular transport genes. Genotyping would enable us to clinch a diagnosis.

Learning points

- ▶ Do not make assumptions to cut corners—you must always consider going back to the basics when patients present for a second time.
- ▶ Common things are common; however, clinical presentations can be atypical.
- ▶ There is value in waiting before performing invasive investigations, particularly if they will not alter patient outcome/management.

Contributors LK wrote the case report. MR had overall responsibility of the patient's care and revised the draft report.

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