Prolonged cholestasis induced by endoscopic retrograde cholangiopancreatography

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The case of a 54-year-old woman who presented with choledocholithiasis and underwent successful endoscopic stone extraction to clear the common bile duct is described. However, her jaundice and liver biochemistry continued to deteriorate despite repeat endoscopic retrograde cholangiopancreatography (ERCP), with further imaging confirming a patent biliary tree. The clinical, radiological and pathological features were in keeping with prolonged cholestasis as a complication of ERCP. The pathophysiology of this unusual syndrome and the therapeutic options available are discussed.

Case report

A previously healthy woman aged 54 years presented with a 3 week history of colicky right upper quadrant pain together with progressive jaundice and pruritus. She also reported the recent onset of dark urine and pale stools. Her only previous medical history was arterial hypertension controlled with atenolol 50 mg daily. There were no notable risk factors for chronic liver disease. Physical examination revealed obvious icterus with scattered excoriation marks but no evidence of bruising, spider naevi, distended abdominal veins or ascites. She was not feverish and was not encephalopathic.

Laboratory blood tests showed an elevated bilirubin of 275 $\mu\text{mol/l}$ (16.2 mg/dl), alkaline phosphatase (ALP) 195 IU/l (30–115) and aspartate transaminase 50 IU/l (5–45). Prothrombin time was 11.8 s (laboratory range 11.0–13.5) and full blood count, C reactive protein, urea, electrolytes and serum amylase were all within normal limits. Trans-abdominal ultrasound demonstrated moderately dilated intrahepatic bile ducts and a dilated common bile duct (CBD) measuring 10 mm in diameter. There were multiple calculi visible in both the CBD and in the contracted gallbladder. The patient was prescribed oral ciprofloxacin 500 mg twice daily and endoscopic retrograde

cholangiopancreatography (ERCP) was arranged.

At ERCP, duodenal intubation revealed a bulging papilla and the cholangiogram confirmed multiple stones in the CBD (figure 1). A sphincterotomy was performed and a balloon trawl extracted multiple small stones with effective clearance of the duct confirmed on a closing cholangiogram. The fully inflated balloon was able to traverse the sphincterotomy, which was considered sufficiently wide to allow spontaneous passage of any further stones.

However, the patient remained jaundiced and liver biochemistry 3 days after the ERCP demonstrated a further deterioration, with bilirubin now 488 $\mu\text{mol/l}$ (28.7 mg/dl), ALP 177 IU/l and aspartate transaminase 64 IU/l. A second ERCP was therefore carried out on day 10 to exclude persistent choledocholithiasis. On this occasion, there was a mildly dilated CBD but no intraductal stones and the retrieval balloon easily traversed the widely patent sphincterotomy (figure 2).

Despite this apparent confirmation of effective duct clearance, the patient continued to deteriorate clinically and biochemically, as evidenced by progressive jaundice, intense pruritus, anorexia and nausea associated with rising levels of bilirubin and ALP. At this stage ciprofloxacin was stopped and she was prescribed ursodeoxycholic acid (UDCA) at a dose of 15 mg/kg daily in addition to cholestyramine 4 g three times a day.

A comprehensive laboratory screen was performed for parenchymal liver disease. Serological tests for hepatitis viruses A, B, C and E, cytomegalovirus and Epstein-Barr virus were all negative. Antismooth muscle, antimitochondrial, antinuclear, antineutrophil cytoplasmic and antiliver/kidney microsomal autoantibodies were also negative. Serum copper, caeruloplasmin, ferritin and α_1 -antitrypsin were all

within the normal range. A blood film, reticulocyte count and haptoglobin estimation showed no evidence of haemolysis. Repeat ultrasonography revealed normal hepatic echotexture and a CT scan confirmed normal splenic, superior mesenteric, portal and hepatic veins.

In view of the persistently abnormal liver biochemistry it was decided to carry out a percutaneous liver biopsy and this was performed on day 22 when the bilirubin and ALP levels had almost peaked. Histology revealed secondary features of severe cholestasis with abundant extracellular and intracellular bile (figure 3). The normal lobular architecture was well preserved

Figure 1 Cholangiogram at initial endoscopic retrograde cholangiopancreatography showing a dilated common bile duct with multiple filling defects due to gallstones.

Figure 2 Cholangiogram taken at repeat endoscopic retrograde cholangiopancreatography showing no further gallstones within the common bile duct despite trawling the duct with an inflated balloon catheter.

without any significant hepatocellular necrosis or collagen deposition. Specific stains demonstrated no abnormal iron deposition, no evidence of α_1 -antitrypsin deficiency and no increase in copper associated protein. Together with the cholestasis, there was a mixed infiltrate of lymphocytes and neutrophils within the portal tracts but no oedema, granuloma formation or bile duct proliferation.

The patient remained unwell with anorexia, malaise and pruritus. Although there was no overt hepatic encephalopathy or significant coagulopathy, liver biochemistry continued to deteriorate, with peak levels of bilirubin reaching 770 $\mu\text{mol/l}$ (45.3 mg/dl) and ALP 360 IU/l (figure 4). Throughout this period the patient received full supportive care including nasogastric feeding, cholestyramine and UDCA. From week 6 onwards, both the patient's symptoms and her biochemistry began to resolve and she was discharged home 7 weeks after admission. All clinical parameters continued to improve and liver biochemistry had finally normalised by day 100. A follow-up magnetic resonance cholangiopancreatogram demonstrated a small amount of gas in the CBD compatible with the previous sphincterotomy together with a contracted gall bladder but otherwise a normal appearances of the biliary tree. The patient was subsequently referred for a laparoscopic cholecystectomy, the histology of which revealed typical changes of chronic cholecystitis.

Discussion

Based on the clinical presentation, laboratory tests and abdominal ultrasound scan, our patient initially represented an apparently straightforward case of cholestatic jaundice secondary to stones in the CBD. As the patient was not feverish with a normal blood leucocyte count and C reactive protein, ascending cholangitis was not considered to be a significant contributing factor to her initial presentation. However, the subsequent deterioration despite ERCP and effective duct clearance was quite unusual. Viral, metabolic and

Figure 3 Light microscopy of liver biopsy specimen showing severe intrahepatic cholestasis. Brown pigments represent bile (haematoxylin–eosin stain, original magnification $\times 40$).

immunological causes of liver disease were excluded, leading us to consider whether the endoscopic procedures themselves may have contributed to her prolonged illness.

ERCP has become an invaluable diagnostic and therapeutic tool in the management of pancreatobiliary disorders with an increasing scope of application.¹ Together with sphincterotomy and balloon trawl of the CBD, it is currently the gold standard therapeutic intervention for obstructive jaundice due to stones in the extrahepatic bile ducts. Stone extraction at ERCP is effective in well over 90% of cases,² usually leading to prompt clinical and biochemical resolution of icterus. In contrast, our patient developed a progressive cholestatic illness following successful CBD clearance.

Prolonged cholestasis is a very rare but recognised complication following ERCP and extraction of CBD stones. There are few similar reports in the literature and we believe our patient represents a further occurrence of this syndrome. In our case, the peak of hyperbilirubinaemia occurring 10–14 days post-ERCP followed by the onset of resolution after approximately a month (figure 4), corresponds with the two cases reported by Lee and colleagues³ and the single case reported by Saritas and colleagues.⁴ The histological features on liver biopsies are also compatible.

Figure 4 Progression of liver biochemistry parameters. Both bilirubin (Bili) and alkaline phosphatase (ALP) levels continued to rise following endoscopic retrograde cholangiopancreatography (ERCP) and gallstone removal (block arrows indicate timing of the two ERCPs) and peaked during week 4 after admission. Levels gradually declined and were eventually normalised 3 months after initial presentation. Data based on bilirubin are measured in $\mu\text{mol/L}$ with ALP and aspartate transaminase (AST) expressed in IU/L.

In each of these reported cases, the initial ERCP was performed for suspected choledocholithiasis, confirmed in Saritas *et al* and in one of the two cases described by Lee *et al* (the other had a filling defect demonstrated on cholangiography but a stone was not retrieved despite sweeping the duct).

The exact mechanism for the prolonged jaundice post-ERCP remains unclear. However, it has been postulated that this may be directly related to the radiocontrast medium used for the procedure, perhaps due to an idiosyncratic adverse reaction resulting in disruption of the hepatocyte canalicular membrane or interruption of transport pumps with subsequent intrahepatic cholestasis and jaundice.^{3,4}

The osmolality and ionic nature of radiological contrast agents are thought to underlie many of the systemic reactions to their intravenous use. It has therefore been hypothesised that the low osmolar agents (such as Omnipaque; GE Healthcare) might have a reduced incidence of ERCP complications compared with the higher osmolar media (such as Hypaque; GE Healthcare, Amersham, UK, as used in our patient). However, randomised trials and a subsequent meta-analysis have not shown any significant difference between these agents in the incidence of post-ERCP pancreatitis or other local complications.⁵ Given its scarcity in the literature, there are insufficient data to associate the risk of post-ERCP cholestasis with the osmolality of contrast agent used.

Similarly, the volume of contrast medium used in our case was unremarkable, with 20 ml administered on the first occasion and approximately 30 ml used at the second, post-sphincterotomy, ERCP.

Interestingly, both high and low osmolar contrast media can exhibit crystal formation leading to a pseudomicroolithiasis similar to calcium bilirubinate.⁶ Although microolithiasis may irritate the bile duct or pancreas, it seems unlikely to be the causative mechanism of the prolonged cholestasis seen here, given the widely patent sphincterotomy and adequate biliary drainage achieved.

Regardless of the pathophysiological mechanism, the overall prognosis of post-ERCP cholestasis seems favourable with no long term consequences reported so far. Fortunately, this was true for our patient who went on to make a full clinical and biochemical recovery. However, in similar circumstances, other differential diagnoses should be considered, not least after ensuring the adequate clearance of ductal stones.

Cholestatic jaundice is not uncommonly a complication of sepsis, hypotension or hypoxia during critical illness.⁷ However, our patient remained afebrile, well oxygenated, maintained a normal blood pressure and did not have a significantly raised CRP throughout this episode.

A further possible differential diagnosis would be an adverse drug reaction to the fluorinated quinolone antibiotic ciprofloxacin our patient was prescribed

by the admitting physician. The exact mechanism of quinolone induced liver injury remains unknown⁸ although a mixed pattern of both hepatocellular and cholestatic liver injury has been described supported by liver histology that is typically a combination of cholestasis and hepatocyte necrosis.⁹ However, our patient's liver biopsy did not show evidence of hepatocellular injury.

There are no published randomised trials of medical therapy for post-ERCP cholestasis. In the few published case reports, UDCA and cholestyramine therapies have usually been tried in the first instance and this combination was successful in our patient. A favourable response to glucocorticoids has also been reported in cases refractory to treatment with UDCA, and plasmapheresis has been employed successfully in some patients.^{3,4} Given the potential for spontaneous resolution, it has been suggested that UDCA could be reserved for those who have failed to improve after 2 weeks post-ERCP, with steroids being added for those whose biochemical abnormalities persist on UDCA.³

In conclusion, the case described in this report demonstrates that severe intrahepatic cholestasis can develop and persist after successful ERCP clearance of CBD stones and the clinician should be aware of this uncommon but significant complication. Based on our experience and the cases previously documented, we advocate performing non-invasive imaging in the first instance to exclude retained stones if there is no clinical or biochemical resolution following an initial therapeutic ERCP. However, it should be borne in mind that one pitfall of magnetic resonance cholangiopancreatography following an endoscopic sphincterotomy is the potential to wrongly identify filling defects due to air as retained ductal stones.

To avoid confusion with idiosyncratic drug reactions, prophylactic quinolone antibiotic administration should be limited to the circumstances recommended in clinical guidelines.^{10,11}

Prolonged idiopathic cholestasis following ERCP appears to have a good prognosis and resolution may occur spontaneously or following therapy with UDCA, cholestyramine or glucocorticoids.

Competing interests None.

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