Case report

Primary sclerosing cholangitis in beta-thalassemia with suspected pigment stone: a diagnostic confusion

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Abstract

Primary sclerosing cholangitis is a chronic inflammatory disease resulting in progressive fibrosis of the biliary tract. The diagnosis is made by demonstrating a beaded appearance in the cholangiography while excluding the secondary causes of sclerosing cholangitis. We report a 27-year-old Sri Lankan female who presented with cholestatic jaundice, whose beta-thalassemia carrier state and pigment stones led to a misdiagnosis as common bile duct obstruction. The magnetic resonance cholangiopancreatography confirmed the diagnosis.

Keywords: Primary sclerosing cholangitis; Cholestatic; Beaded appearance; MRCP; Case report

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Introduction

Primary sclerosing cholangitis (PSC) is a chronic progressive inflammatory disease causing fibrosis of the biliary tract. It is mainly seen in Northern Europe and America, rarely in South Asia [1]. The diagnosis is made by demonstrating a beaded appearance in the cholangiography while excluding the secondary causes of sclerosing cholangitis [2]. We report a Sri Lankan woman with transfusion-independent beta-thalassemia who presented with cholestasis attributed to pigment stones but was later diagnosed as PSC using magnetic resonance cholangiopancreatography (MRCP).

Case presentation

A 27-year-old Sri Lankan woman, previously in good health, was admitted with non-colicky right hypochondriac pain and fever for seven days. She has been a housewife and a mother of a two-year-old, having no history of consuming alcohol or smoking. On admission, she had features of obstructive jaundice, such as deep and tea-coloured urine but no pale stools. She noticed losing weight over the previous two months. She had deep jaundice, hepatosplenomegaly,

and negative Murphy's sign on examination. She has had mild jaundice since her early twenties.

Her initial white cell count was 10500/µl (4000-10000/µl), and her platelet count was 323000/µl (150000-400000/µl). The haemoglobin level was 10.7 g/dl (11-17 g/dl), and red blood cells were microcytic hypochromic. The blood picture displayed features of haemoglobinopathy as evidenced by the presence of markedly hypochromic, microcytic red cells with numerous target cells. She had never received a blood transfusion. Her direct agglutinin test was negative, excluding autoimmune haemolysis. Haemoglobin electrophoresis confirmed beta-thalassemia trait. Her liver function tests were deranged (Table 1). Considering the clinical picture, the patient was managed with antibiotics for possible cholecystitis or cholangitis. The abdominal ultrasonography done on the third day showed hepatosplenomegaly, periportal thickening, and gallbladder wall thickening with a gall stone of nine mm diameter but no common bile duct dilation, suggesting resolving cholecystitis.

With antibiotics, the fever settled, but the jaundice deepened with pruritus. The blood culture was positive for coliforms, for which intravenous cefepime 2 g and metronidazole 500 mg 8 hours were administered. The liver function on day 26 revealed a worsening cholestatic picture. Her serum amylase level was raised. The contrast-enhanced computerized tomography (CECT) of the abdomen demonstrated acute pancreatitis and hepatosplenomegaly with focal hypodense areas in the caudate lobe of the liver and peri splenic varices suggesting parenchymal liver disease with portal hypertension. A linear hypodense area in segment IV of the liver suggested focal intrahepatic duct dilation with no choledocholithiasis. The previously seen gallstone was still inside the gall bladder. She was symptomatically managed with colestyramine, ursodeoxycholic acid, and antibiotics. The magnetic resonance cholangiopancreatography (MRCP) done on day nine was reported as normal, and the patient was discharged on the 33rd day with a plan for interval cholecystectomy (Figure 1). With the finding of gallstones in this beta-thalassemia trait patient, hepatitis and pancreatitis were thought to be due to obstruction by a possible but undetected common bile duct stone, which must have passed. HIV, Hepatitis B and C serology were negative. Absent Kayser-Fleischer rings and normal serum ceruloplasmin levels excluded Wilson's disease. Haemochromatosis was excluded by a serum ferritin level of 412 µg/l (13-232 µg/l) without clinical features, such as endocrine failure and cardiomyopathy. The antinuclear factor, anti-smooth muscle antibody, and anti-mitochondrial antibody were negative. The serum calcium and phosphate levels were normal.

Two days later, she was readmitted with biliary sepsis and acute pancreatitis. Re-reporting of MRCP on day 35 revealed multiple segmented strictures with dilatation of the intervening segment, giving the intrahepatic biliary canaliculi a beaded appearance (Figure 2), suggesting sclerosing cholangitis. Endoscopic retrograde cholangiopancreatography (ERCP) was performed on day 38 to exclude dominant bile duct stricture. It demonstrated segmented strictures in the right and left hepatic ducts, giving the beaded appearance. A 10 French gauge 10cm long plastic stent was inserted. Three cycles of total plasma exchange were done on day 72, and the ALP level improved from 150 U/L to 84 U/L. A liver biopsy was performed, but the histology revealed normal architecture of the liver. Following that, the interval cholecystectomy was done on the 89th day. The patient remained well for a couple of weeks, but worsening cholestatic jaundice led to a second ERCP on the 95th day, at which the stent was replaced with a 10 French gauge 7cm long stent as the previous was dislodged. The cholangiogram at that time revealed the same beaded appearance as the previous ERCP, with no gallstones. Although antibiotic coverage was given at the ERCP, the already-formed intrahepatic biliary strictures and hypoalbuminemia increased the patient's susceptibility to biliary sepsis. She was admitted to the hospital with two more episodes of ascending cholangitis, the latter requiring intensive care, where she succumbed to sepsis and multiorgan failure.

Most of the secondary causes for sclerosing cholangitis were excluded in this patient. No surgical interventions had been performed on this patient before, and she did not have a history of cholelithiasis or pancreatitis. Choledocholithiasis was not demonstrated in the multiple imaging modalities. It is unlikely to be portal hypertensive biliopathy in this patient as she only had early signs of developing portal hypertension. No malignant lesions were identified in the liver or other organs in her CECT of chest, abdomen, and pelvis. The MRCP did not suggest the presence of cholangiocarcinoma, a secondary cause, and a complication of primary sclerosing cholangitis. Eosinophilic cholangitis and mast cell cholangiopathy involving the liver diffusely were excluded as the

histology was normal. The possibility of human immunodeficiency virus associated cholangiopathy was unlikely as her HIV status was negative. Hence, primary sclerosing cholangitis was the only possible diagnosis.

Table 1: Liver enzymes, CRP and serum amylase at the first hospital admission. R factor < 2 indicates cholestatic liver injury

	Normal range	**Day 3**	**Day 9**	**Day 12**	**Day 17**	**Day 20**	**Day 22**	**Day 26**	**Day 30**
Aspartate aminotransferase (U/l)	10-35	60	39		50	67	44	134	102
Alanine transaminase (U/l)	10-40	60	24		25	25	26	31	26
Alkaline phosphatase (U/l)	30-120		155	166	185	95	88	178	77
R factor			0.5		0.4	0.8	0.9	0.5	1.0
Gamma-glutamyl transferase (U/l)	7-50		77	21					66
Total bilirubin (µmol/l)	5-21	429	652	938	861	811	517	648	441
Direct bilirubin (µmol/l)	<3.4		327	443	623		258	432	233
C reactive protein (mg/l)	0.5		4.7	5.9	1.57	201	114	16.5	21.6
Amylase (U/l)	28-100							1256	257

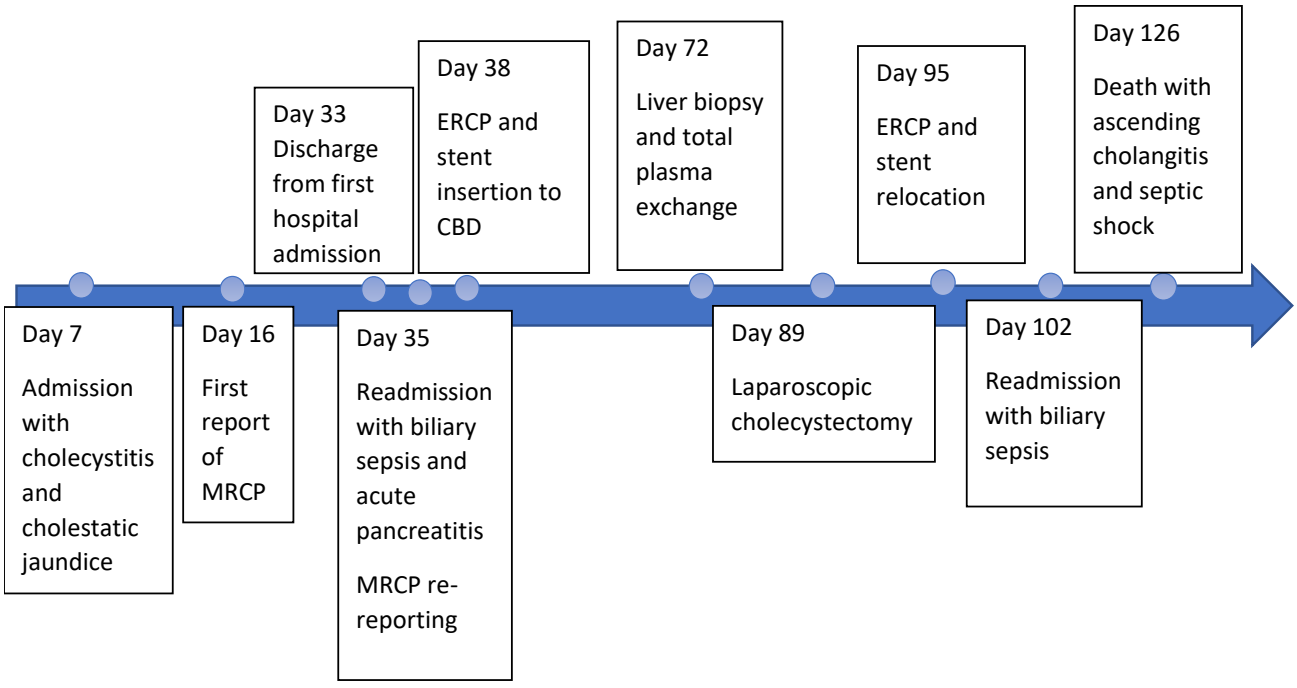

Figure 1: Timeline of the events

Discussion

Primary sclerosing cholangitis, being a rare disease in South Asia, tends to be missed as a diagnosis in our setting, which partly owes to the limited access to the diagnostic modality, MRCP. Thalassemia, on the contrary, is a common disease in Sri Lanka, and beta-thalassemia carrier state is a common encounter in day-to-day practice. Therefore, pigment stones are commonly seen, which causes confusion when making the diagnosis for this patient. This case highlights the importance of suspecting PSC in patients presenting with cholestatic jaundice whose diagnosis is unclear despite its rarity in the region.

The diagnosis of primary sclerosing cholangitis is made by the presence of biliary strictures, giving the characteristic beaded appearance on imaging and exclusion of possible causes that would give rise to secondary sclerosing cholangitis [2]. At the initial presentation of this patient, the cholestasis was attributed to a possible gallstone obstructing the common bile duct, which was supported by the presence of calculus cholecystitis in the ultrasonography. As the HPLC confirmed the beta-thalassemia carrier state, a common condition in this region, the gallstones were explained as pigment stones. However, multiple imaging modalities failed to demonstrate a single intraductal calculus despite the patient's worsening cholestasis. Therefore, MRCP, which is of limited availability, was done, which gave the first clue in making the diagnosis, the beaded appearance of the intrahepatic bile ducts. On the other hand, one study has found that 25% of PSC patients have gallstones or cholecystitis [3].

The serum markers anti-smooth muscle antibody and p-ANCA are associated with primary sclerosing cholangitis, which was negative in this patient. P-ANCA is present in 30-80% of patients [4]. Hence, they are not necessary in making the diagnosis [2]. The liver histology obtained by percutaneous liver biopsy revealed a normal histology. The primary sclerosing cholangitis has a patchy involvement; therefore, the liver biopsy may not display the expected concentric periductal fibrosis, giving an "onion skin" appearance [2]. The patchy cirrhotic changes seen in the liver of the CECT abdomen of this patient can be explained by this pathology.

Exclusion of secondary causes for sclerosing cholangitis is necessary to diagnose primary sclerosing cholangitis. The known secondary causes are cholangiocarcinoma, IgG4-related sclerosing cholangitis, choledocholithiasis, portal biliopathy, HIV, cholangiopathy, systemic mastocytosis, Langerhan's histiocytosis and recurrent pyogenic cholangitis [5]. The limiting factor in evaluating this patient was not having access to the immunoglobulin G4 (IgG4) level measurement. Had it been high, there is a place for steroid treatment [2]. However, it is an unlikely diagnosis without lymphoplasmacytic infiltration in liver histology.

Primary sclerosing cholangitis is a less common disease in South Asia. At the same time, it is more common among males [1,6]. The lack of data about the prevalence and behaviour of primary sclerosing cholangitis in the region can cause a delay in the diagnosis.

Other autoimmune conditions associated with PSC are inflammatory bowel disease, rheumatoid arthritis, autoimmune thyroiditis, myasthenia gravis, insulin-dependent diabetes mellitus and coeliac disease [2,7]. Known complications of PSC are cholangitis, pruritus, fat-soluble vitamin deficiency, metabolic bone disease, cholangiocarcinoma, dominant bile duct strictures, and cirrhosis [2,5]. Treatment for primary sclerosing cholangitis was done with ursodeoxycholic acid and colestyramine symptomatically [2], as we did in this patient. Avoidance of ERCP helps reduce the risk of introducing infections. Instead, non-invasive methods like MRCP and dynamic liver MRI/CECT are preferred [2]. Dominant bile duct strictures are seen in 36-50% of these patients. They can be addressed with stenting, reducing the progression of liver cirrhosis. Liver transplantation is the definitive treatment [2,8].

Although the pathogenesis of PSC is considered of autoimmune origin, none of the immunosuppression therapies have been proven beneficial [2]. Plasma exchange was done with the intention of reducing serum bilirubin levels. This patient showed improvement after plasma exchange, as indicated by the normal ALP levels [9]. However, its effectiveness could not be observed as the patient deteriorated with recurrent episodes of septic cholangitis.

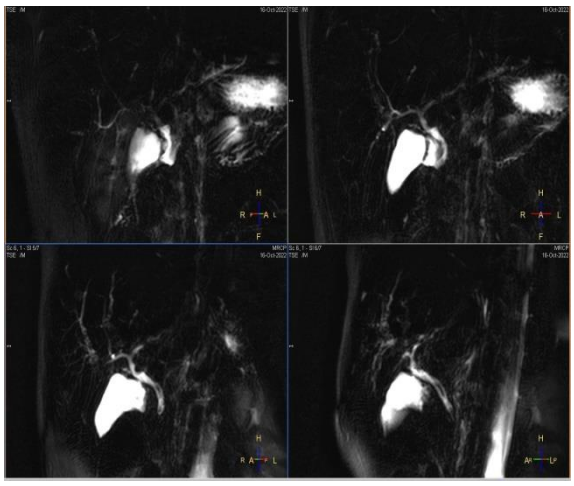

Figure 2: Beaded appearance of the biliary tree in magnetic resonance cholangiopancreatography (MRCP)

Conclusion

Primary sclerosing cholangitis is an uncommon disease with poor outcomes. The threshold for MRCP should be lowered in evaluating patients for cholestatic jaundice to diagnose the condition rather than serum biomarkers. Plasma exchange may benefit in achieving remission in PSC, which needs further research.

Consent

Informed written consent was obtained from the patient's mother as the patient is deceased.

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