Primary Sclerosing Cholangitis in Very Early Age: Two Case Reports

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Abstract

Primary Sclerosing Cholangitis (PSC) is a rare, chronic, progressive cholestatic liver disease which affects intrahepatic and extrahepatic bile ducts. That eventually progresses to end stage liver disease that requires liver transplantation. It mostly occurs in adolescent males and boys. Pediatric disease appears milder in contrast to adult-onset PSC. The diagnosis is made by Magnatic Resonance Cholangio-pancreatography (MRCP). Though there is no practical guideline available in pediatric patients for treating PSC UDCA is prescribed chronically in over 80% of patients. There is close association of PSC with inflammatory bowel disease and autoimmune hepatitis in children. So the treatment is complex in case of children. We reported here two cases of PSC, because of rarity of this disease in such a young age.

Keywords: *Primary Sclerosing Cholangitis (PSC), Inflammatory Bowel Disease (IBD), Magnatic Resonance Cholangio Pancreatography (MRCP), Ursodeoxycholic Acid.*

Introduction

Primary Sclerosing Cholangitis (PSC) is a chronic, progressive cholestatic liver disease which affects intrahepatic and extrahepatic bile ducts.[1] This rare disease is caused by chronic inflammation and fibrosis of bile ducts that leads to multifocal biliary strictures.[2] It eventually progresses to end stage liver disease that requires liver transplantation. The natural history of this disease is very variable. It may be asymptomatic for long time or may progresses early during childhood.[3] It may have fluctuating disease course where symptoms may flare up intermittently.[4] Pediatric disease appears milder in contrast to adult-onset PSC. The diagnosis is made by Magnatic Resonance Cholangiopancreatography (MRCP), which shows a characteristic feature of multifocal strictures and focal dilation of the bile ducts, causes to a beaded appearance.[5] Liver biopsy should be performed in case of children because there may be associated autoimmune hepatitis (Overlap syndrome). The cause of PSC is not well known. Various proposed mechanisms are likely to play as etiology. The most common mechanisms are bile acid toxicity, gut liver axis, alteration of gut microbiota, increased gut permeability.[6,7] There is close association of PSC with Inflammatory Bowel Disease (IBD) in children.[8] IBD may occur concomitantly with PSC, precedesor develops later in disease course. We reported two cases of PSC, because of rarity of this disease in such a young age.

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Case 1

An eighteen month old immunized boy, only issue of his non-consanguineous parents admitted in the department of Pediatric Gastroenterology of BSMMU on mid September, 2021. His presenting complaints were jaundice, pale stool and dark urine for two months. He also had irregular fever for same duration. There was no history of hematemesis and melena, abdominal pain, pruritus, blood transfusion, major or minor surgery, rash, arthralgia, diarrhea, no family history of such type of illness. On examination, he was mildly pale, deeply icteric. Vitals were within normal limit. Anthropometrically he was underweight and stunted. Abdominal examination revealed hepatosplenomegaly and mild ascites. Other systemic examination revealed normal findings. Laboratory investigation revealed that hemoglobin: 9.2gm/dl, WBC count - $11x10^9$/L, Differential count of WBC: N -60%, L - 33%, M - 7%. Platelet count was $268x10^9$/L, ESR - 40 mm in 1st hour. Liver function test was done. Serum bilirubin was raised (10.75mg/dl). Serum direct bilirubin was 4.35gm/dl, S. ALT - 89U/L. S. Gamma Glutamyl Transferase (GGT): 582U/

L (Reference range 0-30 IU/L), which was highly increased. S. Alkaline Phosphatase was not done because it is usually increased in this age group. S. Prothrombin Time and INR: 12.8 sec, 1.07. S. Albumin: 31gm/L. Abdominal ultrasonography revealed hepatomegaly with heterogeneous hepatic parenchyma, intrahepatic biliary tree are mildly dilated with diffuse wall thickening having beaded appearance. Common bile duct, measuring about 0.9 cm, lumen, narrowed with diffuse wall thickening. MRCP showed intrahepatic biliary tree are mildly dilated and distorted with beaded appearance (Figure-1 & 2). Liver biopsy was done. Histopathology result showed feathery degeneration, cholestasis in the periportal area and mild proliferation of bile ductule with periportal infiltration of lymphocytes and neutrophils. It also revealed lobular inflammation and periductal fibrosis (Figure-3). S. Autoantibodies were normal. ANA, pANCA, ASMA, Anti LKM1 were in normal range. S. IgG was normal: 12.3 mg/L (Reference range 3.13-11.70 mg/L). Viral markers was normal (Anti HAV IgM and Anti HEV IgM - negative). S. Alpha Fetoprotein (AFP): 1.33 ng/ml (Reference range 10-20 ng/ml). So, PSC was diagnosed on the basis of MRCP and liver biopsy. Upper gastrointestinal endoscopy showed no esophageal varices. Colonoscopy was postponed at the time of diagnosis of PSC as there was no symptoms of bloody diarrhea. It will be performed on the next follow up. The child was treated with Ursodeoxycholic Acid (UDCA) at the dose of 15 mg/kg/day on two divided doses. Injectable antibiotics (Ceftazidime and Amikacin) was given during hospital stay. We discharged the patient with UDCA therapy. We followed up the patient with Serum GGT, PT-INR and Albumin.

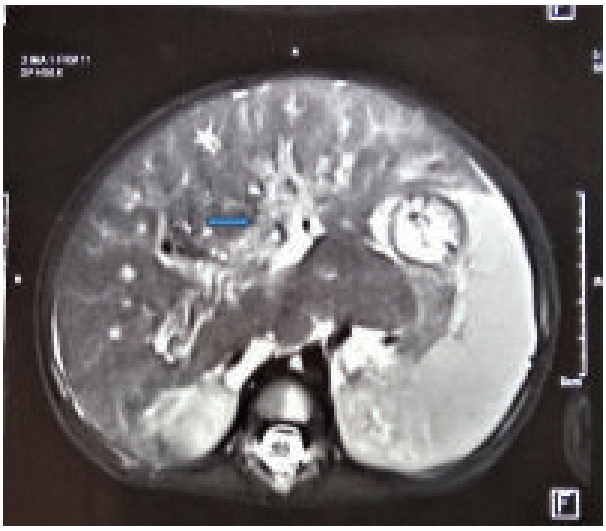

Figure-1: *MRCP showed intrahepatic biliary tree are mildly dilated and distorted (Case 1)*

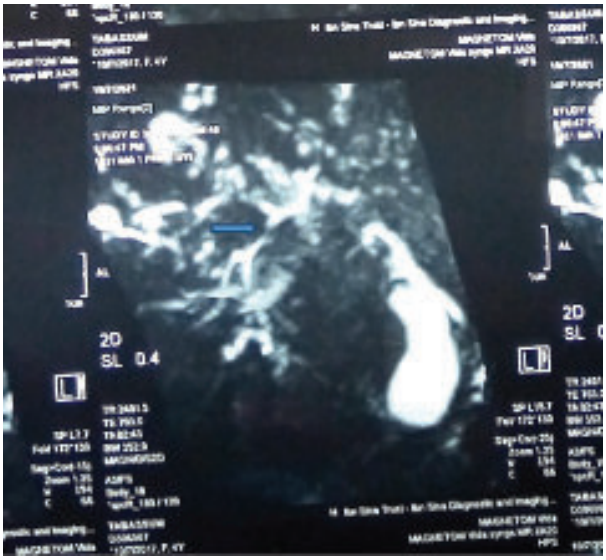

Figure-2: *MRCP showing mild dilatation in intrahepatic biliary channels giving rise of beaded appearance (Case 2)*

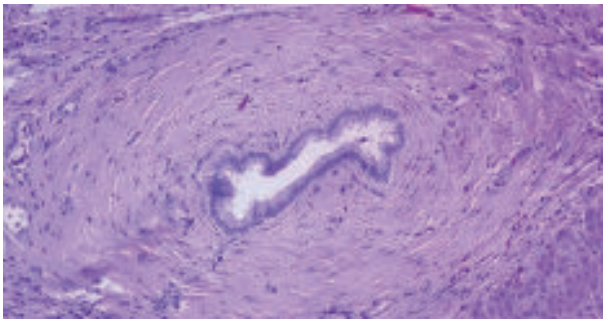

Figure-3: *H & E stain: Lobular inflammation and periductal fibrosis (Case 1)*

Case 2

A 3 years 7 months old immunized girl, 2nd issue of non-consanguineous parents got admitted into the department of Pediatric Gastroenterology, BSMMU with the complaints of swelling of abdomen for 1 and ½ years, which was gradually increasing day by day. She also complained of irregular fever and occasional abdominal pain for same duration. She also had anorexia and was not growing well for same duration. There was no history of jaundice, hematemesis and melena, blood transfusion, pruritus, major or minor surgery, rash, arthralgia, no family history of such type of illness. On examination, she was mildly pale, not icteric. Vitals were within normal limit and anthropometrically underweight and stunted. Abdominal examination revealed hepatosplenomegaly.

Ascites was absent. Other systemic examination revealed normal findings. Laboratory diagnosis revealed that Hemoglobin:10gm/dl (Reference range11-13gm/dl), WBC count $10x10^9$/L, DC of WBC N - 60%, L - 33%, M - 7%, PLT count $300x10^9$/L, ESR 85 mm in 1st hour. Serum ALT: 139 U/L (Reference range 7-40 U/L), S. GGT:1734U/L (Reference range 0-30 IU/L) which was significantly raised, S. ALP: 1080 U/L, PT and INR was 13.4 sec and 1.14, Serum Albumin: 42 gm/L (Reference range 3.5-5.5 gm/L), S. bilirubin was within normal range (1.92m g/dl). USG showed hepatomegaly. CT scan of Abdomen showed grossly dilatation of intra hepatic biliary tree and hepatosplenomegaly. MRCP revealed mild dilatation in intrahepatic biliary channels giving rise of beaded appearance (Figure-3). Liver Biopsy was done and histopathology report showed moderate infiltration of chronic inflammatory cells, small number of polymorphs and bridging fibrosis, marked piecemeal necrosis, moderate lobular necrosis, suggestive of moderate chronic hepatitis. Anti LKM1- negative (1.92 U/ml), S. IgG: 16 mg/L (3.13-11.70 mg/L), ASMA - negative, ANA - negative. Viral markers were negative. Upper gastrointestinal endoscopy showed no varices. Colonoscopy was performed and no features of colitis was present. We diagnosed the patient as Primary Sclerosing Cholangitis. The girl was discharged with UDCA and asked to come for follow up.

Discussion:

PSC in children is rare. It mostly occurs in adolescent males and boys.[9] The mean age of presentation is 13.8 years.[10] The largest pediatric cohort of 781 patients revealed a median age of onset at 12 years, 61% male predominance, 76% with IBD, 33% with AIH-PSC overlap syndrome.[11] Here we discussed about two patients who presented at very early age. Pediatric patients with PSC have various nonspecific complaints at presentation like fatigue, abdominal pain, and diarrhea. Asymptomatic patients have high GGT, ALT, AST as an incidental finding.[12] Elevated liver enzymes may be found in preexisting IBD.[13] They may also present with features of cholestatic disease like jaundice, pruritus, pale stool and dark urine. Our patient (case-1) presented with features of cholestatic disease and case-2 presented with nonspecific symptoms. Rarely patients may present with features of decompensated liver disease and portal hypertension (ascites, varices, encephalopathy).[14] Our patients showed no features of decompensation. Adult onset PSC differs from pediatric onset PSC in many aspects. The use of ALP is not a reliable biomarker for assessing PSC in children because it may be raised in the setting of rapid bone growth. So, GGT is considered as reliable marker in children.[15] Pediatric PSC studies revealed that only 53%-81% patients had raised ALP compared with 94%-100% of patients with elevated GGT.[1] Pediatric onset PSC is a slowly progressive disease than adult onset PSC. Though it may develop end stage liver disease about ten years after diagnosis and require liver transplantation.[11,16] Autoimmune Hepatitis (AIH) may occur simultaneously in case of Pediatric onset PSC which is called overlap syndrome. AIH-PSC overlap syndrome is diagnosed on the basis of elevated liver enzymes, MRCP and/or biopsy consistent with PSC along with positive autoantibodies and histology consistent with AIH (interface hepatitis, plasma cell infiltrate).[17] Our patients had no features of AIH as evidenced by negative autoantibodies and no interface hepatitis in histopathology. So, liver biopsy has a great importance in case of children to detect autoimmune hepatitis. We know that MRCP is sufficient to diagnosis PSC. Because, MRCP has high sensitivity and specificity for diagnosing PSC.[18] MRCP is preferred investigation over ERCP. Because ERCP causes post procedure complications like bacterial cholangitis, pancreatitis, hemorrhage and perforation. So, ERCP is reserved for therapeutic purposes like sphincterotmy, stenting, balloon dilatation.[19] ERCP is also difficult to perform in very young children. Cholangiocarcinoma as a complication is rare in case of children (1%) in relation to adult onset PSC.[20] Though annual screening of Cholangiocarcinoma with CA 19-9 is necessary for adolescents. But routine screening is not obligatory for young children.[21] Medical management of pruritus includes UDCA, rifampicin and naltrexone. Medical refractory severe pruritus is an indication of liver transplantation. Our patients did not present with pruritus. Adults with PSC has a distinct presentation which is called IgG4 associated PSC.[22] IgG4 associated PSC is rare in case of children. Pathogenesis of PSC is not well established, but proposed most common mechanism is bile acid toxicity.[23] Hydrophobic bile acid is hepatotoxic which is present in high concentrations in PSC appear to be cytotoxic within the biliary tree. PSC patients may lack an effective bicarbonate buffer system between cholangiocytes and the biliary lumen,[24] aggravating this effect. UDCA is a hydrophilic

bile acid which is hepatoprotective and is readily absorbed orally. UDCA increases hydrophilic bile acids portion in bile. UDCA therapy with longer duration should be reserved for those who show a dramatic biochemical response and normalization of GGT. While there is detrimental effect with high dose (25-30 mg/kg/d),[25] it should be started with low dose (15mg/kg/d). Though role of UDCA in PSC is inconclusive, UDCA is prescribed chronically in over 80% of patients with PSC. There is no practical guideline available in pediatric, patients for treating PSC. The largest retrospective study of pediatric PSC patients showed that survival was similar in UDCA-treated and untreated children.[26]

Children with PSC have IBD in most cases.[27] Gut-liver axis is main hypothesized pathogenic mechanism which is common for both, PSC and IBD.[28] The mechanisms for developing PSC include an inappropriate immune response in genetically susceptible individuals,[29] a pathogenic change in the fecal microbiome leading to the accumulation of toxic bile acid species and a following inappropriate inflammatory response,[30] migration of gut-activated mucosal lymphocytes to the liver, disruption of the intestinal epithelial barrier due to inflammation.[31] Although the relationship between PSC and ulcerative colitis (UC) indicates a likely common pathogenesis, the two conditions may occur at different times. PSC may occur years after colectomy for UC, and UC may first develop after liver transplantation has been performed for PSC.[11,32] First-degree relatives of patients with PSC have more chance to develop PSC and ulcerative colitis (UC), supporting a genetic basis to these conditions.[11] Our patients did not have any family history of PSC and ulcerative colitis. In a large cohort of 2744 IBD patients (1188 UC; 1556 Crohn disease [CD]), 57 had PSC (48 UC-PSC, 9 CD-PSC). The prevalence of PSC was higher in UC than CD (4.04 versus 0.58 percent, $p<0.001$).[33]

Liver transplatation is the ultimate therapy for PSC that has progressed to end stage liver disease. Complications of portal hypertension and end stage liver disease such as: variceal bleeding, ascites, spontaneous bacterial peritonitis and hepatic encephalopathy are the most common clinical reasons to perform liver transplantation for PSC.[33] PSC frequently recurs (rPSC) in the transplanted liver. rPSC is diagnosed when PSC-like ductal lesions and cholestasis occur six months or more after liver transplant.[34]

Conclusion

PSC in children is a rare condition. Diagnosis of PSC is more accurate by performing MRCP. But this diagnostic facility is not available in all centers of Bangladesh. The availability of MRCP makes diagnosis more possible in tertiary care centers. Even more, diagnostic criteria is different from adult PSC. The children may be presented with autoimmune hepatitis and IBD along with PSC. So, more studies are necessary to treat these children with more comprehensive strategies.

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