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Case report

Autoimmune hepatitis-primary sclerosing cholangitis overlap syndrome in a 10-year-old girl with ulcerative colitis

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= Abstract =

Autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and primary biliary cirrhosis (PBC) are chron liver diseases. Overlap syndrome is defined as a condition in which the clinical, biochemical, and histological fe autoimmune diseases are overlapped. Thus, it is difficult to appreciate overlap syndrome as an actual diagnostic a few cases of the overlap syndrome of AIH and PSC have been reported, especially in children. Moreover, PSC is to be the most frequent liver disorder associated with inflammatory bowel diseases such as ulcerative colitis. W case of AIH-PSC overlap syndrome in a child who was diagnosed as having ulcerative colitis. (Korean J Pediatr 504-507)

Key Words : Autoimmune Hepatitis, Primary Sclerosing Cholangitis, Overlap Syndrome, Ulcerative Colitis, Inflamm Diseases

Introduction

Autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) are immune-mediated chronic liver diseases and have often been regarded as separate disease entities. It has been possible to distinguish between these autoimmune diseases based on the clinical, biochemical and histological features in the majority of cases. In recent years, however, there have been a few cases that were difficult to diagnose as a definite disease because of coexistence of diagnostic features, which is termed as overlap syndrome. While overlap syndrome of AIH and PBC is frequent among adults, overlap between AIH and PSC has rarely been reported, especially in children. Meanwhile, PSC is known to be associated with inflammatory bowel diseases (IBD) such as ulcerative colitis (UC).

We report one case of AIH-PSC overlap syndrome in a 10-year-old girl who had been diagnosed and treated for UC.

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Case report

A 10-year-old girl was referred with a 1-year history of diarrhea, abdominal pain and weight loss. She was found to have elevated liver enzymes in her routine school examination 2 years ago but did not undergo any clinical investigations. One year later, she was admitted to a private hospital for abdominal pain and bloody stool with diarrhea. Colonoscopic examination showed no significant findings. However, her symptoms persisted and she lost weight for about 1 year. She was readmitted to the hospital and the second colonoscopic biopsy was performed. The diagnosis of UC was made and treatment with mesalazine was initiated 1 month prior to referral to our hospital.

Physical examination revealed 10 kg weight loss over 1 year. She also showed mild tenderness in the right lower abdominal quadrant, although the liver was not palpable and there were no other signs of chronic liver failure or cholestasis.

She exhibited a marked increase in aminotransferase levels (AST 229 IU/L, ALT 492 IU/L) in association with an increase in ALP (614 IU/L) and γGT (393 IU/L) activity, while her total bilirubin (0.8 mg/dL) level was normal. Hypergammaglobulinemia was detected with increased IgG

(2,843 mg/dL) and normal IgM (270 mg/dL) levels. Positive circulating antibodies were also found. Antinuclear autoantibody (ANA) and anti-smooth muscle antibody (SMA) were positive with titers of 1:160 and 1:80, respectively. Perinuclear-staining antineutrophil cytoplasmic antibody (pANCA) was also detected with a titer of 1:160, while antimitochondrial antibody (AMA) was negative. The serology for viral hepatitis (IgM anti-HAV, HBsAg, anti-HBc, anti-HBs and anti-HCV antibodies, IgM for cytomegalovirus, Epstein-Barr and herpes simplex viruses) was all negative.

Colonoscopic examination revealed mucosal friability and diffuse hyperemic spots in the entire colon. Biopsy showed crypt atrophy and distortion with heavy eosinophil and lymphoplasma cell infiltration which was consistent with active UC (Fig. 1).

Liver biopsy showed portal lymphoplasmacytic inflammation and bridging fibrosis. A periductal edema and concentric fibrosis around the interlobular bile duct ("onion-skin appearance") was found with positive immunostaining of cytokeratin 7 and CD3, which are indicative of bile duct damage and destruction (Fig. 2). Magnetic resonance cholangiopancreatography (MRCP) showed mild dilatation of common bile duct (maximal diameter 6.8 mm) and irregular dilatation of intrahepatic duct that was compatible with PSC (Fig. 3).

Diagnostic criteria for AIH were fulfilled with a score of 14 according to the revised scoring system proposed by the

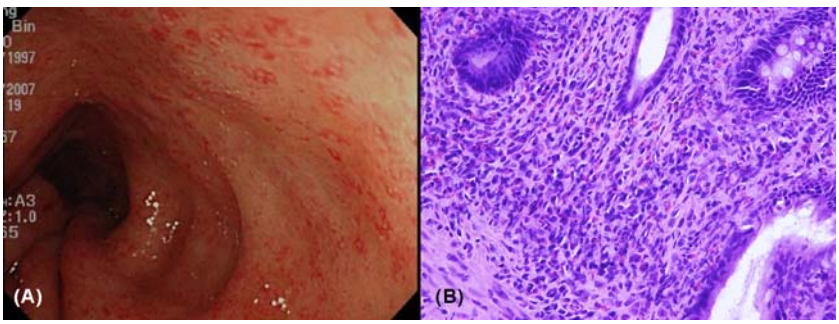

Fig. 1. The colonoscopy shows friability and diffused hyperemic spots in the colon (A) and a colon biopsy represents crypt atrophy and distortion with heavy eosinophil and lymphoplasma cell infiltration [H&E stain, ×200 (B)].

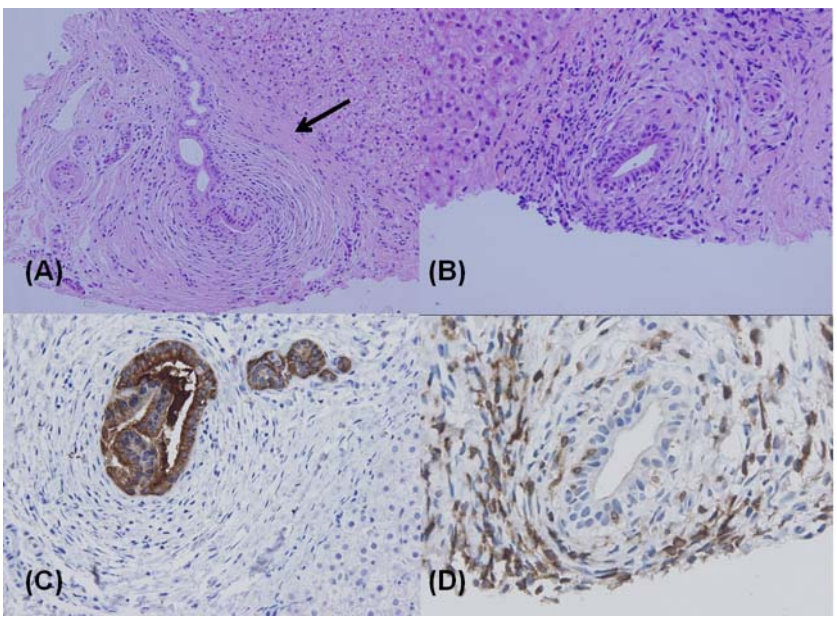

Fig. 2. The A), B) liver biopsy shows concentric fibrosis around the interlobular bile duct (onion-skin appearance: arrow) and mild lymphocytic infiltration around and within interlobular bile ducts [H&E stain, ×100 (A) and ×200 (B)]. Positive immunostaining of cytokeratin 7 (C) and CD3 (D) reveals bile duct damage [×200 (C) and ×400 (D)].

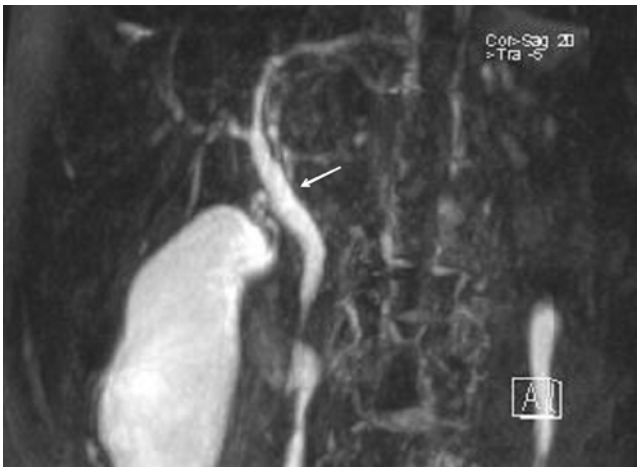

Fig. 3. Magnetic resonance cholangiopancreatography reveals mild dilatation of the common bile duct (maximal diameter is 6.8 mm: arrow) and mild irregular dilatation of intra-hepatic ducts.

International Autoimmune Hepatitis Group[1]. Therefore, the diagnosis of AIH-PSC overlap syndrome accompanied by UC was made. Prednisolone (1 mg/kg/day initially, followed by stepwise reduction) was added to mesalazine she had been taking upon referral. The treatment led to a good biochemical response and clinical improvement within two months. Serum AST (42 IU/L), ALP (175 IU/L) and IgG (1,648 mg/dL) returned to normal, and pANCA and SMA were negative. However, an attempt to withdraw the steroids led to a biochemical relapse. Since her aminotransferase (AST 504 IU/L, ALT 1,042 IU/L), ALP (409 IU/L) activity and total bilirubin (1.2 mg/dL) levels were elevated, azathioprine (25 mg/day, increasing later to 75 mg/day) with ursodeoxycholic acid (UDCA) (10 mg/kg) were introduced and the prednisolone (1 mg/kg/day) was restarted. After achieving improvement in biochemical parameters, the steroids were gradually tapered off over 3 months and discontinued under maintenance treatment with azathioprine, UDCA and mesalazine. She is in good clinical condition on this regimen with normal IgG, ALP, AST, bilirubin and γGT.

Discussion

AIH is characterized by liver histology, hypergammaglobulinemia and circulating autoantibodies including ANA, SMA or anti-liver-kidney microsomal autoantibodies (LKM-1). The diagnosis of AIH is reached by a scoring system established by the International Autoimmune Hepatitis Group (IAHG) in 1999, with "definite AIH" having scores >15 and "probable AIH" having scores of 10-15[1].

PSC is characterized by inflammation and progressive fibrosis of the intrahepatic and/or extrahepatic bile ducts[2, 3]. The diagnosis of PSC can be made by cholangiography and/or histology of the liver parenchyme. The characteristic histological features are periductal "onion-skin" fibrosis and inflammation with portal edema. In recent years, MRCP has been established as the preliminary noninvasive method of diagnosing PSC, especially in children[3, 4].

PSC is accompanied by IBD, particularly UC in about 53-81% of cases[5, 6]. Approximately 5-10% of patients with UC will have coexisting PSC[7]. The UC associated with PSC is characteristically mild, asymptomatic and runs a quiescent course. It is associated with rectal sparing and more severe right sided disease. It also has a high risk of colorectal malignancy, which necessitates routine colonoscopic surveillance[8]. Bowel symptoms may have developed before the nonspecific symptoms of PSC as fatigue, nausea and weight loss. Therefore, UC is usually diagnosed several years before PSC[7].

In our patient who was diagnosed as having UC, we suspected that she had associated PSC or AIH-PSC overlap syndrome because of high serum IgG level and the presence of autoantibodies, even though she had no cholestatic features on physical examination and laboratory tests. MRCP and histological findings in combination with serologic parameters confirmed the diagnosis of AIH-PSC overlap syndrome.

Overlap syndrome is generally defined as a condition with diagnostic features of more than one disease. In recent years, however, the term has been used to define autoimmune conditions in which clinical, biochemical and histological features of AIH, PSC or PBC are overlapped[9]. It occurs in approximately 20% of all patients with autoimmune liver diseases[10]. AIH-PSC overlap syndromes appear to be more common in childhood[6]. Most of the reported overlap cases were originally diagnosed as AIH and the diagnosis of PSC was made years after demonstration of characteristic bile duct changes on cholangiography[5, 6, 11, 12]. Therefore, investigations should be undertaken to rule out underlying PSC in children presenting with features of AIH.

Overlap syndrome is also considered to be associated with IBD (59-89%)[5, 6]. However, the presence of IBD is not a useful parameter to screen for overlap syndrome.

AIH-PSC overlap syndrome shows good response to treatment with immunosuppressive drugs, even if they are less efficient than in AIH. Therefore, overlap syndrome

should be suspected in the case of little response to immunosuppressant in a patient with AIH. Immunosuppressive therapy, such as prednisolone, together with UDCA, is often prescribed in children[5, 12]. Liver transplantation is required when a child progresses to biliary cirrhosis and hepatic decompensation[6, 12].

Recognition of overlap syndrome is of clinical significance in case of autoimmune liver diseases or IBD to enable timely and effective treatment. Children with chronic autoimmune liver disease with high levels of serum IgG, GGT and ALP should be tested for PSC, which should be ruled out by MRCP. Due to the high incidence of IBD in PSC and in overlap syndrome, especially in the case of positive pANCA level, early colonoscopy may be important. It is possible to diagnose and differentiate the infrequent overlap syndrome based on immunoserological and clinicopathological profiles.

한 글 요 약

궤양성 대장염에 동반된 자가면역성 간염-원발성 경화성 담관염의 중복 증후군 1예

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자가면역성 간염, 원발성 담관성 간경화증, 원발성 경화성 담관염은 대표적인 자가 면역성 간질환이다. 이 각 질환의 임상적, 조직학적, 혈청학적 특징이 혼재되어 어느 한 질환으로 진단하기 어려운 경우를 중복증후군(overlap syndrome)이라 하고, 최근 소아에게서도 드물게 보고되고 있다. 한편 경화성 담관염은, 염증성 장질환에서 가장 흔히 동반되는 간담도계질환으로 알려져 있다. 저자들은 궤양성 대장염으로 진단된 환아에게서 간조직 검사, 혈청검사, 방사선 검사 등을 통해 자가면역성 간염-원발성 경화성 담관염의 중복증후군을 진단하였기에 보고하는 바이다. 염증성 장질환 환아에게서 자가 면역성 간질환 또는 중복증후군 동반여부를 염두에 두어 임상적, 조직학적, 혈청학적 검사를 통해 적절한 진단과 치료가 필요하겠다.

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