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Ulcerative Colitis Associated with Primary Sclerosing Cholangitis: Two Case Reports and a Review of the Japanese Literature with Special Reference to HLA Typing

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ABSTRACT. We treated two cases of ulcerative colitis (UC), which were complicated by primary sclerosing cholangitis (PSC). Both patients had pancolitis type of UC, and their laboratory data, endoscopic retrograde cholangiography, and histologic findings of the liver biopsy were all compatible with the diagnosis of PSC. Assessment in histocompatibility leukocyte antigen (HLA) typing revealed that both patients had HLA CW7 antigen. In addition, three of the ten cases of UC and PSC reported in Japan, in which HLA typing have been specified, have HLA CW7. These findings suggest that genetic predisposition with the viewpoint of conventional HLA type may partly play a role in the coexistence of UC and PSC.

Key words: primary sclerosing cholangitis — ulcerative colitis — HLA typing

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease which is characterized by fibrosing inflammation of the extra-, intra-, or both hepatic bile duct.[1,2] It has been well established that there is a close relationship between PSC and inflammatory bowel diseases (IBD), and this is especially the case for ulcerative colitis (UC).[3] Approximately 70%-90% of patients with PSC have coexisting UC,[3] and alternatively, PSC develops in about 5%-10% of patients with UC in western countries.[4]

Major histocompatibility complex has been known to be linked to immunoregulatory genes, and the association between specific histocompatibility leukocyte antigens (HLA) and several autoimmune disease has been established. Furthermore, it has been described that HLA-B8 and DR3 were frequently identified in UC complicated with PSC in western countries.[5,6] Possible correlation of HLA typing with UC coupled with UC, however, has not been clarified in our country, probably due to much less number of subjects.

We recently encountered two such cases in both of which their HLA typing could be investigated. The clinical details in one case have been reported elsewhere.[7] In this report, the other case have been mainly described, and the HLA type in Japanese patients with PSC plus UC were reviewed in the literature.

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CASE REPORT

Case 1

A 76-year old female was admitted to our hospital, because of diarrhea and rectal bleeding.

The patient had initially been pointed out mild liver damage at the neighboring clinic, when she was 57-year of age. She had had neither histories of alcohol ingestion, and abdominal surgery, nor laboratory data of positive antibody against hepatitis viruses, thus the etiology of her liver damage had remained undetermined. She manifested diarrhea and hematochezia during three months' period prior to the admission to our hospital.

Physical examination revealed that she was mildly anemic, and the liver was palpable at the right hypochondrium. Tenderness was not evident on her abdomen. Laboratory data identified mild anemia (hemoglobin; 9.1 g/dl) without leukocytosis. Platelet count was increased ($45.1 \times 10^4/mm^3$). Serum GOT (37 IU/L) and GPT (40 IU/L) were slightly elevated. In addition, her serum levels of γ-GTP (597 IU/L) and ALP (634 IU/L) showed extraordinary

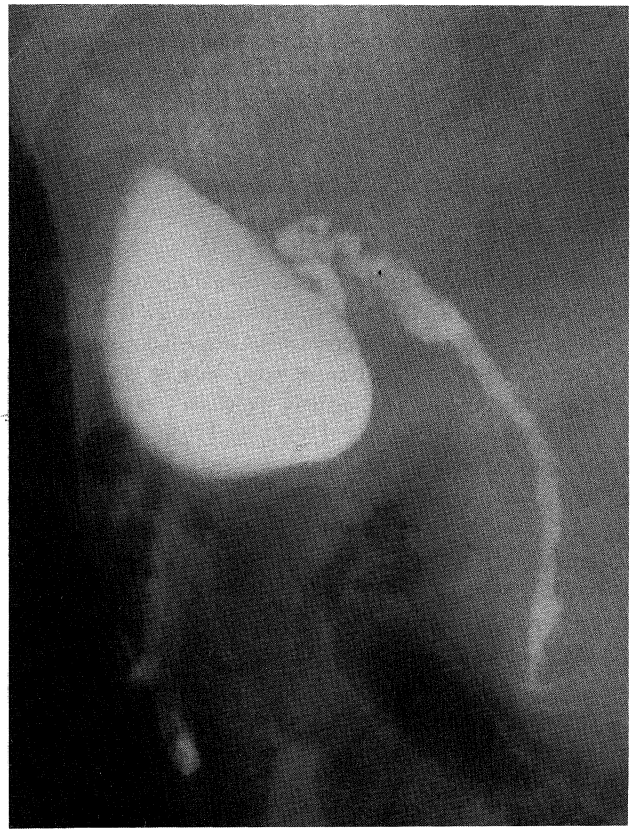

Fig 1. Endoscopic retrograde cholangiography in Case 1 shows irregularities within the wall of the common bile duct. The intrahepatic bile duct can not be identified, because of a stenosis in the proximal portion of the common bile duct.

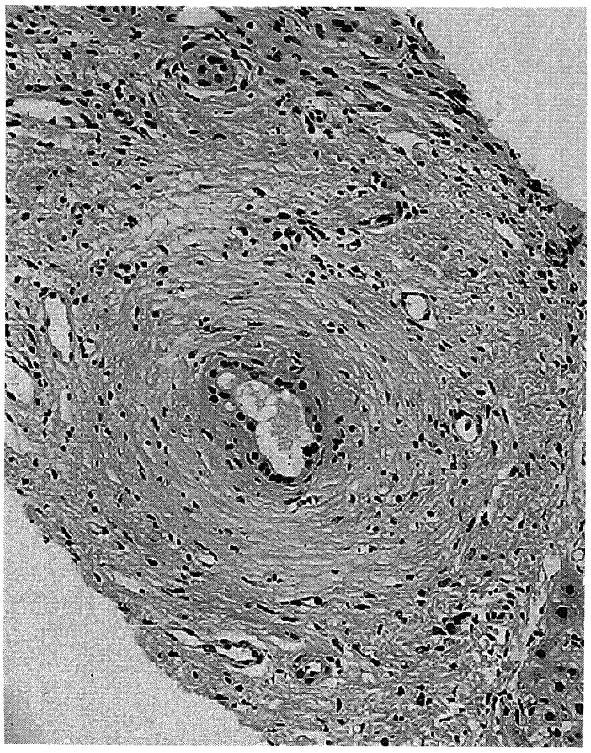

Fig 2. Microscopic examination of the liver biopsy specimen in Case 1 identifies concentric fibrosis surrounding the interlobular bile duct (onion like pericholangial fibrosis) (H & E, original magnification × 100).

high values. Abdominal ultrasonography showed that the liver was enlarged with irregular margin, but cholelithiasis was not evident. Endoscopic retrograde cholangiography (ERC) revealed irregular wall of the common bile duct, the proximal portion of which was so stenotic that the contrast material could not pass through (Fig 1). Because these observations suggested the diagnosis of PSC, percutaneous liver biopsy was further performed. Histological examination of the biopsy specimen revealed that there was chronic inflammatory infiltrate in the area of the portal tract and concentric fibrosis surrounding the interlobular bile duct (Fig 2). These histologic features were compatible with PSC.

Because the diagnosis of PSC was established, and diarrhea and hematochezia persisted, barium enema examination and colonoscopy were further performed. Both of these examinations revealed that the colon was affected by granular mucosa accompanied by small ulcers. The involvement extended from the rectum to the hepatic flexure (Fig 3). These findings conformed to ulcerative colitis of pancolitis type.

She was subsequently treated by oral sulphasalazine. Her diarrhea and hematochezia improved four weeks after the treatment, and the patient has been followed up as outpatient at our institution.

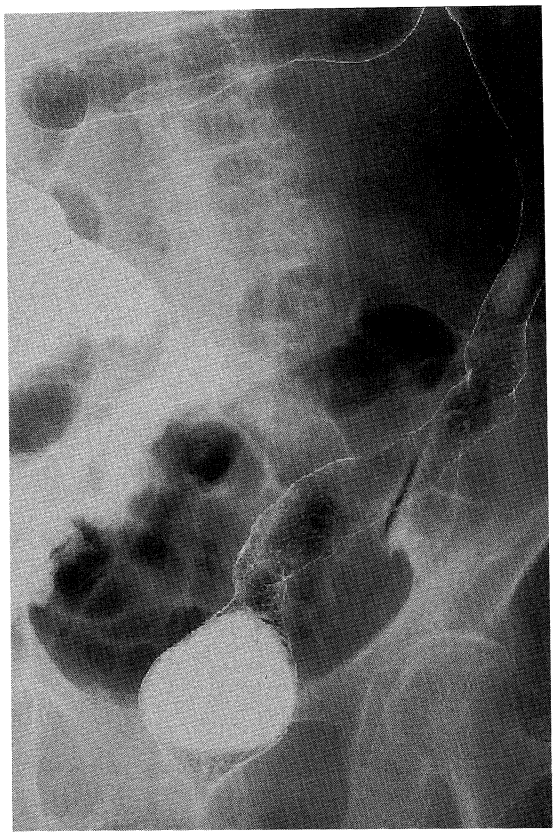

Fig 3. Barium enema study in Case 1 shows lead-pipe appearance and tiny barium flecks found throughout the colon.

Case 2

We treated another case of 16-year old male. The patient was initially diagnosed as suffering from UC when he was 13-years of age. During the subsequent period of treatment as an outpatient, his laboratory data revealed liver damage. While he was suspected of having sulphasalazine-induced hepatitis, further examination identified that he had PSC, because both ERC and liver biopsy both revealed characteristic feature of the disease. The details of this patient have previously been reported from our institution.[7]

HLA typing

We reviewed all the cases of UC accompanied by PSC reported in the Japanese literature, and listed up cases in which each patient's HLA typing has been clearly described. A total of 12 such cases, including those presented in this report, could be identified.[8–17] As indicated in table 1, HLA type of either A2 (7 of 12 cases), DR2 (6 cases), A24 (5 cases) or CW7 (5 cases) were frequently identified in the cases. Three cases had any one of the four HLA types, three cases had any two, and five cases had any three of the HLA types, whereas none of the types were identified in the remaining one patient.

DISCUSSION

PSC is a disease characterized by chronic and fibrosing inflammation of the intrahepatic and extrahepatic biliary tract. This disease progresses to biliary fibrosis, liver cirrhosis, portal hypertension, and premature death from hepatic failure.[1,2] Although the pathogenesis of PSC still remains unknown, it has been well established that the condition frequently occurs in cases of IBD, especially in those of UC.

In contrast to these investigations, there have been little informations regarding the incidence of UC in Japanese patients with PSC. So far as we reviewed, descriptions of the coexistence of both UC and PSC are limited to only 33 case reports, including our two patients, thus the true prevalence of UC in patients with PSC have not been ascertained. Kashihara *et al*[18] previously reviewed the Japanese literature, and they found 10 cases of UC among 55 PSC patients. The rarity of the association may have been derived from much lower incidence of UC in Japan than in western countries, since the prevalence of UC is at least two to five-fold greater in the latter.[19,20] There remains, however, another possibility that counterpart of the two diseases, especially PSC in patients with UC, has been overlooked, because the diagnosis of PSC is based upon ERC and liver biopsy, which are not routinely applied for patients with UC.

Because of such high incidence of UC in PSC, it has been postulated that intestinal bacteria or bacterial toxin may have a role in the pathogenesis of PSC.[21] In more recent years, common autoimmune mechanisms, such as humoral anti-cytoplasmic antibodies (ANCA), have been suggested in the pathogenesis of UC and PSC.[22] However, the less incidence of UC and PSC in Japan than in Western countries suggests that there may be genetic predispositions in the coexistence of the two diseases.

It has been confirmed that HLA haplotypes B8 and DR3 are risk factors for the development of PSC.[5,6] HLA-B8 and DR3 are, however, genetically less frequency found in general population in our country, and furthermore, these two haplotypes were not specified in any of our two patients and 10 other cases of UC and PSC reported in Japan. These findings may be a possible explanation of low incidence of UC and PSC in Japan. HLA-DR2, which is another but less strong risk factor for PSC,[21] was identified in 58% of the cases, but this haplotype does not seem to be specific for UC and PSC, because the type is reported to be found in 70% of Japanese patients with UC.[22] Other two haplotypes, HLA-A2 and A24, are genetically frequent in general populations. Thus from the results of our review, HLA-CW7 was suggested as one of the possible HLA types specific to Japanese patients with UC complicated by PSC.

Review of 33 cases in the Japanese literature revealed that pancolitis type of UC and younger age are risk factors for PSC.[7] Our Case 1, however, was diagnosed as having UC at the age of 76. Although it still remains unknown which of the two diseases, either UC or PSC, preceded in this case, her UC seems to have been overlooked because of less severe gastrointestinal symptoms. Thus, the possibility of UC should have been seriously considered during the observation period for her liver damage. This concept may increase opportunities for the diagnosis of UC and PSC.

TABLE 1. HLA type in reported cases of UC accompanied by PSC in Japan

Author (Ref number)	Patient		
	Age	Sex	HLA type
Tobori, *et al* (5)	35	F	A2, A9, BW39, CW3, CW7, DR2
Ishikawa, *et al* (6)	16	M	A2, A9, B52, DR2
Okayama, *et al* (7)	46	M	A24, A31, B40, BW48, CW3, DRW9
Hashimoto, *et al* (8)	17	F	A9, A10, B5, B15, CW3, DRW9
Hosokawa, *et al* (9)	23	M	A2, BW46, DW61, DR2, DR4
Hosoda, *et al* (10)	20	F	A24, B7, B39, DR4
Takekoshi, *et al* (11)	44	F	A11, A24, B39, DR4
Matsuhashi, *et al* (12)	24	M	A2, AW33, BW39, BW44, CW7, DR2
Adachi, *et al* (13)	57	F	A2, A24, B46, B60, CW1, CW4, DR4, DR9, DR53, DQ3
Meguro, *et al* (14)	23	F	A2, B39, B52, CW7, DR2
Present case 1	76	F	A2, B39, B52, CW7, DR2
Present case 2	17	M	A24, A31, B7, CW7, DR1

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