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HLA Antigens in Primary Sclerosing Cholangitis

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Primary sclerosing cholangitis (PSC) is an uncommon liver disease and its etiology is unclear. However, PSC was shown to be associated with certain HLA antigens, such as HLA AI, B8, or DR3, suggesting the presence of underlying abnormal autoimmunity, although the number of patients in the earlier studies was rather limited.[1–3] In this study, we analyzed HLA antigens in a relatively large number of patients with PSC.

MATERIALS AND METHODS

The subjects of this study were 133 North American Caucasian PSC patients who received orthotopic liver transplantation at the University Pittsburgh Medical Center (Pittsburgh, Pa) from December 1981 to May 1991. Of those, 77 patients had ulcerative colitis (UC), 9 had Crohn's disease, and 10 had hepatobiliary carcinoma in addition to PSC.

HLA typing was performed by the standard National Institutes of Health method using the best commercially available HLA typing trays.

Since the HLA typing had been done over the 10-year period, the patients were divided into 2 groups according to when their HLA typing was performed (group no. 1: 78 patients from December 1981 to December 1988 and group no. 2: 55 patients from January 1989 to May 1991).

HLA phenotype frequency of 1,145 North American Caucasians served as control and chi-square test was used for statistical analysis.

RESULTS

In both groups no. 1 and 2, the phenotype frequencies of HLA-B8, DR3, and DR6 in patients with PSC were significantly higher than those observed in control (Table 1). In addition, the significance was consistent regardless of the presence of UC, Crohn's disease, or hepatobiliary carcinoma.

There was an increased frequency of HLA-A1 and a decreased frequency of HLA-DR1 in patients from group no. 1; however, there were no such trends in group no. 2. Similarly, higher frequencies of A24 and A26 and a decreased frequency of DR7 were observed in patients of group no. 2 but not in group no. 1.

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DISCUSSION

DR3 or DR6 antigens were highly associated with a presence of autoimmune diseases such as myasthenia gravis, Sjogren's syndrome, and insulin-dependent diabetes mellitus. From this study, it appeared that PSC seemed to be associated with certain HLA phenotypes, particularly, B8, DR3, and DR6, suggesting that some autoimmune disorder could be present in patients with PSC.

It is possible that DR3 or DR6 alleles might be highly disease restricted; however, the analysis of class II haplotype by cellular, biochemical, and molecular techniques has revealed extensive genetic heterogeneity within serologically defined DR types. Thus, the association with PSC cannot simply be explained by the direct linkage with DR3 or DR6 gene products. The epitopes of DR3 as well as DR6 are expressed on DRβ1 molecules. Such DR antigens have strong linkage disequilibrium with other alleles, particularly DRβ3 or DRβ4 legions. In fact, approximately half of the DR3 found was reported to have DR52a, which is expressed on DRβ3 molecule, as was DR6.[4] DR52b is also found in about half of DR3 and DR6.[4] Thus, it is possible that class II antigens expressed on DRβ3 molecules could be associated with PSC. In fact, Prochazka et al[3] reported that all patients with PSC had DR52a, although our preliminary study revealed that only two thirds of patients with PSC had DR52a. Nevertheless, it is possible that PSC could simply be associated with DRβ3 class II antigen, and an increased frequency of B8 could be simply explained by a strong linkage disequilibrium between such DRβ3 class II antigens and B8.

In some autoimmune disorders, such as myasthenia gravis (which is also associated with DR3) it was reported that a certain peptide binds readily with myasthenia gravis-associated class II products, which would trigger an activation of lymphocytes, resulting in autoimmune disorder.[5] If there is an underlying autoimmune disorder in PSC, it would be probable that lymphocyte activation must be triggered by some undefined PSC-associated peptide which would specifically bind to DR3 or DR6, or DRβ3 gene products.

References

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Table 1

HLA Phenotype Frequencies in Patients With Primary Sclerosing Cholangitis

		Primary Sclerosing Cholangitis			
		1981–1988		1989–1991	
HLA Antigen	**Percent of Controls**	**Percent of patients**	***P*-value**	**Percent of patients**	***P*-value**
A1	25.7	42.3	$P < .01$	36.7	NS
A2	46.6	44.9	NS	38.2	NS
A3	26.0	23.1	NS	21.0	NS
A24	12.8	14.1	NS	23.7	$P < .05$
A26	7.2 (n = 1,029)	5.1 (n = 78)	NS	16.4 (n = 55)	$P < .05$
B7	18.7	21.8	NS	20.0	NS
B8	17.1	43.6	$P < .001$	36.7	$P < .001$
B39	3.6	1.3	NS	3.6	NS
B44	26.1 (n = 1,029)	16.7 (n = 78)	NS	16.4 (n = 55)	NS
DR1	20.0	8.0	$P < .05$	11.8	NS
DR2	25.3	21.3	NS	27.5	NS
DR3	22.2	40.0	$P < .05$	39.2	$P < .01$
DR4	27.3	17.3	NS	15.7	NS
DR5	19.4	18.7	NS	17.6	NS
DR6	7.2	40.0	$P < .001$	43.1	$P < .001$
DR7	23.6	20.0	NS	9.8	$P < .05$
DR8	5.3	1.3	NS	2.0	NS
DR9	3.0	NA		0.0	NS
DR10	1.2	NA		2.0	NS
Blank		32.0		25.5	
DR3 or 6	29.3 (n=1,145)	69.3 (n = 75)	$P < .001$	76.5 (n = 51)	$P < .001$