Chronic Active "Lupoid" Hepatitis and HLA System; Report of 6 Cases

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During the 12 years from 1977 to 1988 in Tottori University Hospital, 6 cases (4.2%) with chronic active "lupoid" hepatitis were encountered among 143 patients with histologically proven chronic active hepatitis. HLA antigens were studied; BW 22 and CW 1 were strongly associated, and A 11 was rather associated with the rare disorder in Japan. These results suggested that Japanese patients with chronic active "lupoid" hepatitis have different HLA markers from those in Caucasian patients, which may be attributable to rare specificity in the HLA system rather than different mechanisms of pathogenesis.

Key words: BW 22, CW 1, Japanese patient

Viral hepatic diseases including type A, B, and non A non B hepatitis are more prevalent than alcoholic liver diseases in Japan compared to Europe and the United States (1). In contrast, patients with hepatitis B surface antigen (HBsAg)-negative chronic active "lupoid" hepatitis are rare in Japan (2). Mackay and Morris have reported the association of certain specificities of the human major histocompatibility system, human leucocyte antigen (HLA) A 1 and B 8, with autoimmune active chronic hepatitis (3). Since then, several reports on the association of certain specificities of HLA with chronic liver diseases have been reported in Caucasians and Africans (4-7). In Japan, the relationship of the HLA system to HBsAg-negative chronic active "lupoid" hepatitis has not yet been extensively studied (8-10). In this report, the correlation of 6 clinically apparent patients with chronic active "lupoid" hepatitis and the specific Japanese HLA system was studied.

SUBJECTS AND METHODS

During the 12 yr from 1977 to 1988, 143 cases with histologically proven chronic active hepatitis were admitted to Tottori University Hospital. The

143 cases included 98 cases with HBsAg-positive patients, 36 cases with non A non B patients, 2 cases with alcoholic liver diseases, 1 case of drug hepatitis and 6 cases (4.2%) of chronic active "lupoid" hepatitis which fulfilled the diagnostic criteria (11), including histologic lesions, positive serological tests for auto-antibodies and negative HBsAg.

Typing for A, B, and C locus antigens was performed on the B cell deleted peripheral blood lymphocyte population using a microlymphocytotoxicity technique with the standard incubation time (12). Typing for D related (DR) antigens was performed using the enriched B cell population in a microlymphocytotoxicity method with a prolonged incubation time at room temperature (13). The antisera used was UCLA antisera as reported by Opelz and Terasaki (14) and assayed in the BML Corporation (Tokyo). Statistical analyses were performed by the chi square test with the two-sided test, and p values were calculated from X^2 correlation values.

RESULTS

The clinical, hematological and biochemical data of 6 patients with chronic active "lupoid" hepatitis are shown in Table 1. These 6 cases were all females

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Table 1. Clinical Hemotological and Biochemical Data of 6 Patients with Chronic Active "Lupoid" Hepatitis

	Case 1 (N.H)	Case 2 (I.M)	Case 3 (T.M)	Case 4 (F.N)	Case 5 (M.T)	Case 6 (T.S)
Clinical						
Sex/Age (yr)	69/F	69/F	62/F	52/F	61/F	36/F
Hepatitis B surface antigen	(-)	(-)	(-)	(-)	(-)	(-)
Hepatitis C virus antibody	N.D.	N.D.	N.D.	N.D.	(-)	(-)
Alcohol intake	(-)	(-)	(-)	(-)	(-)	(-)
Blood transfusion	(-)	(-)	(-)	(-)	(-)	(-)
Symptoms	Slight fever	Fever	Fever dyspnea	Fatigue	Upper abdominal pain Emaciation	Headache Dizziness
Signs						
Jaundice	(-)	(-)	(-)	(-)	(-)	(-)
Hepatomegaly	(+)	(+)	(+)	(-)	(+)	(-)
Splenomegaly	(-)	(+)	(+)	(-)	(+)	(-)
Palmar erythema	(-)	(-)	(-)	(-)	(-)	(-)
Vascular spider	(-)	(-)	(-)	(-)	(-)	(-)
Ascites	(-)	(-)	(-)	(-)	(-)	(-)
Associated conditions	None	None	Pulmonary hypertension	None	None	Hashimoto's disease
Liver biopsy	CAH	CAH	CAH	CAH	CAH	CAH
Response to corticosteroids	Good	Good	Good	Good	Good	Good
Hematological and biochemical						
Hemoglobin (12-15)(g/dl)	10.7	7.8	10.6	12.6	13.4	11.9
Red blood cell (330-490)($\times 10^6/\text{mm}^3$)	293	242	337	427	426	383
White blood cell (3,300-8,200)(mm^3)	3,200	4,300	2,300	4,100	3,600	5,200
Platelet (12-34)($\times 10^4$)	10.7	16.3	2.4	13.7	8.4	21.5
ESR (3-11)(mm/h)	103	151	100	15	24	39
Bilirubin (0.2-1.0)(mg/dl)	1.1	0.7	1.7	0.7	0.7	0.7
SGOT (<40)(U/l)	26	46	91	151	72	72
Alkaline phosphatase (3-12)(K-AU)	16	42	11	11	12	12
Total protein (6-8)(g/dl)	9.5	9.5	9.0	8.2	8.9	8.9
Albumin (3.5-5.0)(g/dl)	3.3	2.5	2.7	4.0	4.4	4.4
Gamma globulin (0.8-1.7)(g/dl)	4.5	5.2	5.2	2.5	3.1	3.1
Prothrombin time (70-140)(%)	52	90	91	107	92	92
Antinuclear factor	(+)	(+)	(+)	(-)	(+)	(+)
Antibody to DNA	(-)	(+)	(-)	(+)	(+)	(+)
Smooth muscle antibody	(+)	(+)	(+)	(+)	(+)	(+)
Mitochondrial antibody	(-)	(-)	(-)	(-)	(-)	(-)
LE cell test	(+)	(+)	(-)	(-)	(+)	(+)

Values given in parentheses are normal ranges.

CAH, chronic active hepatitis; ESR, erythrocyte sedimentation rate; SGOT, serum glutamic oxaloacetic transaminase; K-AU, King-Armstrong units; N.D., not done

from age 39 to 69 (mean 59 ± 11 yr). All 6 patients were HBsAg negative, with no prior history of alcohol intake or blood transfusion. Hepatitis C virus antigen (anti-HCV) was negative in 2 patients and not examined in the other 4 cases. The histological lesions of all 6 cases were chronic active

hepatitis. Three out of 6 cases were associated with anemia and a markedly increased erythrocyte sedimentation rate. All cases showed a high level of serum gamma-globulin (greater than 2.5 g/dl). Various autoantibodies were positive in each case, whereas the mitochondrial antibody was consistently

Table 2. HLA Loci in Chronic Active “Lupoid” Hepatitis

Case No.	HLA-Loci			
	A	B	C	DR
Case 1	A 24	BW 54(22)	CW 1	DR 2
	A 11			DR 4
Case 2	A 26(10)	BW 22	CW 1	DR 2
	A 11	BW 67		DR 4
Case 3	A 9	BW 22	CW 1	DR 2
	A 11			
Case 4	A 9	BW 5	CW 1	DR 2
	A 11	BW 22		DRW 8
Case 5	A 24	BW 54(22)	CW 1	DR 4
		BW 59		
Case 6	A 2	BW 22	CW 1	DR 4
	A 31	BW 61	CW 3	

negative in all cases. There was no consanguinity in the 6 patients. HLA typing including A, B, C and DR antigens is shown in Table 2. Statistical analyses were calculated using chi square tests. The strong association with BW 22 and CW 1 and relatively strong association with A 11 is shown in Table 3.

DISCUSSION

Chronic active hepatitis is the histological expression of a variety of distinct disease status, including

hepatitis B and non A and non B viral infection (16, 17), drug reaction (18), Wilson’s disease (19), alpha-1-antitrypsin deficiency (20) and alcoholic liver disease (21). The diagnosis of these 6 patients was confirmed to be HBsAg-negative chronic active “lupoid” hepatitis. These patients were associated with fever of unknown origin (3 cases), asymptomatic hepatomegaly (4 cases), and anemia (3 cases). The laboratory findings of an increased erythrocyte sedimentation rate, high gamma-globulin levels, positive autoantibodies in serum as well as histological findings are all characteristic of this condition. In Japan, patients with HBsAg-negative chronic active “lupoid” hepatitis are rare; only 100 cases had been reported prior to 1988 (2). In fact, there were only 6 cases out of 143 cases (4.2%) with chronic active hepatitis during a 12-yr period in our hospital. Regarding the age of these patients, there was two peaks, the thirties and sixties, and the total of both generations consisted of 87% of all cases reported (22).

In Caucasians chronic active “lupoid” hepatitis has a strong association with the B locus allele (3); the highest reported relative risk for this allele is 15.4 (4). Subsequently, family studies (7) showed that, in 14 families with a patient positive for B and DRW

Table 3. Statistical Analysis of HLA in Japanese Patients with Chronic Active “Lupoid” Hepatitis

HLA		Chronic active “lupoid” hepatitis n = 6 (%)	Japanese control+ n = 884–950(%)	p values
A	11	66.7	17.2	N.S. (0.05*)
A	9	50.0	59.6	
A	26	16.7	18.7	
A	2	16.7	43.2	
A	31	16.7	15.3	
BW	22	100.0	22.1	0.0003
BW	67	16.7	1.6	N.S.
BW	59	16.7	4.2	N.S.
BW	5	16.7	36.4	N.S.
BW	61	16.7	16.8	N.S.
CW	1	100.0	32.1	0.003
CW	3	16.7	46.5	N.S.
DR	2	66.7	36.1	N.S.
DR	4	66.7	41.4	N.S.
DRw	8	16.7	12.6	N.S.

The statistical test was performed by chi square test (two-sided test).
*Fisher’s test (one-sided test)
+ Histocompatibility Testing 1980¹⁴⁾

3, a haplo type containing B 8 and DRW 3 was present in alle 14 of the index cases, and the A 1, B 8, DW 3 haplo type was present in 10. Moreover, an increased frequency of DR 3 in Caucasian patients with chronic active "lupoid" hepatitis was reported by Galbraith et al (5) and Lindberg et al (6).

As already mentioned, to date, there have been no well documented cases in the literature of the HLA system in HBsAg-negative active "lupoid" hepatitis in Japanese patients. Ito et al (8) reported that 8 cases of autoimmune chronic hepatitis which met the criteria of Mackay and Morris (3) were not associated the any specificities of HLA. Miyamori et al (9) reported that Japanese patients with autoimmune hepatitis showed a somewhat higher frequency of HLA-A 10 compared to the controls.

The present data showed that the existence of A 11, BW 22 and CW 1 was a common characteristic in 6 Japanese patients, but HLA typing B 8 and DW 3 which are found in patients in Europe and the United States were not common. The frequencies of BW 22 and CW 1 are 22.1% and 32.1%, respectively, in the normal population (15). BW 22 can be divided into three components BW 54, 55, 56; BW 54 is a Japanese-specific HLA antigen.

In the present series, the number of chronic active "lupoid" hepatitis patients is small, but it seems likely that there is a strong association with HLA-BW 22, and CW 1 is rather closely related to these rare disease entities in Japan. The reasons for the differences between these results and those of Miyamori et al (9) are unknown. In the present study, five of the six patients were elderly women. Since the HLA B 8 and DRW haplotype is associated with chronic active "lupoid" hepatitis (7), the HLA data in elderly women may differ from that in young women.

As the frequency of HLA B 8 and DR 3 in Japanese controls is 0.2% and 3.2%, respectively (15), the race specificity warrants studies on HLA antigens in different races. It has suggested that gene interactions involving more genes than the HLA-linked gene may be implicated in patients with autoimmune hepatitis (7). Although it is not clear whether or not the differences in race exist, there is no doubt that the frequency of HLA-BW 22 is lower in Caucasian patients, while HLA 8 is rare in Japanese patients.

Among Japanese cirrhotic patients of cryptogenic etiology, probably of viral etiology, increased frequencies of HLA B 8 and BW 22 were found as compared with normal Japanese controls (23). It is suggested, therefore, that there is a difference in HLA between chronic active "lupoid" hepatitis and cryptogenic cirrhotic groups, which may indicate the involvement of a different mechanism in the pathogenesis. Further studies of HLA antigens with a large series of chronic active "lupoid" hepatitis patients should be performed.

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