HLA-B*51 in Patients with Recurrent Aphthous Stomatitis

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Accepted September 11, 2008.

Sir,

Recurrent aphthous stomatitis (RAS) is one of the most common inflammatory ulcerative diseases affecting the oral mucosa. While the clinical features of RAS are well defined, the precise aetiology of the disease is unknown. Oral aphthous ulcers frequently occur as a first clinical feature of Behçet's disease (BD) and constitute one of the major criteria for the diagnosis. It is difficult to differentiate RAS and oral ulcers of BD. This differentiation is very important in countries that have higher prevalence of BD (1, 2). In contrast to BD (3, 4), only a few reports on the frequency of HLA-B*51 in patients with RAS have been published (5, 6). In this study, HLA-B*51 was examined in Turkish patients with RAS and with BD, in comparison with healthy control subjects. In addition the relationship between this antigen and the clinical features of RAS and BD was analysed.

MATERIALS AND METHODS

The study was conducted on 101 patients with RAS (42 males, 59 females; mean ± standard deviation (SD) age 31.8 ± 12.4 years, age range 11–66 years) who were seen at the Department of Dermatology, Meram Medical School, Konya, Turkey, during a period of 2 years. These patients had oral ulcers at least once during a 2-month period, and had active lesions when examined by us. We included only those patients with RAS not attributed to any associated conditions such as coeliac disease, etc. The diameter of the RAS lesions was noted at examination (2). The control group consisted of 100 patients with BD (39 males, 61 females; mean age 34.6 years, age range 14–72 years) fulfilling the criteria of the International Study Group (7) diagnosed at the same centre and 97 healthy controls (44 males, 53 females; mean age 34.3 years, age range 13–77 years). The study was approved by the institutional ethics committee and all subjects signed an informed consent form. For the patients with RAS and BD, the clinical characteristics of the diseases were recorded. The pathergy test was performed in all patients with RAS and BD. Genomic DNA was extracted from peripheral blood using a commercially available kit (Vivantis Inc., Bandung, Indonesia). Two-step polymerase chain reaction (PCR) assays were used to detect the HLA-B5 and followed by HLA-B*51. PCR amplification of the DNA segments containing HLA-B5 and HLA-B*51 was performed as described previously (8). The proportions of the antigen between the patients and controls were compared using a χ^2 test. The relationships between HLA-B*51 and the clinical features of RAS and BD were evaluated using logistic regression analysis (Enter method).

RESULTS

HLA-B*51 was found in 46 patients with RAS (45.5%), 63 patients with BD (63%) and 45 healthy control subjects (46.3%). There was no difference between the patients with RAS and healthy controls ($p = 0.905$). Compared with healthy controls, the patients with BD had a higher frequency of HLA-B*51 ($p = 0.019$). Aphthae smaller than 10 mm (minor aphthae) and larger than 1 cm (major aphthae) were detected in 92 (91%) and 9 (8.9%) patients with RAS, respectively. Grouped multiple aphthae (> 5 lesions) (herpetiform aphthae) were not detected in any patient with RAS at examination. There was no association between subphenotype of RAS and HLA-B*51 ($p = 0.64$). Positive pathergy reaction (PR) was detected in 4 patients with RAS (3.9%). HLA-B*51 was positive in 3 of them and these 3 patients had first-degree relatives who had RAS with no other clinical manifestations. The frequency of HLA-B*51 in male and female patients with RAS was 41.3% and 58.6%, respectively. HLA-B*51 in patients with RAS was not associated with the clinical variables of the disease ($p > 0.05$) (Table I). We also investigated the relationship between HLA-B*51 antigen and clinical features of BD. There was a statistical significance only in genital ulcer ($p = 0.017$) (Table II).

DISCUSSION

This study found no difference in HLA-B*51 between patients with RAS and healthy controls ($p > 0.05$). The frequency of HLA-B*51 in our patients with RAS was similarly low to that of healthy controls. Although the association between RAS and BD is known, there are few reports of the association between HLA-B*51 and RAS. The first significant association between

Table I. *Relationship between patients with recurrent aphthous stomatitis (RAS) and HLA-B*51*

Clinical characteristics	Total	HLA-B*51 positive	*p*-values[a]
Male, *n* (%)	42	19 (45.2)	0.77
Female, *n* (%)	59	27 (45.7)	
Age, years, mean ± SD	31.8 ± 12.4	31.6 ± 12.5	0.73
Duration of the disease, years, mean ± SD	5.9 ± 4.9	5.6 ± 4.8	0.24
Positive pathergy test, *n* (%)	4	3 (75)	0.16
Major aphthae, *n* (%)	92	41 (44.5)	0.72
Minor aphthae, *n* (%)	9	5 (55.5)	
Herpetiform aphthae, *n* (%)	–	–	
Family history of RAS, *n* (%)	35	16 (45.7)	0.18
Family history of BD, *n* (%)	3	2 (66.6)	0.11

[a]In comparison with healthy subjects.
SD: standard deviation; BD: Behçet's disease.

 doi: 10.2340/00015555-0592
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Table II. *Relationship between patients with Behçet's disease (BD) and HLA-B*51 (n = 100)*

Clinical characteristics	Total	HLA-B*51 positive	*p*-values[a]
Male, *n* (%)	39	25 (64.1)	0.29
Female, *n* (%)	61	38 (62.2)	
Age, years, mean ± SD	34.6 ± 10.3	34.6 ± 10.5	0.69
Duration of the disease, years, mean ± SD	7.5 ± 6.2	7.9 ± 6.4	0.15
Oral ulcer, *n* (%)	77	51 (66.2)	0.12
Genital ulcer, *n* (%)	37	28 (75.6)	**0.017**
Papulopustular lesion, *n* (%)	44	30 (68.1)	0.50
Erythema nodosum, *n* (%)	33	23 (69.6)	0.29
Uveitis, *n* (%)	11	6 (54.5)	0.83
Arthralgia/arthritis, *n* (%)	42	26 (61.9)	0.58
Positive pathergy test, *n* (%)	25	16 (64)	0.99
Family history of RAS, *n* (%)	9	6 (66.6)	0.58
Family history of BD, *n* (%)	19	11 (57.8)	0.52

[a]In comparison with healthy subjects. Significant value shown in bold.
SD: standard deviation; RAS: recurrent aphthous stomatitis.

HLA-B*51 and RAS was reported by Shohat-Zabarski et al. (5) in Israeli patients with RAS. In their study, HLA-B*51 was found in 23% of the patients with RAS and in 9% of control subjects. This association was not confirmed in reports from Turkey and Korea (6, 9). The Korean study (6) used a two-step polymerase chain reaction method using sequence specific primers (PCR-SSP) similar to the present study and found HLA-B*51 in 16.1% of the patients with RAS and 15.7% of the healthy controls. However, in our study the frequency was clearly higher, both in the patients with RAS (45.5%) and controls (46.3%), possibly due to the different ethnic origin of the subjects and perhaps also due to some technical differences.

There are a few reports about the familial aggregation of patients with RAS. In a previous study, first-degree relatives with RAS have been reported for more than 42% of patients with RAS. HLA-B*51 was found in about 27% of these patients who had first-degree relatives with RAS (5). In this study, family history of RAS in first-degree relatives was detected in 34.6% of RAS patients and HLA-B*51 was positive in 45.7% of these patients. An association between positive family history of RAS or BD and HLA-B*51 was not detected statistically in either disease. Although a higher frequency of pure RAS reported among relatives of patients with BD by Arber et al. (4), it was not found in our patients with BD. We found that the percentage of family history of pure RAS was less than family history of BD in the patients with BD. There was similar condition in the patients with RAS.

The association of HLA-B*51 with BD has been confirmed in different ethnic groups and the association between HLA-B*51 and some clinical features of BD have been described (3, 10, 11). We found a significant association between HLA-B*51 and BD, and a positive association between genital ulcer and HLA-B*51. We did not detect an association between HLA-B*51 and the patients with RAS in the Turkish population. In addition, a familial association with HLA-B*51 was not found in the patients with RAS or BD. These findings suggest that the involvement of other genetic and/or environmental factors maybe responsible for the disease development and/or progression in RAS. The high frequency of HLA-B*51 in the Turkish population seems to attribute to the high prevalence of BD in this country. In addition, a more detailed analysis of HLA-B*51 sub-alleles may reveal an association between RAS and BD.

ACKNOWLEDGEMENT

This study was partially supported by the ORVA Pharmaceutical Research Foundation.

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