The histocompatibility antigen in asbestos related disease

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Abstract

Thirty nine phenotypes of human leucocyte antigens (HLA)-A-B-DR and DQ were obtained from 99 asbestos workers (one woman and 98 men). Presence or absence of antinuclear antibodies and rheumatoid factor was determined in 91 of them. Workers were divided into five groups: asbestos workers with no apparent disease (AW; $n = 17$), diffuse benign pleural disease (PD; $n = 31$), asbestosis (AS; $n = 24$), asbestosis with lung cancer (AS-CA; $n = 14$), and mesothelioma (M; $n = 13$). Compared with AW, several trends of differences of HLA antigen prevalence were found in patients with asbestos related disease, but these did not achieve statistical significance when p was corrected (p_{corr}) by number of analyses undertaken. Analysis of the results obtained in previous studies together with the results of this study showed that compared with AW, AS patients had decreased prevalence of HLA-DR5 ($p_{\text{corr}} < 0.02$). Reasons for the differences in results of previous studies and statistical methods commonly used to compare prevalences of HLA antigen are discussed.

It has been recognised that for a given cumulative exposure to asbestos dust, only a fraction of the exposed workers or animals develop one or more of the asbestos related diseases (benign pleural disease, asbestosis, mesothelioma, and lung cancer).¹⁻³ The pathology of these diseases remains, however, controversial and the question "why is one person affected and not the man who works beside him?" remains unanswered.

Several studies have found alterations of humoral immunity in asbestos workers such as an increase in

circulating immunoglobulins,⁴⁻⁷ autoantibodies,⁴⁻¹⁰ and the complement components.⁵ Other studies have shown alterations of the lymphocyte subsets in the peripheral blood of asbestos workers with and without asbestosis.^{7,11}

The fibrotic response to asbestos fibres could be genetically controlled; there is evidence from animal models that susceptibility to interstitial lung disease may be modified by immune and non-immune related genes.¹² The human leucocyte antigen (HLA) has been linked with the immune response capability and close associations between some types of HLA and immunological conditions such as ankylosing spondylitis have been established.¹³ Several studies investigating associations between types of the HLA system and the occurrence of asbestosis have been published with inconsistent and sometimes conflicting results.¹⁴⁻²¹ All but one of these studies²¹ investigated the loci of the class I HLA (HLA-A-B-C) but not class II (HLA-DR, DQ, and DW). Recently a predisposition to development of idiopathic pulmonary fibrosis has been associated with one of the B cell autoantigens, HLA-DR2.²²

In this study we investigated class I and class II HLA in patients with different types of asbestos related disease and compared prevalences of HLAs between different groups using the data obtained in this and previously published studies.

Patients and methods

PATIENTS

We studied 98 white men and one white woman. Their mean age (range) was 59 (35-79). They were divided into five groups: asbestosis (AS; $n = 24$), benign pleural disease (PD; $n = 31$), asbestosis and lung cancer (AS-CA; $n = 14$), mesothelioma (M; $n = 13$), and heavy asbestos exposure (two years or more) with no apparent disease (AW; $n = 17$).

The diagnosis of asbestosis was made on the basis of a history of exposure to asbestos and shadowing on chest radiographs or high resolution computed tomography (HRCT) scans consistent with interstitial fibrosis. Asbestos bodies were detected in bronchoalveolar lavage fluid in the 11 patients in whom this was carried out.

Pleural disease and opacities suggestive of asbes-

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tosis were present on chest radiographs in all patients with lung cancer and asbestosis was confirmed by HRCT in four patients on whom this was performed. Pathological evidence of asbestosis was obtained from the two patients who underwent lobectomy. Histological confirmation of lung cancer was available for all patients with this disease and the cell types were small cell carcinoma (9), squamous cell carcinoma (4), and adenocarcinoma (one patient).

The diagnosis of mesothelioma was made on the basis of progressive chest pain, weight loss, and irregular pleural thickening with reduction of thoracic volume on chest radiographs. A histological diagnosis was obtained during life in 12 patients and at postmortem examination in one patient. Immunohistochemical stains were used as well as routine histological methods.

Patients classified as having benign pleural disease had plain chest radiographic evidence of pleural plaques or pleural thickening of at least 1b grade on the International Labour Office (ILO) scale (length of pleural disease of more than a quarter of the lateral chest wall and maximum width more than 0.5 cm)²³ with or without involvement of the costophrenic angles. The diagnosis of interstitial fibrosis was ruled out on the basis of HRCT in all patients.

Those patients with past occupational exposure to asbestos and in whom the chest radiographs had shown no evidence of pleural disease and pulmonary opacities of less than 1/0 were classified as AW. A diagnosis of asbestosis was ruled out on the basis of HRCT in all patients.

Exposure to asbestos was through lagging in 35, stripping asbestos in 16, loading and unloading asbestos in the shipyards (the docks) in 21, building trade in 17, and driving lorries occasionally loaded with asbestos in six patients. Non-occupational (domestic) asbestos exposure had occurred in four patients.

Thirty five patients were current smokers (smoked during the past three months), 52 were ex-smokers (smoked more than 20 lifetime packs and no cigarettes during the last three months), and 12 were non-smokers (smoked less than 20 lifetime packs and no cigarettes during the last three months).

None of the patients had any clinical evidence of connective tissue disease, had received corticosteroids for at least three months, or had clinical symptoms of any viral disease during six weeks before the blood samples were taken. In patients with lung cancer, blood was withdrawn before any chemotherapy.

METHODS

Blood withdrawal

Blood (50 ml) was withdrawn using a butterfly needle (gauge 19) and was divided into four tubes: 18 ml of blood in 2 ml of 3.8% citrate for HLA typing, 20 ml

with 200 units of preservative free heparin for lymphocyte separation, 2 ml with ethylene diamine-tetra-acetic acid for full blood cell count and differential white blood cell count, and 10 ml untreated for detecting rheumatoid factor and antinuclear antibodies.

HLA typing

Thirty nine phenotypes of HLA-A-B, DR, and DQ were obtained from the fresh blood using a standard National Institute of Health 2-stage complement dependent microlymphocytotoxicity assay defining eight HLA-A and 17 HLA-B types according to methods described by Amos and Pool,²⁴ Gibofsky *et al*²⁵ and Terasaki²⁶; DR and DQ types were obtained using a similar method except that the target cells were B lymphocytes isolated using metal beads coated with monoclonal anti-DR antibodies.²⁷

Rheumatoid factor and antinuclear antibodies

Rheumatoid (antiglobulin) factors were measured by standard techniques; the differential agglutination tests²⁸ with sheep cells coated with rabbit globulin and the latex slide agglutination test²⁹ with latex particles coated with human FII fraction. Rheumatoid factor was considered present when the latex test was positive at a serum dilution of 1/80 or more.

Antinuclear factors were measured and titred by a standard double layer immunofluorescent technique. Cryostat sections of rat liver were used as a substrate, test sera were diluted 1:10, and fluorescein isothiocyanate conjugates of goat antihuman γ globulin were applied. The immunoglobulin class of antinuclear factors was identified by the same immunofluorescent method using fluorescein isothiocyanate conjugates of monospecific horse antihuman IgM, IgG, and IgA (Red Cross blood transfusion, Amsterdam).

STATISTICAL ANALYSIS

Prevalences of HLA types were compared using Fisher's exact test or χ^2 with Yates' correction.³⁰ Values were corrected according to the Sidak-Dunn method^{31 32} using the equation:

$$p_{\text{corr}} = 1 - (1 - p)^n$$

where p_{corr} = p corrected and n = number of analyses undertaken.

The strength of association between an HLA type and an asbestos related disease was estimated by calculating the relative risk (RR) as: incidence among asbestos related disease group/incidence among Aw group. The 95% confidence interval (95% CI) of the RR was calculated using the χ^2 value found in the significance test as follows:

$$95\% \text{ CI} = \text{RR}^{(1 \pm 1.96/\sqrt{z})}$$

Results were considered to be significant when $p_{\text{corr}} < 0.05$.

Table 1 Demographic data

	Group				
	AS (n=24)	AS-CA (n=14)	M (n=13)	PD (n=31)	AW (n=17)
Age (mean (SD)):	62 (10.6)	66.3 (4.5)	58 (6.4)	55 (10.6)	53 (8.5)
Pack-years (mean (SD)):	41† (28)	55*‡ (29)	32 (26)	23 (17.6)	23 (36)
Duration of exposure to asbestos (mean (SD)):	9.3 (7.5)	10.9 (9.1)	11 (11)	10.5 (8.6)	12 (6)
Time since first exposure to asbestos (mean (SD)):	38.2 (10.8)	42 (9.7)	34 (6)	32.6 (11.2)	32 (5.5)

*p < 0.02 compared with AW; †p < 0.0001 compared with PD; ‡p < 0.009 compared with PD.

Table 2 A comparison of prevalence of HLA antigens in patients with asbestosis (AS) and asbestos workers without any evidence of asbestosis (AW) in several studies

HLA	Matej <i>et al</i> ¹⁵		Evans <i>et al</i> ¹⁶		Gregor <i>et al</i> ¹⁷		Huuskonen <i>et al</i> ¹⁸	
	AW (n=112)	AS (n=22)	AW (n=27)	AS (n=37)	AW (n=80)	AS (n=92)	AW (n=37)	AS (n=64)
A:								
1	23	2	14	14	28	34	4	10
2	53	14	16	18	38	48	21	39
3	20	5	12	6	24	20	15	29
9	26	3	5	10	10	10	8	14
10	10	4	2	2	8	9	3	1
11	11	2	5	4	11	15	2	4
19	—	—	—	—	20	24	8	9
28	4	0	2	4	8	7	6	10
B:								
5	14	0	6	2	11	11	2	8
7	21	5	7	6	22	17	12	24
8	19	2	10	10	20	31	4	11
12	19	5	10	18	20	26	3	12
13	6	3	2	2	3	6	1	3
14	6	0	3	4	8	8	0	0
15	6	1	0	1	10	11	6	16
16	11	2	1	0	5	4	4	5
17	11	2	3	5	7	9	0	0
18	5	1	3	8	7	9	7	3
21	5	0	2	2	3	7	0	0
22	4	0	3	1	4	4	0	0
27	11	6	3	2	4	11	11	9
35	16	5	—	—	11	7	10	16
37	13	3	—	—	2	3	0	1
40 *	—	—	—	—	12	9	9	11
W4	—	—	—	—	—	—	17	28
W6	—	—	—	—	—	—	36	57

AW = asbestos workers with no evidence of asbestosis; AS = patients with asbestosis. Figures shown in parentheses are percentages. — = An HLA had not been typed in the correspondent study.

The study by Merchant *et al*¹⁴ was not included in this comparison because the patients are included in the study by Gregor *et al*.¹⁵ Results are not significantly different in any study.

Results

Table 1 shows the demographic data. Duration of exposure to asbestos, or time since first exposure were not significantly different between the groups. Pack-years of smoking were higher in the AS-CA than in the AW and PD groups (p < 0.02 and p < 0.0001 respectively; Mann-Whitney U test) and higher in the AS group than in the PD group (p < 0.009; Mann Whitney U test).

There were no significant differences in the frequencies of any HLA between the AW group and any of the study groups.

Presence of absence of antinuclear antibodies and rheumatoid factor was determined in 91 patients.

There was no difference in the prevalence of any HLA between patients in whom antinuclear antibodies were (n = 19) or were not (n = 72) detected. Similarly there were no differences in prevalence of any HLA in those patients in whom rheumatoid factor was present (n = 6) or absent (n = 85).

A review of publications showed that HLA A and B antigens have been investigated in a total of 355 asbestos workers with no disease (AW) and 289 patients with asbestosis (AS) in studies by Matej *et al*,¹⁵ Evans *et al*,¹⁶ Gregor *et al*,¹⁷ Huuskonen *et al*,¹⁸ Vergnaud *et al*,²⁰ and the current study. The HLA DR 1-7 antigens have been investigated in 49 AW and 64 AS patients in the study by Begin *et al*²¹ and

our current study combined. Compared with the AW group, the AS group had a decreased prevalence of HLA-DR5 ($p_{\text{corr}} < 0.02$). Tables 2 and 3 show the detailed results of our study and previous studies combined.

Discussion

We found no differences in prevalence of HLA antigens between AW patients and patients with

other types of asbestos related disease. Unlike the results of Merchant *et al*¹⁴ and Gregore *et al*¹⁷ who suggested an increase in HLA-B27 in AS patients, the prevalence of HLA-B27 was similar in all the study groups. The results of this study were also at variance with those by Huuskonen *et al*¹⁸ who found that HLA-B18 and B27 were higher in AW than AS patients. No difference was found in prevalence of the HLA-B12 antigen between AS and AW groups, unlike the results obtained by Evans *et al*¹⁶ who

Vergnaud <i>et al</i> ²⁰		The current study		Total	
AW 58	AS 57	AW 17	AS 24	AW (n = 355)	AS (n = 289)
27	17	2	9	98 (28)	86 (30)
27	26	10	12	165 (46)	157 (54)
12	19	5	3	88 (25)	82 (28)
—	—	5	2	54 (18)a	39 (17)a ¹
—	—	2	2	25 (8)a	18 (8)a ¹
5	7	2	2	36 (10)	34 (12)
4	7	3	9	37 (17)b	49 (21)b ¹
3	4	3	1	26 (7)	26 (10)
8	10	5	2	46 (13)	33 (11)
15	13	7	3	84 (24)	68 (24)
18	9	0	3	71 (20)	55 (19)
18	16	2	9	72 (20)	86 (30)
3	4	0	1	15 (4)	19 (7)
14	0	2	2	33 (9)	16 (6)
7	6	1	2	30 (8)	37 (13)
—	—	1	2	21 (7)a	13 (6)a ¹
6	4	1	4	28 (8)	24 (8)
3	8	1	0	26 (7)	29 (10)
—	—	1	2	11 (4)a	11 (5)a ¹
4	2	0	2	15 (4)	9 (3)
8	10	2	2	39 (11)	40 (11)
5	10	1	2	45 (14)c	40 (16)c ¹
—	—	1	0	16 (6)d	7 (4)d ¹
4	6	1	5	26 (14)b	51 (22)b ¹
—	—	11	15	28 (52)c	43 (49)e ¹
—	—	15	15	51 (94)c	72 (82)e ¹

The total numbers of patients differ from n = 355 and n = 289 in some instances. These are shown by superscripts. The numbers are a297, a'232, b216, b'230, c328, c'252, d270, d'195, e54, e'72.

Table 3 Analysis of the prevalence of HLA-DR antigens in the current study and the study by Begin *et al*²¹

HLA	Begin <i>et al</i> ²¹		The current study		Total	
	AW (n = 32)	AS (n = 40)	AW (n = 17)	AS (n = 24)	AW (n = 49)	AS (n = 64)
DR						
1	21 (66)	28 (70)	4 (24)	6 (25)	25 (51)	34 (53)
2	10 (31)	22 (55)	4 (24)	4 (16)	14 (29)	26 (41)
3	14 (44)	3 (8)	1 (6)	5 (21)	15 (31)	8 (13)
4	17 (53)	14 (35)	4 (24)	6 (25)	21 (43)	20 (32)
5	27 (84)	11 (28)	5 (29)	5 (21)	32 (65)	16 (25)†
7	38*	44*	2 (12)	5 (21)		

Numbers in parentheses are percentages.

*Obviously these figures were misprinted because the frequencies exceed the total number of patients.

†RR = 2.6, (95% CI 1.6–4.2); $\chi^2 = 16.8$; $p_{\text{corr}} < 0.02$.

suggested an increase in this antigen in those with advanced asbestosis compared with an AW group. Only one of the previous studies had investigated class II; that of Begin *et al*²¹ who recently reported the results for HLA-D 1-7 only (table 3).

The results obtained by analysis of the combined data from several studies showed no difference between AS and AW patients except that in the combined analysis of this study and that of Begin *et al*²¹ the prevalence of HLA-DR5 was higher in AW compared with AS patients suggesting that it is associated with resistance to developing asbestosis.

Three possible reasons for the inconsistency of the results between studies are as follows: firstly, asbestosis in previous studies was excluded on the basis of clinical and chest radiographic grounds. Since the introduction of HRCT, studies have shown that 15-30% of patients with pulmonary densities of less than 1/0 on chest radiography have evidence of asbestosis on HRCT.³³⁻³⁴ Those patients would have been classified as AW in earlier studies. Secondly, some patients in the exposed group may later develop asbestosis, cancer, and mesothelioma, hence classifying this group as AW may be correct only for the time of assessment. Thirdly, the level of significance used differed between studies. Whereas most earlier studies took the conventional $p < 0.05$ as significant, recent ones corrected the significance level for the number of analyses undertaken.

Svejgaard *et al* suggested that two major types of error exist when investigating the prevalence of HLAs. A type I error, the most common, is the assumption of a true association when in fact one does not exist. Conversely, a type II error is rejection of the hypothesis of an association where one exists. The method of statistical analysis is crucial in minimising both types of error. Fisher's exact test when applicable or χ^2 with continuity (Yates) correction are the two methods commonly used to compare the prevalence of HLA-antigens between disease and control groups.³⁰ Because of the high number of antigens, the possibility of obtaining significant results by chance with conventional $p < 0.05$ is fairly high. Woolf³⁵ suggested correcting the significance level by multiplying (p) by the number of analyses undertaken and accepting the results as significant when the corrected p (p_{corr}) is less than < 0.05 .

In the current study p was corrected according to the method of Sidak³¹ and Dunn³²; and $p_{\text{corr}} < 0.05$ was accepted as the significance level.

Pack-years of cigarette smoking in AS and AS-CA patients were higher than in PD and AW patients, whereas the duration of exposure to asbestos and time since first exposure did not differ between types of asbestos related disease. These results are consistent with several studies that have found an increase in radiographic opacities suggestive of asbestosis in

asbestos workers who smoked compared with those who did not.³⁶⁻³⁸

In conclusion, our data show no significant associations between types of HLA and types of asbestos related disease by data from this study and a previously reported study combined suggest a possible protective effect of HLA-DR5 against asbestosis.

We thank Dr C Darke for his valuable assistance in preparing the manuscript.

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Accepted 17 February 1992

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