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Human leukocyte antigens class II genes are associated with cancer development in the autoimmune rheumatic diseases

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ABSTRACT

Objective. To determine the association between HLA class II alleles and the probability of developing cancer in patients with autoimmune rheumatic diseases. **Material and methods.** A matched case control study was conducted in which patients with autoimmune rheumatic disease who later developed malignancy (solid or lymphoproliferative) were compared with matched controls suffering from the same auto-immune rheumatic disease and with similar disease duration. The rheumatic diseases included rheumatoid arthritis, systemic lupus erythematosus, primary Sjögren syndrome, dermatomyositis-polymyositis, and systemic sclerosis. HLA-DR typing was performed by sequence-specific primers after DNA amplification by PCR (PCR-SSP). Statistical analysis was conducted by conditional logistic regression. **Results.** HLA-DRBI*02 and DRBI*03 were found to be significantly associated with the probability for developing cancer (OR = 5.2 and 4.9, respectively), independent of family history of rheumatoid arthritis and cancer, recurrent sore throat, alopecia, and clinical activity of rheumatoid arthritis. **Conclusions.** The results suggest an association between HLA class II alleles with the probability of developing a malignant neoplasm in patients suffering from an autoimmune rheumatic disease.

Key words. Autoimmune rheumatic disease. Cancer. HLA. MHC. Genetic association.

Los genes de los antígenos leucocitarios humanos clase II están asociados con el desarrollo de cáncer en las enfermedades reumáticas autoinmunes

RESUMEN

*Objetivo. Determinar la asociación entre los alelos HLA de clase II y la probabilidad de desarrollar cáncer en pacientes con enfermedades reumáticas autoinmunes. Material y métodos. Estudio de casos y controles pareado en el que los pacientes con enfermedad reumática autoinmune, que desarrollaron posteriormente un tumor maligno (sólido o linfoproliferativo), fueron comparados con controles pareados por la misma enfermedad reumática autoinmune, sin cáncer y con una duración similar de la enfermedad. Las enfermedades reumáticas incluyeron artritis reumatoide, lupus eritematoso sistémico, síndrome de Sjögren primario, dermatomiositis-polimiositis y esclerosis sistémica. La tipificación de HLA-DR fue realizada por iniciadores secuencia específico después de la amplificación de ADN por PCR (PCR-SSP). El análisis estadístico se realizó mediante regresión logística no condicional. Resultados. Los HLA-DRBI*02 y DRBI*03 estuvieron asociados significativa-mente con la probabilidad de desarrollar cáncer (OR = 5.2 y 4.9, respectivamente) independiente de la historia familiar de artritis reumatoide, cáncer, faringoamigdalitis recurren-te, alopecia y actividad clínica de artritis reumatoide. Conclusiones. Los resultados sugieren una asociación entre los alelos HLA de clase II con la probabilidad de desarrollar una neoplasia maligna en pacientes que sufren de una enfermedad reumática autoinmune.*

Palabras clave. Enfermedad reumática autoinmune. Cáncer. HLA. MHC. Asociación genética.

INTRODUCTION

The relationship between autoimmune rheumatic diseases and cancer is a matter of concern, and there is evidence to support a heightened risk for developing both solid or lymphoproliferative malignancies in many of the rheumatic diseases as well.[1,2]

In rheumatoid arthritis (RA), the relationship has been established mainly with lymphoproliferative malignancies, and the relative risk (RR) reported has ranged from 1.4-8.7.[3-6] In systemic lupus erythematosus (SLE), the RR for lymphoproliferative neoplasm has been reported to range from 4.12-5.48, while the risk for malignancy of all sites is between1.3 and 2.6.[7-11] Highest risk for development of cancer has been described in Sjögren syndrome, which for lymphoma entertains an RR of 33.3-43.8; for cancer at any site, the risk is 2.2.[12-14] In dermatomyositis and polymyositis (DM/PM), relationships have been found mainly with solid tumors, and DM appears to be more frequently associated with cancer when compared with PM, with risks ranging between 2.4 and 8.3 and 0.9 and 1.8, respectively.[15-17] The risk of solid tumor at any site in patients with systemic sclerosis (SSc) is between 1.3 and 2.4, and in lymphoproliferative neoplasm, this is 4.5–9.6; however, the most strongly associated malignancy is that of the lung, with a risk lying between 4.5 and 16.5.[18-20]

The factors involved in the development of malignancy in the autoimmune rheumatic diseases are not clear, and although the immunosuppressive treatment employed to reduce autoimmune disease activity has been suggested as a susceptibility factor, many of the reported risks have been independent of such drugs,[1,3,7,12,16] indicating the existence of factors that could predispose to cancer development.

In a case-control family study to investigate the susceptibility of cancer in first-degree relatives of patients with SSc, an important increased risk for cancer development was found [odds ratio (OR) = 3.79], suggesting that a common genetic or environmental factor may be involved in the development of cancer and SSc.[21] One of the predisposing genetic factors can be the human leukocyte antigen genes (HLA) located within the major histocompatibility complex (MHC) region because there is a relationship between these antigens and the probability of having certain autoimmune rheumatic disease or even cancer.

There is a well-known relationship between HLA-DRBI*04 and RA in several ethnic groups.[22] In SLE, there is an association with HLA-DRBI*02 and DRBI*03.[23] In primary Sjögren syndrome (pSS), the antigens most frequently associated in population-based studies are HLA-B*08, DRBI*03, and DRBI*15.[24] In DM/PM, HLA-B*08 and DQA1*0501 have been associated in several ethnic groups.[25]

On the other hand, there is a relationship between specific HLA alleles and the probability of developing certain neoplasms. For instance, cancer of the uterine cervix demonstrates an important and consistent association with the antigens DQw3 and HLA-DRBI*05.[26] Other malignancies that demonstrate important associations comprise testicular cancer, hepatocellular carcinoma, and prostate carcinoma, which are associated with HLA-B*41, B*15, and B*14, respectively.[27] In lymphoproliferative disorders, Hodgkin disease has been associated with HLA-B*35 and DPB1*0301,[28] and HLA alleles B*08 and A*03 have been described in chronic myeloid leukemia.[29]

OBJECTIVE

To determine whether there is an association between class II MHC alleles and the development of malignancy (solid or lymphoproliferative) in Mexican Mestizo patients with autoimmune rheumatic diseases.

MATERIALS AND METHODS

Study design

We conducted a matched case-control study with two controls per case that was approved by the Committee for Ethics in Research of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ). Cases included Mexican Mestizo patients with a diagnosis of autoimmune rheumatic disease who developed a malignancy subsequent to this diagnosis. Controls comprised Mexican Mestizo patients with autoimmune rheumatic disease who did not develop a malignant neoplasm, and these were matched with cases by rheumatic disease and disease-evolution time (±1 year). All patients were seen at the INCMNSZ, a tertiary-care referral centre in Mexico City, including both incident and prevalent individuals.

Diseases diagnoses were based on criteria conventionally accepted for their classifications including RA,[30] SLE,[31] pSS,[32] DM/PM,[33] and SSc,[34] because these are the five most frequent autoimmune rheu-

matic diseases seen at our institution.[1] Malignancies included were both solid and lymphoproliferative according to the International Classification of Diseases (ICD), 10th edition, codes C00–C80 and C81–C96, respectively. Cancer diagnoses were established or confirmed at our institution by both clinical examination and histopathological studies.

A questionnaire was designed to collect information from the clinical charts of cases and controls regarding family history of rheumatic diseases and cancer, infectious diseases in infancy, comorbidity, autoimmune rheumatic disease (dates of onset and diagnosis), clinical manifestations at rheumatic-disease onset (± 1 year of diagnosis), clinical manifestation during the autoimmune rheumatic-disease course, time using antirheumatic drugs (chloroquine, hydroxychloroquine, prednisone, azathioprine, cyclophosphamide, methylprednisolone pulses, methotrexate, sulfasalazine, gold salts, D-penicillamine, 6-mercaptopurine, cyclosporine, or chlorambucil) during total evolution time of the rheumatic disease and time during which there was rheumatic clinical activity.

The rheumatic clinical activity was assessed taking into account the periods of activity and remission during evolution according to the clinical rheumatologist criterion registered at the clinical charts. When activity was not recorded in the clinical charts, changes in the treatment were taken to define beginning and end of activity periods. For both time utilizing antirheumatic drug and time under rheumatic activity, indexes were obtained dividing the sum of total periods under treatment or activity by total evolution time of the rheumatic disease. Evolution time comprised the period from diagnosis of rheumatic disease to date of last medical consultation

In cases, additional information was obtained concerning dates of onset and diagnosis of neoplasm, clinical manifestations of the tumor, histopathologic diagnosis, cancer remission, and treatment.

HLA typing

After obtaining signed informed consent, a 10-ml blood sample was drawn into tubes containing EDTA, and genomic DNA was extracted by salting-out method. Class II HLA-DRBI alleles were determined with "low resolution" genotyping by PCR amplification of genomic DNA with sequence-specific primers (PCR-SSP).[35] Briefly, PCR reactions were performed in a geneamp 2400 system (Applied Biosystems, Foster City, CA, USA) with a final volume of 10 mL. An initial denaturation step of 94 °C for 2 min was followed by 10 cycles of 94 °C denaturation for 10 sec, 65 °C annealing and extension for 60 sec, and finally 20 cycles of 94 °C denaturation for 10 sec, 61 °C annealing for 50 sec, and 72 °C extension for 30 sec. After amplification, PCR products were loaded into 2% agar gel containing 0.5 μg/mL of ethidium bromide, electrophoresed for 20 min at 15 V/cm, and examined under ultraviolet (UV) light. Individual alleles were assigned for the specific pattern of the appropriately sized bands.

Statistical analysis

Comparisons of continuous variables between cases and controls were tested by Mann-Whitney U test. Corrected χ^2 statistics or Fisher exact test (two-tailed) was applied to evaluate differences in proportions for categorical variables. Because of the matched design, uni- and multivariate conditional logistic-regression analyses were conducted to estimate the probability of developing malignant neoplasm comparing each class II HLA as main effect, employed as binary variable, and deriving odds ratio (OR) by means of the exponential of regression coefficients. Ninety five percent confidence intervals (95% CI) and p values are reported for the OR. Construction of multivariate models included testing for variables associated with a p value < 0.15 in univariate analysis. The final selected model was the more parsimonious one. The statistical software package STATA 8.0 was used for the calculations.

RESULTS

We studied 32 cases matched with 64 controls. As a result of matching, there were no differences in distribution by rheumatic disease ($p = 1.0$). Distribution of cases and controls according to rheumatic disease and malignancy are shown in table 1. Solid tumors were the malignancies more frequently observed; oncologic surgery was indicated in 21 cases, chemotherapy in five, radiotherapy in two and four received more than one type of treatment. Twenty one cases achieved remission of the neoplasm at the cut-off time of study.

In cases, mean age at time of neoplasm diagnosis was 48.9 ± 12.4 years, and mean time between rheumatic-disease diagnosis and neoplasm diagnosis was 4.4 ± 5.3 years. When cases were compared with controls, there were no differences for age between the two groups at the time of the study ($p = 0.69$), age at rheumatic-disease initiation ($p = 0.43$), age at

Table 1. Distribution of cases (solid and lymphoproliferative neoplasm) and controls according to autoimmune rheumatic disease.

Rheumatic disease	Cases			
	Solid n (%)	LP n (%)	Controls n (%)	Total n (%)
RA	17 (53.1)	1 (3.1)	36 (56.3)	54 (56.3)
SLE	7 (21.9)	1 (3.1)	16 (25.0)	24 (25.0)
SSc	2 (6.3)	0 (0.0)	4 (6.3)	6 (6.3)
pSS	1 (3.1)	2 (6.3)	6 (9.4)	9 (9.4)
DM/PM	1 (3.1)	0 (0.0)	2 (3.1)	3 (3.1)
Total	28 (87.5)	4 (12.5)	64 (100)	96 (100.0)

LP: Lymphoproliferative neoplasm. RA: Rheumatoid arthritis. SLE: Systemic lupus erythematosus. SSc: Systemic sclerosis. pSS: Primary Sjögren's syndrome. DM/PM: Dermatomyositis/polymyositis.

Table 2. Age and intervals of time in cases and controls.

	Cases (n = 32) Mean ± SD	Controls (n = 64) Mean ± SD	p
Age (years)	53.3 ± 13.2	51.9 ±15.3	0.69
Rheumatic disease initiation* (years)	39.4 ± 12.9	37.3 ±15.8	0.43
Rheumatic disease diagnosis (years)	44.5 ± 13.9	42.3 ±15.6	0.45
Evolution according to initiation (years)	13.9 ± 7.7	14.7 ±7.3	0.47
Evolution according to diagnosis (years)	8.8 ± 6.6	9.6 ±5.5	0.35

*First manifestation attributable to disease.

Table 3. Rheumatic and cancer family history and infectious disease history in infancy between cases and controls.

Clinical variable	Cases (n = 32) n (%)	Controls (n = 64) n (%)	p
Family history			
• Rheumatic disease*	11 (34.4)	10 (15.6)	0.03
-RA	9 (28.1)	6 (9.4)	0.01
-SLE	2 (6.2)	3 (4.7)	1.00
-Other†	3 (9.4)	1 (1.6)	0.10
• Cancer*	12 (37.5)	13 (20.3)	0.07
-Lung	2 (6.2)	3 (4.7)	1.00
-Colon	2 (6.2)	1 (1.6)	0.26
-Other‡	11 (34.4)	6 (9.4)	0.002
History in infancy			
-Measles	9 (28.1)	16 (25.0)	0.74
-Chicken pox	8 (25.0)	15 (23.4)	0.86
-Mumps	3 (9.4)	5 (7.8)	1.00
-Recurrent sore throat	2 (6.2)	18 (26.1)	0.01
-Rubella	1 (3.1)	0 (0.0)	0.33
-Other§	2 (6.3)	3 (4.7)	1.00

*Any type of rheumatic disease and cancer, respectively. †Osteoarthritis and gout. ‡Mainly liver and breast. §Whooping cough and one other unspecified disease. RA: Rheumatoid arthritis. SLE: Systemic lupus erythematosus.

rheumatic-disease diagnosis (p = 0.45), and rheumatic-disease evolution according to initiation and to diagnosis of rheumatic disease (p= 0.47 and 0.36 respectively) (Table 2). In addition, we found no differences in distribution by gender (81.3% females in cases and 89.1% in controls; p = 0.29), and there

were no differences in mean number of classification criteria for each rheumatic disease ($p > 0.05$).

Family history of rheumatic disease was more frequent in cases than in controls ($p = 0.03$). In contrast, family histories of cancer demonstrated no differences ($p = 0.07$) (Table 3). Additionally, table 3 shows the distribution of infectious-disease history in infancy. A difference was found for recurrent sore throat that was lower in cases than in controls ($p = 0.01$). In distribution of comorbidity by group, hypertension, depression, and diabetes mellitus were higher in cases than in controls; nonetheless, we found these differences not to be statistically significant (Table 3).

Mean proportion of antirheumatic medication administered during total rheumatic-disease evolution demonstrated no differences except in patients who were administered colchicine (Table 4). Mean proportions of rheumatic-disease activity indices during total rheumatic-disease evolution were lower in cases than in controls (0.09 ± 0.15 and 0.12 ± 0.14, respectively; $p = 0.04$).

According to gene frequencies, the most frequent allele in both groups was HLA-DRBI*04 ($p = 0.44$). The HLA-DRBI*03 allele was significantly increased in the case group as compared with that of the controls ($p = 0.04$), and other HLA alleles showed no significant differences between both groups, as shown in table 5.

In univariate analysis, only the HLA-DRBI*03 allele was associated in a significant manner with an increased risk for developing cancer [OR (95% CI) = 2.1 (1.0-4.4); $p = 0.046$]. In multivariate analysis each allele HLA-DRBI was analyzed; nevertheless, only HLA-DRBI*02 and -DRBI*03 alleles exhibited an important association [OR (95% CI) = 5.2 (1.08–25.34) and OR (95% CI) = 4.9 (1.02–24.13), respectively]. These HLA allele associations are

Table 4. Time under antirheumatic medication in cases and controls expressed as mean proportion of total disease duration.

Antirheumatic drug	Cases n = 32 mean (SD)	Controls n = 64 mean (SD)	p
Chloroquine	0.36 (0.44)	0. 37 (0.36)	0.41
Prednisone	0.49 (0.71)	0.30 (0.71)	0.06
Azathioprine	0.09 (0.20)	0.03 (0.10)	0.41
Cyclophosphamide(oral)	0.03 (0.12)	0.0005 (0.003)	0.44
Cyclophosphamide(iv)	0.02 (0.10)	0.0 (0.0)	0.15
Methotrexate	0.30 (0.41)	0.39 (0.58)	0.70
Sulfasalazine	0.03 (0.08)	0.03 (0.08)	0.86
Gold salts	0.0 (0.0)	0.007 (0.05)	0.31
D-penicillamine	0.07 (0.23)	0.14 (0.28)	0.69
6-mercaptopurine	0.0006 (0.003)	0.004 (0.02)	0.69
Colchicine	0.04 (0.19)	0.0 (0.0)	0.04

iv: Intravenous.

Table 5. HLA-DRBI gene frequencies in cases and controls.

HLA-DRBI	Cases n = 32 n (gf)	Controls n = 64 n (gf)	p
DRBI*04	18 (0.281)	43 (0.335)	0.44
DRBI*03	16 (0.250)	17 (0.132)	0.04
DRBI*02	10 (0.156)	12 (0.093)	0.19
DRBI*06	5 (0.078)	14 (0.109)	0.49
DRBI*08	5 (0.078)	15 (0.117)	0.40
DRBI*05	4 (0.062)	10 (0.078)	0.77
DRBI*01	3 (0.046)	11 (0.085)	0.39
DRBI*09	2 (0.032)	0 (0.000)	0.11
DRBI*07	1 (0.015)	5 (0.039)	0.66
DRBI*10	0 (0.000)	1 (0.007)	1.00

gf: Gene frequencies.

Table 6. Multivariate conditional logistic-regression analysis model to estimate probability for developing malignancy.

Variable	OR (95% CI)	p
HLA-DRBI*02	5.2 (1.08–25.34)	0.040
HLA-DRBI*03	4.9 (1.02–24.13)	0.046
Rheumatoid-arthritis family history*	27.6 (2.9–256.8)	0.004
First-degree relatives with cancer family history†	44.2 (2.7–723.6)	0.008
Recurrent sore throat	0.06 (0.006–0.64)	0.019
Alopecia	0.009 (0.0001–0.75)	0.037
Rheumatoid disease activity	0.005 (0.00001–1.8)	0.080

*Independent of the affected region. †Cases: Abdominal, neck, liver, breast, prostate. Controls: Brain, liver, and kidney. **OR:** Odds ratio. **CI:** Confidence interval.

independent of family history of rheumatoid arthritis, family history (first-degree relatives) with cancer, recurrent sore throat, alopecia, and clinical activity of rheumatoid arthritis (Table 6).

DISCUSSION

Relationships between autoimmune rheumatic diseases and malignant neoplasms have been widely discussed together with the possible factors implicated in attempting to elucidate the mechanisms of association;[3,4,6-21] nonetheless, the latter mechanisms are not known. Sakkas, *et al.*, found an increased risk for cancer in first-degree relatives of patients with SSc;[21] these findings suggest that a common genetic factor could be involved in the occurrence of cancer in autoimmune rheumatic diseases. Our results indicate a possible relationship between HLA-DRBI*03 and -DRBI*02 with the risk for developing malignant neoplasms (solid or lymphoproliferative) in autoimmune rheumatic diseases. To our knowledge, there is no other study that describes an association between HLA alleles and development of malignancy in autoimmune rheumatic diseases.

The HLA system could be implicated in the development of a malignancy in autoimmune rheumatic diseases alone or on interacting with other genes of the MHC. It is recognized that variations in MHC lead to a susceptibility to neoplasm development, and there is evidence suggesting that the immune system plays a protector role in tumorigenesis. In cancer, HLA peptide complex-stimulated T-cell responses are not sufficiently effective for eliminating tumor cells, and the loss of HLA expression has been reported in tumors.[36,37]

In HLA-associated diseases, certain HLA alleles usually appear to be necessary for disease development; however, not all individuals with an allele will develop the condition, indicating that other factors are required in combination with or independent of the presence of particular HLA alleles for the disease to occur. Development of cancer in autoimmune rheumatic disease may be primarily associated with an HLA locus or with another MHC region gene that is closely linked with HLA. Hence, the association may also reflect a role for non-classical HLA genes that are genetically linked to HLA loci. Tumor necrosis factor alpha (TNFα) is of particular interest; TNFα is a multifunctional cytokine predominantly produced by macrophages that mediates necrosis of solid tumors encoded by a gene within the MHC class III region.[38] Another possibility is the role of oncogenes, which is suggested for the association of the HLA-DQB1*0301 allele with colorectal carcinomas, and which is probably due to the ability of HLA DQB1*0301 to encode molecules to recognize and present processed peptides containing a certain K ras mutation (13Gly-Asp) more efficiently than other HLA molecules.[39]

Although cytotoxic and immunosuppressive therapy employed in these patients could explain the relationship between rheumatic disease and neoplasm, some of the excessive risk described has been determined in the absence of these drugs in RA, SLE, and pSS.[1,3,4,7,12] Therefore, it is important to note that we found no differences with respect to antirheumatic treatment between cases and controls; thus, immunosuppressive drugs did not explain a higher risk for developing neoplasms, at least in this study.

Paraneoplastic rheumatic syndromes are those cancer-associated rheumatic disorders that occur at a distance from the primary tumor or metastases and may precede by no longer than two years, appear concomitantly with or following the diagnosis of cancer. In contrast to paraneoplastic syndromes, malignant transformation in the course of rheumatic disorders may be as long as 20 years.[40,41] Therefore, if an autoimmune rheumatic disease and

malignancy develops within a short time, it may be difficult to distinguish between a paraneoplasia from a secondary tumor. In inflammatory myopathies this temporal relation is particularly unclear. DM is strongly associated with malignancy since it is diagnosed in about 25% of patients with disease onset above the age of 50 and usually develops within two years from the diagnosis of DM.

A paraneoplastic mechanism has been proposed based on the observation of complete remission of myositis after resection of tumor without the use of corticosteroids.[15,42] Bradford-Hill's criteria are useful for evaluation of a causal relationship between cancer and rheumatic disorders. The criteria includes strength; consistency; specificity; temporality; biological gradient; plausibility; coherence; experiment, and analogy.[43] In applying those criteria to the study of the association of PM/DM with cancer, good evidence that solid tumors are determinants of DM has been found based on temporality, strength, consistency, plausibility, coherence and analogy; nevertheless, the evidence that solid tumors are determinants of PM was not convincing.[44] In our study we attempted to reduce the paraneoplastic syndrome effect by selecting patients whose diagnosis of rheumatic disease occurred prior to the presence of cancer; nonetheless, we are unable to exclude the possibility that some patients could have developed a paraneoplastic syndrome.

Other factors related with age or disease duration could be involved in the development of neoplasms in patients with autoimmune rheumatic diseases; however, there were no differences in disease-duration time or other variables such as age at cut-off time and age at rheumatic-disease initiation or diagnosis between cases and controls. We think that the risk for developing neoplasms was not dependent on rheumatic-disease duration or on patient age because we controlled these in the design or in the analyses.

Differences in time with rheumatic disease activity between cases and controls were found; cases showed a lower time with rheumatic activity than controls. Thus, rheumatic-disease activity could diminish the probability of initiating a malignant pathologic process.

We have no explanation for the finding related with a lesser probability of cancer in the presence of recurrent sore throat. On the other hand, the protective role of alopecia in SLE has been a consistent observation in previous studies conducted by our group.[45]

This work is limited by the small sample size. Due to the long evolution period of both the rheumatic disease and the malignant neoplasm, large cohorts based on retrospective in combination with prospective data will be ideally designed in order to reach sufficient statistical power to demonstrate the associations.

To ascertain whether the HLA system is associated with development of cancer in rheumatic diseases, confirmation is necessary by means of additional studies in this area.

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