The relationship between human leukocyte antigens (HLA) and renal cell carcinoma

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Abstract

Etiologies of Renal Cell Carcinoma (RCC) are not clear despite of the fact that many risk factors have been suggested. Especially in high stages RCC can affect the immune system in various ways. Human Leukocyte Antigens (HLA) may play a complementary role in the activation between the tumor and immunity. Our aim was to determine the existence of the relationship between HLA system and RCC. By using the standard microlymphocytotoxic method of Terasaki in our study, the HLA A, B, DR and DQ antigen types of 20 patients with RCC Stage T1 and T2 were compared with the control group consisting of healthy 30 people. In our RCC patient group, HLA-A23(9) and DQ7(3) antigens were significantly higher than the control group statistically (p=0.005, p=0.0028; respectively). HLA-A10, DQ1, DR10 and B44 antigens were significantly higher in the control group than the patient group (p=0.011; for all).The findings made us suggest that the people, carrying the antigens which were detected in the patient group, were at high risk for RCC and the people, carrying the protective antigens that were detected in the control group were at less risk for RCC. There may be a dramatic regression for the patients who underwent immunotherapy and HLA expression, which is known to play role in tumor biology, may direct the effects of immunotherapeutic agents. Immunologic description and destruction is avoided in case of change or disappearance of HLA expression by cancer cells. Further investigations which will be performed in our population in the future will be more illuminating to confirm those results. We have concluded that, HLA profiles may be evaluated for detection the people at risk of RCC, the prognosis of the patients and their treatments.

KEY WORDS: renal cell carcinoma (RCC), human leukocyte antigens (HLA), immunity

Introduction

Renal Cell Carcinomas (RCC) are responsible for approximately 3% of the adult cancers and they compose 85 % of the primary malignant renal tumours. Most of the studies, performed in developed countries indicate that the incidence and mortality of RCC, increases dramatically especially in 5th and 6th decades. This result could be partly due to the developed diagnostic procedures of the urologists and improved techniques and partly due to the reflection of a real increase in the incidence of RCC. Other than smoking there has been not detected any promoting main factor, having a connection with RCC. Amount of possible risk factors have been put forward. Important cell cycles genes like p53, several genetic changes in control genes, chemical, physical, biological agents that deform the DNA were evaluated as possible carcinogens. Genetic predispositions are important as well. Cytogenetic studies make us think that both sporadic and genetic forms are related to the structural changes in the 3rd chromosome [1, 2, 3]. In genetic analysis it has been displayed that deletion of DNA occurs and Von Hippel-Lindau (VHL) suppressor gene is localized in the short arm of the 3rd chromosome [4, 5]. The chromosome changes which are observed in RCC contain translocations and deletions on the short arm of the 3rd chromosome. In now days the investigation of the relation between the HLA, the improvement of treatment of tumour which is closely related to the immune system and formation mechanisms are still continuing. It is known that HLA antigens are important in every single step, from the development to the spreading of the tumour [6, 7]. The incidence of the HLA and its relation with diseases, displays a differences according to different populations [8-17]. It emphasizes that the relation between HLA and the diseases should be investigated and the data should be evaluated for every one of the populations. Starting from this point, in our research we investigated the existence of relation between RCC and HLA. For this purpose we investigated the incidence of frequencies of HLA Class I A and B, Class II DR and DQ antigens by determining the HLA tissue types in blood species of RCC patients who applied to our clinic.

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Materials and Methods

Patients

Our study was performed on two groups, the patient group which consisted of patients with RCC and the control group consisted of healthy people. Our RCC patient group was including 20 patients and control group included 30 healthy kidney donors who applied to Istanbul University, Cerrahpaşa Faculty of Medicine between 2000-2001 years. The mean age of the patient group was 60.85 ± 1.19 and it was consisted of 7 (35%) females and 13 (65%) males. The mean age of the control group was 47.54 ± 12.85 and it consisted of 10 (33.3%) females and 20 (66.6%) males of healthy donors. For this purpose, the patients were subjected according to general inquiries; physical examination, urinary system ultasonography, intravenous pyelography, abdominopelvic computed tomography, urine cytology and HLA determination.

HLA analysis

Blood species were taken before the radical nephrectomy in order to avoid changes in HLA profiles which could occur due to transfusion process. Determination of HLA types was studied by microlymphosythotoxic method on commercial plaques which contain each specification (ONELAMDA-USA) [14]. The determination of HLA tissue types by microlymphosythotoxic method is a reliable, practical method which doesn't require many materials and saves time. The longest diameter in the pathologic specimen of nephrectomy material was accepted as the tumour dimension. Stage and pathologic classifications of all cases were arranged according to 1997 TNM classification system [15]. Fuhrman grading system was used for histopathologic grading.

Statistical analysis

Statistical analysis was accomplished by using SPSS in Windows computer programe. Chi square and Fischer exact tests were applied to control and patient groups in order to find out any important statistical difference between HLA types. The results were multiplied by 77 to reach the corrected p values (tested total HLA subtypes amount). In the next step, Odds Ratio (OR) was calculated by using ($a^+ X b^- / a^- X b^+$) formulation in order to show HLA subtypes differences statistically.
(a^+: patient percentage of the specific HLA type.)
(a^-: patient percentage of the non- specific HLA type)
(b^+: control percentage of the specific HLA type)
(b^- : control percentage of the non-specific HLA type)

Results

In the presented study 8 (40%) cases with RCC cases were in stage T1, while 12 (60%) cases were in stage T2, metastasis wasn't detected in any of the patients. 8 patients were evaluated as grade 2 and 12 patients were evaluated as grade 3. The tumour diameter was found as ≤ 7 cm in 13 patients and > 7 cm in 7 patients. Histopathological evaluation revealed that from 20 patients, 4 were observed to have grade 1 and clear cells, 6 were observed to have grade 2 and clear cells, 4 were observed to have grade 1 and clear and granular cells, 6 were observed to have grade 2 and clear and granular cells subtypes (Table 1). The increase of HLA-A23(9) and HLA-DQ7(3) antigens in the RCC group were statistically significant when they were compared with the control group according to HLA tissue type determinations (p=0.005, p=0.028 in respect). On the other hand HLA-B44(12), HLA-DR10, HLA-A10 and HLA-DQ1 antigens were detected significantly higher in the control group, which consisted of healthy people, than the RCC group (p=0.011 in all) (Table 2). Some HLA subtypes were detected neither in patient nor in the control group. A statistical difference doesn't exist between the patient and control groups in regard of distribution of sexes (p>0.05). Smoking which is one of the risk factors was only detected in 53.3% (12 cases) of the patient group and was in 35% (10 cases) of the control group. This difference was statistically significant (p<0.05). OR was calculated as 15.61 for the allele which contained HLA-A23 and as 3.71 for the allele which contained HLA-DQ(7). HLA-A23 (9), HLA-B(22) and HLA-DR15(2) antigens were significantly higher in stage T1 than the other stages (p=0.005, p=0.017, p=0.0497 in respect), besides HLA DR4 antigen was more significant in grade 2 than the other grades (p=0.038, p=0.0365 in respect). In our research which was performed on the base of the 1997 TNM classification, there wasn't detected a statistical correlation between HLA antigens and the tumour diameters in RCC patients.

TABLE 1. Baseline characteristics of patient and control groups.

	Patient Group	Control Group
Number of patients	20	30
Mean age	60.85±1.15	47.54±12.85
Sex	13 Males, 7 Females	20 Males, 10 Females
Stage		
T1	8	-
T2	12	
Grade		
1	-	
2	8	-
3	12	
Pathology		
Clear cells	10	-
Clear +granular cells	10	

Discussion

In 1931, by indicating the parallelism between the blood transfusion and organ transplantations, Landsteiner pointed

TABLE 2. Percentages of HLA alleles in patient and control groups

HLA Type	Control (%)	Patient (%)	p value*	HLA Type	Control (%)	Patient (%)	p value*
A1	18.47	20		B41	1.08	-	
A2	44.02	56		B44(12)	11.95	2	p=0.011
A3	24.45	22		B49		22	
A10	8.15	4	p=0.011	B50(21)	1.08	-	
A11	15.21	-		B51(5)	26.63	34	
A13	-	6		B52(5)	0.54	-	
A19(32)	0.54	-		B53	0.54	-	
A19	12.50	6		B55(22)		6	
A23(9)	4.34	34	p=0.005	B57(17)	0.54	6	
A24(9)	17.39	12		B60(40)	5.97	10	
A25(10)	5.43	6		B62(15)	2.71	6	
A28	0.56	-		B63(15)	0.54	-	
A29(19)	3.26	6		B65(14)	0.54	-	
A29	-	-		B67	3.26	-	
A30(19)	5.43	10		DR1	9.78	-	
A31	1.08	-		DR2	1.08	-	
A31(19)	1.08	-		DR3	3.8	-	
A32	0.54	-		DR4	14.67	22	
A32(19)	2.17	6		DR5	3.8	-	
A33(19)	1.08	-		DR7	5.43	6	
A68(28)	1.08	6		DR8	15.76	6	
B5	5.43	-		DR9	7.06	6	
B7	11.95	-		DR10	14.13	2	p=0.011
B8	15.76	22		DR11(5)	41.39	54	
B12(44)	0.54	-		DR12(5)	7.06	-	
B12	1.08	-		DR13(6)	12.50	10	
B13	7.60	6		DR14(6)	15.21	12	
B14	5.97	6		DR15(2)	28.80	22	
B15	2.17	-		DR18(3)	16.30	10	
B16	5.43	-		DQ1	18.69	2	p=0.011
B17	11.41	-		DQ2	1.63	-	
B18	5.97	10		DQ3	5.43	-	
B21	4.89	-		DQ4	47.82	78	
B22	7.60	12		DQ5	2.17	-	
B27	9.78	-		DQ6(1)	32.06	50	
B35	28.26	28		DQ7	3.26	-	
B37	7.6	12		DQ7(3)	4.60	62	p=0.028
B38(16)	2.71	-					
B40	1.08	-					

* The ones which are significant statistically are given their p values. The ones which aren't given their values, are insignificant statistically (p>0.05).

out that tissues must have had a similar feature as the blood types had [14]. Several diseases were observed more frequently in the people who carry the HLA alleles belonging to the disease. When RCC and relation with HLA and MHC (Major Histocompatibility Complex) are investigated in medical literature, only few publications were found [3, 6]. The studies, which investigated the relation between HLA and the tumours, thus, investigated the relation between HLA and RCC, started in 1970's and have been going on in now days [6, 7, 18, 19]. In these studies it was searched whether an affirmative or preventive relation between HLA antigens and RCC existed. It's well known that HLA antigens differ in every population in the meaning of stage, grade, prognosis, response to the treatment and survey of the different tumours. It's obvious how important it is to perform HLA studies in different populations for the same disease. The differences between our results and results of other populations indicate the importance of the evaluation of HLA for every single population. The quantitative and qualitative changes in the antigen expression of this molecule, which is on the surface of the tumour cells, are important in the antitumoral immune response. Brasanac et al. [6, 7] investigated the relation between RCC and HLA in 1999. In this study, it was notified that HLA Class I expression was decreasing in the cells of RCC patients and the tumour was developing aggressively when the cellular antitumoral immune response was disrupted in the tumours in which Class I expression was low [6, 7]. In the study, performed in Yugoslavia when a strong relation between the deficiencies of Class I expression and stage T3 and T4 was detected to be existing, HLA-A23 and B antigens

were detected significant in stage T1, which information verifies the fact that the tumor is able to reach stage T1 in the presence of Class I antigens [6]. After the p value was corrected, even though it had lost its value, the significant frequency of HLA-A23 that we had observed in our patients, wasn't published before. The statistical relation which was detected in Brasanac's et al. studies [6, 7] between the grade degree and reduction of expressions of class I antigens, wasn't detected in the reduction of expressions of class II antigens and the increase in the frequencies of HLA-DR8 and DR4 in grade 2 and 3 is worth attention. The statistical relation between the deficiencies of class I expressions and the increase of the tumor diameter of Brasanac [6] wasn't confirmed in our study. In 2000, Kojima et al. evaluated the relation between RCC and HLA class II antigens [20]. In the mentioned study, subtypes of class 2 antigens were investigated as well, besides the expressions of subtypes of HLA-DR4 and DR12 were found significantly higher in the RCC patients compared with those in the control group [20]. We attained the result that RCC and class I and II antigens are related to each other. Those results that we attained are partly parallel with Kojima's [20]. But our subtypes of class 2 were different than Kojima's subtypes. Kojima et al. informed that, when HLA profiles of RCC patient group and the control group are compared in Japanese population, HLA-DR4 and DR12 were frequent in the patient group and those antigens were thought to be related to the disease [20]. When result's of Kojima et al. [20] study were compared to our results, there was a difference in the aspect of frequency of HLA-DQ7 antigens, but there was a similarity in the aspect of HLA-DQ7 antigen belonging to class II. The results belong to Turkish people and when the difference they display is compared with the results of other researches, it is outstanding, in the meaning of "population". When it's taken into consideration that HLA antigens are different for populations, the importance of separate investigations of HLA and the diseases in every population, will come out. Brasanac et al. [7] confirmed the relation of HLA DR, DQ, DP with RCC, the existence of class II antigens but with a bad expression. In our study we found that HLA-A23 and DQ7 increased and this was in concert with the results of Brasanac [6, 7] in the aspect of DQ antigens. It's also observable there as well that the relation of RCC with HLA patients differ for populations. The results of our study support and confirm the data of the previous literature [6, 7, 20]. No mechanism is defined on the relation of HLA system and RCC in medical literature investigation. However, the disrupted immune function of cellular immunity in RCC patients was defined for many times in the studies of 1970's and 1980's. T cellular lymphopenia, especially T-helper cellular lymphopenia, and the disrupted increase of the T cells to immunogenetic reaction are defined [21]. The mechanisms which are defined above indicate that RCC is in activation with the immune system in various ways. It was put forward that the reduction of MHC on the surface of tumour cells could protect the neoplastic cells from the immune system [21]. That's why studies like tumour inoculation focused on the relation between the tumour cells and HLA molecules may be productive [22]. To define the relation between subtypes of HLA and RCC by making use of the relation of HLA system and immunity, may help us to define the activation between the tumour and immune system and to direct the treatment [22, 23]. Studies which plan to form an inoculation which arises especially a restrictive HLA-A2 immune response, based on HLA class I, against tumour antigens in RCC cancers, are notified [23]. The number of cases isn't enough in each group. However, the more similar studies in different pathologic stages of RCC in every group we have and the more facts we have, the more possibilities we will have to focus on its relation with HLA system and ratio of the survey in every group.

Conclusion

Human Leukocyte Antigens (HLA) may play a complementary role in the activation between the tumour and immunity. Our aim was to determine the existence of the relationship between HLA system and RCC. The increase of HLA-A23(9) and HLA-DQ7(3) antigens in the RCC group were statistically significant. On the other hand HLA-B44(12), HLA-DR10, HLA-A10 and HLA-DQ1 antigens were detected significantly higher in the healthy people group.

Declaration of interest

Authors do not have any commercial affiliations, or potential conflicts of interest associated with this work submitted for publication.

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