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Human leukocyte antigens class I and II in patients with idiopathic granulomatous mastitis

Hande Koksal

Saglik Bilimleri University, Faculty of Medicine, Konya Education and Research Hospital, Department of General Surgery, Yeni Meram Cad, Number: 97, Konya, Turkey

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ABSTRACT

Background: To determine the distribution of human leukocyte antigens (HLA) in patients with idiopathic granulomatous mastitis (IGM).
Methods: The study included 48 patients diagnosed with IGM and 50 controls consisting of healthy donor candidates.
Results: The frequencies of HLA-A*10, HLA-A*2403, HLA-B*18 and HLA-DR*17 antigens were significantly higher in the patient group than control group ($p = 0.012$, $p = 0.012$, $p = 0.0001$ and $p = 0.005$, respectively). However, the frequencies of HLA-A*29, HLA-B*14 and HLA-DR*1 were lower in the patient group than control group ($p = 0.027$, $p = 0.013$ and $p = 0.015$, respectively).
When patients without/with relapse were compared, there was a significant difference in HLA-A*3 ($p = 0.048$) and HLA-A*32 ($p = 0.011$).
Also, the patients with relapse and control group were compared in respects of HLA-A*10 ($p = 0.0006$), HLA-A*24 ($p = 0.035$), HLA-A*32 ($p = 0.011$), HLA-B*18 ($p = 0.035$), HLA-B*103 ($p = 0.035$) and HLA-DR*17 ($p = 0.006$).
Conclusion: These findings may help to explain etiopathogenesis but still, further studies on this subject with more patients in different geographic regions are needed.

Introduction

Idiopathic granulomatous mastitis (IGM) is a rare benign inflammation of the mammary gland described by Kessler and Wolloch for the first time.[1] Different etiologic causes including hormonal imbalance, autoimmunity, microbial agents, smoking and α1-antitrypsin deficiency have been reported up to now but the etiology of IGM is still unclear.[2,3] There are strong hypothesis on autoimmune process's role in many publications.[2–5] An interesting point is that; significant proportion of IGM related publications in English literature is made up of developing countries located at the similar geographical zone including Turkey, China, South Korea, and Saudi Arabia.[3]

The human leukocyte antigens (HLAs) are expressed on cell surface and regulate the immune response. So far, a lot of studies have been conducted to investigate whether there is a relationship between HLA and various diseases.[6,7] For this reason, conducting HLA studies in different populations for the same disease is obviously important. The studies showing the relationship between HLA antigens and diseases can give vital information on etiology, determination of risk, prevention of the disease, to understand whether they are genetically transmitted, and consequently to reach a molecular pathogenesis, to plan treatment approach and prognosis.[6,7]

To our knowledge, there are no studies on relationship between HLA and IGM up to now. The aim of this study is to investigate whether there is a relationship between HLA antigens and IGM in Turkish population.

Materials and methods

In this study, 48 patients with histopathologically proven IGM (patients group) were included. The control group consisted of 50 healthy transplantation candidate donors.

Genomic DNA was extracted from lymphocytes in peripheral blood of the patients with IGM and healthy controls using QIAamp DNA Blood Mini kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's instructions.

E-mail address: drhandeniz@yahoo.com.

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Polymerase chain reaction sequence-specific oligonucleotide method (PCR-SSO) combined with Luminex technology was carried out using "HLA SSO Typing" commercial kit (Lifecodes, USA). The protocol comprised the DNA amplification process using a group specific primer, hybridization with sequence-specific oligonucleotide probes (SSO), analyzing on a special device (Luminex 100) (Lifecodes, USA) and software interpretation (MATCH IT TM N DNA Software) (Lifecodes, USA). All procedures were performed according to the manufacture's' instructions.

The present study was approved by the Local Ethics Committee (Selcuk University, No: 2018/117) and conducted in accordance with Helsinki Declaration. Informed consents were obtained from all participants.

Statistical analysis

Median values were used to analyze demographic characteristics. For comparing categorical variables and comparison between groups, Pearson chi-square test or Fischer's exact test was used (parametric data, non-parametric data, respectively). In the statistical analyses; p value was regarded as significant if < 0.05. The association between IGM and HLAs was estimated by risk ratios and 95% confidence intervals.

Results

In this study, 48 patients diagnosed as IGM after pathologic examination and 50 healthy volunteers for transplantation donor candidates were included in the study.

Patients' characteristics

There were 48 patients with histologically proven IGM with median age 33 years (range, 21–68 years) at diagnosis. Median parity number was 3 (range, 0–6). In 33 patients (68.7%), the lesion was central while in 15 patients (31.3%), the lesion was located peripherically.

The symptoms and signs were mass (n: 48, 100%), pain (n: 39, 81.3%), erythema (n: 34, 58%), axillary lymphadenopathy (n: 22, 45.8%), skin involvement (n: 20, 41.7%), ulceration (n: 8, 18.8%), sinus formation (n: 7, 14.6%), nipple retraction (n: 6, 12.5%), and peau d' orange (n: 3, 6.3%). Five patients (10.4%) had erythema nodosum.

Treatment modalities were drainage plus antibiotic (n: 36, 75%), only antibiotic (n: 6, 12.5%), wait and watch (n: 4, 8.3%) and surgery plus drainage plus antibiotic (n: 2, 4.2%)

The frequencies of HLAs

The frequencies of HLA class I and II antigens in IGM and control groups are given in Table 1.

The frequencies of HLA-A*10, HLA-A*2403, HLA-B*18 and HLA-DR*17 antigen were significantly higher in the patient group than control group (12.5% vs 0%, $p = 0.012$; 12.5% vs 0%, $p = 0.012$; 22.9% vs 0%, $p = 0.001$ and 14.6% vs 0%, $p = 0.005$, respectively). However, the frequencies of HLA-A*29, HLA-B*14 and HLA-DR*1 were lower in the patient group than controls (0% vs 12%, $p = 0.027$; 0% vs 14%, $p = 0.013$; and 4.2% vs 22%, $p = 0.015$, respectively).

There was no difference in HLA frequencies and central or peripheral localization of the lesion ($p > 0.05$).

The common HLAs in IGM patients with erythema nodosum (n: 5) were HLA-A*24 (n: 2), HLA-A*2403 (n: 2), HLA-B*35 (n: 2), HLA-B*44 (n: 2) and HLA-DR*8 (n: 2).

When patients without relapse were compared with patients with relapse (Table 2), there was a statistically significant difference

Table 1
Distribution of human leukocyte antigen class I and II antigens in the idiopathic granulomatous mastitis and controls.

HLA antigens	Patients		Control		p	Risk ratio	95% Confidence Interval	
	n	%	n	%			Lower	Upper
Class I antigens								
A*1	9	18.8	3	6	NS			
A*2	17	35.4	20	40	NS			
A*3	10	20.8	11	22	NS			
A*10	6	12.5	0	0	0.012	2.19	1.753	2.738
A*11	8	16.7	6	12	NS			
A*23	9	18.8	3	6	NS			
A*24	8	16.7	14	28	NS			
A*2403	6	12.5	0	0	0.012	2.19	1.753	2.738
A*26	8	16.7	8	16	NS			
A*28	3	6.3	0	0	NS			
A*29	0	0	6	12	0.027	2.09	1.689	2.588
A*30	4	8.3	7	14	NS			
A*31	1	2.1	1	2	NS			
A*32	5	10.4	2	4	NS			
A*33	3	6.3	4	8	NS			
A*66	0	0	1	2	NS			
A*68	4	8.3	3	6	NS			
A*69	1	2.1	1	1	NS			
A*210	1	2.1	0	0	NS			
B*5	1	2.1	0	0	NS			
B*7	0	0	2	4	NS			
B*8	4	8.3	4	8	NS			
B*13	3	6.3	6	12	NS			
B*14	0	0	7	14	0.013	2.116	1.703	2.629
B*15	1	2.1	3	6	NS			
B*16	3	6.3	0	0	NS			
B*18	11	22.9	0	0	0.0001	2.351	1.842	3.002
B*22	1	2.1	0	0	NS			
B*27	2	4.2	3	6	NS			
B*35	13	27.1	12	24	NS			
B*37	2	4.2	1	2	NS			
B*38	3	6.3	7	14	NS			
B*39	1	2.1	2	4	NS			
B*40	0	0	5	10	NS			
B*41	3	6.3	4	8	NS			
B*44	7	14.6	5	10	NS			
B*46	1	2.1	0	0	NS			
B*48	1	2.1	0	0	NS			
B*49	8	16.7	4	8	NS			
B*50	0	0	2	4	NS			
B*51	9	18.8	14	28	NS			
B*5103	1	2.1	0	0	NS			
B*52	1	2.1	1	2	NS			
B*53	0	0	1	2	NS			
B*54	0	0	1	2	NS			
B*55	1	2.1	3	6	NS			
B*56	2	4.2	0	0	NS			
B*57	2	4.2	4	8	NS			
B*58	1	2.1	3	6	NS			
B*61	4	8.3	0	0	NS			
B*62	2	4.2	0	0	NS			
B*64	2	4.2	0	0	NS			
B*65	2	4.2	0	0	NS			
B*101	1	2.1	0	0	NS			
B*103	4	8.3	0	0	NS			
BW*4	0	0	2	4	NS			
BW*6	0	0	5	10	NS			
Class II antigens								
DR*1	2	4.2	11	22	0.015	0.154	0.032	0.738
DR*3	7	14.6	11	22	NS			
DR*4	9	18.8	13	26	NS			
DR*7	2	4.2	5	10	NS			
DR*8	3	6.3	4	8	NS			
DR*9	2	4.2	0	0	NS			
DR*10	2	4.2	1	2	NS			
DR*11	18	37.5	18	36	NS			
DR*12	2	4.2	3	6	NS			
DR*13	9	18.8	9	18	NS			
DR*14	1	2.1	3	6	NS			
DR*15	6	12.5	9	18	NS			

Table 1 (*continued*)

HLA antigens	Patients		Control		p	Risk ratio	95% Confidence Interval	
	n	%	n	%			Lower	Upper
DR*16	1	2.1	1	2	NS			
DR*17	7	14.6	0	0	0.005	2.220	1.769	2.785
DR*18	0	0	1	2	NS			
DR*45	1	2.1	0	0	NS			

HLA: human leukocyte antigen, NS: Not significant.

Table 2
Comparison of HLA class I and II antigens in the idiopathic granulomatous mastitis without/with relapse.

HLA antigens	No relapse (n: 36)		Relapse (n: 12)		p	Risk ratio	95% Confidence Interval	
	n	%	n	%			Lower	Upper
HLA-A*3	10	27.8	0	0	0.048	1.462	1.178	1.814
HLA-A*32	1	2.8	4	33.3	0.011	0.011	0.006	0.583

HLA: human leukocyte antigen.

in patients with relapse in respect of HLA-A*3 (27.8% vs 0%, p = 0.048) and HLA-A*32 (2.8% vs 33.3%, p = 0.011). Also, IGM patients with relapse and control group were compared (Table 3), HLA-A*10 (25% vs 0%, p = 0.0006), HLA-A*24 (16.7% vs 0%, p = 0.035), HLA-A*32 (33.3% vs 4%, p = 0.011), HLA-B*18 (16.7% vs 0%, p = 0.035), HLA-B*103 (16.7% vs 0%, p = 0.035) and HLA-DR*17 (25% vs 0%, p = 0.006) frequencies were detected to be higher in IGM patients.

Discussion

The etiology of IGM, which is a benign inflammatory disease, is still unknown. To date, many etiological factors including hormonal disturbances, autoimmune factors, micro-organisms, smoking and α1-antitrypsin deficiency have been emphasized.[2,3] Recently, especially studies on autoimmunity in the etiology of IGM have been drawing attention.[2–5]

Altintoprak and colleagues[8] studied the anti-nuclear antibody and extractable nuclear antigen levels for the investigation of autoimmunity in the etiology of IGM. However, the authors were unable to demonstrate the presence of an autoimmune basis for IGM in this study. In another study by Yigitbasi et al.,[9] interleukin-33 and soluble ST2 receptor of interleukin-33 were investigated in IGM and breast cancer patients. Both interleukin-33 and soluble ST2 receptor of interleukin-33 were higher in breast cancer and IGM than control group; but the levels of the soluble ST2 receptor of interleukin-33 were lower in IGM than breast cancer. Ozel and colleagues[10] investigated rheumatoid factor, antinuclear antibody and anti-double stranded DNA antibodies serologically in IGM patients. Rheumatoid factor was positive in 6 of 8 patients, antinuclear antibody and anti-double stranded DNA antibodies were positive in same 2 patients. Also, these 2 patients' rheumatoid factor was positive. With these findings, autoimmunity should be kept in mind in the etiology of IGM. In addition to these studies, the association of idiopathic granulomatous mastitis with some rheumatologic symptoms or findings, such as arthritis or erythema nodosum, further suggests autoimmune etiology strongly.[11–15] Moreover, the good response of patients to steroids also supports the autoimmunity.[13,16–19] Although rare, granulomatous mastitis associated with Sjögren's syndrome was reported.[20]

Table 3
Comparison of HLA class I and II antigens in the idiopathic granulomatous mastitis with relapse and control.

HLA antigens	Relapse (n: 12)		Control (n: 50)		p	Risk ratio	95% Confidence Interval	
	n	%	n	%			Lower	Upper
HLA-A*10	3	25	0	0	0.0006	6.556	3.593	11.962
HLA-A*24	2	16.7	0	0	0.035	6.000	3.407	10.565
HLA-A*32	4	33.3	2	4	0.011	4.667	1.984	10.977
HLA-B*18	2	16.7	0	0	0.035	6.000	3.407	10.565
HLA-B*103	2	16.7	0	0	0.035	6.000	3.407	10.565
HLA-DR*17	3	25	0	0	0.006	6.557	3.593	11.962

HLA: human leukocyte antigen.

Some diseases such as narcolepsy (HLA-DR*2), ankylosing spondylitis (HLA-B*27), Reiter' disease (HLA-B*27), rheumatoid arthritis (HLA-DR*4), hemochromatosis (HLA-A*3), psoriasis (HLA-Cw*6), celiac disease (HLA-DR*3) and multiple sclerosis (HLA-DR*2) have well-established genetic linkages to the HLAs system.[6]

After these studies suggesting autoimmunity in etiopathogenesis; we aimed to investigate the presence of HLA susceptibility in patients with IGM.

In our study comparing the frequencies of HLA class I and II antigens of IGM and control group, we found that the frequency of some HLA antigens including HLA-A*10 (12.5% vs 0%), HLA-A*2403 (12.5% vs 0%), HLA-B*18 (22.9% vs 0%), and HLA-DR*17 (14.6% vs 0%) was high in the patient group and this finding is statistically significant. However, the frequencies of some of them including HLA-A*29 (0% vs 12%), HLA-B*14 (0% vs 14%) and HLA-DR*1 (4.2% vs 22%) were significantly lower. Different interpretations can be made about antigens with statistically significant difference in our study. For example, in the study of Fellerhoff and colleagues,[21] they showed the relationship between schizophrenia and Chlamydophila infections. Also, this risk has been shown to be increased in carriers of HLA-A*10 genotype. In our study, HLA-A*10's frequency was higher in IGM patients than controls. Can the high frequency of HLA-A*10 in our study suggest a similar relationship to us? Balke et al.[22] showed that HLA-A*24 predisposes to a delayed antigen spreading of humoral autoimmunity, whereas HLA-A*24 and -B*18 are associated with accelerated progression of advanced subclinical autoimmunity in first-degree relatives of patients with type 1 diabetes. In our study, the high incidence of both HLA-A*2403 and HLA-B*18 antigens may indicate that IGM may be associated with humoral immunity and autoimmunity. The frequencies of HLA-A*10, HLA-A*24, HLA-A*32, HLA-B*18, HLA-B*103 and HLA-DR*17 of the IGM patients developing relapse were higher than controls.

Idiopathic granulomatous mastitis is an entity that the etiology is not defined or understood so it is difficult to treat. Many hypotheses suggest an abnormal function of immune system due to an unknown agent; either host antigen or extraneous trigger agent. Additionally, the concomitant autoimmune diseases in IGM like arthritis, erythema nodosum and Sjögren's syndrome; and the benefits of using steroids in some cases also impress to think about immune dysregulation in the etiopathogenesis of this disease. This paper examines the HLA types of patients who have had diagnosis of IGM, and comparing the differences with healthy volunteers. This population may provide the opportunity for great insight into this problem.

However, without having a data about the frequency of HLA in other countries where IGM is widely encountered, it would not be correct to comment on why the frequency of certain antigens is low and some antigens are high. In the light of this study some points about etiopathogenesis of this disease can be highlighted with encouraging many studies on this subject worldwide. We were able to identify specific HLA types which were statistically significant among the patients and healthy volunteers. Furthermore, among those who had been diagnosed as IGM, there were significant

differences in some HLA types between the patients who relapsed and who did not.

When the treatment approaches of the patients were evaluated, the significant part of the treatment was symptomatic treatment, in the form of antibiotics and drainage. It was not possible to treat according to the frequency of HLA because of not accepted data worldwide. But the findings of HLA distribution in patients who require steroids or another immunosuppressive medication is valuable.

As a result, this paper provides great insight into this problem, its results should be confirmed in other populations also. We think that this study will likely form the basis for future research on this topic.

In conclusion, the prevalence of some HLA antigens including HLA-A*10, HLA-A*2403, HLA-B*18 and HLA-DR*17 in patients with IGM is higher or some of them including HLA-A*29, HLA-B*14 and HLA-DR*1 were lower than in the control group which may help to explain etiopathogenesis. Therefore, the studies on this subject with more patients in different geographic regions are needed.

Disclosure statement

The author has no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.01.038.

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