Sarcoid arthropathy and the association with the human leukocyte antigen. The Icelandic Sarcoidosis Study

D. Petursdottir[1], S.O. Haraldsdottir[2], K. Bjarnadottir[3], T. Jonsson[3], T. Gislason[2,4], S. Gudmundsson[3], B. Gudbjornsson[1,4]

[1]Centre for Rheumatology Research, [2]Department of Respiratory Medicine, [3]The Icelandic Blood Bank, Landspitali - University Hospital, Reykjavík; [4]Faculty of Medicine, University of Iceland, Reykjavík, Iceland.

Abstract

Objective

The aim of the present study was to evaluate whether certain HLA antigens were risk factors for developing sarcoid arthritis and whether HLA antigens appear to account for the phenotype and the resolution of the arthritis condition in an unselected nationwide cohort.

Methods

The Icelandic Sarcoidosis Study (ISS) contains all tissue-verified cases of sarcoidosis in Iceland since 1981. Of a total of 234 cases, 39 patients were identified with arthritis and of those 36 delivered a biosample for the study. The patient cohort has previously been described in detail. DNA was isolated from EDTA blood and HLA antigen typing was performed. A total of 544 Icelandic stem cell donors acted as controls.

Results

*HLA-B8 and HLA-B14 antigens were more common among those who suffered from sarcoid arthritis (24% vs. 11%, $p<0.01$; 6.5% vs. 2.4%, $p<0.05$). DRB1*03 was also found more frequently in patients with sarcoid arthritis compared to controls (28% vs. 11%, $p<0.001$), while DRB1*04 was less frequently reported (5.6% vs. 17%, $p<0.01$). No differences were found in the HLA-A distribution between the groups. A higher proportion of patients with chronic arthritis had HLA-A11 than those with resolving joint problems (60% vs. 3.8%).*

Conclusion

Our nationwide study of patients with sarcoid arthritis further supports the conclusion that genetics may strongly influence the development and the clinical course of the disease. Furthermore, some HLA antigens may even be protective for the disease. Thus, classification of the major histocompatibility complex may have clinical implications.

Key words

arthritis, HLA, nationwide study, sarcoidosis

Dyrleif Petursdottir, MD
Sigridur Olina Haraldsdottir, MD
Kristjana Bjarnadottir, MSc
Thorbjorn Jonsson, MD, PhD
Thorarinn Gislason, MD, PhD
Sveinn Gudmundsson, MD, PhD
Bjorn Gudbjornsson, MD, PhD

Please address correspondence to:
Prof. Bjorn Gudbjornsson,
Centre for Rheumatology Research,
Landspitali - University Hospital,
v/Hringbraut,
101 Reykjavik, Iceland.
E-mail: bjorngu@landspitali.is

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Introduction

Sarcoidosis is a multi-organ granulomatous disorder characterised by accumulation of epithelioid and mononuclear cells together with $CD4^+$ T-cells (1). Sarcoidosis affects people of all racial and ethnic groups, and occurs at all ages, although it usually develops before the age of 50 years, with an incidence peak of 20 to 39 years of age (2). The incidence of sarcoidosis varies widely throughout the world, probably because of differences in environmental exposures and genetic background, e.g. the prevalence of human leukocyte antigen (HLA) (3). Racial differences in incidence rates and in clinical appearances, with reports of disease clustering in families, further support the conclusion that genetic factors may be significant players in the pathogenetic processes of sarcoidosis (2, 4-7).

Two main categories of genetic studies in sarcoidosis have been reported: studies on the major histocompatibility complex (MHC) and non-MHC studies. Many HLA genes, which are located on chromosome six, have been investigated for association with sarcoidosis based on the assumption that disease-associated HLA molecules present specific antigenic peptides in such a way that recognition by specific T lymphocytes results in the initiation of a granulomatous inflammatory response with pathologic consequences.[8,9] However, only a small number of HLA antigens have been consistently associated with sarcoidosis and sarcoid arthritis (8).

The first reported association between sarocoidosis and specific gene products was the association between the class I HLA-B8 antigen and acute sarcoidosis (10). Subsequently, HLA class II antigens, encoded by HLA-DRB1 and DQB1, have also been consistently associated with sarcoidosis (3, 11, 12). In this regard, the association between Löfgren's syndrome and the extended HLA-DRB1*0301/DQB1*0201 haplotype is probably the most extensively reproduced (8).

This article focuses on the relationship between the human leukocyte antigens and the clinical presentation of the arthritic condition among patients with tissue-verified sarcoidosis.

Material and methods

Patients and controls

The Icelandic Sarcoidosis Study (ISS) contains all tissue-verified cases of sarcoidosis in Iceland diagnosed beginning in 1981. In 2004, a total of 234 individuals, all of Icelandic Causiasian heritage, had been indentified with tissue-verified sarcoidosis. A history of arthritis or periarticular inflammation was found in 39 (20.1%) cases among these patients. We have previously published data on the prevalence, clinical manifestation and long-term prognosis of this patient cohort with a history of sarcoid arthritis (13, 14). One patient died during the observation period and two were living abroad at the time of the present study. Thus, 36 patients were invited to participate in the study. The demographics of the present patient cohort and their disease itinerary have previously been described in detail (Table I) (14).

All participants received an information letter by post and they had to sign an informed consent agreement before the visit during which where they were included in the present study.

As controls, 544 healthy blood donors (males 78%) registered in the Icelandic Stem Cell Donor Registry, were used for comparsion.

Methods

DNA was isolated from EDTA blood samples using QIAamp (Qiagen, Düsseldorf, Germany). Samples were typed for HLA-A and -B using the conventional lymphocytotoxicity test. Patient samples were typed for HLA-DRB1 using sequence-specific primers (PCR-SSP, Dynal, Oslo, Norway). Control samples were typed for HLA-DRB1 by a Luminex-based PCR-SSO typing method (One Lambda Inc, Canoga Park, CA, Product information LAB-Type SSO Typing Tests). The HLA typings were performed at The Blood Bank, University Hospital, Iceland.

HLA typing with the lymphocytotoxicity test gives serological results, while typing with the Luminex gives allele-based results with asuggested serology. To compare the groups the suggested serology for broad antigens within the control samples for class I was used.

Both methods gave identical allele resolution for class II.

Data collecting

All data were registered in File Maker Pro3 and analysed using the GraphPad Prism 5 for Windows (GraphPad Software, San Diego, CA). We used antigen carrier frequencies for statistical analysis. A difference in distribution of carriage of alleles in different groups was assessed with Fisher's exact test. Statistically significant differences between patients and controls were defined as a *p*-value of 0.05 or less.

The Hospital Ethics Committee (05-039) and the Data Protection Authority in Iceland (S2425/2005) approved the study protocol.

Results

Forty-four individuals, who had been registered with joint symptoms in the ISS data base, alive in 2005 and living in Iceland, were invited to participate in the present study. Of these, three individuals did not respond to the invitation letter and the fourth individual declined to participate in the study. Thus, 40 of the 44 individuals listed in the database, or 91% accepted the invitation to come for a clinical evaluation and a blood test in accordance with the study protocol. However, four cases did not have a confirmed history of inflammatory joint disorder or their joint problem was attributable to other causes. Thus, 36 individuals underwent HLA typing.

No statistical differences were observed in the HLA-A antigen frequencies of individuals with a history of sarcoid arthritis and the control group of stem cell donors (Fig. 1). The antigen frequency of HLA-A19 demonstrated the largest differences or 19% for the sarcoid arthritis group and 12% for the control group of healthy stem cell donors, but it did not reach a statistically significant difference (p=0.096).

The antigen frequency for HLA-B8 was 24% in the sarcoid arthritis group compared to 11% in the control group (p=0.0033, Fig. 2). For HLA-B14 the frequency was 6.5% for the sarcoid arthritis group and 2.4% for the control group (p=0.0383, Fig. 2). The two patients carrying the HLA-B8 and B14 antigens, were two and five years older respectively at the time of diagnosis, than those who did not carry these antigens. There were fewer sarcoid arthritis patients HLA-B27 positive than the healthy controls, but the difference did not reach significance (2.9% *vs*. 7.9%; p=0.229).

Table I.

	Total (n=36)	female (n=21)	male (n=15)
Age of diagnosis mean years ± SD	45 ± 10	46 ± 10	43 ± 10
Age of inclusion mean years ± SD	52 ± 10	53 ± 8	51 ± 11
Chronic arthritis (n)	5	5	0
Erythema nodosum (n)	12	10	2
Uveitis/Iritis (n)	7	3	4
Smoking history (n)			
Never smokers	21	15	6
Ex-smokers	10	5	5
Smokers	5	1	4

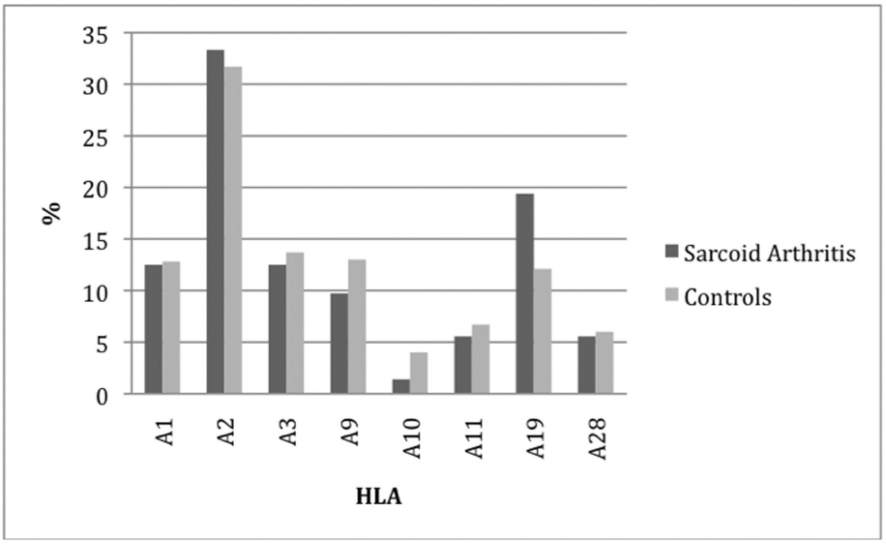

Fig. 1. HLA-A antigen frequencies among individuals with confirmed sarcoid arthritis (n=36) compared to control group of healthy stem cell donors (n=544).

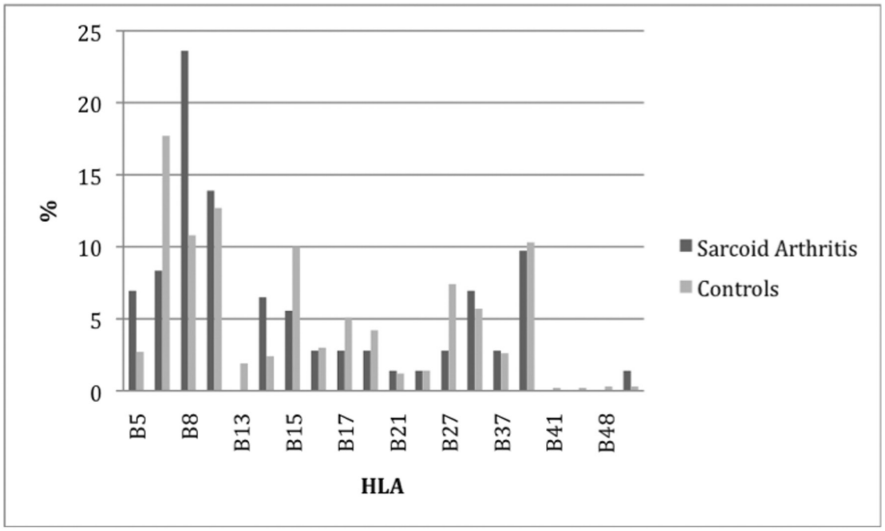

Fig. 2. HLA-B antigen frequencies among individuals with sarcoid arthritis (n=36) compared to control group of healthy stem cell donors (n=544).

The frequency of the DRB1*03 allele was 28% in the sarcoid arthritis group and 11% in the control group (p=0.0002). In comparison, the frequency of HLA-DRB1*04 was only 5.6% in the sarcoid arthritis group, but 17% in the control group of healthy stem cell donors (p=0.0117). The patients without the DRB1*04 allele were a mean eight years older at the time of diagnosis than those who did not carry this allele (mean 45 years *vs*. 37 years of age), but in contrast patients who carried the DRB1*03 allele had a mean age of 46 years at the time of diagnosis while those who did not have this allele had a mean age of 42 years.

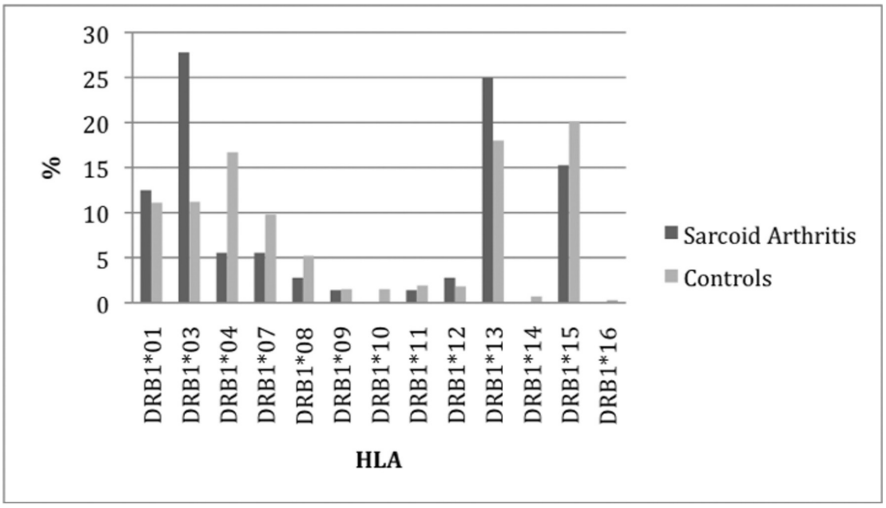

Fig. 3. HLA-DRB1 allele frequencies among individuals with sarcoid arthritis (n=36) compared to control group of healthy stem cell donors (n=544).

Chronic arthritis and HLA

As previously reported by our group (14), five patients (14%) had had chronic polyarthritis for more than six months. The HLA-A11 antigen was found in three of these five patients (60%) with a history of chronic arthritis, while only one patient (3.8%) had resolving arthritis (p=0.0074). Those individuals who were HLA-A11 positive had a mean age of 47 years, while those who were negative for that allele had a mean age of 44 years at the time of diagnosis.

No other significant differences regarding the HLA-A or HLA-B antigens or the HLA-DRB1 alleles were observed in the distribution frequencies between those patients with a history of chronic arthritis and the group of individuals with resolving arthritis or in respect to other clinical presentation of their arthritis condition. Neither were there any statistical differences regarding the investigated HLA types between the patients with a history of erythema nodosum, iritis or uveitis and the patients with no extra-pulmonary symptoms except for their arthritides condition.

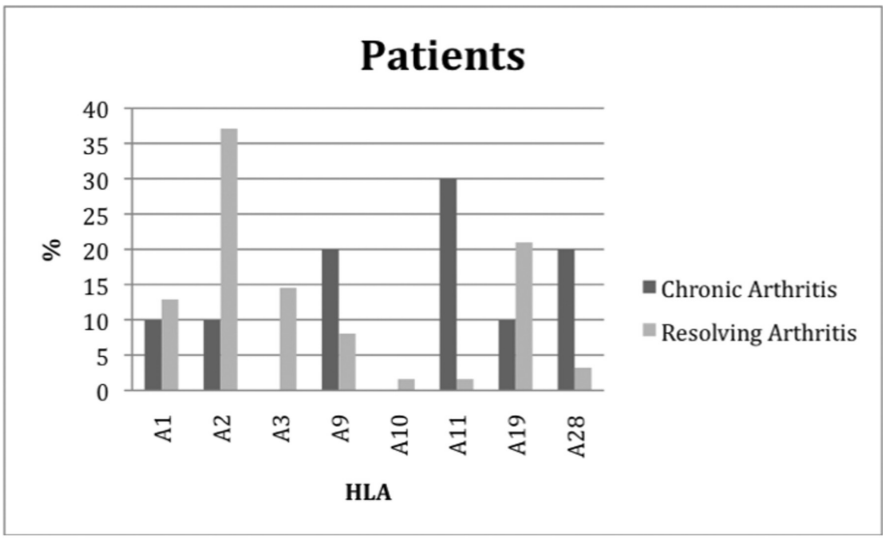

Fig. 4. HLA-A antigen frequencies among individuals with chronic sarcoid related arthritis (n=5) compared to those who had a history of time- limited or resolving arthritis (n=31).

Discussion

In the present study, we have focused on a group of individuals who suffered from sarcoidosis, which in all cases were tissue-sample verified and who also had a history of arthritides. All cases came from a nationwide cohort that was reported (13, 14). Our main findings in this study were in context with previous reports of sarcoidosis and the major histocompatibility complex in general; however, we focused solely on patients with a history of arthritis related to their sarcoidosis, while previous studies only included sarcoidosis in general and a few studies Löfgren's syndrome (8). This is the first study, to our knowledge, on the present issue in this patient group of sarcoid arthritis.

The HLA-B7 and HLA-B8 antigens have been consistently reported to be associated with sarcoidosis (1). Furthermore, HLA-B8 has also been associated with sarcoidosis of acute onset and short duration in a number of studies across racial boundaries (15-20). These two antigens, *i.e*. HLA-B7 and HLA-B8, seem to have an independent association with sarcoidosis without connection to the MHC class II genes, *i.e*. HLA- DRB1 (20). In our group of patients with sarcoid arthritis we confirmed the findings of increased prevalence of the HLA-B8 antigen, but we did not find significantly increased frequencies of HLA-B7. On the contrary, our patient group had increased frequencies of the HLA-B14 antigen, which has been reported to be associated with both persistent sarcoidosis in Scandinavians (21) and pulmonary tuberculosis (22). However, none of our patients had a history of tuberculosis, while all of our patients had tissue-verified sarcoidosis.

As previously mentioned, the HLA-B7 antigen has been reported to be associated with persistent sarcoidosis (20). Five of our patients developed a chronic arthritis condition, *i.e*. they suffered from their arthritis for more than six months. This subgroup of patients did not have a higher frequency of the HLA-B7 antigen, but instead they had a significantly increased frequency of the HLA-A11 antigen.

Our findings of increased frequencies of DRB1*03 in our patient group with sarcoid arthritis are also consistent with other reports of the association between the haplotype HLA-DRB1*03/DQB1*02 with Löfgren's syndrome (23, 24). The association between DRB1*03 has also been shown to be associated with a good prognosis in patients diagnosed with Löfgren's syndrome (23) and has been linked to acute sarcoidosis with a short duration of illness (24). However, we did not find that association in our study. Furthermore, the finding of low frequencies of DRB1*04 is also consistent with other reports and suggests that this haplotype may be a protective marker for sarcoidosis in Scandinavia, Central Europe and Asia (21, 25-27).

The present and previous studies on the HLA system strongly support the conclusion that genetic factors play a significant role in the risk of developing both sarcoidosis and sarcoid arthritis, but also that it may have an important influence on the course of the disease. In our previous study of sarcoid arthritis (14) only one patient reported that he had a first degree relative with sarcoid arthritis, while one third of our patient population had a family member with a history of some autoimmune disorder. However, a twin study in Scandinavian demonstrated an 80-fold increased risk of developing sarcoidosis in monozygotic twins, while the risk was further increased in dizygotic twins up to seven-fold (28).

Since no disease specific autoantibodies have been described for sarcoidosis, as in many other systemic inflammatory and auto-immune disorders, further studies of a possible antigen or antigens that may interphase with the HLA-system, *e.g*. HLA-DR1*03, are highly of interest. Especially, as Sarcoidosis is frequently found on the differential diagnostic list when clinicians are evaluating complex cases (29, 30).

The present study was based on a nationwide cohort on a subgroup of patients with sarcoid arthritis based on both tissue-verified diagnosis of sarcoidosis and re-evaluation of their arthritis problems by the researchers. Thus, our study population was rather homogeneous compared to previous studies on this issue which included in general all patients with sarcoidosis or subgroups such as Löfgren's syndrome. Furthermore, all patients in the present study were of Icelandic Caucasian heritage. However, although our study covered more than two decades, it only included 36 patients with sarcoid arthritis, which results in various limitations in respect to analysis and conclusions. In the future it would be of interest to collect all known cases in Iceland with clinical signs of sarcoid arthritis or Löfgren's syndrome, irrespective of whether the diagnostic criteria were based on tissue samples or only on clinical grounds, as mentioned above, and run a similar analysis of the HLA classes to elucidate whether those who develop an arthritis condition associated with their sarcoidosis have differences in their HLA antigens compared to those who suffer from limited pulmonary disease.

In conclusion, our study of patients with sarcoid arthritis from a nation-wide patient cohort with tissue-verified sarcoidosis has confirmed previous reports on the association of several HLA classes with sarcoidosis, such as HLA-A8, HLA-A14 and HLA-DRB1*03, while some alleles may be protective for the disease, *e.g*. HLA-DRB1*04. Furthermore, other alleles may influence the course of the disease, *e.g*. HLA-A11. Further studies are needed on this issue of the association of HLA classes and sarcoid arthritis before it can be recommended that the classification of the major histocompatibility complex in patients suffering from sarcoid arthritis may have clinical implications in daily clinical praxis.

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