Association of *HLA-DRB1* shared epitope alleles and immune checkpoint inhibitor-induced inflammatory arthritis

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Funding: This work was supported by the National Institute of Arthritis, Musculoskeletal and Skin Disorders (P30-AR070254, K23-AR061439), Jerome L. Greene Foundation, the Passano Foundation, the Camille Julia Morgan Arthritis Research and Education Fund, The Scherr Family Foundation and Joanne and Adam Rogers, and an investigator-initiated study funded by Bristol-Myers Squibb.

Financial interests of authors: LCC has received research funding from Bristol-Myers Squibb. COB has received research funding from and served as a consultant for Bristol-Myers Squibb. AAS has served as a consultant for Bristol-Myers Squibb.

Abstract

Objective: To evaluate the frequency of HLA class I and II alleles associated with traditional forms of inflammatory arthritis (IA) in patients with immune checkpoint inhibitor (ICI) induced IA as compared to population controls.

Methods: High-resolution HLA typing was performed on 27 patients with ICI-induced IA and 726 healthy controls. Genotyping at the shared epitope (SE) locus (HLA DRB1) was performed on 220 rheumatoid arthritis (RA) cases. Allele-positivity rates and frequency of having at least one SE allele were compared using Fisher's exact test between ICI-induced IA and healthy controls. Frequency of having at least one SE allele was also compared between ICI-induced IA and RA cases.

Results: Twenty-six patients with ICI-induced IA were of European descent, and one was African American. In those 26 patients, 16 (61.5%) had at least one SE allele, significantly different from healthy controls of European descent, in whom 299 (41.2%) had at least one SE allele (OR 2.3, p=0.04). The allele-positivity rate of DRB1*04:05 was also higher in the ICI-induced IA group. The ICI-induced IA population and RA patients of European descent did not differ in frequency of having at least one SE allele, but ICI-induced IA patients were more likely to be autoantibody-negative for rheumatoid factor and anti-cyclic citrullinated peptide antibodies.

Conclusion: Patients with ICI-induced IA of European descent were more likely to have at least one SE allele than healthy controls. Further studies are needed to validate these findings and investigate whether a unique immunogenetic framework increases risk for different immune related adverse events.

Introduction

Class I and II human leukocyte antigen (HLA) alleles are important genetic risk factors for a variety of autoimmune diseases[1]. Associations with particular HLA alleles have informed models of pathogenesis for autoimmunity, such as in RA, where increased presentation of citrullinated antigens by HLA class II shared epitope (SE) is hypothesized as relevant to underlying immune biology[2].

Immune-related adverse events (irAEs) from immune checkpoint inhibitor (ICI) therapy can be considered novel immune mediated diseases. ICIs, used in the treatment of a variety of malignancies, block negative costimulatory molecules, leading to increased immune activation[3]. As a result of activation of T cells and downstream effects, a variety of inflammatory syndromes known as irAEs can occur. Rheumatic irAEs include inflammatory arthritis (IA), sicca syndrome, vasculitis, myositis, and scleroderma[4 5]. IA appears to be the most common rheumatic irAE, with prevalence estimates of 5% or higher[6].

Although IA is a fairly common side effect of ICI therapy, the majority of treated patients do not develop this adverse event. Also, a wide range of tumor types in patients with ICI-induced IA have been reported[7]. This raises the intriguing hypothesis that a predisposing genetic factor may influence which patients develop IA due to ICI treatment.

ICI-induced IA shares some important similarities to classic forms of inflammatory arthritis. Patients can have small joint polyarthritis, similar to rheumatoid arthritis (RA), and can have early erosive disease[8]. There are key differences, however, that suggest a separate immune pathogenesis from RA. First, patients are not predominantly female. Second, most patients lack traditional autoantibodies, rheumatoid factor (RF) and anti-cyclic citrullinated peptides (CCP).

Additionally, patients may have features more consistent with spondyloarthritis such as enthesitis, reactive arthritis with conjunctivitis and urethritis, or inflammatory back pain[7].

In this pilot study, we aimed to evaluate whether class I and II HLA alleles that are associated with classic forms of inflammatory arthritis were more prevalent in patients with ICI-induced IA when compared to healthy population controls. We also explored other potential HLA associations with complete high-resolution typing of the HLA-A, -B, -C, -DRB1 and -DQB1 loci.

Patients and Methods

Inclusion and exclusion criteria:

Patients over the age of 18 with rheumatologist-confirmed ICI-induced IA were included in the study if they had a DNA sample available for analysis. Patients with preexisting systemic autoimmune disease before ICI treatment were excluded.

Healthy controls were identified from potential bone marrow donors of European descent who had high resolution HLA typing performed at our institution.

Patients with physician-diagnosed RA (also of European descent) were drawn from a longitudinal cohort of patients followed for research at our institution and were included if they had a DNA sample available for analysis.

Demographic and clinical data:

Information on demographics, oncologic history, ICI treatment, and autoantibodies is collected as a part of an ongoing prospective cohort study of patients with ICI-induced IA. This study was

approved by the Johns Hopkins Institutional Review Board (IRB # 00035182) and patients signed informed consent in order to participate.

HLA typing:

High resolution HLA typing was performed at the CLIA-certified Immunogenetics Laboratory at John Hopkins University by NGS using the TruSight HLA Sequencing Panel and the MiSeq System (illumina®, San Diego, CA). HLA types were assigned using the Assign TruSight HLA Analysis software. HLA- DRB1*01:01, 01:02, 04:01, 04:04, 04:05, 04:08, 10:01, 14:02 were designated as SE alleles[9 10].

Statistical analysis:

The frequency of having at least one SE allele was compared between the ICI-induced IA group and healthy controls and between the ICI induced IA group and RA cases. The statistical assessment was made on Stata v.14 (StataCorp LLC, College Station, TX, USA) using Fisher's exact test. P-values, odds ratios (OR) and 95% confidence intervals (CI) were also obtained. At each of the HLA-A, -B, -C, -DRB1 and -DQB1 loci, allele-positivity rates for the four-digit HLA alleles were also compared between cases and controls. Only the top 25 most frequent alleles at each locus were compared, and the rest were grouped together for analysis. Given the exploratory nature of this study, no adjustment for multiple comparison was applied.

Results

Demographics, oncologic history, and clinical features of ICI-induced IA: Twenty-seven patients with ICI-induced IA were included. The average age was 60.2 (SD 12.1) years, and 12 patients (44.4%) were female. Melanoma was the most common tumor type (N=9), followed by non-small cell lung cancer (N=6). Other tumor types were renal cell carcinoma, basal cell carcinoma,

squamous cell carcinoma, Merkel cell carcinoma, colon cancer, endometrial cancer, esophageal cancer, breast cancer, and mycosis fungoides (Supplementary Table 1). Twenty-six patients were of self-identified European descent, and one was African-American. Nine patients were treated with anti-PD-1/CTLA-4 combination therapy, and 18 patients were treated with anti-PD-1 or PD-L1 monotherapy (with or without an investigational agent, e.g. anti-CD73, anti-LAG3). Most patients lacked autoantibodies traditionally seen in RA; two were positive for RF (7.4%) and two were positive for anti-CCP antibodies (7.4%).

HLA allele frequencies compared to population controls: For this analysis, only the 26 patients of European descent were included. First, SE alleles were grouped together and the probability of having at least one SE allele was compared. In ICI-induced IA, 16 (61.5%) had at least one SE allele, while 299 (41.2%) of the population control group had at least one SE allele (OR 2.3, p=0.04). Next, class I and II alleles known to be associated with traditional forms of IA (i.e. RA, psoriatic arthritis, ankylosing spondylitis) were evaluated. These included the DRB1 SE alleles (analyzed individually), B*08:01, B*15:01, B*27:05, C*06:02, and DRB1*03:01[11-13]. When individual alleles were examined for associations, some showed frequency deviations in cases with ICI-induced IA (Table 1). HLA DRB1*04:05 was enriched in the ICI-induced IA population (OR 8.6, p=0.04). Also included in Table 2 are associations for other individual HLA alleles not increased in traditional forms of IA, but with p-values approaching statistical significance (Table 1). There were trends toward higher prevalence of HLA A*03:01 (OR 2.2, p= 0.07), HLA B*52:01(OR 5.0, p=0.08) and HLA C*12:02 (OR 5.2, p=0.07) in ICI-induced IA. Patients with ICI-induced IA had a trend toward lower prevalence of DQB1*03:01 (OR 0.4, p= 0.06).

Within the group of ICI-induced IA patients, we evaluated whether clinical characteristics differed between patients with and without SE allele. Interestingly, some clinical features were only seen in patients lacking SE alleles. Specifically, inflammatory back pain, trigger fingers, prominent enthesitis and the case of reactive arthritis were seen in patients without SE alleles. None of these features were seen in the SE positive group. Small joint involvement including the small joints of hands and wrists, typically thought of as RA-like, was seen in those with and without SE alleles.

Comparison of ICI-induced IA to RA population: The probability of having at least one SE allele did not differ between patients of European descent with ICI-induced IA and RA patients of European descent (Table 2). There was a trend toward the RA patients being more likely to be homozygous for SE alleles, with 23.6% of RA cases being homozygous versus just 7.7% of ICI-induced IA (p=0.15). There were significant differences in RF and anti-CCP positivity (Table 2). There were no patients with ICI-induced IA who were positive for both RF and anti-CCP antibodies, as compared to the RA population, where 49.3% were double positive.

Discussion

In this study of high-resolution HLA typing in ICI-induced IA, patients of European descent were more likely to be positive for SE alleles than population controls. There were also suggestions of other HLA allelic associations with ICI-induced IA. There was not a significant difference in prevalence of SE between patients with ICI-induced IA and those with RA of European descent. As previously shown, patients with ICI-induced IA were unlikely to have RF or anti-CCP antibodies[7 14 15], and this was significantly different from the RA comparator population.

This is one of the first studies to evaluate immunogenetics in patients who develop an irAE due to ICI therapy. A smaller study of acute onset type 1 diabetes due to anti-PD-1 therapy showed four out of five patients had HLA subgroups DRB01* 03 or 04, which are associated with type 1 diabetes risk in the general population[16]. Another study of patients with metastatic melanoma treated with ipilimumab suggests that having CTLA-4 gene variant 1661A>G may predispose patients to developing endocrine irAEs[17]. These data evaluated with the present study suggest that a patient's immunogenetic framework may increase the risk for developing irAEs like IA due to ICI therapy. This pilot study is hypothesis-generating for future genetic studies in irAEs. That SE appears to be enriched in this population was a surprising finding, given this population is mostly anti-CCP negative. Two patients with RA-like ICI-induced IA have been previously reported to have HLA-DRB1*01:01, one of whom was positive for anti-CCP[18]. While seronegative RA has been found to be associated with SE[19], potential mechanisms underlying this are less clear. The trends observed toward higher prevalence of several class I alleles are also intriguing given associations of various class I alleles with ankylosing spondylitis, peripheral spondyloarthritis, and psoriatic arthritis. Certain clinical features in subsets of patients with ICI-induced IA such as enthesitis, reactive arthritis-like presentation, and inflammatory back pain are seen in spondyloarthritis. Interestingly, there was no association with HLA B27, the allele most strongly associated with ankylosing spondylitis. This may suggest more similarity with peripheral spondyloarthritis or psoriatic arthritis in pathogenesis, rather than ankylosing spondylitis.

Our study also found that HLA B*52:01 and C*12:02 may be associated with ICI-induced IA. Interestingly in the Japanese population, the HLA-B*52:01-C*12:02 haplotype has been associated with ulcerative colitis and Takayasu's arteritis[20] and HLA-C*12:02 has been

associated with late-onset psoriasis[21], suggesting potential relevance of these alleles to the development of autoimmune disease.

With increasing evidence that tumor response to ICIs is improved in patients who develop irAEs[22-24], there may be shared genetic associations between response and toxicity. HLA typing and response to ICIs was recently evaluated in a large study of patients with melanoma and non-small cell lung cancer; both patient and tumor HLA class I genotypes influenced tumor response to ICI therapy[25]. Specifically, patients with the HLA-B44 supertype had extended survival, while HLA-B62 supertype was associated with worse outcomes. Further genetic investigations could evaluate tumor response and irAE development concurrently.

The study was limited primarily by sample size, which was due to the naturally rare occurrence of ICI-induced IA at a single institution. As a result, smaller effect sizes were unlikely to be detected. Also, the cases of ICI-induced IA were not entirely clinically homogenous, which could lower the statistical power of detecting an association. When a larger sample is available, it may be useful to look at groups by pattern of joint involvement or other clinical features to see if differing associations exist by subgroup (e.g. whether those with enthesitis have differing HLA associations from those with small joint polyarthritis or whether those with multiple irAEs have differing HLA associations versus patients with ICI-induced IA alone). It will also be informative to study HLA associations in a broader group of ICI-treated patients to define whether these alleles are risk factors for ICI-induced IA or other types of irAEs.

In summary, we observed a potential risk association between the presence of SE alleles and ICI-induced IA in this pilot study of high-resolution HLA typing. Larger studies are needed to confirm this association and to examine whether distinct HLA alleles associate with unique phenotypes of ICI induced IA.

Key words

inflammatory arthritis, cancer immunotherapy, immune checkpoint inhibitors, immunogenetics

Key messages

- Shared epitope alleles were more common in immune checkpoint inhibitor-induced inflammatory arthritis than in population controls

- The immune checkpoint inhibitor-induced inflammatory arthritis population did not differ from RA patients in frequency of having at least one shared epitope allele

- A patient’s immunogenetic framework may influence the development of immune related adverse events

Table 1: Comparison of allele-positivity rates for select HLA class I and II alleles and prevalence of having at least one SE allele in ICI-induced IA vs population controls of European descent

HLA allele/s	Odds ratio (95% CI) ICI-induced IA vs. controls	p-value*
A*03:01	2.2 (0.9, 5.1)	0.07
B*08:01	0.9 (0.3, 2.6)	0.56
B*15:01	2.2 (0.7, 5.9)	0.12
B*27:05	0.6 (0.0, 4.0)	1.00
B*52:01	5.0 (0.5, 24.1)	0.08
C*06:02	0.9 (0.3, 2.7)	1.00
C*12:02	5.4 (0.6, 26.8)	0.07
DQB1*03:01	0.4 (0.1, 1.1)	0.06
DRB1*03:01	1.1 (0.4, 2.9)	0.81
DRB1*04:05	8.6 (1.7, 43.4)	**0.04**
At least 1 SE allele	2.3 (1.0, 5.1)	**0.04**
*p-values < 0.05 significant (bold)		

Table 2: Shared epitope in European descent subset of ICI-induced IA compared to ethnically matched RA controls

	ICI-induced IA N= 26	RA N= 220	p-value*
Positive for SE (at least 1 allele)	16 (61.5%)	145 (65.9%)	0.66
Number of shared epitope alleles	Two alleles: 2 (7.7%) One allele: 14 (53.8%) Zero allele: 10 (38.5%)	Two alleles: 52 (23.6%) One allele: 93 (42.3%) Zero allele: 75 (34.0%)	0.15
CCP positive	2 (7.7%)	142 (64.6%)	**<0.01**
RF positive	2 (7.7%)	122/215 (56.7%)	**<0.01**
RF and CCP double positive	0 (0%)	106/215 (49.3%)	**<0.01**
*Fisher's exact test. CCP: anti-cyclic citrullinated peptide antibodies; RF: rheumatoid factor.			

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Supplementary Table 1: Demographic and Clinical Features of Patients with ICI-induced IA

Patient	Sex	Age	Tumor type	ICI Regimen	Autoantibodies	SE Present	# SE Alleles	Clinical features of IA
1	Female	45	Melanoma	PD-1/CTLA-4	None	Yes	1	Initial knee pain and swelling; additive course with wrists, fingers, shoulders, elbows
2	Male	35	Melanoma	PD-1/CTLA-4	None	No	0	Reactive arthritis: urethritis, conjunctivitis, knee and ankle swelling
3	Female	55	Endometrial cancer	PD-1, anti-CD73	None	No	0	Wrist, shoulders, fingers involved. Significant tenosynovitis on US.
4	Female	53	Melanoma	PD-1/CTLA-4	None	No	0	Knees and shoulders initially, then PIPs
5	Male	59	Basal cell	PD-1/CTLA-4	None	Yes	1	Wrists, ankles, MCPs, PIPs
6	Male	59	NSCLC	PD-1	None	No	0	Elbows, shoulders, PIPs, MCPs
7	Female	73	Mycosis Fungoides	PD-1	Low + CCP	Yes	1	Knees, then PIPs, MCPs, and wrists
8	Male	59	Melanoma	PD-1/CTLA-4	None	Yes	1	Swelling and pain in shoulder (unilateral), found to have resorptive bone lesion; then mild arthritis in MCPs, PIPs
9	Male	82	Merkel cell	PD-1	High + RF	Yes	1	Swelling in wrist first, then pain and stiffness in shoulders and hips
10	Female	59	NSCLC	PD-1	ANA 1:80 speckled	No	0	Knees and ankles
11	Male	54	NSCLC	PD-1	None	No	0	Trigger fingers, inflammatory back pain, elbow involvement
12	Female	45	Breast cancer	PD-1	None	Yes	1	Swelling in one knee, then shoulders, MCPs, PIPs
13	Male	58	RCC	PD-1/CTLA-4	None	Yes	1	Ankle first involved (erosion on MRI), PIPs, elbows
14	Male	81	NSCLC	PD-1	None	Yes	2	Shoulders and hips, followed by wrists, MCPs
15	Male	40	Melanoma	PD-1/CTLA-4	Anti-smooth muscle	Yes	1	MCPs, PIPS, MTPs, then plantar fasciitis and elbow involvement
16	Female	68	Basal cell	PD-1	None	Yes	2	Wrists, ankles, PIPs and MCPs
17	Male	68	Esophageal	PD-1	Moderate + RF	Yes	1	MCPs, PIPs, wrists, knees

18	Female	54	Melanoma	PD-1/CTLA-4	None	No	0	Knees, ankles, wrist. Trigger fingers.
19	Male	58	Squamous cell	PD-1	Anti-beta-2 glycoprotein/ cardiolipin IgM	Yes	1	Shoulders, PIPs, wrists
20	Male	86	Melanoma	PD-1	None	Yes	1	PIPs, MCPs, then shoulders
21	Male	64	Melanoma	PD-1	Anti-beta-2-glycoprotein IgM	Yes	1	Shoulders, knees, PIPs
22	Male	57	NSCLC	PD-1	None	No	0	Ankles, wrists, dactylitis of index finger
23	Female	60	RCC	PD-1, then PD-1 + anti-LAG-3	None	Yes	1	Wrists, MCPs, knees
24	Female	65	Pancreatic cancer	PD-1	Moderate + CCP	Yes	1	Shoulders, MCPs, PIPs, wrists
25*	Female	70	NSCLC	PD-1	None	No	0	Knees, then PIPs, MCPs
26	Female	67	Colon cancer	PD-1	None	No	0	PIPs first, then knees, elbows, hips
27	Male	51	Melanoma	PD-1/CTLA-4	None	No	0	PIPs, MCPs, Achilles enthesitis, wrists, knees, ankles

SE: shared epitope; NSCLC: non-small cell lung cancer; RF: rheumatoid factor; CCP: anti-cyclic citrullinated peptide antibodies; ANA: anti-nuclear antibodies; RCC: renal cell carcinoma. *: Patient 25 was of African descent, all others of European descent. MCP: metacarpophalangeal joint. PIP: proximal interphalangeal joint. MTP: metatarsophalangeal joint.