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ORIGINAL ARTICLE

Immune checkpoint inhibitor-induced inflammatory arthritis: a novel clinical entity with striking similarities to seronegative rheumatoid arthritis

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Abstract

Objective To determine the clinical and serologic similarities and differences between inflammatory arthritis induced by immune checkpoint inhibitors (IA-irAE) and rheumatoid arthritis (RA).

Methods In this retrospective cross-sectional comparative study, 20 patients with IA-irAE were age and sex matched to 40 seropositive and 40 seronegative RA patients. Electronic medical records were reviewed from diagnosis of inflammatory arthritis through May 2019. Arthritis characteristics, treatment, and relevant laboratory and serologic studies were captured.

Results Clinically, IA-irAE differed from seropositive and seronegative RA with respect to disease duration (4.18 versus 11.59 and 13.3 months, respectively, $p = 0.005$ (IA-irAE vs seropositive RA), $p = 0.002$ (IA-irAE vs seronegative RA)), polyarticular joint involvement at presentation (75% versus 97.5% and 100%, $p = 0.013$, $p = 0.003$), absence of erosive changes (5.9% vs 43.6% and 53.8%, $p = 0.005$, $p = 0.001$), mean prednisone dose (24.7 mg versus 16.53 mg and 15.68 mg, $p = 0.008$, $p = 0.005$), and use of methotrexate (5.0% versus 85.0% and 70.0%, $p < 0.0001$, $p < 0.0001$). Serologically, IA-irAE closely resembled seronegative RA. ANA positivity was seen in a minority of patients and did not differ significantly between all groups; however, the ANA staining pattern (speckled) was similar between IA-irAE and seronegative RA (100% versus 75%, respectively) and was not commonly observed in seropositive RA (18.2%).

Conclusion IA-irAE is a new subset of IA that resembles seronegative RA immunologically. Our findings suggest that further study of IA-irAE might provide a window into underlying pathogenic mechanisms of early-stage seronegative RA.

Key Points

- *Comprehensive comparison of clinical features between inflammatory arthritis irAE (IA-irAE) and regular rheumatoid arthritis indicates IA-irAE as a new subset of inflammatory arthritis.*
- *IA-irAE resembles seronegative RA immunologically, suggesting that study of IA-irAE may provide a window into underlying pathogenic mechanisms of early-stage seronegative RA.*

Keywords Immune checkpoint inhibitor · Inflammatory arthritis · Immune-related adverse events · Rheumatoid arthritis

Introduction

The introduction of immune checkpoint inhibitors (ICIs) dramatically improved the morbidity and mortality rates for various cancer types. There are currently seven FDA-approved monoclonal antibodies that target either CTLA-4, programmed death 1 (PD-1), or its ligand PD-L1. These immune checkpoints normally function to down-regulate T cell activation and function. By blocking these co-inhibitory pathways of T cells, ICIs promote T cell-mediated antitumor immunity but may lead to a break in self-tolerance [1], manifesting as systemic or organ-specific autoimmunity. These adverse

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events, mediated by activation of the immune response, are termed immune-related adverse events (irAEs). The most commonly involved organs in irAEs are the gastrointestinal tract, endocrine glands, and skin [2].

Rheumatologic irAEs (Rh-irAE) are less common, but are being increasingly recognized by oncologists and rheumatologists alike because of the rapid expansion in the use of ICIs and their potential for profound negative impact on patients' quality of life. Inflammatory arthritis irAE (IA-irAE) is the most common Rh-irAE and has the potential to become a chronic disease persisting even after ICI cessation [3]. To date, three subtypes of IA-irAE have been described according to their arthritis pattern: a subtype of polyarticular arthritis similar to RA, a subtype similar to the spondyloarthopathies (characterized by axial joint involvement and inflammatory back pain), and reactive arthritis (conjunctivitis, urethritis and oligoarthritis) [4]. The most common pattern among IA-irAE is polyarticular arthritis [5, 6]. To date, most studies on IA-irAE are descriptive and retrospective. Several outstanding questions remain to be explored. Specifically, can our experiences in treating rheumatoid arthritis apply to IA-irAE? Is IA-irAE a distinct subset of rheumatoid arthritis? More importantly, as IA-irAE is presumably triggered by a defined event (the administration of ICI), could the study of similarities and differences between IA-irAE and RA provide us fresh insight into the elusive etiology underlying rheumatoid arthritis?

The aim of this study is to identify the similarities and differences between IA-irAE and seronegative and seropositive rheumatoid arthritis. We compared the clinical characteristics of IA-irAE patients with polyarticular arthritis to age- and sex-matched patients with seronegative and seropositive RA, to explore any phenotypic links between IA-irAE and RA.

Patients and methods

Study subjects and ethics statement This is a retrospective, cross-sectional comparative study. Institutional review board approval was obtained prior to initiation of the study (IRB number PR12-007618-07). All data were gathered retrospectively. Twenty cancer patients with de novo inflammatory arthritis of the peripheral joints after the initiation of ICI therapy (ipilimumab, nivolumab, pembrolizumab, or combination) in Mayo Clinic in Rochester were included in this study. Cases of IA-irAE were identified based on the clinical diagnosis of a managing rheumatologist (19/20 patients) or oncologist (1/20 patients). Inflammatory arthritis was clinically defined as the presence of at least one characteristic feature of synovitis (joint swelling, warmth, erythema, or morning stiffness lasting > 1 h). Oligoarthritis was defined as less than or equal to four affected joints, and polyarthritis as > 4 affected joints. IA-irAE patients were excluded if they had any history of preexisting inflammatory arthritis or other rheumatic diseases (e.g., systemic lupus erythematosus, Sjögren's syndrome, scleroderma, myositis, vasculitis, or gout). RA patients with a new or recent diagnosis (made within 1 year of referral to Mayo Clinic in Rochester, Minnesota) and seen in the Division of Rheumatology at Mayo Clinic in Rochester after January 1, 2010, were identified for comparison. All RA patients fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria [7]. RA patients with diagnosis of cancer, infection, other co-existing or concomitant rheumatic diseases, and those on biologic therapies were excluded. Forty seropositive (RF and/or ACPA positive) RA patients and 40 seronegative RA patients were identified. These RA patients were age and sex-matched to the IA-irAE patients in a 2:1 ratio.

Variables extracted Clinical data including patient demographics, arthritis characteristics, laboratory findings, and treatment during their first encounter in rheumatology were extracted for analysis. Demographic information included age, gender, BMI, family history of rheumatic disease, and smoking history. Clinical characteristics related to arthritis included disease duration (the time from patient-reported initial presence of joint symptom to first established IA diagnosis), morning stiffness, joint first involved, arthritis pattern, and presence of erosive changes documented by radiology report (with most common modality being X-ray). Lab findings included serologic testing (i.e., RF, anti-cyclic citrullinated peptide/anti-CCP, antinuclear antibodies/ANA, anti-extractable nuclear antigen antibodies/ENA, HLA-B27, sedimentation rate, and c-reactive protein), complete blood count, liver enzymes (i.e., alanine aminotransferase, aspartate aminotransferase), renal function (i.e., creatinine), creatine kinase, alkaline phosphatase, and uric acid. For lab findings reported as less than the lowest limit of detection, the values of lowest limit were used for analysis. Medication use including glucocorticoids (GC) and disease-modifying antirheumatic drugs (DMARDs) by the treating rheumatologist at the first encounter were abstracted.

Statistical analysis For comparisons of the binary data, Chi-squared test or Fisher exact test (when at least one cell had expected count of less than 5) was used. For comparisons of the continuous data, Mann-Whitney *U* test (rank-sum test) was used. A $p < 0.05$ was considered significant. Continuous data are expressed as mean (standard deviation), and categorical data are expressed as positive number/test number (%). All statistical calculations were done using SPSS25.0 software.

Results

Characteristics of IA-irAE patients The clinical characteristics of 20 IA-irAE patients are summarized in Table 1. All patients

presented with peripheral arthritis. The most common arthritis pattern was polyarthritis (75%), either with involvement of both small and large joints (55%) or large joint predominant (20%). No obvious gender predominance was found in these patients. The most common malignancy was metastatic melanoma (12/20, 60%), other types of cancer included lung adenocarcinoma (5/20, 25%), gastric adenocarcinoma (1/20, 5%), colon cancer (1/20, 5%), and angioimmunoblastic T cell lymphoma (1/20, 5%). No obvious association was found between malignancy type and arthritis pattern. At the time of chart review, the cancer status was stable or in remission in the majority of patients (16/20, 80%). In 13 patients, IA-irAE was induced by anti-PD-1 monotherapy (pembrolizumab or nivolumab), one patient by anti-CTLA4 (ipilimumab) monotherapy, and 6 by combination anti-PD-1 and anti-CTLA4. There were no statistically significant differences in clinical presentation as stratified by immunotherapy type (data not shown.)

Table 1 Clinical features of patients with IA-irAE

	Value
Characteristics	
Patients	20
Age, mean (SD)	65.85 (9.73)
Gender, male/female	11/9 (55%/45%)
ICI type	
Pembrolizumab (anti-PD-1)	11 (55%)
Nivolumab (anti-PD-1)	2 (10%)
Ipilimumab (anti-CTLA-4)	1 (5%)
Ipilimumab and nivolumab	3 (15%)
Ipilimumab continued with pembrolizumab	3 (15%)
Malignancy	
Metastatic melanoma	12 (60%)
Lung adenocarcinoma	5 (25%)
Other cancers	3 (15%)
Cancer stable or in remission	16 (80%)
Pattern of arthritis	
Polyarticular, large joint predominant	4 (20%)
Polyarticular, small joint and large joint	11 (55%)
Oligoarticular/monoarticular	5 (25%)
Other irAEs	
Dermatitis	10 (50%)
Colitis	4 (20%)
Hepatitis	2 (10%)
Pneumonitis	2 (10%)
Hypophysitis	2 (10%)
Others	2 (10%)

Values in table are presented as mean (SD) or *n* (%)

SD standard deviation, *ICI* immune-checkpoint inhibitor, *irAE* immune-related adverse events

IA-irAE is clinically distinct from RA To discern any similarities and differences between IA-irAE and RA, each IA-irAE patient was matched with two RA patients on the following parameters: age, sex, and seropositivity (i.e., if the IA-irAE patient was seronegative, they were matched to two seronegative RA patients, and if the IA-irAE was RF positive, they were matched to two RF positive RA patients, and so on). Results are presented in Table 2. The peripheral polyarthritis predominant IA pattern of IA-irAE was very similar to RA. Compared with matched RA, IA-irAE patients had shorter disease duration before their first established IA diagnosis, less erosive changes, lower hemoglobin and lymphocytes counts, and higher levels of alkaline phosphatase. Little difference was found in immunological characteristics. Systemic glucocorticoid was used as initial therapy in the majority of patients, both IA-irAE and RA, but the mean dose of GC used in IA-irAE patients was slightly higher than in RA. DMARDs were used in three IA-irAE patients, specifically, hydroxychloroquine (HCQ) in two patients and methotrexate (MTX) in one. MTX was the most common DMARDs used in RA patients. Fifteen patients with IA-irAE had documentation regarding their response to GC. Only two responded poorly to GC. Among the 13 IA-irAE patients who initially responded well to GC, 11 had documentation regarding arthritis symptoms during prednisone taper. Of those patients, symptoms of arthritis were recurrent in eight IA-irAE patients (8/11, 72.7%) during GC tapering or stoppage.

IA-irAE patients are serologically similar to patients with seronegative RA We compared IA-irAE patients to an age- and sex-matched cohort of seropositive RA and seronegative RA in Table 3. This differs from the comparison outlined in Table 2 in that IA-irAE patients were not additionally matched based on seropositive status.

IA-irAE patients are different from both seropositive RA and seronegative RA in terms of disease duration, presence of morning stiffness, erosive changes, lymphocyte count, hemoglobin level, and treatment regimen. Serologically, IA-irAE patients were largely different from seropositive RA, but similar to seronegative RA. The frequency of positive anti-CCP and RF was significantly lower in IA-irAE compared to seropositive RA. Of the three IA-irAE patients with positive serologies, the titers of RF and anti-CCP were low (i.e., RF was 16, 17, 16 IU/mL; anti-CCP level was 48.4 U; the reference ranges are as follows: RF < 15 IU/mL and anti-CCP < 20 U). In our seropositive patients, RF and anti-CCP were found in high titers (i.e., greater than 3 times of the upper limit of normal). The low frequency and titer of RF and anti-CCP in patients with IA-irAE were similar to that seen in seronegative RA. The positivity of ANA was not significantly different among groups, but the staining pattern of positive ANA by immunonhistochemistry was different among groups. Among those four IA-irAE patients with positive ANA, all had a

Table 2 Comparison between IA-irAE and age, gender, and serologically matched RA

	IA-irAE ($n = 20$)	RA ($n = 40$)	p value
Basic characteristics			
Gender, M/F	11/9	20/20	0.715
Age, year	65.85(9.73)	65.08(8.44)	0.808
BMI, kg/m^2	29.63(7.51)	29.25(4.30)	0.764
Positive family history of rheumatic diseases	8/20(40.0%)	14/40(35.0%)	0.705
Positive smoke history	12/20(60.0%)	22/40(55.0%)	0.713
Arthritis characteristics			
Disease duration, m	4.18(3.76)	13.30(12.79)	0.001
Presence of morning stiffness	14/19(73.7%)	38/40(95.0%)	0.018
Onset with hand arthritis	6/20(30.0%)	17/38(47.4%)	0.275
Symmetric	10/17(58.8%)	26/36(72.2%)	0.329
Polyarthritis	15/20(75.0%)	40/40(100.0%)	0.001
Erosions	1/17(5.9%)	23/40(57.5%)	0.000
Immunological characteristics			
Positive RF or anti-CCP	3/18(16.7%)	6/40(15.0%)	1.000
RF positivity	3/18(16.7%)	5/40(12.5%)	0.694
Anti-CCP positivity	1/18(5.6%)	5/40(12.5%)	0.655
RF level in patients with positive RF, IU/mL	16.67(0.58)	327.6(261.45)	0.036
Anti-CCP level in patients with positive anti-CCP	48.40(−)	239.2(24.15)	0.333
ANA positivity	5/16(31.3%)	6/36(17.1%)	0.281
ANA titer in patients with positive ANA	1:300.00(247.66)	1:390.00(595.43)	0.686
ANA staining pattern, speckled	4/4(100.0%)	2/4(50.0%)	0.429
HLA-B27 positivity	0/4(0.0%)	2/16(12.5%)	1.000
Sedimentation rate, mm/h	24.25(15.91)	25.48(25.07)	0.463
C-reactive protein, mg/L	25.93(26.70)	30.63(35.21)	0.752
Complement C3, mg/dL	131.71(28.77)	124.57(20.50)	0.535
Complement C4, mg/dL	26.43(6.45)	26.29(6.40)	0.805
Lab findings			
Leukocyte, × 10^9/L	8.27(2.88)	7.52(2.10)	0.482
Neutrophils, × 10^9/L	5.77(2.85)	4.82(1.72)	0.317
Lymphocytes, × 10^9/L	1.39(0.49)	1.78(0.56)	0.016
Monocytes, × 10^9/L	0.63(0.25)	0.67(0.27)	0.565
Eosinophils, × 10^9/L	0.21(0.14)	0.19(0.20)	0.371
Basophils, × 10^9/L	0.053(0.028)	0.04(0.017)	0.102
Hemoglobin, g/dL	12.27(1.66)	13.80(1.57)	0.002
Platelet Count, × 10^9/L	283.70(122.16)	302.30(105.93)	0.189
Alanine aminotransferase, U/L	19.25(7.85)	21.94(7.76)	0.324
Aspartate aminotransferase, U/L	22.11(11.38)	22.48(4.22)	0.294
Creatinine, mg/dL	0.97(0.32)	0.98(0.21)	0.519
Alkaline phosphatase, U/L	100.92(41.48)	65.44(14.66)	0.012
Creatine kinase, U/L	90.8(63.45)	83.91(35.16)	0.775
Uric acid, mg/dL	5.37(0.72)	5.27(1.27)	0.84
Treatment			
Systemic use of GC	15/20(75.0%)	34/40(85.0%)	0.481
GC dose, mg	24.73(10.71)	16.99(7.07)	0.010
Use of MTX	1/20(5.0%)	30/40(75.0%)	0.000
Use of HCQ	2/20(10.0%)	6/40(15.0%)	0.707

Data were presented as mean (SD) or number positive/number tested (%)

SD standard deviation, *ICI* immune-checkpoint inhibitor, *IA* inflammatory arthritis, *BMI* body mass index, *RF* rheumatoid factor, *CCP* cyclic citrullinated peptide, *ANA* antinuclear antibody, *GC* glucocorticoids, *MTX* methotrexate, *HCQ* hydroxychloroquine

speckled pattern (4/4, 100.0%). In the seropositive RA group, among 11 patients with staining pattern data, 2 had a speckled pattern (2/11, 18.2%), while 9 had a homogeneous pattern. In the seronegative RA group, among four patients with data on ANA staining pattern, the majority (3/4, 75.0%) had a speckled pattern. Furthermore, the titer of ANA tended to be lower in patients with IA-irAE and seronegative IA than in seropositive RA, although the difference did not reach statistical significance. Several other autoantibodies were measured in IA-irAE patients and most were negative (anti-dsDNA, 0/10, anti-Ro, 0/12, anti-la, 0/12, anti-SM, 0/12, anti-RNP, 1/12). In all, IA-irAE patients share more features with seronegative RA patients based on the low prevalence of seropositivity (and low titer of antibodies when positive) and the prevalence and staining pattern of the ANA (speckled).

Table 3 Comparison between patients with IA-irAE and age- and sex-matched seropositive RA or seronegative RA

	IA-irAE ($n = 20$)	Seropositive RA ($n = 40$)	Seronegative RA ($n = 40$)	P_1	P_2
Basic characteristics					
Gender, M/F	11/9	15/25	20/20	0.197	0.715
Age, year	65.85(9.73)	61.93(9.45)	63.35(9.77)	0.221	0.500
BMI, kg/m^2	29.63(7.51)	28.37(5.94)	29.83(5.02)	0.747	0.621
Positive family history of rheumatic diseases	8/20(40.0%)	10/39(25.6%)	17/40(42.5%)	0.257	0.853
Positive smoke history	12/20(60.0%)	22/39(56.4%)	23/40(57.5%)	0.792	0.853
Arthritis characteristics					
Disease duration, m	4.18(3.76)	11.59(12.18)	11.13(11.07)	0.005	0.002
Presence of morning stiffness	14/19(73.7%)	37/39(94.9%)	39/40(97.5%)	0.032	0.011
Onset with hand arthritis	6/20(30.0%)	19/36(52.8%)	14/39(35.9%)	0.100	0.651
Symmetric	10/17(58.8%)	31/39(79.5%)	26/36(72.2%)	0.188	0.329
Polyarthritis	15/20(75.0%)	39/40(97.5%)	40/40(100.0%)	0.013	0.003
Erosions	1/17(5.9%)	17/39(43.6%)	21/39(53.8%)	0.005	0.001
Immunological characteristics					
Positive RF or anti-CCP	3/18(16.7%)	40/40(100.0%)	0/40(0.0%)	0.000	0.026
RF positivity	3/18(16.7%)	33/39(84.6%)	0/40(0.0%)	0.000	0.026
Anti-CCP positivity	1/18(5.6%)	33/40(82.5%)	0/40(0.0%)	0.000	0.310
RF level in patients with positive RF, IU/mL	16.67(0.58)	205.15(217.67)	–	0.001	–
Anti-CCP level in patients with positive anti-CCP	48.40(−)	216.31(64.56)	–	0.118	–
ANA positivity	5/16(31.3%)	12/33(36.4%)	6/37(16.2%)	0.724	0.275
ANA titer in patients with positive ANA	1:300.00(247.6)	1:567.27(476.5)	1:110(60)	0.343	0.200
ANA staining pattern, speckled	4/4(100.0%)	2/11(18.2%)	3/4(75.0%)	0.011	1.000
HLA-B27 positivity	0/4(0.0%)	0/4(0.0%)	2/19(10.5%)	–	1.000
Sedimentation rate, mm/h	24.25(15.91)	19.72(14.72)	24.66(24.96)	0.367	0.365
C-reactive protein, mg/L	25.93(26.70)	17.99(21.90)	27.93(35.37)	0.203	0.913
Complement C3, mg/dL	131.71(28.77)	133(−)	126.25(19.56)	0.750	0.694
Complement C4, mg/dL	26.43(6.45)	23(−)	27.25(6.52)	0.500	0.613
Lab findings					
Leukocyte, × 109/L	8.27(2.88)	7.14(2.12)	7.43(2.01)	0.203	0.404
Neutrophils, × 109/L	5.77(2.85)	4.55(1.70)	4.83(1.62)	0.153	0.316
Lymphocytes, × 109/L	1.39(0.49)	1.90(0.65)	1.72(0.53)	0.005	0.031
Monocytes, ×1 09/L	0.63(0.25)	0.63(0.22)	0.64(0.26)	0.808	0.762
Eosinophils, × 109/L	0.21(0.14)	0.15(0.12)	0.18(0.21)	0.052	0.166
Basophils, × 109/L	0.053(0.028)	0.043(0.024)	0.040(0.016)	0.114	0.091
Hemoglobin, g/dL	12.27(1.66)	13.59(1.43)	13.92(1.57)	0.006	0.001
Platelet count, × 109/L	283.70(122.16)	284.24(74.13)	301.68(104.58)	0.390	0.214
Alanine aminotransferase, U/L	19.25(7.85)	21.32(8.12)	22.6(10.19)	0.423	0.373
Aspartate aminotransferase, U/L	22.11(11.38)	20.79 (6.08)	23.55(6.12)	0.776	0.201
Creatinine, mg/dL	0.97(0.32)	0.85(0.18)	1.00 (0.20)	0.161	0.357
Alkaline phosphatase, U/L	100.92(41.48)	82.85(22.95)	65.44(14.66)	0.270	0.012
Creatine kinase, U/L	90.8(63.45)	37.72(43.50)	83.4(28.52)	0.222	0.612
Uric acid, mg/dL	5.37(0.72)	5.49(1.63)	5.23(1.32)	1.000	0.769
Treatment					
Systemic GC use	15/20(75.0%)	29/40(72.5%)	33/40(82.5%)	0.836	0.511
GC dose, mg	24.73(10.71)	16.53 (7.86)	15.68(7.79)	0.008	0.005
Use of MTX	1/20(5.0%)	34/40(85.0%)	28/40(70.0%)	0.000	0.000
Use of HCQ	2/20(10.0%)	5/40(12.5%)	8/40(20.0%)	1.000	0.471

Data were presented as mean (SD) or number positive/number tested (%)

SD standard deviation, *ICI* immune-checkpoint inhibitor, *IA* inflammatory arthritis, *BMI* body mass index, *RF* rheumatoid factor, *CCP* cyclic citrullinated peptide, *ANA* antinuclear antibody, *GC* glucocorticoids, *MTX* methotrexate, *HCQ* hydroxychloroquine, P_1 *p* value of the comparison between IA-irAE and seropositive RA, P_2 *p* value of the comparison between IA-irAE and seronegative RA

Discussion

This study provides a preliminary description of the similarities and differences between IA-irAE and RA. Based our study, we found that IA-irAE resembles seronegative RA in certain immunological characteristics. This interesting observation could suggest a shared underlying mechanism. For example, one could hypothesize, based on these findings, that IA-irAE is a disease process more likely dependent on autoreactive T cells rather than B cell-based autoantibody production. More detailed immunological study of IA-irAE patients with regards to the degree of immunoglobulin complex formation and complement fixation, among others, compared to RA, are lacking and are important next steps.

In our study, the most commonly utilized ICIs were the anti-PD-1 agents (i.e., pembrolizumab or nivolumab).

Similarly, in previous studies, these agents were the most commonly associated with IA-irAE [8, 9]. While this may simply relate to the more widespread use of anti-PD-1 agents clinically, it may also suggest an important role of PD-1 in IA pathogenesis. A role for PD-1 in inflammatory arthritis has been suggested from animal studies and RA patients alike. However, the link between PD-1 polymorphism and inflammatory arthritis was not consistently observed and it remains controversial how PD-1 signaling contributes to humoral immunity and systemic inflammatory autoimmune diseases [10]. Consistent with other studies, IA-irAE patients' cancers responded favorably to ICI treatment, suggesting that rheumatic autoimmunity aids anti-tumor immune response through undefined mechanisms [6, 8].

Some clinical manifestations of IA-irAE distinguish it from RA, such as disease duration, presence of morning stiffness, and lack of erosive changes. Cappelli et al. reported that erosive changes were presented in two of four IA-irAE patients with imaging data (determined by ultrasound), as early as their first evaluation by rheumatologist, indicating that early erosive changes might develop in patients with IA-irAE [9]. In contrast, in our study, only one patient presented with erosive changes in the hands, confirmed by X-ray. Given the cross-sectional nature of our study, the prevalence of erosive disease could have been underestimated given the lack of long-term follow-up data and the absence of advanced joint imaging for the majority of patients at initial diagnosis. The disease duration is relatively short in IA-irAE patients, likely due to the close monitoring of adverse events in ICI-treated patients and quick referral to rheumatologists in our dedicated referral program. A recent study by Braaten et al. demonstrated that ICI-induced IA can become a long-term chronic disease instead of a self-limited phenomenon [3], suggesting that IA-irAE might be a harbinger of a novel, chronic clinical entity with longstanding impact on patients' quality of life. Thus, prospective study with long-term follow-up is needed to understand the prevalence of erosive arthritis in IA-irAE and the chronicity of symptoms.

The low prevalence of RF and anti-CCP antibodies, and their low titer when observed, in patients with IA-irAE has been reported previously [3, 6, 11]. Interestingly, the ANA staining pattern of IA-irAE was quite different from seropositive RA, while similar to seronegative RA, suggesting that different autoantigens could be present among the IA subsets. ENA and anti-dsDNA autoantibody were also investigated in some of those patients with positive ANA and most were negative, which could indicate two possibilities: first, that specific autoantibodies are lacking in this patient subset or second, the possibility that rarer or novel autoantibodies could be present in IA-irAE and a subset of seronegative RA. This observation highlights the critical needed for additional prospective studies with relevant biospecimen collection, in IA-irAE and irAE in general.

The immunological mechanisms involved in the pathogenesis of IA could be divided into antibody-dependent or -independent pathways [12]. The seropositive RA is a typical type of antibody-dependent IA, as autoantibodies produced can be present in serum years before the onset of arthritis, and may have direct role in mediating joint damage [13]. The pathogenic basis of seronegative RA is largely unknown although current evidence suggests the possibility of an antibody-independent pathway [12]. Our study provides clinical observations that support the hypothesis that antibody-independent mechanisms may contribute to both IA-irAE and seronegative RA. Clearly, more dedicated research into the autoantibody profile between these two disease subsets are warranted. Our results also imply that dysregulation of PD-1 signaling may play an important role in IA-irAE and seronegative RA.

This study is limited by its retrospective, cross-sectional design which precludes the ability to capture longitudinal, long-term outcome data. We are reporting novel observations from the second largest cohort of de novo peripheral arthritis induced by ICI to date. We were not able to demonstrate any meaningful differences in characteristics based on ICI type or sex due to the small sample size. Furthermore, we did not have data on the autoantibody status previous to ICI therapy. Thus, a prospective analysis of immunological features before and after ICI therapy in a large IA-irAE cohort is warranted.

Conclusion

IA-irAE is a new subset of IA presumably triggered by a defined event (the administration of ICI). IA-irAE more closely resembles seronegative RA than seropositive RA. As patients with IA-irAE are at a relatively early stage (short disease duration, lack of erosive changes) when they are diagnosed with IA, the study of IA-irAE may provide us a good opportunity to unravel the characteristics, biomarkers, or underlying immunological mechanisms of early stage seronegative RA.

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Compliance with ethical standards

Disclosure None.

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