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Clinical presentation of immune checkpoint inhibitor-induced inflammatory arthritis differs by immunotherapy regimen

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Abstract

Introduction—Immune checkpoint inhibitors (ICIs) are a class of cancer immunotherapy, increasingly utilized to treat malignancies. Inflammatory arthritis (IA) is a potential consequence of ICI use, but there is limited information to guide evaluation and management of this immune-related adverse event (irAE). This study aimed to characterize clinical phenotypes, IA treatment and response in the largest cohort of patients with ICI-induced IA reported to date.

Methods—Patients with rheumatologist-confirmed IA occurring during or after ICI treatment with no prior history of autoimmune disease were included. Data were analyzed by ICI treatment regimen; treatments included combination CTLA-4/PD-1 inhibition, anti-PD-1 or anti-PD-L1 monotherapy. Relationship to the development of other irAEs, management of IA, and outcomes of IA management were evaluated.

Results—Of 30 patients identified, those treated with combination ICI therapy were more likely to present with knee arthritis, to have higher levels of C-reactive protein, to have already had another irAE, and to have a reactive arthritis-like phenotype. In contrast, patients treated with ICI monotherapy were more likely to have initial small joint involvement and to have IA as their only irAE. Ten patients required additional immunosuppression beyond corticosteroids, with TNF-inhibitors and/or methotrexate. Tumor progression while on non-corticosteroid immunosuppression was not seen in those with initial tumor response to ICIs.

Conclusion—These data suggest that distinct IA phenotypes may emerge with exposure to different ICI regimens. The majority of patients referred to rheumatology required systemic immunosuppression to manage their IA symptoms. Tumor progression was not seen in patients requiring TNF-inhibitors.

Keywords

inflammatory arthritis; cancer; immunotherapy; immune checkpoint inhibitor

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Introduction

Immune checkpoint inhibitors (ICIs), used in the treatment of advanced stage cancers, have revolutionized the field of oncology. They act by blocking negative co-stimulatory molecules on T cells, antigen presenting cells, and tumor cells¹. The blockade of these inhibitory molecules allows for unchecked T cell activation and a subsequent immune response targeting tumors. There are currently six FDA-approved ICIs targeting cytotoxic lymphocyte antigen 4 (CTLA-4: ipilimumab), programmed cell death protein 1 (PD-1: nivolumab, pembrolizumab), or programmed death ligand 1 (PD-L1: atezolizumab, durvalumab, avelumab) for an ever increasing range of indications and with many more ICI agents in development.

The growing use of ICIs has created a new and increasing population of patients referred to rheumatology for management of immune-related adverse events (irAEs). Immune-related AEs broadly refer to inflammatory or immune-mediated off-target tissue effects that occur as a result of ICI use. These toxicities may involve nearly every organ system, and range widely in severity and management requirements². Rheumatologic irAEs have been described in case series and reports including inflammatory arthritis (IA), sicca syndrome, myositis, vasculitis, and polymyalgia rheumatica^{3–5}. Epidemiologic data, such as the incidence of rheumatologic irAEs, is lacking, but IA appears to be the most common type of rheumatologic event⁶⁷.

Although well established guidelines exist for management of irAEs like colitis and pneumonitis, there have been only preliminary recommendations for evaluating and treating ICI-induced IA⁸⁹. This may stem from a lack of consistent reporting of rheumatologic irAEs in clinical trials, the non-life threatening nature of IA, or a lack of recognition of musculoskeletal symptoms by treating providers. The range of arthralgia reported in clinical trials in agents targeting CTLA-4, PD-1, or PD-L1 has ranged from 1–43%⁶, but no accurate estimates exist for the incidence of IA. The requirement of immunosuppression for treatment of ICI-induced IA has been documented in case series of 12 or fewer³⁴¹⁰¹¹ as have the unique clinical features of ICI-induced IA, including a group of patients with a clinical phenotype similar to reactive arthritis⁴. Treating patients for ICI-induced IA is complicated by their history of active or recently treated cancer and concerns of using immunosuppression in the context of ICI therapy, especially given the lack of published evidence on long-term outcomes.

With this study, we aim to characterize the presentation and longitudinal course for a cohort of patients with the novel rheumatologic entity, ICI-induced IA. Specifically, we evaluated the detailed clinical presentations of ICI-induced IA, whether these phenotypes differed by ICI regimen, long-term outcomes including persistence of arthritis, and possible effects of anti-rheumatic drugs on tumor progression.

Patients and Methods

Patients

Patients in this retrospective longitudinal cohort study were seen for clinical care in the Johns Hopkins Division of Rheumatology. They were included if they were age 18 or older and were treated for any malignancy with either anti-PD-1 or anti-PD-L1 monotherapy, or combination immunotherapy with anti-PD-1/CTLA-4. No patients with arthritis from anti-CTLA-4 monotherapy were referred. All patients underwent comprehensive rheumatologic evaluation and had rheumatologist confirmed IA as determined by physical examination and patient history. Patients were excluded if they had pre-existing systemic autoimmune disease, if they were on a blinded clinical trial where their immunotherapy agent was unknown, or if they were missing baseline rheumatologic clinical data including joint counts and description of clinical phenotype. This study was approved by the Johns Hopkins Institutional Review Board (IRB00144789).

Clinical measures

Information on timing of symptom onset, pattern of joint involvement, and severity of disease activity obtained at baseline clinic visits was extracted from the medical record. Longitudinal visits in rheumatology from January 1st, 2013, up to July 1st, 2017 were evaluated for IA treatment and response to IA treatment. Information about other irAEs and cancer response was obtained from oncology and rheumatology documentation in the medical record. Whether a patient's tumor responded to immunotherapy was determined clinically by the treating oncologist.

Statistical analysis

Summary statistics were calculated for demographic and clinical variables and for treatment requirements in the entire cohort and for subgroups divided by ICI treatment regimen. Clinical, demographic and treatment variables for each ICI regimen group (PD-1/PD-L1 monotherapy and CTLA-4/PD-1 combination therapy) were compared by Wilcoxon Rank Sum tests for continuous variables and Fisher's exact test for categorical variables. Time from ICI initiation to development of individual irAEs was calculated in months and graphically examined in box plots. Lag time to IA diagnosis from symptom onset was compared across groups based on initial joint involvement and number of concomitant irAEs with the Kruskal Wallis test.

Results

Patient demographic features, oncologic history and family history

Thirty patients with ICI induced IA were included. Patients had a median age of 59 years (range 36–83) and 40% were female (Table 1). Tumor types included metastatic melanoma, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), colorectal cancer (CRC), Hodgkin or cutaneous lymphoma, renal cell carcinoma (RCC), duodenal carcinoma, Merkel cell carcinoma, basal cell carcinoma of the skin, and squamous cell carcinoma of the skin. Sixteen patients were treated with anti-PD-1/PD-L1 monotherapy, and 14 patients were treated with combination anti-CTLA-4/PD-1 therapy; 23 of these patients were in clinical

trials. Compared to the ICI monotherapy group, patients treated with combination therapy were significantly younger by 7.5 years ($p=0.01$) and more likely to have metastatic melanoma as their underlying cancer. Ten of the 29 patients with treatment response data (34.5%) had a complete anti-tumor response. Six patients (20%) had a first degree relative with autoimmune disease. The family history of autoimmune diseases included rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, myasthenia gravis, and juvenile idiopathic arthritis, and two patients had more than one first degree relative with autoimmune disease.

Baseline IA clinical features

Patients most commonly had one or both knees affected as the first joint (56.7%, Table 1). Those who received combination therapy were more likely to have knee involvement first, and none had initial small joint involvement; in contrast, initial small joint involvement was more common in the monotherapy group (Table 1). C-reactive protein levels were significantly higher in those treated with combination therapy. Three patients developed IA concurrently with sterile urethritis and conjunctivitis, a reactive-arthritis like presentation; all received anti-CTLA-4/anti-PD-1 combination therapy and had colitis as an antecedent irAE. All patients with reactive arthritis-like IA were HLA B27 negative. Also notable was the presentation of stenosing tenosynovitis (i.e. trigger fingers) in two other patients preceding the development of synovitis.

Patients were assessed for autoantibodies. One had low level anti-CCP antibodies, and one was positive for a high titer rheumatoid factor. Low titer anti-nuclear antibodies (1:80) were seen in two patients. All patients positive for anti-citrullinated peptide antibodies, rheumatoid factor, or anti-nuclear antibodies were in the monotherapy treatment group (Table 1).

Relationship to other irAEs

Most patients (68.7%) in this cohort had an additional irAE in addition to IA. Colitis was the most common non-rheumatologic irAE with 10 patients (31.3%) also having colitis during their course. Thyroid disease, pneumonitis and skin rash were the next most common irAEs (Table 1). Some more unusual irAEs that occurred in these patients, included pancreatitis and myocarditis (Table 1).

The time course for developing irAEs was similar to that previously reported in anti-CTLA-4 studies, with colitis tending to develop first (Figure 1A)². IA development was variable (1 to 24 months) in time to development after ICI initiation (Median time to symptom onset 5 months; mean (SD) 6.2 (5.3) months).

These data suggest that there may be a delay in recognition of IA as an irAE by treating providers. Diagnosis of IA followed patient-reported initial development of joint symptoms by an average of 5.2 months (SD 6.6), but the longest time between symptom onset and diagnosis by a rheumatologist was 26 months. There was no significant difference in lag time from symptom onset to IA diagnosis by the number of concomitant non-rheumatologic irAEs ($p=0.23$). There was a significant difference in lag time to diagnosis of IA by category of initial joint presentation ($p<0.01$). Those with initial small joint involvement had 10

months longer lag time to IA diagnosis than those with the knees as the initial joints involved (Figure 1B).

Management of Inflammatory Arthritis and Outcome

Twenty four (80%) patients required systemic corticosteroids for IA management. Ten patients (33.3%) required additional immunosuppression (Table 2). Additional immunosuppression was started if IA had not improved after 1-3 months of corticosteroid use following ICI cessation. The requirement for corticosteroids did not differ by ICI treatment regimen, but those treated with combination CTLA-4/PD-1 inhibition were more likely to require additional immunosuppression. TNF-inhibitors (TNFi), with or without methotrexate, were required for 7 patients, and Methotrexate (MTX) monotherapy was used in 3 patients. The duration of TNFi use ranged from 2–16 months. All TNFi-treated patients had clinical improvement in their arthritis. Of those receiving TNFi, 4 had a complete tumor response at the time of TNFi initiation, with none having tumor progression on TNFi (duration: 3–16 months). Of the MTX monotherapy-treated patients, 3 had a complete or sustained partial tumor response to ICI therapy, and did not develop progressive cancer during the 2–12 months of IA management follow up.

Specific TNFi used included infliximab, etanercept, and adalimumab. Some patients needed only a short course of TNFi, 2–3 months, while other remained on TNF-I for over a year and flared if attempts to taper were made. None of these patients were treated concurrently with MTX or TNF-I while receiving ICI therapy.

Persistence of IA after ICI cessation was evaluated in the subset of patients with visits at least 3 months after their ICI cessation. Among 21 patients, 18 (85.7%) still had symptoms of IA after ICI discontinuation (Table 2).

Discussion

In this retrospective cohort study, the clinical features of patients with ICI-induced IA differed by the ICI regimen used to treat their cancers. Specifically, combination therapy was associated with higher levels of CRP and higher likelihood of having a large joint affected first in the arthritis course. All instances of reactive arthritis-like presentation were also in the combination therapy group and were noted in patients who had previously had colitis. Patients on PD-1 or PD-L1 monotherapy were more likely to have IA as their first irAE and more likely to have initial small joint involvement similar to RA. There was a lag time from the time symptoms of IA developed to diagnosis of 5 months on average, and those with initial small joint involvement had significantly longer lag times than those with knee involvement suggesting a delay in recognition of this irAE phenotype among treating providers. Patients in this cohort were also commonly found to have persistence of IA requiring immunosuppression for treatment. In follow-up thus far of patients treated with TNF-inhibitors and/or methotrexate, loss of cancer response to ICIs has not been observed in those who originally responded.

This study represents the largest cohort of patients with ICI-induced IA to date and is the first effort to evaluate clinical characteristics of IA based on ICI treatment regimen. This is

critical information, not just for rheumatologists as they try to recognize subgroups in ICI-induced IA and diagnose patients with this new entity, but also for oncology providers who are usually first to encounter patients with ICI-induced IA and subsequently refer patients to rheumatology. The substantial lag time between ICI-induced IA symptom onset and diagnosis has also not been previously described. Persistence of ICI-induced IA is notable when compared to some other immune related adverse events², and this delay in diagnosis and treatment may be one contributing factor to persistence. Long-term follow up of those treated with immunosuppression for ICI-induced IA has not been previously published. In this limited number of patients, the data suggest that TNFi or methotrexate may be useful to treat IA without affecting cancer outcomes.

The clinical insights from this work are hypothesis-generating for immunologic mechanisms underlying ICI-induced IA and other irAEs. That patients treated with different ICI regimens presented differently suggests a link between specific types of immune activation and phenotype. The association of colitis with arthritis in the combination therapy group may suggest that the Th17 response is a driver. Indeed, in one study of colitis as an irAE, IL-17 levels at baseline and after six weeks of treatment were associated with development of severe colitis¹². It is interesting to note that all cases of reactive arthritis were seen in the ICI combination treated group, which may also speak to the role of Th17 cells in pathogenesis¹³. These observations could also be explained by tumor type influencing immune pathogenesis, however, as significantly more melanoma patients were in the combination therapy group. Tumor type has influenced development of other irAEs, such as in pneumonitis, which is more common in patients with lung cancer¹⁴. Vitiligo is a unique side effect to melanoma and is correlated with an improved tumor response¹⁵. If there is shared expression of certain immunogenic proteins by particular tumors and in the joint, an analogous situation to melanoma and vitiligo could occur for inflammatory arthritis.

That initial small joint involvement in this study was more common with PD-1/PD-L1 inhibition may also be relevant to the underlying immunologic mechanisms of this toxicity. In murine models of IA and in human RA, the potential role of PD-1 in pathogenesis has been recognized,¹⁶¹⁷ and there may be overlap between RA and those patients with ICI-induced IA who have similar disease clinically. In this cohort, few patients were positive for RF and CCP, differing from a recent report of seropositive ICI-induced IA patients¹⁸, but consistent with other case series³. Some patients excluded from this analysis due to participation in a blinded trial or use of a novel ICI have these autoantibodies, but they still comprise <10% of all patients seen at our center, suggesting a novel mechanism in the majority of ICI-induced IA. By studying the underlying immune mechanisms of ICI-induced IA, we may gain insight into classical rheumatologic disease in addition to guiding treatment for ICI-induced IA based on understanding of pathogenesis.

This study was limited in its focus on only patients with ICI-induced IA, without a control group of ICI-treated patients without IA. As a result, the rate of other irAEs and timing of development of other irAEs cannot be compared to a wider patient population to determine how these patients may differ. Our results regarding timing of non-rheumatologic irAEs were consistent with previous studies, however, with colitis being an earlier irAE when compared to pneumonitis², for example. Longitudinal outcomes were only available in a

subset of patients due to competing risk of death in patients with malignancy, and because seven patients remained on ICI therapy at the time of data analysis. There was likely a referral bias contributing to the severity of arthritis seen in the study population; patients with mild or self-limited IA may have been less likely to be referred to rheumatology and successfully managed by oncologists. Patients also received immunosuppression for other irAEs in some cases, which may have masked their arthritis symptoms leading to a delay in referral to rheumatologist's attention later than symptom development or not at all. Finally, patients were excluded if they were on an investigational immunotherapy agent in combination with an immune checkpoint inhibitor targeting PD-1, PD-L1, or CTLA-4, which limited our total number of patients.

In summary, ICI-induced IA can have variable clinical presentations, and some of this variation can be explained by the ICI regimen used. There is a considerable lag time from the patient-reported onset of joint symptoms to diagnosis of ICI-induced IA, particularly in those with initial small joint involvement. Finally, the experience thus far with using immunosuppression in ICI-induced IA has been reassuring in terms of cancer outcomes, but more studies are needed to confirm this finding.

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Figure 1.

- a) Time to develop irAE after ICI initiation (time to symptoms for IA, time to diagnosis for others)
 b) Time to develop IA symptoms and for IA diagnosis in groups by first joint involvement

Table 1

Demographic and clinical variables at initial evaluation

	All patients (n = 30)	PD-1/PD-L1 monotherapy (n=16)	Combination CTLA-4/ PD-1 therapy (n=14)	p-value *
Age: median (IQR)	59 (54–68)	65 (55–73)	57.5 (45–59)	0.01
Female sex: N (%)	12 (40%)	9 (56.3%)	3 (21.4%)	0.07
Tumor Type: N (%)	Melanoma: 7 (23.3%) NSCLC: 12 (40%) Other: 11 (36.7%)	Melanoma: 1 (6.3%) NSCLC: 9 (50%) Other: 6 (37.5%)	Melanoma: 6 (42.9%) NSCLC: 3 (21.4%) Other: 5 (35.7%)	0.04
Complete tumor response [^] : N (%) N =29	Yes: 10 (34.5%)	Yes: 6 (40%)	Yes: 4 (26.7%)	0.70
First joint/s affected: N (%)	Knee: 17 (56.7%) Other large: 7 (23.3%) Small joint/s: 6 (20%)	Knee: 7 (43.8%) Other large: 3 (18.8%) Small joint/s: 6 (37.5%)	Knee: 10 (71.4%) Other large: 4 (28.6%) Small joint/s: 0 (0%)	0.03
# Swollen joints: median (IQR)	7 (4–10)	8.5 (5–10.5)	6 (4–10)	0.50
Reactive arthritis triad: N (%)	Yes: 3 (10%)	Yes: 0 (0%)	Yes: 3 (23.0%)	0.08
CRP (mg/dL) median (IQR)	2.6 (0.2–7.2)	0.5 (0.2–3.5)	4 (0.5–9.2)	0.03
Additional irAE present: N (%)	None: 10 (33.3%) 1 irAE: 12 (40%) >1 irAE: 8 (26.7%)	None: 7 (43.8%) 1 irAE: 7 (43.8%) >1 irAE: 2 (12.5%)	None: 3 (21.4%) 1 irAE: 5 (35.7%) >1 irAE: 6 (42.9%)	0.18
Types of additional irAE **	Colitis: 10 Thyroid disease ⁺ : 5 Pneumonitis: 4 Hypophysitis: 2 Rash: 4 Sicca: 3	Colitis: 2 Thyroid disease: 2 Pneumonitis: 3 Rash: 2 Sicca: 1 Pancreatitis: 1	Colitis: 8 Thyroid disease: 3 Pneumonitis: 1 Hypophysitis: 2 Rash: 2 Sicca: 2 Myocarditis: 1	
Time to first irAE Dx (months): median (IQR) Total N = 22	3 (1.3–12)	10 (3–16)	2 (1–4.25)	0.20
Time to IA Sx (months): median (IQR)	5 (2–8)	3.5 (1.5–7)	5.75 (5–8)	0.20
Time to IA Dx (months): median (IQR)	9 (4–17)	7 (3.5–19)	9.5 (6–16)	0.72
IA as 1 st IRAE: n (%)	16 (53.3%)	12 (75%)	4 (28.6%)	0.03
CCP positive: n (%)	1 (3.3%)	1 (6.3%)	0 (0%)	1.0
RF positive: n(%)	1 (3.3%)	1 (6.3%)	0 (0%)	1.0
ANA positive: n(%)	2 (6.7%)	2 (12.5%)	0 (0%)	0.49

Bold values indicate statistical significance.

* Comparison of PD-1/PD-L1 monotherapy to combination therapy.

** Some patients had more than one additional irAE; every irAE is noted. Wilcoxon Rank Sum test used for continuous data and Fisher's exact test for categorical.

[^]: Clinical response defined by treating oncologist.⁺: Thyroid disease was defined as new onset hypothyroidism or thyroiditis during immune checkpoint inhibitor treatment. CRP: C reactive protein. CCP: anti-cyclic citrullinated peptide antibodies. RF: rheumatoid factor. ANA: anti-nuclear antibodies.

Table 2

Treatment requirements for IA and outcomes

Variable	All patients (n=32)	PD-1/PD-L1 monotherapy (n=18)	Combination CTLA-4/PD-1 therapy (n=14)	p-value [*]
Required systemic corticosteroids: N (%)	24 (80%)	11 (68.9%)	13 (92.9%)	0.18
Maximum dose of steroids for IA [^] : median (IQR) N = 23	40 (20–60)	40 (20–40)	40 (20–60)	0.32
Required additional immunosuppression: N (%)	10 (33.3%)	2 (12.5%)	8 (57.1%)	0.02
Type of additional immunosuppression ^{**} : N (%) Total N = 10	TNF-inhibitor: 7 MTX: 3	TNF-inhibitor: 0 MTX: 2	TNF-inhibitor: 7 MTX: 1	0.07
Persistence of symptoms > 3 months after ICI cessation Total N = 21	18 (85.7%)	8 (72.7%)	10 (100%)	0.21

^{*} Comparison of PD-1/PD-L1 monotherapy to combination therapy.

^{**} Some patients on TNF-inhibitors were also on methotrexate and are included in the TNF-I group.

[^] Prednisone equivalents