Annals of Case Reports
Chaffin K and Samlowski W. Ann Case Rep: 8: 1384
www.doi.org/10.29011/2574-7754.101384
www.gavinpublishers.com

Research Article

Clinical Outcome of Function-Limiting Immune Arthropathy during Checkpoint Inhibitor Therapy: A Case Series

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Citation: Chaffin K, Samlowski W (2023) Clinical Outcome of Function-Limiting Immune Arthropathy during Checkpoint Inhibitor Therapy: A Case Series. Ann Case Report. 8: 1384. DOI:10.29011/2574-7754.101384

Received: 24 July 2023, **Accepted:** 28 July 2023, **Published:** 31 July 2023

Abstract

Function-limiting arthropathy is an uncommon toxicity of immune checkpoint inhibitor therapy. We analyzed the clinical features and outcome of this toxicity in a series of cancer patients. Patients treated with methotrexate, infliximab, or adalimumab were identified in our patient care database. Individual patient records were reviewed for concomitant checkpoint inhibitor treatment to analyse patient characteristics and clinical outcome. Sixteen patients were identified that met study requirements. Ten patients developed seronegative arthropathy consisting of severe arthralgia's and morning stiffness as a de novo immunologic adverse event. Five patients eventually achieved symptom resolution and five required ongoing treatment. Arthritis-related toxicity caused a treatment delay in 5/10 of these patients, but only one required treatment discontinuation. Six additional patients had pre-existing symptomatic inflammatory arthritis. Four reported flares during treatment, two achieved complete symptom resolution with treatment and two require ongoing therapy. Only one of these six patients had a treatment delay. Median time to onset of arthropathy was 1.3 ± 1.5 months in patients with pre-existing arthritis versus 5.2 ± 10.7 months in patients who developed arthropathy as an adverse event (p=.037). There is relatively little information about function-limiting arthropathy associated with checkpoint inhibitor treatment. Median time to symptoms was significantly shorter in patients with pre-existing arthritis versus those who developed arthropathy due to treatment. Patients with flares of pre-existing arthritis during treatment were more likely to achieve resolution of their symptoms and less likely to have treatment delays than patients who develop de novo arthropathy.

Keywords: Methotrexate, Infliximab, Adalimumab, Ipilimumab, Nivolumab, Pembrolizumab, Immune Related Adverse Event

Abbreviations: ADL: Activities Of Daily Living; BORR: Objective Response Rate; CR: Complete Response; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; ICI: Immune Checkpoint Inhibitors; IRAE: Immune Related Adverse Event; NCCN: National Comprehensive Cancer Network; SD: Standard Deviation; SITC: Society For Cancer, Immunotherapy

Introduction

Immune checkpoint inhibitors (ICI), especially PD-1 and CTLA-4 directed monoclonal antibodies, have dramatically changed the treatment options in multiple malignancies. A small but increasing percentage of solid tumor patients (e.g., melanoma, non-small cell lung and renal cancer), ranging from 10-40% currently achieve a durable complete remission (CR) following

treatment [1-5]. The normal function of inhibitory immune checkpoints, such as PD-1 and CTLA-4 is to inhibit persistent T cell activation, thereby reducing the risk of autoimmunity [6,7]. Therefore, it is not surprising that the major toxicities of antibodies that block these inhibitory signals include a variety of immune related adverse events (irAE) [8]. The exact pathogenesis of individual irAE remains poorly understood. Side effects are closely related to the timing of immunotherapy administration and generally resemble known autoimmune diseases [8]. The incidence and severity of irAE is dependent on many different factors including the class of ICI (e.g., CTLA-4 versus PD-1) or combination utilized, host related factors, and a potential pre-existing predisposition to autoimmune disease [9]. ICI-induced irAE can involve virtually every organ system. A 2019 systematic review found that 66.0% of patients treated with PD-1 antibodies developed at least one irAE of any grade and 14.0% of patients developed an irAE of grade 3 or higher [10]. The incidence of grade 3 and 4 toxicity with combined PD-1 and CTLA-4 blockade is much higher [11]. In one study, joint pain was noted in about 3.8% of patients undergoing PD-1 or PD-L1-directed monotherapy [12]. In most patients, symptoms responded to treatment interruption and glucocorticosteroid administration. A small percentage of patients required more intensive therapy to control symptoms. While arthropathy can greatly impair quality of life and potentially lead to lasting joint damage, little information is available concerning longer term outcomes. Due to their immune enhancing activity, physicians have been hesitant to administer ICIs to patients with pre-existing autoimmune arthritis as they may be at higher risk of toxicity. In fact, most clinical trials have excluded patients with pre-existing autoimmune conditions, such as inflammatory arthritides [13]. The exclusion of this subset of patients has created a significant knowledge gap regarding the efficacy and safety of ICIs in patients with pre-existing arthritis. In this current retrospective patient series, we have described our experience in cancer patients who developed severe function-limiting arthropathy. The goal was to analyse the patients who developed arthropathy as a de novo irAE, as well as the treatment outcome in a small number with functionally significant pre-existing autoimmune arthritis.

Results

Patient Demographics

Over the interval between 3/31/2015 and 3/31/2022, 588 patients were treated with checkpoint inhibitor therapy in this clinic (WS). A total of 16 patients who developed treatment-related arthropathy or had pre-existing autoimmune arthritis were identified. Baseline patient characteristics are shown (Table 1). Ten patients (63%) were female and 6 (37%) were male. The median age was 65 ± 9.42 (SD, standard deviation) years. The youngest patient was 44 years old at time of cancer diagnosis, while the oldest patient was 77. One patient was Hispanic, the remaining 15 (94%) were Caucasian. Patient specific comorbidities are described (Table 1). Based on the demographics of this practice, 15 patients (94%) were treated for metastatic melanoma and one patient had stage IV sarcomatoid renal cancer.

UPN	age	Gender	race	cancer	primary	site of metastasis	stage	pretreatment comorbidities	ESR*	CRP*	Arthritis onset
1	68	F	C	MM	leg	SQ, LN, Lung	IV	pulmonary fibrosis			Pre-existing PA
2	48	F	C	MM	face		IVC	HTN, bells palsy		4.69	Pre-existing PA
3	70	F	C	MM	extr	LN, liver, lung	IV	HTN, breast cysts, seizures	23	1.3	Pre-existing RA
4	65	F	C	MM	extr	LN	IVC	COPD, xerostomia, vitiligo, asthma, non-melanoma skin cancer			Pre-existing RA
5	68	F	C	MM	wrist	LN, lung	IVB	iron deficiency anemia	7	<0.5	Pre-existing RA
6	61	M	C	MM	trunk	LN, gastric mucosa	IV	depression, HTN, HLP	4	0.9	Pre-existing RA
7	46	F	C	MM	ear		IIIB				IRAE
8	65	M	C	MM	scalp	lung	IVB	HCL, BPH , TIA,	2	0.6	IRAE
9	44	M	H	MM	extrr		IIIC	HTN, HCL			IRAE
10	67	F	C	MM	trunk	LN, Lung	IIIB	glaucoma, HTN	1	1.5	IRAE
11	77	M	C	MM	face	SQ	IIIC	HTN, HLP			IRAE
12	63	F	C	MM	extr	LN	IIIB	DM, HTN, a-fib, SAA	55	4.5	IRAE
13	72	M	C	RCC	kidney	lung	IVB	HTN, PE, osteoarthritis			IRAE
14	69	F	C	MM	wrist	LN, lung	IVC	hypothyroidism			IRAE
15	59	F	C	MM	extr	LN	IVA				IRAE
16	62	M	C	MM	trunk	SQ	IVA				IRAE

UPN, unique patient number; M, male; F, female; C, Caucasian; H, Hispanic; MM, malignant melanoma; RCC, renal cell carcinoma; extr, extremity; SQ, subcutaneous tissue; LN, lymph node; HTN, hypertension; PE, pulmonary embolism; DM; Diabetes Mellitus, BPH, benign prostatic hyperplasia; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; a-fib, atrial fibrillation; SAA, splenic artery aneurism; HCL, hypercholesterolemia; HLP, hyperlipidemia; ESR, erythrocyte sedimentation rate (mm/h); CRP, C-reactive peptide (ml/dl); ANA, antinuclear antigen; RF, Pre, pre-existing arthropathy; PA, psoriatic arthritis; RA, rheumatoid arthritis; IRAE, immune-related adverse event. *Indicates pre-treatment value, if available

Table 1: Baseline patient Characteristics.

Patients with Arthropathy as an irAE

Function-limiting arthropathy that developed as a de novo irAE during ICI treatment was identified in 10 of 588 (1.7%) ICI treated patients. This included 9 patients with melanoma and 1 with renal cancer. Four of these patients had had received nivolumab monotherapy. Six patients were treated with combined PD-1 plus CTLA-4 blockade. Two were treated with the standard nivolumab (1 mg/kg) + ipilimumab (3mg/kg) regimen, while four patients received the alternate dosing regimen [nivolumab (3 mg/kg) + ipilimumab (1mg/kg)] [14]. Median time to onset of function-limiting arthropathy was 5.16 ± 10.7 months (SD) from start of immunotherapy with a range of 1.5 to 35.5 months. The median number of ICI doses administered prior to onset of arthropathy was 7 (range 1-14). Once arthropathy was controlled, 9 patients were able to resume treatment. The median number of ICI doses eventually administered was 12.5 (range 4-14). The median treatment duration was 10.9 months (range 3.6 - 15.1 months). The clinical characteristics of arthritic symptoms experienced by the 10 irAE patients is described in more detail (Table 2). These patients developed function-limiting arthralgias and morning stiffness without joint redness, swelling, or effusion. Most patients developed an elevated C-reactive protein and erythrocyte sedimentation rate as inflammatory markers (Figure 1A and 1B). No patient had detectable anti-nuclear antibodies, rheumatoid factor, double stranded DNA antibodies or citrullinated peptide antibodies. Of the ten patients with ICI induced arthropathy, one patient (10%) permanently discontinued treatment due to difficulty controlling symptomatic arthritis, five patients (50%) had treatment delays for arthritis treatment and were subsequently able to resume therapy. One patient (10%) had treatment delayed due to unrelated causes (COVID-19 pneumonia) and was able to continue planned treatment. Only one patient was hospitalized due to iatrogenic hypopituitarism, due to abrupt discontinuation of glucocorticosteroid treatment. Three patients (30%) had no alterations in their treatment schedule. Six patients developed additional ICI-related toxicities concurrently with the onset of arthropathy (Table 2). All ten patients were first treated with non-steroidal anti-inflammatory agents and low dose steroids. Two patients subsequently improved with escalated therapy consisting of high-dose steroids alone, one received steroids + infliximab, two received steroids + methotrexate, four received steroids + methotrexate + infliximab, and one received steroids + methotrexate + infliximab + rituximab. Arthritis as an irAE proved difficult to treat. Five patients (50%) continued to have persistent symptomatic arthritis after discontinuation of ICI therapy in remission despite ongoing arthritis treatment. Five patient (50%) had complete resolution of arthropathy symptoms following immunosuppressive therapy. Despite immunosuppressive treatment with steroids and other agents, 6 of the 10 patients with irAE arthropathy (60%) responded to treatment with complete remissions. Median progression-free survival (PFS) was not reached at a median follow-up of 28 months (range 1 to 56.0 months) (Figure 2A). Two-year PFS was 60.0%. The median overall survival (OS) of patients with irAE arthropathy was also not reached (range 7.5 to 66.0 months) (Figure 2B). Two-year OS was 88.8%. Four patients who achieved a radiographically confirmed complete remission electively discontinued treatment [15,16].

UPN	CKI	dose #	TT	non-arthritic CKI toxicity	Peak ESR*	Peak CRP*	CKI treatment changes	current status	nature of arthritic flare	anti-inflammatory therapy	arthritis treatment response	PFS (mo)	OS (mo)
7	N	13			78	3	CKI delay	NED	arthritis, morning stiffness	S, INF, M	active, ongoing treatment	20.5	20.5
8	N+I, Nm	13		rash, hypothyroidism	34	192	CKI delay	NED	delayed onset seronegative arthritis	S, M,	active, ongoing treatment	19.4	19.4
9	N	6		myopathy	25	18.6	CKI d/c	NED	myalgias, arthralgias	S, M, INF, R	active, ongoing treatment	8.9	9.9
10	N, N+I, Nm, P	14	B/E	rash, headache, fatigue, colitis hypotension	19	62.1	CKI delay	PD	seronegative arthritis	S, INF	active, ongoing treatment	4	36.1
11	N	12			10	0.4	None	NED	delayed onset seronegative arthritis	S	resolved	36.1	36.1
12	N	14	B/E		20	16.2	CKI delay **	NED	arthralgias	S	resolved	26.2	26.2
13	N+I, Nm	6	Cabo	erythema nodosum, HTN	115	242	CKI delay	NED	severe arthritis	S, INF, M	resolved	7.5	7.5
14	N+I, Nm	4	B/E		16	17.2	CKI delay	PD	severe arthritis	S, INF, M	resolved	6.5	8.5
15	N+I	14		visual blurring, photophobia, DVT, blistering lesions	80	41	None	NED	inflammatory arthritis with flexion contraction of the fingers	S, M	active, ongoing treatment	66	66
16	N+I	11		chills, fatigue	111	20.6	None	PD	arthralgias and achiness	S, INF, M	active, ongoing treatment	8.5	11.7

UPN, unique patient number; N, nivolumab; Nm, nivolumab maintenance; I, ipilimumab; P, pembrolizumab; TT, targeted therapeutic agent; Cabo, cabozantinib; B/E, binimetinimbi / encorafenib; ; DVT, deep vein thrombosis; PFS, progression free survival from start of treatment; OS, overall survival; NED, no evidence of disease; PD, disease progression; D-other, died of other causes; DOD, died of disease; S, steroids; INF, infliximab; M, methotrexate; R, rituximab. * indicates peak value. ** due to covid-19 pneumonia.

Table 2: Treatment Related Arthritis Patient Outcomes.

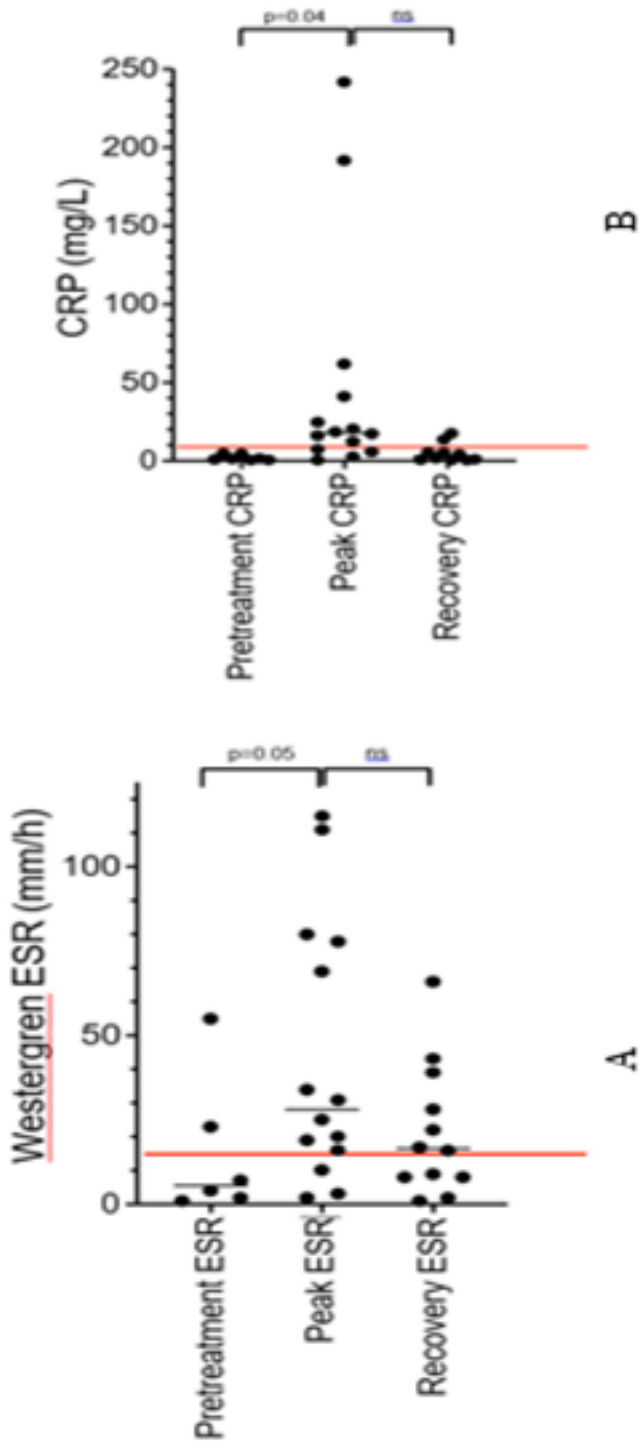

Figure 1: Inflammatory markers at diagnosis of arthropathy and during recovery. The line indicates the upper limit of normal. Panel A: Westergren erythrocyte sedimetation rate (ESR), Panel B: C-reactive protein (CRP).

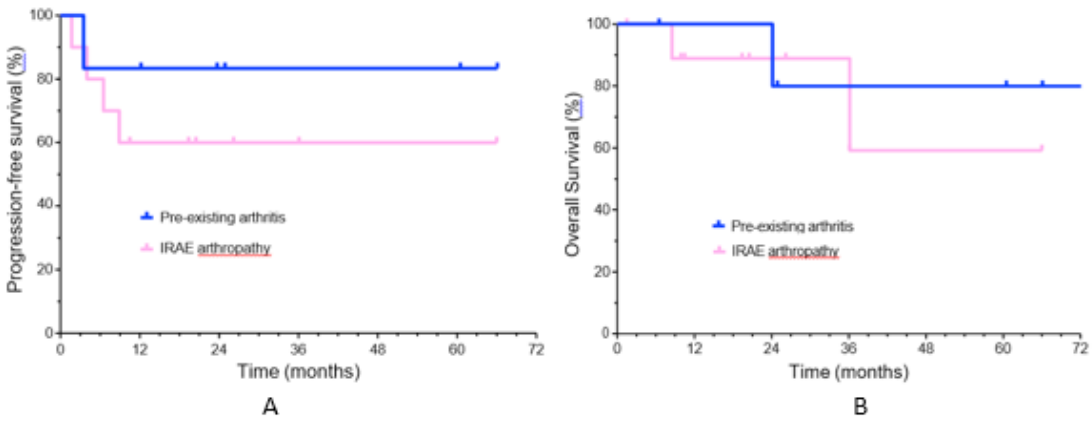

Figure 2: Clinical outcome of arthropathy patients. Panel A: Progression free survival, Panel B: Overall survival.

Patients with pre-existing psoriatic or rheumatoid arthritis

Six patients had a pre-existing diagnosis of symptomatic inflammatory arthritis, prior to ICI treatment for metastatic melanoma (Table 3). This represented 1.0% of total treated patients. Four (66%) had rheumatoid arthritis and 2 (33%) had psoriatic arthritis. The patients with pre-existing rheumatoid arthritis had elevated rheumatoid factor and citrullinated peptide antibodies. Three of these four patients were already receiving immunosuppressive drug therapy prior to the initiation of ICI treatment. Their regimens included methotrexate, adalimumab, and methotrexate + infliximab, respectively. One of these patients received ipilimumab monotherapy and one patient received nivolumab monotherapy. Four patients were treated with ipilimumab plus nivolumab regimens. The median number of ICI doses administered across all ICI regimens was 7 (range 2-17). The median number of ICI doses administered prior to onset of increased arthritis symptoms was 2 (range 1-6). The median overall treatment duration was 6.4 months (range 1.4 - 15.3 months). Four of the six patients reported an arthritis flare. The individual symptoms are described (Table 3). Two patients experienced increased arthralgias and two patients experienced arthralgias with associated joint swelling. The time to arthritis flare following initiation of ICI therapy was only 1.34 ± 1.53 months (range 0.9 – 4.6 months). Statistical analysis showed a significant difference in time to onset versus patients who developed de novo arthropathy (p=.037). No patients with pre-existing arthritis required hospitalization for treatment-related toxicities. Only one patient had treatment discontinued due to exacerbation of arthritis, two patients had treatment discontinued due to non-arthritic complications (infusion reactions and rash, respectively), and three patients had no change in planned treatment.

All six patients with pre-existing arthropathy experienced additional non-arthritis related grade 2-4 treatment related toxicities (Table 3). One patient died (while in complete remission) from interstitial pulmonary fibrosis that may have been exacerbated by infliximab therapy for arthritis. Three patients were on ongoing ant-rheumatic therapy at the start of ICI therapy, and only one of these patients experienced a mild arthritic flare during ICI treatment. Despite pre-existing autoimmune arthritis, 4 patients achieved a complete remission, while two patients progressed after ICI treatment (Figure 2A and 2B). Median PFS and OS were not reached. At 2 years, PFS of patients treated with ICI with pre-existing autoimmune arthropathy was 83.3% (range 3.5 to 66.1 months). OS of these patients was 80% at 2 years (range 6.5 to 106.4 months).

UPN		CKI	dose #	TT	pre-existing arthritis	baseline therapy	other CKI toxicities	ESR*	CRP*	Treatment modification	current status	nature of arthritic flare	arthritis flare therapy	current state of arthritis	PFS (mo)	OS (mo)
1		N+I, Nm	6		PA		pulmonary fibrosis *	69	12.2	CKI D/C	D-other**	arthralgias	INF, S	resolved	23.7	24.1
2		I, N	4,4		PA		periorbital swelling **, eye tearing			CKI D/C ***	NED	arthralgias, intermittent leg swelling	INF, S	active, ongoing treatment	66.1	66.1
3		N+I, Pm	4	P	RA	M	rash, hypotension	2	7.5	CKI D/C ***	PD	no flare		stable on medication	3.5	6.5
4		N	17		RA	S, M, R	sjogren syndrome, diarrhea, COPD exacerbation, vitiligo		5.5	None	NED	joint pain and swelling	INF, S	stable on medication	60.5	60.5
5		I	8		RA	M, F	fatigue	3		None	PD	no flare		stable on medication	12.2	106.4
6		N+I	2		RA		rash, diarrhea, dizziness, colitis, fatigue	31	24.5	None	NED	joint aches, morning stiffness	INF, S	stable on medication	24.9	24.9

UPN, unique patient number; N, nivolumab; I, ipilimumab; Nm; nivolumab maintenance; P, palbociclib; Pm, pembrolizumab maintenance; TT, targeted therapeutic agent; PFS, progression free survival from start of treatment; OS, overall survival; NED, no evidence of disease; PD, disease progression; D-other, died of other causes; DOD, died of disease; S, steroids; INF, infliximab; M, methotrexate. * indicates peak value. ** likely due to infliximab. *** due to non-arthritic toxicity.

Table 3: Pre-existing Arthritis Patient Outcomes.

Discussion

Arthralgias are frequently reported following ICI treatment (1%-43% of treated patients) [17,18]. As arthralgias may also occur as a sequalae of the malignancy, or due to pre-existing degenerative arthritis, this creates diagnostic and management challenges. In contrast, severe function-limiting inflammatory arthropathy appears to be a relatively infrequent complication of ICI therapy (1-7% incidence) [10,12,19-21]. Development of function-limiting arthropathy was particularly significant during adjuvant therapy, as these patients were healthy individuals whose cancer had been completely resected.

Patients with Arthropathy as an irAE

In our patient cohort, the incidence of de novo function-limiting arthritis that developed during ICI treatment was 1.7%. It should be noted that the current CTCAE toxicity grading system is inadequate to characterize this toxicity, as it requires signs of inflammation, erythema, or joint swelling; irreversible joint damage, which were not seen in clinically severely symptomatic patients. In our patients, arthropathy was most frequently observed following combined CTLA-4 plus PD-1 therapy. Both we and other have occasionally observed ICI-induced arthropathy after PD-1 monotherapy [22]. The median time to onset of de novo arthropathy in our series was 5.2 ± 10.7 months (SD) from the start of treatment. The time to onset is similar to that reported by other investigators [23]. An unusual finding was that two of our patients had significantly delayed onset of arthropathy occurring seven months and two years after the end of ICI therapy. This has also been observed by other investigators [24]. In our series, de novo ICI induced arthropathy generally presented as the acute onset of severe arthralgias and morning stiffness. Unlike patients with rheumatoid arthritis and lupus, patients did not develop physical evidence for arthritis (joint redness, swelling, or effusions). Both large and small joints appeared equally affected. These symptoms severely impacted quality of life and daily function. Laboratory findings generally included an elevation of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) without specific serologic markers for rheumatoid arthritis or lupus. This constellation of clinical symptoms and laboratory results had also been reported by other investigators [22,25], suggesting a novel inflammatory syndrome. Only rarely does ICI induced arthropathy overlap other known autoimmune syndromes, such as rheumatoid arthritis and lupus [19,22]. Management strategies for ICI induced inflammatory arthritis recommended by the Society of Immunotherapy of Cancer (SITC) and the National Comprehensive Cancer

Network (NCCN) suggest a tiered approach depending on severity [25,26]. These guidelines suggest that patients undergo a thorough rheumatologic examination, radiologic imaging, and laboratory testing including ESR, CRP, rheumatoid factor, anti-CCP and ANA [25]. Our experience suggests that the ESR and CRP are most likely to be informative. For mild arthritis (mild joint pain, inflammatory symptoms, and joint swelling that does not inhibit activities of daily living), NCCN guidelines recommend continuing immunotherapy with administration of NSAIDS or low dose corticosteroids [26]. For moderate arthritis symptoms that limits activities of daily living, physicians should consider holding immunotherapy and administering prednisone 0.5 mg/kg/day for 4-6 weeks with a slow taper. For function-limiting arthritis that limits self-care activities physicians should hold immunotherapy and prescribe methylprednisolone or prednisone 1 mg/kg/day. If there is no improvement by week 2 of steroid treatment, physician should consider additional disease modifying anti-rheumatic drugs (methotrexate, sulfasalazine, infliximab, tocilizumab, azathioprine, leflunomide, or IVIG). Physicians can consider resuming therapy upon stabilization or adequate management of symptoms. However, function-limiting symptoms may require permanent discontinuation of ICI therapy. We have evaluated these strategies in a community setting. We found that arthritis as an irAE proved challenging to control. Early use of disease modifying antirheumatic agents has been suggested if high-dose steroids are ineffective or cannot be weaned to 10 mg or less prednisone daily within a few weeks [23]. In our series, all ten patients were treated with intensive anti-inflammatory treatment. Two patients responded to high-dose steroids alone. When symptoms did not resolve within 1-2 weeks in the other 8 patients, other anti-rheumatic agents were added in a stepwise fashion. Even after eventual ICI discontinuation when patients achieved a durable remission, five patients (50%) continued to have persistent symptomatic arthropathy. These patients continue to receive arthritis treatment. Persistent arthropathy has also been observed as a long-term complication by other investigators [27]. Our other five patients (50%) eventually had complete resolution of arthropathy symptoms following immunosuppressive therapy. Some investigators have hypothesized that the use of steroids and other immunosuppressive agents may reduce the efficacy of ICI therapy [24]. In contrast, other studies have suggested that development of irAE may have a positive correlation with clinical response [28]. Although the number of patients included in our series is relatively small, the durable remission rate was higher than expected. Two-year progression-free survival was 68.2 %. Thus, immunosuppressive treatment of immune arthropathy did not appear to be detrimental to effective induction of anticancer responses. Treatment delays also did not seem to preclude responses. The potential observation that arthropathy is associated with improvement in anticancer responses will need to be evaluated in a larger multi-institutional cohort of patients.

Patients with pre-existing psoriatic or rheumatoid arthritis

Patients with pre-existing autoimmune arthropathy have generally been excluded from ICI clinical trials [13]. Thus, there is currently relatively little information concerning the safety and efficacy of ICI in patients with pre-existing autoimmune arthritis (e.g., rheumatoid arthritis, psoriatic arthritis, lupus) [29]. In one case series analyzing ICI treatment in patients with rheumatoid arthritis, disease flares occurred in 55-83% of patients. This proved manageable with escalation of steroids and other immunosuppressive agents [30]. In another case series, flares of pre-existing autoimmune disease occurred in 67% patients with 75% of flares becoming completely resolved or stabilized on steroids and additional immunosuppressive agents. In our patient series, the median time to onset for patients experiencing flare of pre-existing autoimmune disease was significantly more rapid than in patients with de novo arthropathy, 1.34 ± 1.53 months ($p=.037$). This observation is supported by other case series [22, 30]. While mild flares of arthritis occurred frequently in our patients, these proved relatively easy to manage. Flares tended to be less debilitating, with less impediment to function than in patients with de novo arthropathy. Three of our patients were already receiving ongoing anti-rheumatic therapy when ICI treatment was initiated. These drugs were continued during ICI treatment. This seemed to decrease the severity of arthritis flares and did not appear to lessen the anticancer response. Overall, clinical complete responses occurred in 4 of 6 of our patients with underlying rheumatoid arthritis or psoriatic arthritis. These responses were durable for at least 2 years (66.7%), despite immunosuppressive therapy [31-33].

Conclusions

Function-limiting ICI-induced arthropathy as an irAE has a unique presentation, different from other inflammatory arthritidies (e.g., lupus, rheumatoid arthritis, psoriatic arthritis). A small percentage (1/7%) of our ICI-treated patients developed severe arthralgias and morning stiffness without joint effusions or joint damage. Laboratory testing usually identified an elevated CRP and ESR, without the elevation of serologic markers for lupus or RA. Based on our experience, early recognition and aggressive treatment with steroids and other disease modifying agents is recommended. Many of our cancer patients improved with antirheumatic therapy. However, there is a significant risk of long-term persistence despite effective antirheumatic therapy. Onset of arthropathy did not seem to have an adverse effect on clinical anticancer responses. Use of ICIs in patients with pre-existing rheumatoid arthritis and psoriatic arthritis appears to be relatively safe and effective, particularly if patients continue their ongoing arthritis treatment. Further information is needed to establish

safety and effectiveness of ICI treatment in other autoimmune conditions (e.g., lupus, scleroderma, vasculitis).

Materials and Methods

Patient identification

We performed a retrospective analysis of patients treated by a single oncologist (WS) with the immunosuppressant drugs infliximab, methotrexate, or vedolizumab for autoimmune disease between 3/31/2015 and 3/31/2022. These individual records were then screened in a HIPAA-compliant iKnowMed database (McKesson, Houston, TX) to identify patients who received these agents for autoimmune arthritis (n=21). Records were evaluated for concomitant ICI administration. Patients with arthritis who were not treated with an ICI were excluded from analysis (n=5). In total, 16 patients with ICI-treated malignancy, with either preexisting autoimmune arthritis or who developed arthropathy, were identified for further analysis.

Data extraction

A chart review of each patient's individual records was performed. Data was extracted into a password protected spreadsheet (Excel) for analysis and subsequently de-identified. This study design has been reviewed by the WCG IRB chair and was deemed exempt from full IRB review. Data acquired for each patient included: age, gender, self-identified ethnicity, comorbid conditions, and current cancer status. Malignancy type, location, stage, and metastatic sites were also recorded. The ICI and targeted therapeutic agents and dosage, start dates, end dates, progression dates, and toxicities were extracted from the electronic record. Any toxicity-related delays in treatment were recorded. The nature of arthritis (pre-existing or de novo treatment reaction), anti-inflammatory regimens used for acute arthritic symptoms, and current state of arthritis response were noted. Characterization of inflammation related laboratory markers was also documented.

Treatment regimens

Patients were treated with standard ICI regimens available at the time of the cancer diagnosis. These included nivolumab (fixed dose of 240 mg every 2 weeks or alternatively 480 mg every 4 weeks), ipilimumab (3 mg/kg every 3 weeks), pembrolizumab (fixed dose of 200 mg every 3 weeks), or as combined therapy with ipilimumab (3 mg/kg every 3 weeks x 4 doses) plus nivolumab (1 mg/kg every 3 weeks x 4 doses) followed by nivolumab maintenance therapy. Some patients were treated with the alternate ipilimumab plus nivolumab dosing scheme identified in the Checkmate 511 trial [14]. A small number of patients with targetable mutations who progressed during initial ICI therapy were offered addition of targeted therapies with continuation of PD-1 antibody therapy. These agents consisted of either palbociclib (100mg/day), cabozantinib (40 mg/day) [34], or encorafenib (150 mg daily) plus binimetinib (30 mg/bid) [35,36].

Response and toxicity assessment

Best objective response rate at 12 months (BORR) was determined using RECIST 1.1 criteria [37]. Patients were monitored for treatment related toxicities at the time of each clinic visit. We attempted to grade toxicity using the CTCAE 5.0 criteria [38], however these criteria proved inadequate. In this grading system, Grade 1 toxicity is characterized as "mild pain with inflammation, erythema, or joint swelling". Grade 2 toxicity is "moderate pain associated with signs of inflammation, erythema, or joint swelling limiting instrumental activities of daily living (ADL)". Grade 3 toxicity is "severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; limiting self-care and ADL". Arthropathy in our patients were characterized by severe joint pain and morning stiffness that markedly limited daily activities, without joint redness or swelling or irreversible joint damage.

Treatment paradigm

In our patients, ICI therapy was interrupted for severe arthralgias and morning stiffness, and immunosuppressive therapy was initiated. The initial management of arthropathy included administration of nonsteroidal agents and glucocorticosteroids, initially 10-20 mg prednisone/day [26]. If unresponsive, weekly methotrexate 7.5 mg po was added. If there was no improvement over 1-2 weeks, infliximab or rituximab were subsequently added. Once patients responded, steroids were slowly tapered (10 mg/week). Treatment with ICI resumed once toxicity subsided to grade 1 or less. If patients achieved a complete response, elective treatment discontinuation was considered as previously described [15,16].

Statistical Analysis

Descriptive statistics were calculated via Excel spreadsheet (expressed as data range, median and standard deviation). Progression free survival and overall survival from start of treatment were additionally calculated via Excel spreadsheet and analyzed via the method of Kaplan Meier [39]. Time from the start of the regiment that triggered arthropathy to the onset of clinical symptoms was calculated. The date of progression, death, or the date of the last clinic visit were used for progression-free and overall survival calculations. The end date of this analysis was 9/1/22.

Conflict of Interest: Neither of the authors have a conflict of interest

Acknowledgments: Supported in part by NIH grant 5U10CA035421. We would like to express our appreciation to patients and their families and the clinical staff of Comprehensive Cancer Centres of Nevada. Critical review of the manuscript by Suzanne Samlowski, M Arch and Aida Loudyi, MD is appreciated.

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