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CLINICAL CASE

Characteristics and treatment of new-onset arthritis after checkpoint inhibitor therapy

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ABSTRACT

Immune checkpoint inhibitors (ICIs) may cause immune-related adverse events (IRAEs). Characterisation and data on treatment of musculoskeletal IRAEs are scarce. In this cohort study, patients receiving ICI therapy who experienced arthralgia were evaluated for the presence of synovitis. Data on demographics, ICI regime, time of onset, imaging and response to therapy of synovitis were prospectively collected. Arthritis was demonstrated in 14 of 16 patients of whom 7 showed monarthritis, 5 had oligoarthritis and 2 had polyarthritis. Patients with ICI-induced arthritis were predominantly male (57%) and seronegative (69%). Regarding the detection of synovitis in staging imaging, moderate sensitivity for contrast-enhanced CT with PET-CT as reference was observed. Disease burden at baseline was high and was significantly reduced after anti-inflammatory treatment. Nine patients were treated with systemic and eight patients with intra-articular glucocorticoids. Six patients who flared on glucocorticoid treatment on tapering were given methotrexate resulting in long-term remission. Patients with synovitis were more likely to have good tumour response. Patients with ICI-induced arthritis were predominantly male and seronegative showing different patterns of arthritis with high disease burden. Good efficacy and safety was observed for methotrexate, particularly for ICI-induced polyarthritis.

Key messages

What is already known about this subject?

- Immune checkpoint inhibitors (ICIs) cause musculoskeletal immune-related adverse events including arthritis. Prospective data on clinical characteristics and treatment of ICI-induced arthritis are needed to improve clinical management of patients.

What does this study add?

- Patients with ICI-induced arthritis were predominantly male and seronegative showing different patterns of arthritis, had a high disease burden, however, were also more likely to have good tumor response.
- ICI-induced arthritis was not self-limiting as disease activity increased upon prednisolone taper. Good efficacy and safety were observed for early treatment with MTX, particularly for ICI-induced polyarthritis.
- PET-CT, but also conventional CT, performed for cancer staging, reliably detect signs of ICI-induced arthritis

How might this impact on clinical practice?

- Remission of ICI-induced arthritis can be achieved by early MTX treatment after initial glucocorticoid failure (increase of activity after taper). Analysis of cancer staging PET-CT but also CT can be helpful for a primary screening of synovitis.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are antibodies targeting inhibitory molecules on T cells, which are exploited by some cancers, such as programmed cell death 1 (PD-1) or cytotoxic T-lymphocyte associated protein 4 (CTLA-4), thereby boosting antitumour responses.[1] The introduction of ICIs, first ipilimumab (anti-CTLA-4), later nivolumab, pembrolizumab (anti-PD-1) and atezolizumab, durvalumab and avelumab (anti-programmed cell death 1 ligand 1) revolutionised cancer treatment by improving survival (and even leading to long-term remission in a portion of patients) for metastatic melanoma and non-small cell lung cancer (NSCLC). Further ICIs (eg, targeting lymphocyte activation gene 3 protein (LAG3)) and combination therapies (combination of ICIs or combination of ICI with other tumour therapies) are under investigation in clinical trials. Given the clinical success of ICIs their indications are rapidly growing.[1] Unfortunately, owing to their non-specific mechanism of activating T cells, ICIs are accompanied by a spectrum of immune-related adverse events (IRAEs) due to inflammatory autoimmune tissue damage.

The most common adverse events affect the dermatological, gastrointestinal and endocrine system.[2] Previous case reports and series reported rheumatic musculoskeletal IRAEs (msIRAEs) including arthritis, tenosynovitis, polymyalgia rheumatica (PMR), sicca syndrome and myositis in patients in the presence and predominantly in the absence of pre-existing autoimmune disease.[3–14] Response to different treatments was reported mostly for non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and biological disease-modifying antirheumatic drugs.

Here, we prospectively studied a homogenous cohort of patients with ICI-induced arthritis (confirmed by imaging and/or synovial fluid analyses), which was treated according to a treatment algorithm containing methotrexate (MTX). We analysed demographic and clinical characteristics, imaging findings and the treatment response in a systematic way, and demonstrate novel data regarding imaging (including positron emission tomography (PET)-CT and therapy (particularly for the conventional synthetic disease-modifying antirheumatic drug MTX) for ICI-induced arthritis.

METHODS

In this cohort study, 12 patients with melanoma and four patients with NSCLC receiving ICI therapy (ipilimumab, nivolumab and/or pembrolizumab as standard care or part of a clinical trial) at the University of Munich who experienced arthralgias were evaluated for the presence of musculoskeletal inflammation by clinical examination, ultrasound and staging imaging studies including MRI and PET-CT scans. Patients were referred by their treating dermatologist or pulmonologist when they experienced new-onset arthralgia after initiation of ICI therapy. Data on demographics, ICI regime, time of onset and response to therapy of msIRAEs and other IRAEs were collected at baseline and during follow-up between January 2016 and November 2017. Laboratory analyses for rheumatoid factor (RF), anticyclic citrullinated peptide (anti-CCP) antibodies, antinuclear autoantibodies (ANA) including antibodies to extractable nuclear antigens and human leucocyte antigen-B27 were performed during consultation according to presenting symptoms. Treatment response to ICI therapy was radiologically assessed and indicated as complete response, partial response, stable disease and progressive disease based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria V.1.1.[15] All patients underwent musculoskeletal imaging, and msIRAEs were confirmed on ultrasound performed by ultrasound-certified rheumatologists or [^{18}F]-2-fluoro-2-deoxy-D-glucose PET-CT scans performed for cancer staging. For a substudy, first CT scans (obtained from initial PET-CT routine cancer staging) and later—to minimise detection bias—fusion PET-CT (as reference) from the same patient (in a total of seven patients) were assessed for signs of synovitis in predefined joint areas (shoulders, elbows, hands including wrists, hips, knees and feet including ankles) by one specialist for radiology together with one specialist for nuclear medicine, who were blinded for patient information beyond oncological information.

Regarding standardised treatment, patients with synovitis were first treated with injection of glucocorticoids and if more than two joints were affected usually in parallel with 20–30 mg of oral prednisolone. Systemic glucocorticoids were tapered within 6 weeks to 2.5 mg. In those patients who flared on tapering MTX was started at a dose of 15 mg weekly. Two patients with mild monarthritis who refused glucocorticoids were treated with NSAIDs. Response to anti-inflammatory treatment was assessed by the change of a numeric rating scale (NRS, range 0–10, 10 being the worst) regarding activity of arthritis as judged by the patient as well as by two independent expert rheumatologists aware of all clinical data but blinded to treatment. Consent was obtained from all participants. Differences between different cohorts of patients were determined by Student's t-test or Fisher's exact test, where applicable using Prism 5.0. The study report followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

RESULTS

Patients demographics and clinical characteristics

Mean age was 63.4±12.6 years, 43% of the patients were female and most patients had stage IV cancer (table 1). Two patients had a family history of rheumatic disease (patients 3 and 7; mother with rheumatic disease, entity not known) but none of the patients had a personal history of rheumatic or autoimmune diseases. Ten of 14 patients (71%) received treatment with nivolumab, 4/14 (29%) with ipilimumab and 4/14 (29%) with pembrolizumab, of which 1/14 (7%) was treated with ipilimumab and pembrolizumab in sequence and 3/14 (21%) with combination therapy of ipilimumab and nivolumab. Regarding the overall response to ICI treatment, 6/14 (43%) patients had a partial response, 5/14 (36%) had a stable disease, 2/14 (14%) had a progressive disease and 1/14 (7%) patient had no evidence of disease.

Other IRAEs included asymptomatic pancreatitis (two patients), vitiligo (two patients), colitis (three patients), pneumonitis (two patients), myasthenic symptoms (one patient) and conjunctivitis (one patient). In 3 of 14 patients, other IRAEs occurred in timely association (4 weeks before or after) to onset of arthritis, one case with mild pancreatitis a week before, the second in parallel with myasthenia and colitis 4 weeks later and the third with colitis 2 weeks prior to (table 1).

Musculoskeletal IRAEs

Of 16 patients with new-onset arthralgias after initiation of ICI therapy, 14 had objective signs of musculoskeletal inflammation (table 2). The two patients with arthralgia were treated with NSAIDs with a good clinical

Table 1 Patient characteristics and IRAEs, except musculoskeletal

Patient	Age	Sex	Cancer type	Cancer stage	ICI	Best overall response to ICI	IRAEs, except MS
1	78	Male	Melanoma	IV	Nivolumab	Partial response	Vitiligo, itching
2	37	Male	Melanoma	III	Pembrolizumab (adjuvant)	No evidence of disease	Colitis
3	75	Female	Melanoma (uvea)	IV	Nivolumab	Partial response	Suspected colitis, vertigo
4	72	Female	melanoma	IV	Nivolumab/ ipilimumab*	Partial response	Vitiligo
5	73	Male	melanoma	IV	Nivolumab/ ipilimumab*	Partial response	Pneumonitis, conjunctivitis
6	79	Female	melanoma (uvea)	IV	Nivolumab/ Ipilimumab*	Stable disease	None
7	49	Male	melanoma	IV	Nivolumab	Progress	Suspected pneumonitis, pancreatitis
8	51	Male	NSCLC	IIIb	Nivolumab	Progress	None
9	65	Male	melanoma (uvea)	IV	Ipilimumab/pembrolizumab	Stable disease	Pruritus, pancreatitis
10	53	Female	melanoma	IV	Pembrolizumab	Partial response	None
11	73	Male	Melanoma	IV	Pembrolizumab	Partial response	Colitis, myasthenic symptoms
12	58	Female	NSCLC	IIIb	Nivolumab	Stable disease	None
13	60	Male	NSCLC	IIIb	Nivolumab	Stable disease	None
14	65	Male	NSCLC	IIIa	Nivolumab	Stable disease	None

*Combination therapy.
Age, refers to age at first onset of musculoskeletal IRAEs; ICI, immune checkpoint inhibitor; IRAEs, immune-related adverse events; MS, musculoskeletal; NSCLC, non-small cell lung cancer.

response. Seven patients presented with monarthritis, five with oligoarthritis (spondyloarthritis-like pattern) and two with polyarthritis (rheumatoid arthritis (RA)-like pattern). Monarthritis presented as omarthritis in all cases. Synovial analysis performed in four patients was consistent with inflammatory arthritis (≥2000 white blood cells/mm^3). PMR-like disease with typical ultrasound findings was evident in five cases concurrent with arthritis. The time from start of ICI therapy to onset of synovitis was highly variable ranging from 1 to 716 days (median 139 days), the time between counselling request and first rheumatologist visit was 9.5±9.3 days and time from start of arthralgia to first confirmation of synovitis was 2.5±4.4 months in our cohort. Extra-articular rheumatic IRAEs were evident in three patients, two patients with sicca syndrome (xerostomia in both, additional keratoconjunctivitis in one) and one patient with myositis.

Laboratory and imaging findings

At first visit in our clinic, C reactive protein (CRP) levels ranged from 5 to 114 (≤5 mg/L). RF was positive in only five patients and at low levels (10.2–21.1 U/mL), all below ≤3xULN (≤10 U/mL). Anti-CCP antibodies were detected in only one case at 98.7 (≤5 U/mL). ANA were positive in nine patients, and anti-Sjögren's syndrome-related antigen A was positive in one patient (anti-SSB negative). The latter patient had xerophthalmia (without xerostomia) but normal Schirmer's and Saxon test (refused salivary gland biopsy) (table 2).

Furthermore, we tested the hypothesis whether synovitis can be detected already on routine cancer imaging when focusing on joint areas in conventional CT scans compared with PET-CT scans. In PET-CT scans available from seven patients (together 41 joint areas evaluable), signs of synovitis were detected solely on CT in 6 (15%) and on PET-CT in 10 (24%) of the 41 joint areas (online supplementary figure 1). Of interest, the sensitivity of solely CT scan (with PET-CT as reference) was 60% and specificity was 94%.

Disease activity, treatment, response to therapy and safety

The baseline mean overall disease burden (assessed by patient NRS for pain) was 7.3±1.0 and was significantly

Table 2 Characteristics of musculoskeletal IRAEs, laboratory and imaging results

Patient	Pattern of arthritis	PMR-like disease	Other MS IRAEs	Latency of MS IRAEs after ICI start (days)	CRP at onset of MS IRAEs (mg/L)	RF/anti-CCP	ANA/ENA	HLA-B27	Synovial fluid cell counts (cells/µL)	Proof of MSI on imaging: US (1), PET-CT (2), CT (3), MRI (4)
1	Oligo	+ve	–ve	174	9.9	–ve /–ve	–ve / –ve	–ve	12 300	1
2	Mono	–ve	–ve	121	≤5.0	–ve /–ve	1:100/ ND	ND	ND	3, 4
3	Mono	+ve	Sicca	289	5.5	–ve /–ve	–ve / ND	–ve	ND	1, 4
4	Poly	+ve	–ve	1	9.8	+ve/+ve	1:400/ –ve	ND	ND	1,2,3
5	Poly	+ve	–ve	48	38.6	–ve /–ve	1:3200/ –ve	–ve	ND	1
6	Oligo	–ve	–ve	143	38.2	–ve /–ve	1:1600/ –ve	ND	ND	1
7	Oligo	–ve	Sicca	43	71.3	–ve /–ve	–ve / ND	–ve	2600	1
8	Mono	–ve	–ve	31	21.2	–ve /–ve	1:800/ –ve	–ve	ND	2
9	Mono	–ve	–ve	716	≤5.0	–ve/–ve	1:200/ –ve	–ve	ND	2, 3, 4
10	Mono	–ve	–ve	253	≤5.0	+ve/ ve	1:100/ ND	ND	ND	1, 4
11	Oligo	–ve	Myositis	76	≤5.0	–ve/–ve	–ve / ND	–ve	20 000	1, 2, 3
12	Mono	–ve	–ve	139	6.8	+ve/–ve	1:400/ –ve	–ve	ND	4
13	Oligo	–ve	–ve	116	48	+ve/–ve	1:12800/ SSA	–ve	6000	1, 2, 3
14	Mono	+ve	–ve	394	114	+ve/–ve	–ve / –ve	–ve	ND	1

MRI (hyperintensity on STIR images and/or prominent contrast enhancement on postcontrast fat-suppressed T1-weighted images).
ANA, antinuclear autoantibodies; anti-CCP, anti-cyclic citrullinated peptide antibodies; CRP, C reactive protein; ENA, extractable nuclear antigens; ICI, immune checkpoint inhibitor; IRAEs, immune-related adverse events; HLA, human leukocyte antigen; MS, musculoskeletal; MSI, musculoskeletal inflammation; ND, not determined; PET-CT, positron emission tomography-CT; PMR , polymyalgia rheumatica with ultrasound features including bursitis or tenosynovitis of shouldersor hips typical for PMR; RF, rheumatoid factor; Sicca, proven by Saxon and Schirmer test; SSA, anti-Sjögren's syndrome-related antigen antibodies; US, ultrasound (proof of synovitis: ≥ grade 2 grey scale or ≥ grade 1 power Doppler findings); +ve, if positive; –ve, if negative.

reduced to 2.0±1.3 (table 3, p<0.0001) in response to treatment. Activity of arthritis, as judged by physician NRS, was also markedly reduced from 4.5±2.1 to 1.0±0.6 after a median of 6 months of anti-inflammatory treatment (for patients 1–13, table 3, p<0.0001). Patient 14 was not included in the analyses for the change of mean arthritis activity, as no follow-up for 1 year was available at the end of our observation period. No patient was started on glucocorticoids for arthralgia (or any other IRAEs in the 4 weeks) before referral to rheumatology. The patients presenting with monarthritis in the absence of PMR features could all be managed with NSAID or local glucocorticoid injection therapy without relapse (median follow-up 418 days). Of all patients, nine were treated with systemic and eight with intra-articular glucocorticoid injection. All patients responded to glucocorticoid treatment. Six patients flared on glucocorticoid treatment on tapering and subsequently received MTX (median follow-up 434 days for patients receiving MTX). Remission of arthritis was achieved in all MTX-treated patients, which was confirmed by ultrasound, and prednisolone could be tapered below 2.5 mg/day. In two patients, prednisolone was not tapered below 2.5 mg because of adrenal insufficiency (patients 1 and 7). The entire patient cohort was followed for a median of 433 days, and throughout the duration of follow-up no safety issues regarding MTX side effects were evident. None of the patients taking MTX showed progression of tumour, except of one patient who already progressed before starting MTX. None of the patients had to stop ICI treatment due to msIRAEs during the follow-up.

DISCUSSION

To summarise, treatment of IRAE is challenging for maintaining the desired antitumour effect of ICI therapy.

Table 3 Therapy and response to treatment of immune checkpoint inhibitor-induced arthritis

Patient	Therapy: 1=intra-articular GC, 2=systemic GC	Increase in disease activity after GC taper	NRS patient before therapy	NRS physician before therapy	NRS patient after therapy	NRS physician after therapy
1	1, 2, MTX	+ve	7,5	7,5	1,0	0,5
2	1	NA	8,0	2	5,0	0,5
3	2	–ve	6,5	4	3,5	1
4	1, 2, MTX	+ve	8,0	7	2,5	1
5	2, MTX	+ve	9,0	8,5	1,0	1,5
6	1, 2, MTX	+ve	7,0	4	1,0	0,5
7	2, MTX	+ve	6,0	2,5	0,0	0,5
8	1	NA	7,0	2,5	1,0	1,5
9	1	NA	8,5	2	1,5	0,5
10	NSAID	NA	6,5	3,5	1,5	0,5
11	1, 2, MTX, SSZ	+ve	6,0	5,5	3,5	2
12	NSAID	NA	5,5	3	3,0	1
13	1, 2	–ve	8,0	7	2,5	2,5
14	2	NA	8,0	4,5	1,5	0,5

GC, glucocorticoid (shoulders injections usually performed subacromial); MTX, methotrexate; NA, not applicable (no systemic GC received; no follow-up after GC-taper for patient 14 yet available); NRS, numeric rating scale; NRS physician, mean of the NRS values from two expert rheumatologists before and after anti-inflammatory treatment for each patient; NSAID, non-steroidal anti-inflammatory drugs; SSZ, sulfasalazine; +ve, if positive; –ve, if negative.

Our study demonstrated that local glucocorticoid injection is effective and sufficient for monarthritis. However, in patients with oligoarthritis or polyarthritis, tapering glucocorticoid therapy was frequently associated with flares. This is the first report on the efficacy and safety of MTX as a glucocorticoid-sparing agent in ICI-induced arthritis.

In our cohort, a predominance of male sex (57%) was observed. This is in contrast to two large early arthritis patient cohorts (not in context to ICI), with rather female preponderance (male sex in Leiden cohort: 34%, Etude et Suivi des POlyar- thrites Indifférenciées Récentes, ESPOIR cohort: 24%).[16] However, our finding is in line with previous reports on ICI-induced arthritis with occurrence mostly in male patients ranging from 50% to 83%, which might suggest that early arthritis induced by ICI seems to have different underlying factors not related to female sex.[3 5–8 11]

Most patients with arthralgias on ICI therapy were proven to have arthritis or PMR-like disease 14/16 (88%) indicating that the majority of patients referred by oncology had true inflammatory disease and thus oncology may be under-referring or should continue referring for arthralgia. In previous studies, the rate of inflammatory disease in patients with arthralgia seemed to be lower, probably due to differences in patient referral strategies.[11 17 18]

Retrospective analysis revealed that the median time from start of arthralgia to first confirmation of synovitis was 2.5±4.4 months in our cohort, suggesting that symptoms were usually not self-limiting. Recently, Cappelli *et al* reported a slightly longer lag from first joint symptoms to diagnosis of arthritis of 5.2±6.6 months.[13]

The median time between counselling request and first rheumatologist visit was 9.5±9.3 days reflecting that patients were rapidly seen after counselling was requested. This is of potential importance since most patients did not receive glucocorticoids at the time of first contact, which could otherwise have interfered with diagnostic measures such as ultrasound, MRI, CRP levels or joint swelling making a definite diagnosis more difficult. The last timeframe has not been reported in studies before.

When patients developed arthralgia, inflammatory manifestations were associated with high disease burden and were not self-limiting as disease activity increased on prednisolone taper (table 3). Pattern of arthritis was heterogeneous, ranging from monarthritis to polyarthritis, consistent with previous case series.[3 6 9 11]

While RF and anti-CCP antibodies were negative in most of our patients (69%), low titre ANA were frequently observed (table 2). Except for one study demonstrating seropositivity in all patients with polyarthritis fulfilling the RA American College of Rheumatology/European League Against Rheumatism criteria,[5] (the latter fact might explain the high frequency), other studies with ICI-induced arthritis, in line with our findings, reported that patients tested were predominantly seronegative (67%–100%).[3 6–8 10 11] These results might indicate that the immune response associated with the induction of msIRAE, unleashed by ICIs, might be driven by activated autoreactive T cells independent of a B cell response

characteristic for RA. However, novel autoantibodies could be involved, which are not detectable by currently available assays.

A substudy evaluating the value of routine cancer imaging for the detection of synovitis, revealed low, however higher than expected, sensitivity (60%) and surprisingly good specificity (94%) for conventional CT compared with fusion PET-CT (the latter taken as the gold standard in the absence of MRI in timely association with PET-CT scans). Although usually not all joint regions were covered by PET-CT (eg, hands, feet, knees) and staging imaging was sometimes performed before maximum of joint pain, already 29% of the patients in our cohort could have been diagnosed for synovitis on positive staging imaging (online supplementary figure 1). A few studies demonstrated a good correlation between fusion PET-CT and MRI (as the gold standard) in the detection of synovitis making PET-CT a feasible reference.[19] Since no data are available regarding sensitivity or specificity of CT compared with PET-CT (or MRI), the data in this paper represent novel findings, which might be useful in the evaluation of arthritis in the context of immunotherapies when PET-CT is routinely performed for cancer staging/follow-up. These findings suggest that careful analysis of PET-CT and conventional CT (in case PET was not performed) focusing on the detection of signs of synovitis could potentially be helpful for treating oncologists, particularly when patients complain about arthralgia.

Regarding tumour response to ICI therapy, most of our ICI-induced arthritis patients had at least stable disease (86%), which is in line with previous observations demonstrating better response to ICI therapy in patients experiencing IRAEs compared with those without IRAEs in general (49% vs 18%)[20] and also for msIRAEs (86% vs 35%).[3 6]

Strengths of this study are the comprehensive clinical assessment including imaging and laboratory analyses and the standardised treatment regime focusing on MTX as a glucocorticoid-sparing agent. In the case of an insufficient response to MTX, we would have favoured treatment with tumour necrosis factor inhibitors as the next step. Limitations of this study are the small number of patients, the potential bias of the clinical assessors and the lack of a control group. Given the rather low numbers of patients with PET-CT, the imaging findings need to be interpreted with caution and further studies validating our data are needed. However, the sample size was comparable with previous reports and assessors of physician-judged arthritis activity and imaging were blinded as mentioned above. Further questions to be addressed are the optimal duration of MTX treatment (step down) and more data on tumour safety.

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