Whole-body MRI in patients with arthralgia or inflammatory arthritis after exposure to immune checkpoint inhibitors: a single-centre prospective imaging study

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Summary

Background Musculoskeletal adverse events due to immune checkpoint inhibitors are common and can present clinically as inflammatory arthritis, polymyalgia rheumatica, or arthralgia. The pathoanatomy of musculoskeletal adverse events related to immune checkpoint inhibitors remains undefined, with a paucity of available imaging data. We aimed to investigate the whole-body imaging phenotype of arthralgia and inflammatory arthritis following exposure to immune checkpoint inhibitors, to fully characterise the pattern of inflammation in these patients and subsequently inform clinical management.

Methods In this prospective imaging study, patients aged 18 years or older with new musculoskeletal symptoms that started during or up to 6 months after receiving an immune checkpoint inhibitor and healthy controls aged 18 years or older, with no personal history of rheumatological autoimmune disease, no active cancer, and no self-reported joint pains in the 4 weeks before their MRI scan date, were recruited at the Leeds Rheumatology department of Chapel Allerton Hospital, Leeds, UK, and underwent gadolinium contrast-enhanced whole-body MRI. Joint, tendon, bursal, entheseal, and whole spinal imaging lesions were graded by two independent masked assessors and consensus reported. Inflammatory whole-body MRI patterns were analysed and patients were followed up for 6 months. People with lived experience of inflammatory arthritis and musculoskeletal toxicity related to immune checkpoint inhibitors highlighted the importance of knowing and understanding imaging findings to help inform risk versus benefit decisions about immunosuppressive treatments.

Findings Between Oct 20, 2021, and May 22, 2024, 60 patients (35 [58%] with arthralgia and 25 [42%] with inflammatory arthritis) and 20 healthy controls were recruited. The mean age of patients was 65 years (SD 11) and that of healthy controls was 62 years (7); 34 (57%) patients were men and 26 (43%) were women, and 12 (60%) healthy controls were men and eight (40%) were women. All patients and healthy controls were White. Median total joint synovitis, joint erosions, enthesitis, and tenosynovitis scores were significantly higher in patients with arthralgia or inflammatory arthritis induced by immune checkpoint inhibitors compared with healthy controls, without significant differences between the inflammatory arthritis and arthralgia subgroups. Acromioclavicular (46 [77%] of 60), glenohumeral (45 [75%] of 60), wrist (43 [73%] of 59), and metacarpophalangeal (35 [59%] of 59) joints were the most frequently affected by synovitis in all patients. There were three distinct global inflammatory patterns: peripheral inflammatory arthritis in 22 (37%) of 60 patients; polymyalgia rheumatica in seven (12%), and an overlapping phenotype of polymyalgia rheumatica and peripheral inflammatory arthritis in 12 (20%). Axial inflammation was only identified in one patient. Four of the five patients requiring disease-modifying antirheumatic drug therapy were in the peripheral inflammatory arthritis group, which also had the highest initial and ongoing glucocorticoid requirement.

Interpretation MRI inflammation and erosions are as prevalent in patients with arthralgia exposed to an immune checkpoint inhibitor as in those with inflammatory arthritis. This finding suggests that the overall burden of musculoskeletal toxicity associated with immune checkpoint inhibitors is currently under-recognised. Patients who develop inflammatory arthritis or arthralgia after exposure to immune checkpoint inhibitors have three main imaging patterns: polymyalgia rheumatica, peripheral inflammatory arthritis, and an overlap of polymyalgia rheumatica and inflammatory arthritis. Patients with peripheral inflammatory arthritis were most likely to require disease-modifying antirheumatic drugs.

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Introduction

Immune checkpoint inhibitors have revolutionised cancer management by substantially improving outcomes in patients with advanced melanoma and other malignancies.[1] These monoclonal antibodies enhance the ability of the immune system to recognise and destroy

Research in context

Evidence before this study

We searched PubMed from database inception to Sept 27, 2024, using the terms ''inflammatory arthritis'' ''arthralgia'', "polymyalgia rheumatica", "musculoskeletal", "immune checkpoint inhibitor", "PD-1", "CTLA-4","PD-L1", "immune related adverse event", "imaging", and "magnetic resonance imaging". We searched for primary research articles and case reports published in English that included imaging findings in patients with musculoskeletal adverse events following initiation of an immune checkpoint inhibitor. Previous imaging studies of joint pain associated with immune checkpoint inhibitors have been retrospective, included small numbers of participants, and have used multiple imaging modalities focusing on symptomatic joint areas without predefined imaging protocols. Arthralgia is a frequently reported symptom after exposure to an immune checkpoint inhibitor but the prevalence of subclinical inflammation on imaging in patients without overt inflammatory arthritis is unknown. Polymyalgia rheumatica, rheumatoid arthritis, psoriatic arthritis, and spondyloarthropathy imaging features have all been identified but the frequency of each imaging phenotype and the patterns of disease that are associated with future disease-modifying antirheumatic drug requirements have not been systematically explored.

Added value of this study

The findings of this imaging study show that MRI subclinical inflammation and erosions are as prevalent in patients with arthralgia alone as in those with inflammatory arthritis after exposure to an immune checkpoint inhibitor. The use of whole-body MRI has enabled patient-level global assessment of the inflammatory burden to identify three distinct patterns of inflammation: polymyalgia rheumatica, peripheral inflammatory arthritis, and an overlap of polymyalgia rheumatica and peripheral inflammatory arthritis. The most frequent inflammatory pattern is peripheral inflammatory arthritis and this group appears most likely to require disease-modifying antirheumatic drug therapy.

Implications of all the available evidence

These results suggest that the overall burden of musculoskeletal toxicity associated with immune checkpoint inhibitors is currently under-recognised and highlights the range and extent of inflammation in all patients presenting with new musculoskeletal symptoms after exposure to an immune checkpoint inhibitor. Rheumatology assessment should be considered by oncologists for patients who develop arthralgia alone. The three patterns of inflammation we have identified could help clinicians recognise the different inflammatory arthritis phenotypes that patients could present with following exposure to immune checkpoint inhibitors. These insights also advance our understanding of how toxicities induced by immune checkpoint inhibitors relate to classical autoimmune diseases. Clinicians should be aware that a peripheral inflammatory arthritis pattern might require higher levels of immunosuppression, and close follow-up should be considered for these patients.

cancer cells by blocking T-cell immune checkpoint receptors (programmed cell death 1 [PD-1] and programmed cell death ligand 1 [PD-L1], and cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]). Although this is an effective antitumour strategy, the enhancement of T-cell activity can alter self-tolerance to healthy tissues and so immune checkpoint inhibitors can cause a wide range of immune-related adverse events.[1]

Musculoskeletal toxicities are the fourth most common immune-related adverse event following exposure to immune checkpoint inhibitors; inflammatory arthritis, polymyalgia rheumatica, and polymyositis have all been reported.[2] Inflammatory arthritis occurs in around 7% of patients, but arthralgia is very common, reported in up to 43% of patients.[3] Unlike other immune-related adverse events induced by immune checkpoint inhibitors, inflammatory arthritis can persist in around half of patients after immunotherapy cessation.[4] Importantly, inflammatory arthritis causes a considerable functional and emotional impact, even after taking into account the underlying cancer and other immune-related adverse events.[5] The indications for immune checkpoint inhibitor therapy are rapidly expanding and rheumatologists will probably encounter musculoskeletal immune-related adverse events more frequently. It is therefore crucial to develop a comprehensive understanding of the clinical and imaging phenotypes of musculoskeletal toxicity induced by immune checkpoint inhibitors to enable rapid diagnosis and optimisation of management strategies.

Current data on patterns of inflammation in inflammatory arthritis induced by immune checkpoint inhibitors are heterogeneous. Some studies report a rheumatoid arthritis-like small joint polyarthritis,[1] whereas others have reported large joint synovitis.[6] Given that these patients are predominantly anti-cyclic citrullinated peptide and rheumatoid factor negative[1], this raises possible associations with spondyloarthropathy and polymyalgia rheumatica. Extracapsular involvement (ie, tenosynovitis, bursitis, and enthesitis) has all been described.[2,7] Features seen in spondyloarthropathies, such as dactylitis, sacroiliitis, and axial inflammation of the facet and costovertebral joints, have also been reported.[2,8,9]

Imaging studies of inflammatory arthritis induced by immune checkpoint inhibitors are scarce and have focused on symptomatic joint regions. This makes it difficult to gauge the overall pattern of disease in patients. Whole-body MRI combines the ability of MRI to provide highly sensitive mulitplanar information on bone and

soft tissues with the ability to image multiple upper and lower limb joints in addition to the spine and pelvis in one acquisition. In this study, we used whole-body MRI to analyse the imaging phenotype of patients with arthralgia or inflammatory arthritis induced by immune checkpoint inhibitors compared with healthy controls. We aimed to establish the pathoanatomical pattern of inflammation to aid diagnosis and management of these patients.

Methods

Study design and participants

For this prospective imaging study, patients aged 18 years or older with new musculoskeletal symptoms that started during or up to 6 months after receiving an immune checkpoint inhibitor treatment (anti-PD-1, anti-PD-L1, or anti-CTLA-4 alone or combined) were recruited via regional oncology services to the Leeds Rheumatology department of Chapel Allerton Hospital, Leeds, UK. Patients with known active inflammatory arthritis before starting an immune checkpoint inhibitor, or suspected inflammatory myositis, were excluded. Other exclusion criteria pertained to MRI safety considerations, including an estimated glomerular filtration rate less than 45 mL/min per 1·73 m² or acutely deteriorating renal function. A physical examination was performed and patients with at least one clinically detectable swollen joint (ie, clinical synovitis) or tenosynovitis on examination were labelled as having inflammatory arthritis, and those without a clinically detectable swollen joint or tenosynovitis were labelled as having arthralgia.

Healthy controls were recruited to undergo whole-body MRI. Healthy controls were aged 18 years or older, had no personal history of rheumatological autoimmune disease, no active cancer, and no self-reported joint pains in the 4 weeks before their MRI scan date. The healthy control group consisted of hospital staff, friends of hospital staff, and relatives or spouses of patients.

Our previous patient and public involvement work has highlighted that people with inflammatory arthritis find imaging investigations to be informative and valuable in understanding their condition and treatment rationale. In the current study, patients highlighted the importance of knowing and understanding imaging findings to help inform risk versus benefit decisions about immunosuppressive treatments.

Ethical approval for this study was obtained by the Leeds West Research Ethics Committee (09/H1307/98). All patients and healthy controls gave informed written consent at the time of recruitment.

Procedures

Baseline demographic data were collected for all participants, and data on immune checkpoint inhibitor type, malignancy type, musculoskeletal symptom onset time, other immune toxicities, personal or family history of autoimmune disease, and current use of glucocorticoids were collected for all patients. Baseline erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody, rheumatoid factor, and anti-cyclic citrullinated peptide concentrations were measured at baseline. If CRP was reported as less than 5 mg/L, the value was taken to be 2 mg/L for the purposes of the analysis.[10] Patient-reported outcome measures, health assessment questionnaire (HAQ) scores, and the global health visual analogue scale (VAS) scores were collected. Early morning stiffness duration, 28 tender joint count, and 28 swollen joint count were recorded.

Whole-body MRI was performed on all participants with gadolinium contrast by use of a 3 Tesla scanner at the NIHR Leeds Biomedical Research Centre (Leeds, UK). A comprehensive MRI protocol was used and included imaging of the joints, axial spine, tendons, entheses, and bursae (full details are provided in the appendix pp 2–3). The dominant hand was imaged in a dedicated coil to ensure a high resolution and very good image quality. The feet and ankles were not imaged as their inclusion would have necessitated an unacceptably long scan duration. This omission was supported by our recent data, which suggest a low of prevalence of ultrasound inflammation in the joints, tendons, and entheses of the feet and ankles in patients treated with immune checkpoint inhibitors.[11] The carpometacarpal and first metacarpophalangeal joint were also excluded due to the high prevalence of osteoarthritis in these joints in the general population, and hence the risk of false positive results with synovitis and erosions.[12]

See Online for appendix

The MRI scans were anonymised and randomly assigned to be scored semi-quantitatively by two experts (DM and ER). Each expert scored independently and was masked to group assignment. Consensus scores were agreed in cases of discrepancy.

A semi-quantitative scoring system, adapted from Freeston and colleagues'[12] whole-body MRI imaging protocol, was applied for synovitis, tenosynovitis, erosions, bursitis, and enthesitis (0=no abnormality, 1=indeterminate abnormality, and 2=definite abnormality). Trochanteric bursitis was scored for the presence of inflammatory change within the greater trochanteric bursa only. The cervical, thoracic, and lumbar spines were scored for bone oedema (0–2) in the vertebral body endplate and anterior corner regions. The sacroiliac joints were scored for subchondral oedema (0–2) and erosions or sclerosis (0–2). All erosions were scored with the Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) criteria. Before the MRI scans, patients were asked to stop taking non-steroidal anti-inflammatory drugs (NSAIDs) for 48 h where possible. No other medications, including glucocorticoids, were withheld.

The participant scans were classified into four pattern groups; polymyalgia rheumatica (extracapsular), peripheral inflammatory arthritis, spondyloarthropathy, and no specific pattern. The polymyalgia rheumatica extracapsular pattern was defined according to a recent

comparable study that compared which MRI sites were most discriminatory between individuals with polymyalgia rheumatica and rheumatoid arthritis.[13] When defining this pattern, there was a recognition that otherwise healthy individuals might have capsular entheseal changes around the greater trochanter. The pattern was designated as follows: bilateral trochanteric bursitis and either bilateral ischial tuberosity or bilateral pubic symphysis with at least one site needing to have a bilateral score of 2.

The peripheral inflammatory arthritis pattern was defined according to whole-body MRI literature on common sites of inflammation in rheumatoid arthritis:[14] a score of 2 in at least two joints or extensor or flexor tendons (not including hips, sternoclavicular, and acromioclavicular joints).

The spondyloarthropathy pattern was defined in line with a previous report on inflammation sites in spondyloarthropathy:[15] sacroiliac subchondral oedema in at least two adjacent slices that was not thought to be

	All immune checkpoint inhibitors (n=60)	Arthralgia* (n=35)	Inflammatory arthritis (n=25)	Healthy controls (n=20)
Mean age, years	65 (11)	63 (12)	68 (10)	62 (7)
Sex				
Male	34 (57%)	21 (60%)	13 (52%)	12 (60%)
Female	26 (43%)	14 (40%)	12 (48%)	8 (40%)
Ethnicity				
White	60 (100%)	35 (100%)	25 (100%)	20 (100%)
Smoking status				
Never smoked	26/59 (44%)	14/34 (41%)	12 (48%)	..
Previous smoker	30/59 (51%)	18/34 (53%)	12 (48%)	..
Current smoker	3/59 (5%)	2/34 (6%)	1 (4%)	..
Malignancy				
Melanoma	30 (50%)	16 (46%)	14 (56%)	..
Lung cancer	11 (18%)	9 (26%)	2 (8%)	..
Renal cancer	8 (13%)	3 (9%)	5 (20%)	..
Mesothelioma	4 (7%)	4 (11%)	0	..
Other	7 (12%)	3 (9%)	4 (16%)	..
Immune checkpoint inhibitor (anti-PD-1 or anti-PD-L1) monotherapy				
Pembrolizumab	26 (43%)	17 (49%)	9 (36%)	..
Nivolumab	8 (13%)	2 (6%)	6 (24%)	..
Atezolizumab	4 (7%)	3 (9%)	1 (4%)	..
Durvalumab	3 (5%)	3 (9%)	0	..
Avelumab	1 (2%)	1 (3%)	0	..
Immune checkpoint inhibitor combined therapy (anti-PD-1 or anti-PD-L1 with anti-CTLA-4)				
Ipilimumab plus nivolumab	18 (30%)	9 (26%)	9 (36%)	..
Personal history of autoimmune disease†	8 (13%)	6 (17%)	2 (8%)	..
Family history of autoimmune disease in first-degree relative‡	11/56 (20%)	7/33 (20%)	4/23 (17%)	..
Time from immune checkpoint inhibitor initiation to musculoskeletal symptom onset, months	3·5 (1·4–11·0)	2·5 (1·0–6·0)	6·0 (2·5–14·0)	..
Rheumatoid factor (>14 IU/mL)	4 (7%)	1 (3%)	3 (12%)	..
Anti-cyclic citrullinated peptide (≥2·99 IU/mL)	0	0	0	..
Antinuclear antibody (bioplex or immunofluorescence) positive	3/59 (5%)	0/34 (0%)	3 (12%)	..
C-reactive protein, mg/dL (n=59)§	7·9 (2·0–21·5)	6·9 (20–19·0)	10·2 (2·0–33·5)	..
Erythrocyte sedimentation rate, mm/h (n=53)	18·0 (9·0–40·0)	20·0 (10·0–33·5)	14·5 (8·3–46·5)	..
Early morning stiffness, min (n=58)¶	45 (10–120)	45 (10–120)	30 (5–75)	..
HAQ score (n=54)‖	0·8 (0·4–1·4)	0·6 (0·4–1·4)	1·0 (0·5–1·5)	..
Global VAS score, 0–100 (n=44)**	50 (30–53)	50 (35–55)	30 (25–50)	..
Tender joint count 28 (n=57)††	2 (1–4)	1 (0–3)	2 (1–5·25)	..
Swollen joint count 28 (n=58)‡‡	0 (0–1)	0 (0–0)	2 (1–3)	..
On glucocorticoids at time of MRI				
Yes§§	7 (12%)	3 (9%)	4 (16%)	..
Hydrocortisone replacement for adrenal insufficiency only	6 (10%)	4 (11%)	2 (8%)	..
No	47 (78%)	28 (80%)	19 (76%)	..

(Table 1 continues on next page)

	All immune checkpoint inhibitors (n=60)	Arthralgia* (n=35)	Inflammatory arthritis (n=25)	Healthy controls (n=20)
(Continued from previous page)				
On glucocorticoids 4 weeks before MRI	3 (5%)	1 (3%)	2 (8%)	..
On DMARDs at time of MRI¶¶	1 (2%)	0	1 (4%)	..
On concurrent chemotherapy or small molecule inhibitors||||	4 (7%)	2 (6%)	2 (8%)	..
Additional immune-related adverse event				
Thyroid dysfunction	12 (20%)	4 (11%)	8 (32%)	
Colitis	11 (18%)	5 (14%)	6 (24%)	..
Dermatological	10 (17%)	6 (17%)	4 (16%)	..
Hepatitis	8 (13%)	4 (11%)	4 (16%)	..
Hypoadrenalism	5 (8%)	3 (9%)	2 (8%)	..
Diabetes	2 (3%)	0	2 (8%)	..
Renal	2 (3%)	1 (3%)	1 (4%)	..
Hypopituitarism	1 (2%)	1 (3%)	0	..
Pancreatic insufficiency	1 (2%)	0	1 (4%)	..
Uveitis	1 (2%)	0	1 (4%)	..
Pneumonitis	1 (2%)	1 (3%)	0	..
No additional immune-related adverse event	22 (37%)	14 (40%)	8 (32%)	..

Data are n (%), n/N (%), median (IQR) or mean (SD). HAQ=health assessment questionnaire. VAS=visual analogue scale. DMARD=disease-modifying antirheumatic drug. *Five patients in the arthralgia group had polymyalgia rheumatica on clinical assessment. †Eight (13%) had a personal history of autoimmune disease: three thyroid dysfunction, one type 1 diabetes, one psoriasis, one ulcerative colitis, one polymyalgia rheumatica, and one giant cell arteritis. ‡11 patients (20%) had a family history of autoimmune disease in a first-degree relative: six inflammatory arthritis, two psoriasis, one vitiligo, one thyroid dysfunction, and one connective tissue disease (Sjögren's disease and systemic sclerosis). §n=24 for inflammatory arthritis group. ¶n=34 for arthralgia group and n=24 for inflammatory arthritis group. ||n=33 for arthralgia group and n=20 for inflammatory arthritis group. **n=27 for arthralgia group and n=17 for inflammatory arthritis group. ††n=33 for arthralgia group and n=24 for inflammatory arthritis group. ‡‡n=34 for arthralgia group and n=24 for inflammatory arthritis group. §§Median prednisolone doses: 9 mg in all immune checkpoint inhibitor group, 5 mg in arthralgia group, and 9·5 mg in inflammatory arthritis group. ¶¶One patient was on methotrexate for joint toxicity at the time of MRI. ||||One patient on encorafenib plus binimetinib, one patient on paclitaxel plus carboplatin, one patient on axitinib, one patient on pemetrexed and one patient in a clinical trial with a 50% chance of being on olaparib.

Table 1: **Baseline characteristics**

linked to joint degeneration or marrow infiltration by the primary tumour. Additionally, spine vertebral corner bone oedema was required in at least one site. At least one abnormality required a score of 2. Bone oedema in the cervical spine or lumbar spine was considered in relation to disc degeneration at these sites and the presence of degenerative changes was ascribed to degenerative arthritis. Finally, the non-specific pattern of inflammation included those not meeting criteria of one of the above patterns.

Patients were followed up over 6 months as per usual clinical care, and data were collected on immune-related adverse events and immunosuppressive medications. Musculoskeletal toxicity was managed according to the strategy outlined below and in accordance with European Alliance of Associations for Rheumatology consensus;[16] NSAIDs were given initially for mild symptoms. For moderate to severe symptoms, glucocorticoids were used at the lowest dose required to control symptoms (either an intra-articular injection or injections or a 120 mg intra-muscular methylprednisolone injection). If a patient required frequent intra-articular or intra-muscular glucocorticoid injections (ie, more frequently than every 12 weeks), oral prednisolone was prescribed. Disease-modifying antirheumatic drug (DMARD) initiation with methotrexate was considered in patients who required more than 10 mg prednisolone per day to control their symptoms. Patients with a polymyalgia rheumatica presentation were started on 15 mg prednisolone orally with the aim to slowly taper, as per usual practice for this indication. Patients with arthralgia and inflammatory arthritis were managed similarly as above and according to symptom severity.

Statistical analysis

For the sample size, we followed the principle of having 12 participants per group for pilot observational studies.[17] A summed total score of 0–26 was obtained for appendicular joint synovitis for each participant and median total score values were presented for each group. Total scores were compared between patients and healthy controls with Mann–Whitney *U* tests. Median differences with 95% CIs were calculated by use of the Hodges–Lehmann estimator. This process was then repeated for appendicular joint erosions (total score 0–34), tenosynovitis in tendons (total score 0–4), enthesitis in entheses (total score 0–24), and bursitis in bursae (total score 0–8).[13]

The presence of all abnormalities at each site was compared between patients and healthy controls with the χ^2 test. Fisher's exact test was used if the χ^2 assumption was violated. Cohen's κ statistic was used to measure inter-rater agreement between the two scorers for all sites. The ϕ correlation coefficient was used to assess the

	Arthralgia (n=35)	Inflammatory arthritis (n=25)	Healthy controls (n=20)	Arthralgia *vs* inflammatory arthritis		Arthralgia *vs* healthy controls		Inflammatory arthritis *vs* healthy controls	
				Median difference (95% CI)	Adjusted p value*	Median difference (95% CI)	Adjusted p value*	Median difference (95% CI)	Adjusted p value*
Appendicular joint synovitis (0–26)	9·0 (5·0 to 12·0)	10·0 (5·0 to 15·5)	2·0 (0·0 to 3·3)	2·0 (–5·0 to 1·0)	0·59	–6·0 (–9·0 to 4·0)	<0·0001	–8·0 (–11·0 to –5·0)	<0·0001
Appendicular joint erosions (0–26)	2·0 (0·0 to 4·0)	2·0 (0·5 to 6·5)	0·0 (0·0 to 1·0)	0·0 (–2·0 to 1·0)	1·000	–1·0 (–2·0 to 0·0)	0·0045	–2·0 (–3·0 to –1·0)	0·0041
Bursitis (0–8)	4·0 (2·0 to 6·0)	2·0 (0·0 to 6·0)	2·0 (0·0 to 2·8)	1·0 (0·0 to 2·0)	0·68	–2·0 (–4·0 to 1·0)	0·0055	–1·0 (–2·0 to 0·0)	0·56
Enthesitis (0–24)	2·0 (0·0 to 3·0)	2·0 (1·0 to 4·0)	0·0 (0·0 to 0·8)	0·0 (–1·0 to 1·0)	1·000	–2·0 (–2·0 to 0·0)	0·0019	–1·0 (–3·0 to –1·0)	0·0009
Tenosynovitis (0–4)	0·0 (0·0 to 1·0)	0·0 (0·0 to 2·0)	0·0 (0·0 to 0·0)	0·0 (–1·0 to 0·0)	0·95	0·0 (0·0 to 0·0)	0·024	0·0 (–1·0 to 0·0)	0·0082

Data are median (IQR) unless otherwise stated. *The p value has been adjusted for pairwise comparisons by use of Bonferroni correction. The adjusted p value threshold is 0·05/3=0·017.

Table 2: **Median MRI inflammation scores in arthralgia and inflammatory arthritis induced by immune checkpoint inhibitors compared with healthy controls**

relationship between physical examination findings (tender joints [present or absent] and swollen joints [present or absent]) and whole-body MRI-detected inflammation (present or absent; appendix p 4). Statistical significance for all tests was defined as p values less than 0·05. The Bonferroni correction was applied directly to the p values for the three pairwise comparisons for each MRI parameter. The adjusted p value threshold is therefore 0·05/3=0·017. The analysis was done with SPSS statistical software (version 28).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Oct 20, 2021, and May 22, 2024, 60 patients (35 [58%] with arthralgia and 25 [42%] with inflammatory arthritis) who met the inclusion criteria were recruited. The mean age of patients was 65 years (SD 11), 34 (57%) were men, 26 (43%) were women, and all patients were White (table 1). 42 (70%) patients were taking anti-PD-1 or anti-PD-L1 monotherapy. 18 (30%) patients were taking combination therapy with an anti-PD-1 or anti-PD-L1 therapy together with an anti-CTLA-4 therapy. The three most common malignancies were melanoma (30 [50%] of 60), lung cancer (11 [18%]), and renal cancer (eight [13%]). 20 healthy controls were recruited from Oct 18, 2023, to March 15, 2024. The mean age was 62 years (SD 7), 12 (60%) were men, eight (40%) were women, and all were White (table 1).

The median time to onset of musculoskeletal symptoms from immune checkpoint inhibitor initiation was 3·5 months (IQR 1·4–11·0). Five (20%) of 25 patients in the arthralgia group had polymyalgia rheumatica according to clinical assessment. The majority (53 [88%]) of patients were autoantibody negative. Seven (12%) patients were prescribed glucocorticoids at the time of MRI (not including those on hydrocortisone replacement for adrenal insufficiency). 38 (63%) had at least one other additional immune-related adverse event. The most common additional immune-related adverse events were thyroid dysfunction (12 [20%]), colitis (11 [18%]), and dermatological manifestations (ten [17%]).

Patients with inflammatory arthritis and arthralgia had significantly higher levels of overall inflammation and erosions compared with healthy controls (table 2). Patients with arthralgia had a median joint synovitis score of 9·0 (IQR 5·0–12·0) and those with inflammatory arthritis had a score of 10·0 (5·0–15·5), compared to healthy controls who had a median score of 2·0 (0·0–3·3). The median erosion scores were 2·0 (IQR 0·0–4·0) for patients with arthralgia and 2·0 (0·5–6·5) for those with inflammatory arthritis compared to 0·0 (0·0–1·0) for healthy controls. There were no significant overall differences between patients with inflammatory arthritis and arthralgia.

Acromioclavicular (46 [77%] of 60), glenohumeral (45 [75%] of 60), wrist (43 [73%] of 59), and metacarpophalangeal (35 [59%] of 59) joint synovitis were frequently identified in patients treated with an immune checkpoint inhibitor. Knee joint synovitis was more frequent in patients with inflammatory arthritis (16 [67%] of 24) than in those with arthralgia (10 [29%] of 35). The wrist joint was the most common site for erosions (29 [49%] of 59). Trochanteric (41 [68%] of 60) and subdeltoid (30 [50%]) bursitis as well as ischial tuberosity (36 [60%]) and pubic symphysis (33 [55%]) enthesitis were also highly prevalent in patients with inflammatory arthritis and those with arthralgia. Vertebral body anterior corner changes and sacroiliac bone oedema and erosions were uncommon. Endplate vertebral body bone oedema was common (34 [57%] of 60) but attributed to degenerative changes or metastases with no significant differences between patients treated with an immune checkpoint inhibitor and healthy controls (table 3).

There was a weak correlation between whole-body MRI-detected inflammation and clinical examination findings in patients with inflammatory arthritis and those with arthralgia (appendix p 4).

	All immune checkpoint inhibitors (n=60)	Arthralgia (n=35)	Inflammatory arthritis (n=25)	Healthy controls (n=20)	Adjusted p value arthralgia *vs* inflammatory arthritis*	Adjusted p value arthralgia *vs* healthy controls*	Adjusted p value inflammatory arthritis *vs* healthy controls*
Appendicular joint synovitis							
Acromioclavicular	46 (77%)	25 (71%)	21 (84%)	8 (40%)	0·77	0·066	0·0066
Glenohumeral	45 (75%)	27 (77%)	18 (72%)	3 (15%)	1·000	<0·0001	0·0004
Sternoclavicular	33 (55%)	20 (57%)	13 (52%)	4 (20%)	1·000	0·023	0·083
Wrist	43/59 (73%)	24/34 (71%)	19 (76%)	8 (40%)	1·000	0·12	0·043
Metacarpophalangeal 2–5	35/59 (59%)	21/34 (62%)	14 (56%)	6 (30%)	1·000	0·096	0·24
Proximal interphalangeal 2–5	15/59 (25%)	6/34 (18%)	9 (36%)	0	0·29	0·17†	0·0069†
Hips	27/58 (47%)	16/34 (47%)	11/24 (46%)	1 (5%)	1·000	0·0039	0·0074
Knees	26/59 (44%)	10 (29%)	16/24 (67%)	3 (15%)	0·011	0·63†	0·0017
Appendicular joint erosions							
Acromioclavicular	19 (32%)	11 (31%)	8 (32%)	4 (20%)	1·000	1·000	1·000
Glenohumeral	20 (33%)	10 (29%)	10 (40%)	0	1·000	0·019†	0·0031†
Sternoclavicular	17 (28%)	11 (31%)	6 (24%)	0	1·000	0·010†	0·065†
Wrist	29/59 (49%)	16/34 (47%)	13 (52%)	2 (10%)	1·000	0·020	0·0089
Metacarpophalangeal 2–5	15/59 (25%)	9/34 (26%)	6 (24%)	4 (20%)	1·000	1·000†	1·000†
Proximal interphalangeal 2–5	3/59 (5%)	0/34	3 (12%)	0	0·20†	1·000	0·49†
Hips	4/58 (7%)	1/34 (3%)	3/24 (13%)	0	0·56†	1·000†	0·46†
Knees	5/59 (8%)	2 (57%)	3/24 (13%)	0	0·97†	1·000†	0·46†
Tenosynovitis							
Hand flexor	21/59 (36%)	11/34 (32%)	10 (40%)	0	1·000	0·011†	0·0031†
Hand extensor	9/59 (15%)	5/34 (15%)	6 (24%)	1 (5%)	0·80†	0·84†	0·27†
Enthesitis							
First costochondral	0	0	0	0	1·000	1·000	1·000
Spinous process L5	1 (2%)	0	1 (4%)	0	1·000†	1·000	1·000†
Anterior inferior iliac spine	4 (7%)	2 (6%)	2 (8%)	1 (5%)	1·000†	1·000†	1·000
Ischial tuberosity	36 (60%)	22 (63%)	14 (56%)	4 (20%)	1·000	0·0066	0·030
Pubic symphysis	33 (55%)	18 (51%)	15 (60%)	2 (10%)	1·000	0·0064	0·0027
Tibial tuberosity	4 (7%)	2 (6%)	2 (8%)	0	1·000†	1·000†	0·91†
Vertebral body bone oedema							
Endplate	34 (57%)	21 (60%)	13 (52%)	16 (80%)	1·000	0·39	0·15
Anterior corner	4 (7%)	1 (3%)	3 (12%)	1 (5%)	0·57†	1·000†	1·000†
Sacroiliac bone oedema	5 (8%)	3 (9%)	2 (8%)	2 (10%)	1·000†	1·000†	1·000†
Sacroiliac bone erosions	3 (5%)	1 (3%)	2 (8%)	1 (5%)	1·000†	1·000†	1·000†
Bursitis							
Subdeltoid	30 (50%)	17 (49%)	13 (52%)	8 (40%)	1·000	1·000	1·000
Trochanteric	41 (68%)	27 (77%)	14 (56%)	9 (45%)	0·25	0·048	1·000

Data are n (%) or n/N (%), unless otherwise stated. *The p value has been adjusted for pairwise comparisons with Bonferroni correction. The adjusted p value threshold is 0·05/3=0·017. †Fishers exact test used as χ^2 assumption of no expected cell count less than 1 and greater than 20% of expected cell counts less than 5 was violated.

***Table 3*: Comparison of whole-body MRI abnormalities**

Cohen's κ analysis for all sites scored was performed. Two measures showed substantial correlation (left ischial tuberosity: κ=0·772, left sacroiliac bone oedema: κ=0·796), while all other measures showed full agreement (κ>0·8) between the two scorers.

All healthy controls showed a minimal or non-specific pattern of inflammation. A polymyalgia rheumatica (extracapsular) pattern of inflammation was identified in seven (12%) of 60 patients. All patients in this group had bilateral trochanteric bursitis and ischial tuberosity inflammation. Six (86%) of these seven patients also had pubic symphysis inflammation. Three (43%) of these patients had score 2 synovitis in one joint (two glenohumeral and one wrist joint synovitis). No score 2 extensor or flexor tendon involvement or score 2 erosions were seen.

A peripheral inflammatory arthritis pattern was seen in 22 (37%) of 60 patients, with five (23%) of 22 patients having just small joint inflammatory arthritis, seven (32%) having just large joints, and ten (45%) having both large and small joints. Seven (32%) of 22 patients had score 2 extensor or flexor tendon involvement, five (23%)

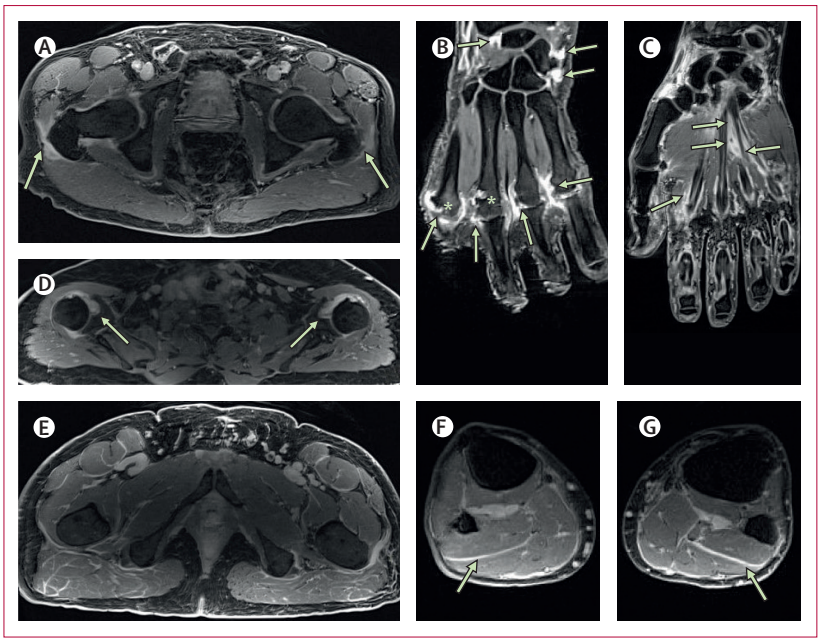

Figure: **Example features seen in overlapping pattern of inflammatory arthritis and polymyalgia rheumatica with whole-body MRI**
(A) Extensive bilateral trochanteric bursitis, which is greater on the right side of the patient (arrows). (B) Extensive metacarpophalangeal and wrist synovitis (arrows) and also extensive second metacarpophalangeal head destruction (denoted by *) and third metacarpophalangeal joint erosion (denoted by *). (C) Extensive flexor tenosynovitis (arrows). (D) Extensive bilateral glenohumeral synovitis (arrows). Examples of myofascial inflammation. (E) Extensive pelvic fascial inflammation. (F) Right knee diffuse fascial oedema. (G) Left knee diffuse fascial oedema.

had bilateral score 2 trochanteric bursitis, and ten (45%) had at least one score 2 erosion.

Notably, 12 (20%) of 60 patients met the criteria for both a polymyalgia rheumatica (extracapsular) pattern and a peripheral inflammatory arthritis pattern, indicating an overlapping imaging phenotype of polymyalgia rheumatica and inflammatory arthritis (figure). Eight (67%) of these 12 patients also had score 2 extensor or flexor tendon involvement and seven (58%) had at least one score 2 erosion (figure A–D).

Only one patient met the criteria for a spondyloarthropathy pattern with sacroiliac bone oedema and anterior corner vertebral body changes. This patient also met the overlapping polymyalgia rheumatica and inflammatory arthritis pattern.

19 patients did not fit any specific criteria but 11 (58%) of 19 could be considered to have incomplete patterns, which almost met a criteria (appendix p 5): two of these had an incomplete polymyalgia rheumatica (extracapsular) pattern (bilateral trochanteric bursitis and either unilateral ischial tuberosity or unilateral pubic symphysis; at least 1 site score 2), six had an incomplete peripheral inflammatory arthritis pattern (score 2 synovitis in one joint or score 1 synovitis in >3 joints) and three had an incomplete overlapping polymyalgia rheumatica and peripheral inflammatory arthritis pattern. No score 2 extensor or flexor tendon involvement was seen. Three (16%) of 19 patients had at least one score 2 erosion.

Evidence of atypical myofascial inflammation was identified in four patients after a systematic review of all scans. Atypical myofascial inflammation was identified at the shoulders, knees, and pelvis, and was generalised in one patient. Two of these patients had a non-specific pattern of MRI inflammation, one had peripheral inflammatory arthritis, and one had overlapping polymyalgia rheumatica and inflammatory arthritis. Examples of patients with myofascial inflammation are shown in the figure (E–G).

The baseline characteristics of patients according to whole-body MRI imaging patterns are summarised in the appendix (pp 6–7). The overlapping polymyalgia rheumatica and inflammatory arthritis group were the oldest with a mean age of 73 years (SD 9), had the fastest symptom onset (median 2 months [IQR 1–3]), and were most likely to be receiving combination immune checkpoint inhibitor therapy (six [50%] of 12). The inflammatory arthritis group had the highest HAQ (median 0·88 [IQR 0·25–1·63]) and global VAS scores (median 50 [30–55]). Interestingly, the polymyalgia rheumatica group was the youngest with a mean age of 59 years (SD 9) and had the lowest inflammatory marker concentrations (median CRP 2 mg/dL [IQR 2–11]). Of the patients with a previous history of autoimmune disease, three (previous history of ulcerative colitis, giant cell arteritis, and psoriasis) had an inflammatory arthritis MRI pattern of inflammation and one (previous history of polymyalgia rheumatica) had a polymyalgia rheumatica MRI pattern.

39 (65%) of 60 patients were followed up for 6 months after whole-body MRI assessment; five (13%) of 39 had polymyalgia rheumatica or extracapsular pattern, 13 (33%) had peripheral inflammatory arthritis, seven (18%) had overlapping polymyalgia rheumatica and inflammatory arthritis, and 14 (36%) had a non-specific pattern (appendix p 8). Of the five patients requiring DMARD initiation to control their symptoms, four (80%) were in the peripheral inflammatory arthritis group. The fifth patient had a non-specific MRI pattern but had myofascial inflammation.

23 (59%) of 39 patients had stopped receiving immune checkpoint inhibitor therapy at 6 months' follow-up; five (22%) of 23 stopped therapy due to completing the immune checkpoint inhibitor treatment, three (13%) due to cancer progression, one (4%) due to patient choice, and 11 (48%) due to other immune-related adverse events. Three patients had their immune checkpoint inhibitor stopped by their oncologists due to musculoskeletal toxicity.

Discussion

This imaging study is, to the best of our knowledge, the largest and most comprehensive characterisation of a prospective cohort of patients who developed new

musculoskeletal symptoms after exposure to immune checkpoint inhibitors. The majority of patients in our cohort (35 [58%] of 60) had arthralgia without clinically apparent synovitis or tenosynovitis. Importantly, these patients had a similar burden of MRI inflammation (synovial, tendon, entheseal, and bursal inflammation, and erosions) to those with clinically apparent synovitis or tenosynovitis. Additionally, despite a median symptom onset of only 2·5 months in those with arthralgia, erosions were frequently identified. Previous imaging observations have also identified early erosive pathology after immune checkpoint inhibitor exposure.[7] This is an important finding as arthralgia without clinically apparent arthritis is reported in up to 43% of patients exposed to immune checkpoint inhibitors.[3] Interestingly, the correlation between MRI findings and physical examination findings in our patients was weak, highlighting the potential importance of imaging investigations in the management of these patients.

The high prevalence of subclinical musculoskeletal inflammation associated with immune checkpoint inhibitors might have wider implications for patients; subclinical autoimmunity might be prevalent in other organ systems in patients who have vague, non-specific symptoms or even in those who are asymptomatic. This has been shown in patients with colitis and myocarditis.[18,19] A high prevalence of subclinical immune-related adverse events could be both beneficial and detrimental; cancer outcomes might be better in some patients with immune-related adverse events (regardless of the grade) than in those who do have any immune-related adverse events.[20]

This study suggests that patients with new arthralgia or inflammatory arthritis after exposure to an immune checkpoint inhibitor have one of four whole-body MRI patterns; overlapping polymyalgia rheumatica and peripheral inflammatory arthritis, peripheral inflammatory arthritis, polymyalgia rheumatica, and a non-specific pattern group. Notably, we describe a distinct overlapping polymyalgia rheumatica and inflammatory arthritis phenotype in a high proportion of patients with arthralgia or inflammatory arthritis induced by an immune checkpoint inhibitor. These patients have erosive peripheral joint synovitis alongside typical extracapsular polymyalgia rheumatica features and a high frequency of hand tenosynovitis. Inflammatory arthritis and polymyalgia rheumatica induced by immune checkpoint inhibitors have been previously reported.[1–2] Polymyalgia rheumatica due to immune checkpoint inhibitors appears to be associated with a higher prevalence of peripheral inflammatory arthritis compared with classical polymyalgia rheumatica.[21] Our data are consistent with these findings, but also show that patients with an overlapping polymyalgia rheumatica and inflammatory arthritis phenotype induced by a immune checkpoint inhibitor frequently have joint erosions and hand tenosynovitis. Although hand tenosynovitis has been reported in classical polymyalgia rheumatica, this condition is typically non-erosive[22] and therefore overlapping polymyalgia rheumatica and inflammatory arthritis induced by an immune checkpoint inhibitor is likely to represent a distinct, more aggressive disease entity. Interestingly, patients with an overlapping polymyalgia rheumatica and inflammatory arthritis phenotype also had the shortest symptom onset (median 2 months) and were most likely to be receiving combination immune checkpoint inhibitor therapy (six [50%] of 12).

Peripheral inflammatory arthritis was the most frequently identified MRI pattern in our cohort (22 [37%] of 60 patients). A rheumatoid arthritis-like presentation with small joint polyarthritis after exposure to an immune checkpoint inhibitor has been described previously.[1] However, in this study the inflammatory arthritis subgroup was not typical of rheumatoid arthritis, as only five (23%) of 22 patients in this subgroup had small joint polyarthritis, with ten (45%) having mixed small and large joint polyarthritis. The shoulder joints were the most frequently affected joints, in keeping with a previous clinical study.[6] 46 (77%) of 60 patients across all groups had acromioclavicular synovitis and 45 (75%) had glenohumeral synovitis. Acromioclavicular joint synovitis was not included in the peripheral inflammatory arthritis pattern definition since it is a well recognised and a common site of osteoarthritis on both X-ray and MRI, and is often asymptomatic.[23] Patients with a peripheral inflammatory arthritis pattern had the highest baseline and ongoing glucocorticoid requirement. They were also the most likely to receive DMARD therapy (four of the five patients requiring DMARDs were in this group). Tenosynovitis, high disease activity, and delay in rheumatology referral were recently shown to increase the likelihood of requiring DMARD therapy.[24] This study is the first to report the imaging phenotype of musculoskeletal toxicity associated with increased DMARD requirement.

A polymyalgia rheumatica MRI pattern was identified in seven (12%) of 60 patients in our cohort. Interestingly, this group had the lowest baseline CRP concentrations (median 2 mg/dL) and glucocorticoid requirement (three [60%] of five patients; appendix p 8). This finding is consistent with recent data suggesting that polymyalgia rheumatica induced by an immune checkpoint inhibitor has a milder phenotype that can be managed with lower corticosteroid requirements than classical polymyalgia rheumatica.[25] These data suggest that polymyalgia rheumatica induced by an immune checkpoint inhibitor might generally be considered a milder form of musculoskeletal toxicity induced by this drug class.

19 (32%) patients in our study did not fit into a polymyalgia rheumatica, inflammatory arthritis, or spondyloarthropathy pattern. The majority (14 [74%] of 19) had a partial or incomplete pattern, suggesting a forme fruste (ie, an atypical or attenuated form of the disease) that might eventually progress into the complete

form. Four (7%) of 60 patients had an unusual pattern of myofascial inflammation, two of whom did not have inflammatory arthritis or polymyalgia rheumatica features. Myofascial inflammation has been reported previously in patients receiving immune checkpoint inhibitors,[26] but the current study reports the highest number of confirmed cases. Myofascial inflammation can be seen in eosinophilic fasciitis, which has also been reported following immunotherapy.[27] However, the four patients in this study who had this MRI feature did not have any of the typical skin signs that would usually be seen in eosinophilic fasciitis, suggesting that this pattern of inflammation is a new but not uncommon entity, which must be considered after immune checkpoint inhibitor exposure.

Finally, only one patient met the criteria for spondyloarthropathy. In line with previous studies, this suggests that spondyloarthropathy is an uncommon manifestation of a musculoskeletal toxicity induced by an immune checkpoint inhibitor.[28] This has important implications for DMARD selection and suggests that patients might respond better to treatments used for inflammatory arthritis or polymyalgia rheumatica over treatments more predominantly used for spondyloarthropathies.

Given that musculoskeletal toxicity induced by an immune checkpoint inhibitor has a defined trigger (ie, release of T-cell regulation in CTLA-4 or PD-1 pathways, or both), it is tempting to speculate that the arthropathy we describe has a unified immunological, and by extension, micro-anatomical basis, distinct from rheumatoid arthritis or polymyalgia rheumatica. Indeed, although our data suggest similarities between inflammatory arthritis phenotypes induced by immune checkpoint inhibitors and classical forms of inflammatory arthritis, there are also some key differences. We report an overlapping phenotype that appears to represent a distinct, more aggressive disease entity. In keeping with previous reports,[1,29] the patients in this study were largely seronegative for autoantibodies associated with rheumatoid arthritis and few had a personal or family history of autoimmune diseases. It is also noteworthy that synovial fluid samples of patients with inflammatory arthritis induced by an immune checkpoint inhibitor show distinct CD8 T-cell signatures compared with those of rheumatoid arthritis.[28] Therefore, it is possible that our whole-body MRI findings define three subgroups that form part of a unique synovial and extracapsular pathology that is part of the same spectrum of inflammatory arthritis, but distinct from classical autoimmune arthritides.

This study has some limitations. As previous reports have shown imaging findings for inflammatory arthritis induced by an immune checkpoint inhibitor that are similar to those observed for polymyalgia rheumatica, rheumatoid arthritis, and spondyloarthropathy, the global MRI patterns of interest were defined a priori based on classical forms of inflammatory arthritis.[1–2,6–9] As a consequence, some patients were labelled as having a non-specific pattern of inflammation as they did not meet imaging criteria for the defined groups. The significance of this non-specific inflammation is unclear and will be important to address through clinical follow-up and repeat imaging. An alternative, unbiased approach would be to take a more agnostic approach to MRI pattern analysis, such as cluster analysis, which could be explored in future studies. We also included four patients with a history of ulcerative colitis, giant cell arteritis, polymyalgia rheumatica, and psoriasis given that a previous autoimmune disease is not a contraindication for being prescribed an immune checkpoint inhibitor. Although none of these four patients had clinical symptoms, signs, or history of inflammatory arthritis or arthralgia, we accept that these patients were at increased risk of developing an inflammatory arthritis before commencing immune checkpoint inhibitor treatment. In terms of the MRI scoring, although the inter-reader agreement between scorers was good, intra reader agreement was not measured. We were unfortunately unable to image the feet or ankles for logistical reasons (excessive scan time). However, preliminary ultrasound data suggest a low prevalence of musculoskeletal inflammation in the feet and ankles.[11] Finally, the follow-up period of 6 months was relatively short, which precludes definitive conclusions on long-term musculoskeletal outcomes. Further follow-up is required for this.

A major strength of this study is the use of whole-body MRI, which has enabled global patient-level assessment, including spinal, synovial, and extra-capsular inflammation. Previous imaging studies in this field have been retrospective, used multiple imaging modalities, and focused on symptomatic joint areas without predefined imaging protocols. The largest of these was a retrospective observational study of 19 patients with new rheumatic symptoms related to immune checkpoint inhibitors, assessed with various imaging modalities.[6] Our study also provides comprehensive descriptions of musculoskeletal toxicity induced by an immune checkpoint inhibitor regardless of the severity of musculoskeletal symptoms, alongside a healthy control group. Larger studies that look at the burden of musculoskeletal toxicity and other organ toxicities in asymptomatic individuals after immune checkpoint inhibitor exposure will be highly informative. Future work is also required to examine cancer outcomes in those with arthralgia alone.

In conclusion, a similar frequency of subclinical inflammation and erosions were identified in a cohort of patients with cancer who developed arthralgia alone compared with those who developed inflammatory arthritis with visible joint swelling. Musculoskeletal toxicity related to immune checkpoint inhibitors is likely to be considerably under-recognised in clinical practice and many patients labelled with non-specific musculoskeletal symptoms might in fact benefit from rheumatological assessment and treatment for

subclinical inflammation.[30] Clinicians should be aware that patients can present with overlapping features of both polymyalgia rheumatica and peripheral inflammatory arthritis. Those with peripheral inflammatory arthritis might be more likely to require DMARDs in addition to glucocorticoids and should be followed up closely. These findings could help to optimise the management of patients who develop musculoskeletal symptoms after exposure to an immune checkpoint inhibitor and also advance our understanding of how toxicities caused by immune checkpoint inhibitors relate to classical autoimmune diseases.

Contributors

KHa, NS, and KM contributed to the study conception and design. KHa, NS, SS, and KM collected the data. KHa, ER, DM, and KM interpreted the data. KHa and LD directly accessed and verified the underlying data. KHa, LD, and KA analysed the data. KHa wrote the initial draft of the manuscript. All authors contributed to subsequent drafts of the manuscript and had full access to all data in the study. All authors approved the final version and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

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