ORIGINAL INVESTIGATIONS

The Debut of Inflammatory Musculoskeletal Pathology in Patients Receiving Anticancer Therapy with PD-1/PD-L1 Pathway Inhibitors

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Objective: *to describe musculoskeletal immune-mediated adverse events (iAEs) associated with the therapy of solid tumors with immune checkpoint inhibitors (ICIs, inhibitors of the PD-1/PD-L1 pathway).*

Patients and methods. *13 patients receiving ICIs therapy with musculoskeletal iAEs were examined. The average age of patients was 59±10 years. All cases had a histologically verified diagnosis of a malignant solid neoplasm: melanoma (n=5), kidney cancer (n=3), bladder cancer (n=2), non-small cell lung cancer (n=1), breast cancer (n=1), cervical cancer (n=1). All patients were prescribed inhibitors of the PD-1/PD-L1 signaling pathway: nivolumab (n=6), pembrolizumab (n=3), atezolizumab (n=3), prolgolimab (n=1). In 7 (54%) patients, in addition to musculoskeletal disorders, other AEs were also detected: thyroiditis (n=3), neuropathy (n=2), rash (n=1), dry syndrome (n=1), hepatitis (n=1). The median time from the start of antitumor immunotherapy (IT) to the onset of musculoskeletal pathology was 20 [9; 48] weeks.*

Results and discussion. *Clinical manifestations of musculoskeletal pathology included: synovitis in 9 (69%) patients, tenosynovitis in 11 (85%), enthesitis in 4 (31%), morning stiffness in the joints for more than 30 minutes in 4 (31%). In 11 cases, musculoskeletal pathology was persistent (in 9 patients with arthritis and 2 with periarthritis) and in 2 – transient. The knee (77%), shoulder (69%) and hand (54%) joints were most frequently affected, with bilateral involvement in 9 (69%) patients. Inflammatory changes in the joints were represented by mono- (n=1), oligo- (n=3) and polyarthritis (n=5), including those involving the small joints of the hands and/or feet (n=5) and predominantly affecting the joints of the lower limbs (n=3). In 3 patients with arthritis, periarticular changes dominated in clinical picture (in 2 patients with symmetrical polyarthritis and severe tenosynovitis, in another 1 patient – with RS3PE syndrome).*

The severity of musculoskeletal pathology was assessed using the CTCAE v5.0 toxicity criteria: grade 1 was documented in 2 (15.5%), grade 2 in 9 (69%), and grade 3 in 2 (15, 5%) patients. Laboratory workup revealed elevation of ESR ≥30 mm/h (median – 34 [14; 42] mm/h) in 7 out of 12 (58%) patients, elevation of CRP level >5 mg/l (median – 7.2 [4.6; 12.9] mg/l) – in 7 out of 10 (70%). In 7 out of 10 patients, antinuclear antibodies (Hep2) were detected in titers: 1:160 (n=2), 1:320 (n=3), 1:640 (n=2). Rheumatoid factor and antibodies to cyclic citrullinated peptide were not detected in any case.

Therapy for musculoskeletal AEs included non-steroidal anti-inflammatory drugs (n=10), oral systemic glucocorticoids – GC (n=5), methotrexate – MT (n=1) and hydroxychloroquine (n=5), intra-articular administration of GC (n=1). Five patients with arthritis required long-term therapy (median duration – 12 [3; 12] months), in 1 patient with polyarthritis and severe tenosynovitis, antitumor IT was interrupted for the duration of the course of MTX treatment.

Conclusion. *It has been shown that musculoskeletal iAEs have heterogeneous manifestations and may require long-term treatment and in rare cases, anticancer therapy interruption. Additional studies and close cooperation between rheumatologists and oncologists are needed to obtain a more complete understanding of the nature and spectrum of musculoskeletal AEs, to identify their clinical, laboratory and instrumental features, and to develop an management of patients algorithm.*

Keywords: *immune checkpoint inhibitors; immune-mediated adverse events; immunotherapy; oncology; rheumatic complications; musculoskeletal pathology.*

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Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that block the natural and anti-tumor activity of the immune system. As a result, T-cell cytotoxic immunity is activated against cancer cells. The first ICI drug was approved by FDA in 2011; this revolutionized oncology and made it possible to successfully treat previously incurable tumors. The scientists who discovered ICI therapy were awarded the Nobel Prize in 2018 [1].

The therapy with ICIs is highly effective but associated with inflammatory immune-related adverse events (irAEs), which can affect various organs and systems including the musculoskeletal system. The true prevalence of irAEs is unknown [2].

According to the meta-analysis of placebo-controlled randomized clinical trials of ICIs, the prevalence of musculoskeletal irAEs is 9.8–12.9% [3]. At the same time, some researchers suggested that musculoskeletal irAEs are not carefully recorded in clinical trials and in real clinical practice their prevalence can reach 22%, which potentially makes them one of the most common irAEs [4].

It is considered that inflammatory arthritis and polymyalgia rheumatica-like syndrome are the most common types of musculoskeletal irAEs. In rare cases the immune-related myositis also occurs. The phenotypic features of musculoskeletal irAEs have been described based on clinical case series and several small retrospective and prospective studies [4]. The treatment algorithm for musculoskeletal irAEs hasn't been completed [4]. In particular, there are conflicting data about the specifics of prescribing glucocorticoids (GC), synthetic basic anti-inflammatory drugs (sDMARDs), and biologic drugs for patients with musculoskeletal irAEs. In addition, musculoskeletal irAEs, unlike most others, are often persistent and require long-term antirheumatic therapy, and we cannot answer the question of how it affects the effectiveness of antitumor treatment [5–7].

The aim of the study was to describe our own experience with musculoskeletal immune-related adverse events (irAEs) in patients with solid tumors receiving immune checkpoint inhibitors (ICIs, PD-1/PD-L1 inhibitors) therapy.

Patients and methods. From January 2020 to June 2021, we observed 13 patients with inflammatory musculoskeletal disorders manifested during the treatment with ICIs. Patients were recruited in The National Medical Research Radiological Centre of the Ministry of Health of the Russian Federation, Federal State Budgetary Institution "N.N. Blokhin Russian Cancer Research Center" of the Ministry of Health of Russia and in V.A. Nasonova Research Institute of Rheumatology. The patients were >18 years old and had a diagnosis of a malignant solid neoplasm, more often melanoma (38%). Nine (69%) patients had a complete or partial response to anticancer treatment, and 4 (31%) had stabilization of the tumor process. All patients received PD-1/PD-L1 inhibitors: nivolumab (n=6), pembrolizumab (n=3), atezolizumab (n=3), prolgolimab (n=1). Seven (54%) patients also had non-musculoskeletal irAEs, more often thyroiditis (n=3, Table 1). A causal relationship between the musculoskeletal manifestations and anticancer drug treatment was assessed as probable in 10 (77%) cases and as possible in 3 (23%) cases according to the Naranjo algorithm [8].

All patients gave their informed consent to assessing and using their data. The study was approved by the local ethics committee of V.A. Nasonova NIIR.

Severity of musculoskeletal disorders were assessed according to the common terminological criteria for adverse events (AEs) - CTCAE (Common Terminology Criteria for Adverse Events) v5.0. [9].

In 10 patients the serum level of antinuclear antibody (ANA, Hep2, measured by indirect immunofluorescence), rheumatoid factor (RF, measured by nephelometric method), antibodies to citrullinated protein/peptide (ACPA, measured by ELISA) and highly sensitive C-reactive protein (CRP) were assessed. In 12 patients, erythrocyte sedimentation rate (ESR, by Westergren method) was measured. In 6 patients ultrasound evaluation of the affected joints was performed.

Detailed data on the features of each case are presented in Table. 2.

Results. Clinical features of musculoskeletal irAEs. Clinical manifestations of musculoskeletal irAEs included synovitis in 9 (69%) patients, tenosynovitis/ tendinitis in 11 (85%) patients, en-

Table 1. Characteristics of the patients with musculoskeletal irAEs (n=13)

Characteristic	Value
Women, n (%)	7 (54)
Mean age, years, M±σ (min – max)	59±10 (43 – 74)
ICI therapy, n (%):	
PD-1 inhibitors	10 (77)
PD-L1 inhibitors	3 (23)
Tumor type, n (%):	
melanoma	5 (38)
kidney cancer	3 (23)
bladder cancer	2 (15)
non-small cell lung cancer	1 (8)
cervical cancer	1 (8)
breast cancer	1 (8)
Non-musculoskeletal irAEs, n (%):	
thyroiditis	3 (23)
neuropathy	2 (15)
rash	1 (8)
dry syndrome	1 (8)
hepatitis	1 (8)

Table 2. Characteristics of the cases of musculoskeletal irAEs

№	Sex	Age, years	Musculoskeletal manifestations and laboratory findings	Therapy of musculoskeletal irAEs	ICI withdrawal	Clinical outcome of musculoskeletal irAEs
1.	Female	62	Symmetric transient arthralgias and synovitis. ANA - 1/320	No		Regression
2.	Female	65	Asymmetric oligoarthritis. ANA - 1/640, CRP - 12.5 mg/L	GC, GH, NSAIDs	+	Partial regression
3.	Female	74	Symmetrical polyarthritis. ANA - 1/640, CRP - 21 mg /L, ESR - 46 mm / h	GC, GH, NSAIDs	+	Regression
4.	Female	45	RS3PE syndrome. ESR - 40 mm/h	No		Partial regression after changing the dosing regimen of atezolizumab
5.	Male	66	Symmetric transient arthralgia, tenosynovitis	No		Regression
6.	Male	65	Synovitis of the knee. ESR - 38 mm/h	Betamethasone intra-articular		Regression
7.	Female	49	Periarthritis of the lower extremities joints	local NSAIDs		Regression
8.	Male	47	Symmetrical polyarthritis. CRP - 5.5 mg / L, ESR - 30 mm / h	NSAIDs		Regression
9.	Female	43	Symmetrical polyarthritis with severe tenosynovitis. ANA - 1/320, CRP - 50 mg / L, ESR - 40 mm / h	GC, GH, MT, NSAIDs. IT interruption	+	Partial regression
10.	Female	54	Asymmetric oligoarthritis, plantar fasciitis. ANA -1/320, CRP - 6.4 mg/L	NSAIDs		Partial regression
11.	Male	65	Symmetrical polyarthritis. CRP - 7.9 mg / L, ESR - 53 mm / h	GC, GH, NSAIDs	+	Regression
12.	Male	58	Symmetrical polyarthritis with severe tenosynovitis. CRP - 227 mg / L, ESR - 81 mm / h	GC, GH, NSAIDs	+	Partial regression
13.	Male	70	Periarthritis of the shoulder joints. ANA - 1/160	NSAIDs	+	Regression

RS3PE syndrome – remitting seronegative symmetrical synovitis with pitting edema; GH – hydroxychloroquine; MT – methotrexate; NSAIDs – non-steroidal anti-inflammatory drugs; ICI – Immune checkpoint inhibitor.

thesitis in 4 (31%) patients, morning stiffness (more than 30 minutes) in 4 (31%) patients. The knee (77%), shoulder (69%), and hand (54%) joints were most commonly affected; bilateral involvement was observed in 9 (69%) cases (Table 3).

In 11 (85%) patients musculoskeletal irAEs were persistent, and only in 2 (15%) – transient. Transient musculoskeletal disorders (№ 1 and 5) were represented by synovitis, tenosynovitis, and symmetrical arthralgia of small and large joints which developed in the first days after initiation of ICI therapy and resolved spontaneously within a few weeks. In the other cases, musculoskeletal irAEs were manifested by persistent inflammatory disorders of the joints and extra-articular tissues.

Arthritis was detected in 9 patients, including mono- (n=1), oligo- (n=3) and polyarthritis (n=5). Arthritis involved the small joints of the hands and/or feet in 5 cases, and predominantly involved joints of the lower extremities in 3 cases. In all cases, arthritis didn't meet the classification or diagnostic criteria for rheumatic disease.

The clinical characteristic of inflammatory arthritis was represented by tenosynovitis more than synovitis in 3 cases. Two patients (№ 9 and 12) had symmetrical polyarthritis with severe tenosynovitis, one patient (№ 4) had remitting seronegative symmetrical synovitis with pitting edema (RS3PE-syndrome) manifested by tenosynovitis and pitting edema of the hands.

Patients № 7 and 13 had only moderate symptoms of periarticular inflammatory changes.

Severity of musculoskeletal irAEs according to CTCAE v5.0. Musculoskeletal irAEs in 9 (69%) cases had grade 2 according to the CTCAE V5.0 classification. Grade 3 musculoskeletal irAEs were found in patients with polyarthritis and severe tenosynovitis.

Laboratory and instrumental features of musculoskeletal irAEs. Ultrasound examination of the affected joints was performed in 6 patients with arthritis. In all cases, we found sonographic signs of synovitis (with abnormal synovial vascularity in patients № 2, 3, 9, 10) and tenosynovitis. In cases № 9 and 12, the signs of tenosynovitis prevailed over synovitis.

Laboratory findings, including elevated ESR and CRP, were available for 7 patients (ESR values were normal before the onset of musculoskeletal irAEs in all cases). The highest CRP values were in patients with

Table 4. Laboratory findings

Characteristic	Value
RF >15 IU/mL, n (%)	0 (0)*
ACPA >5 U /mL, n (%)	0 (0)*
ANA (Hep2) >1/80, n (%)	7 (70)*
ESR ≥30 mm/h, n (%)	7 (58)**
ESR mm/h, Me [25th; 75th percentile], min – max	34 [14; 42], 7 – 81**
CRP >5 mg/L, n (%)	7 (70)*
CRP mg/l, Me [25th; 75th percentile], min – max	7.2 [4.6; 12.9], 0.8 – 227**

* – 10 patients were tested (№ 1–3, 6, 8–13);
** – 12 patients were tested (№1–6, 8–13).

polyarthritis and severe tenosynovitis (№ 9 and 12). RF, ACPA were negative in all cases. The ANA test was positive without any specificities in 7/10 (70%) patients in titers: 1:160 (n=2), 1:320 (n=3), 1:640 (n=2; Table 4).

Treatment of musculoskeletal irAEs. The transient musculoskeletal irAEs did not require additional drug therapy and in both cases resolved spontaneously within a few weeks after onset. In other cases, antirheumatic therapy with NSAIDs (n=9), oral GC (n=5), intra-articular GC (n=1) and DMARDs (n=6) was carried out. Four patients with persistent musculoskeletal irAEs (№ 7, 8, 10, 13) were treated with NSAIDs only and 1 patient with monoarthritis (№ 6) received a single intra-articular injection of betamethasone.

Five patients with arthritis received oral GC (№ 2, 3, 9, 11, 12), while 3 of them (№ 9, 11, and 12) required at least 15–20 mg daily of prednisone. Oncologists prescribed oral GC to three patients: in 2 cases (№ 9 and 12) prednisolone at a dose of 30 mg and 45 mg daily, respectively, due to musculoskeletal irAEs, and in 1 case (№ 2) at a dose of 125 mg daily due to sensory polyneuropathy. In all these patients, the short-term therapy with medium or high doses of oral GC did not lead to stable control of the musculoskeletal pathology. Rapid relapse of symptoms was observed when the GC therapy was discontinued, or the dose was reduced. GH at a dose of 200–400 mg daily was prescribed for all patients receiving oral GC.

In patient № 9, musculoskeletal irAEs had a progressive course despite the therapy with GC. In this case antitumor treatment was interrupted and a 3-month course of MT therapy at a dose of 25 mg weekly was carried out.

Evolution of musculoskeletal irAEs. During the follow-up period of 1.5 years, in patients with transient tenosynovitis/arthralgia, musculoskeletal manifestations did not recur. In 56% (n=5) of patients, arthritis was characterized by a long course and required a long-term treatment – the median duration of antirheumatic therapy was 12 (3; 12) months. Six patients completed ICI therapy for different reasons (№ 2, 3, 9, 11, 12, 13). Subsequently, complete resolution of musculoskeletal symptoms occurred in only 2 patients.

Discussion. Despite the fact that our sample has a very small size and includes a heterogeneous group of patients, it allows us to update the problem of musculoskeletal irAEs associated with ICI therapy.

Inflammatory arthritis was the most common musculoskeletal irAE in our patients. We didn't find a patient with manifestations of myositis due to its rarity. In addition, we didn't detect definite polymyalgia rheumatica in our group of patients.

There are conflicting data about the development of polymyalgia rheumatica-like syndrome in patients receiving ICI in the previous studies. According to some reports, this is the most common inflammatory musculoskeletal irAE [10], in other studies this diagnosis is much less common [7, 11, 12]. In addition, some researchers call into question the high prevalence of polymyalgia rheumatica among musculoskeletal irAEs. They explain it by the fact that in most studies the cases of this irAE didn't meet the classification criteria of EULAR (European Alliance of associations for Rheumatology) / ACR (American College of Rheumatology) 2012. Moreover, in some cases there was no increase in ESR or CRP levels, and most patients with polymyalgia rheumatica-like syndrome had peripheral joint involvement including the knee and small joints of the hands. In some studies, only a clinical assessment of patient with musculoskeletal AEs was performed. At the same time, clinical features of polymyalgia rheumatica-like syndrome didn't differ from those of other musculoskeletal AEs [13].

Based on our data, we also put in doubt the prevalence of polymyalgia rheumatica among musculoskeletal irAEs. Otherwise, the clinical, laboratory and sonographic features of musculoskeletal irAEs we identified coincided with the previous studies [12, 14]. In particular, we didn't find specific autoantibodies (RF or ACPA) in our patients with arthritis. However, the presence of ANA in some cases requires further study, because of possible involvement of the humoral immune response in the pathogenesis of irAEs [15].

As already noted, musculoskeletal irAEs are often persistent and can retain their activity even after ICI therapy interruption, which distinguishes them from other irAEs [5, 7, 16]. At the same time, the standard treatment with short courses of medium or high doses of oral GCs may not lead to stable control of musculoskeletal irAEs, which also happened in 3 of our patients. Unfortunately, there are no clinical trials of the treatment of musculoskeletal irAEs. Our findings and data from other studies demonstrate the need for long-term antirheumatic treatment in some cases. This underscores the importance of further research on the impact of antirheumatic therapy on cancer outcomes [7].

We still cannot answer the question of what exactly musculoskeletal irAEs are. It remains unclear whether these are idiopathic rheumatic disorders or represent new nosological units. In addition,

there are no specific diagnostic tests to distinguish paraneoplastic disease from idiopathic rheumatic disorders. At the same time, musculoskeletal paraneoplastic syndromes are clinically similar to irAEs and may debut or worsen during antitumor treatment with ICI [17–19].

There are no studies on the issue of determining the causal link between the development of musculoskeletal AEs and anticancer therapy with ICI. The classic Naranjo algorithm allowed us to determine only a probable causal link between the musculoskeletal manifestations and ICI therapy in most cases. Thus, additional research is needed to gain a better understanding of the phenomenon of musculoskeletal irAEs.

Conclusion. Our data demonstrated that the musculoskeletal irAEs may be represented by heterogeneous manifestations and require a long-term treatment. In rare cases musculoskeletal irAEs can lead to suspension of the anticancer treatment with ICI. Additional research and cooperation between rheumatologists and oncologists are needed to gain understanding of the nature of musculoskeletal irAEs and identify their clinical, laboratory and instrumental features.

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