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REVIEW

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Rheumatic immune-related adverse events induced by immune checkpoint inhibitors

Hui Zhong | Jiaxin Zhou | Dong Xu | Xiaofeng Zeng

Department of Rheumatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Key laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Beijing, 100730, China

Correspondence
Dong Xu, MD, Department of Rheumatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shuaifuyuan No. 1, Dongcheng District, Beijing 100730, P.R. China.
Email: xudong74@hotmail.com

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Abstract

Immune checkpoint inhibitors (ICIs) block the major inhibitory pathways in T cells, resulting in an augmented antitumor response. Immune-related adverse events (irAEs) are a new class of side effects caused by ICIs and tend to be more prevalent in patients with preexisting autoantibodies and autoimmune diseases. The rheumatic subset of irAEs mainly includes arthralgia, arthritis, myalgia, myositis, vasculitis, sicca syndrome, scleroderma and systemic lupus erythematosus. The most common classification system for AEs, the Common Terminology Criteria for Adverse Events, is of limited use for irAEs, especially rheumatic irAEs. Therapy with glucocorticoid and temporary or permanent discontinuation of ICIs are the cornerstones of irAE treatment, and can be complemented with immunosuppressants (e.g., methotrexate), biologic agents (e.g., tumor necrosis factor inhibitors and interleukin-6 receptor antagonists), intravenous immunoglobin and plasma exchange. Thus, the evaluation and treatment of rheumatic irAEs require multidisciplinary cooperation among physicians. Here, we review the most prevalent ICI-associated rheumatic irAEs.

KEYWORDS
immune checkpoint inhibitors, PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors, rheumatic immune-related adverse events

1 | INTRODUCTION

Immune checkpoint inhibitors (ICIs) block the major inhibitory pathways in T cells, resulting in an augmented antitumor response. The dominant immune checkpoint molecules are the T-cell surface receptors programmed cell death-1 (PD-1), its ligand PD-L1, and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). Several monoclonal antibodies and fusion proteins against these molecules have been approved and are now in clinical use for the treatment of various cancers. Under physiological conditions, PD-1 and CTLA-4 engagement by their ligands PD-L1 and CD80/CD86 serve to curtail T-cell activation and play a positive role in maintaining immune tolerance. In contrast, tumor cell expression of the inhibitory ligands leads to downregulation of the T-cell response, enabling tumor escape from immunosurveillance.[1]

Although ICIs have a beneficial role in activating tumor antigen-specific T cells, they can also lead to aberrant activation of autoantigen-reactive T cells, leading to side effects that resemble autoimmune diseases. The underlying mechanisms of such immune-related adverse events (irAEs) remain unclear. Although some irAEs, including colitis, hepatitis and pneumonitis, have been well-documented, we have a relatively poor understanding of rheumatic irAEs, which include arthralgia, arthritis, myositis, polymyalgia–rheumatica-like (PMR-like) syndrome, sicca syndrome, vasculitis, scleroderma and systemic erythematosus. In this review, we aim to summarize some of the major epidemiological features, risk factors, clinical characteristics and treatments of rheumatic irAEs associated with ICI treatment.

2 | CHARACTERISTICS OF RHEUMATIC IRAES

2.1 | Risk factors for irAEs

2.1.1 | Preexisting autoantibodies

Patients with preexisting autoantibodies are considered more likely to develop irAEs. In a study by Belkhir et al.,[2] two patients who were positive for anti-cyclic citrullinated peptide (CCP) antibodies developed arthritis and were later diagnosed with rheumatoid arthritis (RA).

Another patient[3] who had preexisting diabetes-related autoantibodies developed type 1 diabetes after treatment with the anti-PD-1 antibody nivolumab. In a retrospective cohort study of 137 patients treated with nivolumab or pembrolizumab monotherapy,[4] patients positive for any autoantibodies were more likely to develop irAEs than those who were autoantibody-negative, although the risk of developing severe irAEs was not increased.

2.1.2 | Preexisting autoimmune diseases (AIDs)

Patients with preexisting AIDs are prone to developing irAEs. Abdel-Wahab et al.[5] conducted a systematic review of 123 patients with cancer and preexisting AIDs who were receiving ICIs, and they found that 75% had exacerbation of preexisting AIDs, irAEs or both. Among these patients, 41% had recurrence or worsening of prior manifestations, 25% developed *de novo* irAEs (differing from their preexisting AIDs), and 9% had both. Rate of adverse events (AEs) were similar in patients with active or inactive AIDs (67% *vs* 75%). Patients who were receiving treatment for preexisting AIDs when ICI therapy was initiated had fewer AEs than those who were not receiving treatment (59% *vs*. 83%). Compared with patients treated with the anti-CTLA-4 antibody ipilimumab, patients treated with anti-PD-1/PD-L1 inhibitors reported more AID flares (62% *vs*. 36%) and more *de novo* irAEs (42% *vs*. 26%).

2.2 | Grading of irAEs

The Rheumatology Common Toxicity Criteria (RCTC)[6] reporting system is widely used in rheumatological clinical trials to describe drug-associated AEs, whereas the Common Terminology Criteria for Adverse Events (CTCAE)[7] system is more commonly used in trials of ICIs. However, there are limitations to the value of the CTCAE for classifying rheumatic irAEs, leading to an underestimation of their severity. For example, arthralgia and myalgia are classified as grade 2 AEs by the CTCAE when functional limitation is present, whereas the RCTC classifies these AEs as grade 3. There are also flaws in the application of the RCTC. The RCTC is less accurate in describing functional limitations than the CTCAE, which further subdivides them into limitations of instrumental and self-care activities of daily living. Arthritis and myositis lack evaluation criteria in the RCTC, probably because these two symptoms are commonly seen in nearly all rheumatic diseases and it is difficult to identify which induced these symptoms. Moreover, rheumatic irAEs sometimes present as an AID with disease-specific activity evaluation systems, such as the Disease Activity Score derivative for 28 joints for RA. Whether these disease-specific evaluation systems should be used to evaluate rheumatic irAEs remains an unanswered question. For example, PMR-like syndrome and inflammatory arthritis do not perfectly conform to their own classification criteria, so such disease evaluation systems may not be suitable for irAEs. Moreover, we should bear in mind that the main purpose of disease-specific evaluation systems is to guide treatment. The prognosis of a cancer patient with irAEs is inherently different from that of a cancer-free patient with the same symptoms, further supporting the notion that rheumatic disease-specific evaluation systems may not be appropriate for patients with cancer. In addition, the heterogeneity of irAEs means that accurate evaluation requires the combined efforts of rheumatologists and oncologists, even when using a standardized evaluation system.

TABLE 1 The general clinical features of rheumatic irAEs

	Rheumatic irAEs
Incidence	0.4%–16%[8,9]
Timing of occurrence	5–11.2months[10,11]
Most common manifestation	Arthralgia, arthritis, myalgia, myositis
Autoantibodies	Mostly negative
Severity	Mild to moderate

3 | CLINICAL FEATURES AND TREATMENT OF RHEUMATIC irAES

The general clinical features of rheumatic irAEs are shown in Table 1.

3.1 | Arthritis

Arthritis is characterized by joint pain and swelling. In a randomized controlled phase III study of 834 patients with melanoma, the incidence of arthritis and arthralgia was 1.8% and 9.4%–11.6%, respectively, for patients treated with PD-1 inhibitors compared with 0 and 5.1%, respectively, for patients treated with CTLA-4 inhibitors.[9] The incidence of arthralgia was higher for patients treated with additional agents; namely, 10% for those treated with nivolumab plus ipilimumab[12] and 42.4% for those treated with an ICI combined with a peptide vaccine.[13] A French pharmacovigilance registry documenting grade ≥2 irAEs in 908 patients treated with ICIs showed a prevalence of 1.2% (10 of 868 patients) for arthritis; 0.2% for both RA and psoriatic arthritis (PsA), and 0.7% for seronegative polyarthritis.[14] A single-center retrospective study of 1293 patients reported a prevalence of 2.6% for arthritis,[15] and a retrospective review of radiologic records of 119 patients who received ICIs for metastatic melanoma found that 3.4% of patients had arthritis.[16]

Arthritis can be classified as RA, PsA, or remitting seronegative symmetrical synovitis with pitting edema (RS3PE), but most patients were diagnosed with undifferentiated arthritis.[17] Depending on the number of joints involved, undifferentiated arthritis can be divided into monoarthritis, oligoarthritis and polyarthritis. Knee arthritis is more common in patients receiving combination ICI therapy, whereas small-joint polyarthritis is more prevalent in patients treated with ICI monotherapy.[10] Plasma levels of acute phase reactants are higher in patients treated with combination ICI therapy compared with monotherapy, and these patients are more likely to have a reactive arthritis-like phenotype (inflammatory arthritis with conjunctivitis or uveitis).[10] Notably, tumor progression should always be taken into consideration when making a differential diagnosis. Albayda et al.[18] reported on a patient with metastatic non–small cell lung cancer who developed pain and joint swelling after treatment with combined nivolumab and ipilimumab, but the symptoms were attributed to tumor progression rather than ICIs.

The lag time between the onset of symptoms and the time of diagnosis of inflammatory arthritis in ICI-treated cancer patients varies. The average time is about 5 to 11.2 months,[10,11] but it is significantly shorter for patients with initial knee involvement than for those with small joint involvement, suggesting a delay in recognition of the latter irAE phenotype by treatment providers.[10] The onset of arthritis after ICI therapy also differs between the rheumatic irAE subtypes. RA usually occurs at after 1 month (range, 3 days to 5 months), whereas undifferentiated oligoarthritis and polyarthritis develop at about 3 months (1–9 months and 1 day–24 months, respectively), and undifferentiated monoarthritis develops at about 9 months (1–24 months).[17] Musculoskeletal rheumatic irAEs tend to develop earlier in patients with preexisting rheumatic diseases than in those without (median 4.6 and 38 weeks, respectively).[19]

Most patients with ICI-induced arthritis are seronegative (antinuclear antibodies, rheumatoid factor and/or anti-CCP antibodies).[10,20–22] Among patients with a confirmed diagnosis of RA, 78% and 89% are positive for rheumatoid factor and anti-CCP antibodies, respectively.[2]

Arthritis in patients with rheumatic diseases is generally detected using ultrasound, X-rays, computed tomography (CT) and magnetic resonance imaging (MRI). A study by Leipe et al.[23] examined detection of synovitis in cancer patients undergoing conventional CT or positron emission tomography (PET)-CT, and CT was found to have low sensitivity (60%) but good specificity (90%) compared with PET-CT. A review by Narayan et al.[24] reported good correlation between the ability of fusion PET-CT and MRI to detect synovitis. These findings indicate that regular PET-CT and conventional CT can be helpful in detecting synovitis in ICI-treated cancer patients, especially those with arthralgia.[23]

The Society for Immunotherapy of Cancer Toxicity Management Working Group[25] recommended that ICI-treated cancer patients should receive individualized treatment and be referred to rheumatologists if they have CTCAE grade ≥2 inflammatory arthritis, have symptoms persisting for >6 weeks, or require treatment with >20 mg prednisone (or equivalent) daily that cannot be tapered to <10 mg/day within 4 weeks. The American Society of Clinical Oncology (ASCO) has provided detailed treatment recommendations based on CTCAE-defined AEs.[26] The majority of patients treated with ICIs develop mild-to-moderate arthritis that generally responds well to nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose corticoids. Monoarthritis without PMR can be managed with NSAIDs or intraarticular injection of glucocorticoids.[23] About 80% of patients require glucocorticoids and 30% require disease-modifying antirheumatic drugs; the latter requirement is particularly common among patients receiving combination ICI therapy.[10] Methotrexate has a good safety profile and can be used as maintenance treatment to acquire and maintain long-term remission.[23] A small number of patients with arthritis might need treatment with tumor necrosis factor-α or interleukin-6 (IL-6) inhibitors. ICIs should be discontinued in patients who develop grade ≥2 arthritis. For patients with grade 2 arthritis, ICIs can resume upon symptom control and reduction in prednisone dose to ≤10 mg/day, whereas for patients with grade 3 or 4 arthritis, the decision to resume ICIs should be made in consultation with a rheumatologist when the AEs is grade ≤1.[26]

Notably, some patients treated with ICIs develop PsA despite having no history of psoriasis before ICI therapy.[17] Glucocorticoids are not recommended for traditional PsA because of the risk of deterioration of psoriasis. However, there are no special recommendations for ICI-induced PsA, and a retrospective study[14] and a study of case series[27] reported that this irAE can be successfully managed by glucocorticoids.

3.2 | Myositis

Myositis is characterized by weakness of the proximal limbs and elevated plasma creatine kinase (CK) with or without myalgia. Eye muscle involvement, presenting as ptosis or diplopia in the absence of anti-acetylcholine receptor antibodies,[28] occurs in some patients. A randomized, open label, phase III study reported an incidence of myalgia of 2% among 272 patients treated with nivolumab,[8] whereas a prospective study found that myalgia was present in up to 18.2% of patients treated with PD-1 inhibitors in combination with a vaccine.[13] In another randomized controlled phase III study,[9] the incidence of myositis was 0.4% and 0.7% for patients treated with CTLA-4 and PD-1 inhibitors, respectively, whereas in a retrospective study of 119 patients treated with CTLA-4 inhibitors,[16] 1.7% of patients showed radiological evidence of myositis. The lag time between ICI initiation and myositis onset has been reported to be between 3 and 19 weeks.[28,29] More men than women tend to develop myositis (ratio of 7:3),[28] and the median age of patients who develop myositis is 71 years. Compared with traditional myositis, ICI-induced myositis seldom involves extramuscular organs such as skin or lungs.[28] Most patients with myositis are seronegative for autoantibodies, but a small fraction are positive for one or more of anti-striated muscle antibody, anti-TIF1-γ antibody, antinuclear antibodies, anti-Ro 52 antibody and anti-PM/Scl antibody.[30-32] Paraneoplastic syndrome-associated muscle involvement should be differentiated from ICI-associated myositis.[28] There is no distinct diagnostic border between myositis and myopathy, and some patients with myositis have myasthenia-like symptoms.[32] The overall incidence of ICI-induced myasthenia gravis (MG) is about 0.12%[33]; among these patients, myositis is detected by muscle biopsy in about 0.9%.[34] Compared with patients with traditional MG, ICI-treated MG patients have lower titers of anti-acetylcholine receptor antibodies,[28] much higher levels of CK, and are more likely to have myositis and myocarditis.[33] In general, plasma CK levels increase before the onset of clinical manifestations, and CK levels in patients with myositis are usually much higher than those in patients with ICI-induced MG.[28]

Moreira et al.[29] analyzed data from a registry of side effects and a cancer center database and found that 32% of patients with ICI-induced myositis had myocardial involvement, and among those with ICI-induced myocarditis, 25% coexisted with myositis.[35] Necrotic myositis was the most common histological finding.[28,30] In a study by Liewluch et al.[36] of 654 cancer patients treated with nivolumab and/or pembrolizumab, five cases of myositis were identified, of

which two presented as immune-mediated necrotic myositis, one as dermatomyositis, and two as nonspecific myositis. Touat et al.[28] studied muscle biopsies from 10 patients with ICI-induced myositis treated with nivolumab, pembrolizumab or durvalumab monotherapy or with nivolumab plus ipilimumab cotherapy. Muscle biopsy showed multifocal necrotic myofibers, major histocompatibility complex class I antigens (MHC-I) of sarcolemma and inflammation of endomysium, consisting mainly of CD68-positive cells expressing PD-L1 and CD8-positive cells expressing PD-1, whereas CD20-positive cells were not detected in significant numbers as in other inflammatory myopathies such as dermatomyositis and antisynthetase syndrome.

CK levels do not perfectly reflect the extent of disease severity in patients with ICI-induced myositis; patients with severe muscle weakness might have mild or no elevation of CK,[30] whereas a small fraction of patients with no clinical symptoms may exhibit elevated CK levels. Thus, it is preferable to evaluate myositis based not only on CK levels but also on the severity of muscle weakness, activity capabilities and extraskeletal muscle organ involvement, such as myocardial involvement.[26]

For patients who develop grade ≥2 myositis, ICIs should be discontinued. Those with grade 2 myositis may resume ICIs upon symptom control, normalization of CK levels and reduction in prednisone dose to <10 mg/day, whereas those with grade 3 or 4 myositis may resume ICIs when the AE is grade ≤1 and immune suppression has been discontinued. However, ICIs should be permanently discontinued if any evidence of myocardial involvement develops. Prednisone should be administered at 0.5–1 mg/kg/day for patients with grade 1 or 2 myositis (at least three CK evaluations), and at 1–2 mg/kg/day for those with grade 3 or 4 myositis. For severe or refractory cases, corticoid pulse therapy, plasma exchange, intravenous immunoglobin, immunosuppressants (e.g., methotrexate) and biological agents (e.g., rituximab and infliximab) should be considered.[26] The response to glucocorticoids is generally good, with complete resolution of the irAE in 50% of patients.[28] Those with myocardial or diaphragmatic involvement have a poorer prognosis.[30]

3.3 | Vasculitis

ICI-induced vasculitis is a rare irAE, but the exact frequency is currently unclear. The median time from ICI initiation to vasculitis onset is about 3 months.[37] A systematic review by Daxini et al.[37] reported on 53 patients treated with PD-1/PD-L1/CTLA-4-targeting ICIs who developed vasculitis. Of the 53, 20 were confirmed to have ICI-associated vasculitis based on the 2012 Revised Chapel Hill Consensus Conference nomenclature (five had been treated with anti-CTLA-4, 14 with anti-PD-1 and one with anti-PD-1/PD-L1/CTLA-4 combination therapy). In that study, large vasculitis (giant cell arteritis, isolated aortitis) and vasculitis of the nervous system (primary angiitis of the central nervous system and isolated vasculitis of the peripheral nervous system) were the most commonly reported types of vasculitis, and all events resolved after ICI withholding and/or glucocorticoid administration.

Patients receiving ICIs have also been reported to develop small-vessel vasculitis, such as eosinophilic granulomatosis,[38] which is characterized by asthma, nasosinusitis, eosinophilia, lung shadows and arthritis. About 2.9% of ICI-treated patients have asymptomatic eosinophilia of unknown cause.[39] Other reported forms include small-vessel vasculitis in both hands causing finger pain and ischemia,[40] mesenteric vasculitis causing stomachache[41] and skin vasculitis causing purpura.[42] Most patients are negative for autoantibodies, although Comont et al.[43] reported on a patient with small-vessel vasculitis in both hands who had a high titer of speckled-pattern antinuclear antibodies.

A few studies have reported histological findings for cancer patients with vasculitis. In patients with ICI-induced giant cell arteritis, temporal artery biopsies showed transmural temporal arteritis, with infiltrates in the adventitia and muscularis layers, narrowed lumen and small focal disruptions in the internal elastic lamina.[44,45] Burel et al.[27]reported one case of cryoglobulinemic vasculitis (type III) induced by a PD-L1 inhibitor, and histopathological analysis revealed arterial thrombosis and capillaritis.

Treatment of ICI-induced vasculitis may involve withdrawal of ICIs and initiation of glucocorticoid therapy. Skin vasculitis may benefit from hydroxychloroquine.[42] Plasma exchange[41] is also an option to concomitantly remove the circulating ICIs, pathogenic autoantibodies and inflammatory cytokines.

3.4 | Polymyalgia–rheumatica (PMR)-like syndrome

PMR-like syndrome is characterized by pain, stiffness and restricted movement in the proximal limbs in the absence of myositis or weakness. PMR-like syndrome usually occurs about 3 months after starting ICI treatment[46] and often accompanied by other rheumatic irAEs. For example, about 88% of patients with arthralgia have concurrent PMR-like syndrome.[23] A multicenter and systematic review by Calabrese et al.[46] evaluated 49 patients with ICI-induced PMR-like syndrome. Sufficient data were available for evaluation of PMR in 37 of the 49 cases according to the 2012 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) Classification criteria, and 28 cases fulfilled the criteria. The most common reason for failing to satisfy the criteria was joint involvement, most commonly the knees, followed by the hands and elbows.

Evaluation of ICI-induced PMR-like syndrome is based on the degree of stiffness, pain and limitation of instrumental activities of daily living.[26] Grade 1 AEs can be managed by acetaminophen and/or NSAIDs, whereas treatment of grade ≥2 AEs should include discontinuation of ICIs and low-to-moderate glucocorticoid therapy. If improvement is seen, glucocorticoids should be tapered over the course of 3–4 weeks. If patients fail to improve, they should be treated as for grade 3 AEs, possibly with higher doses of glucocorticoids for an extended period, or with immunosuppressive agents such as methotrexate or IL-6 inhibitors. Compared with traditional PMR, ICI-related PMR requires treatment with higher doses of glucocorticoids. In the study by Calabrese et al.,[46] about 37% of patients required >20 mg/day prednisone and two patients who failed to

respond to this received the anti-IL-6 antibody tocilizumab. For grade 2 AEs, ICIs can be resumed upon symptom control and reduction of prednisone to <10 mg/day, and for grade 3 or 4 AEs, ICIs may be resumed after consultation with a rheumatologist when the AE is considered grade ≤1.[26]

3.5 | Systemic sclerosis (SSc)

SSc is an AID characterized by skin sclerosis. Barbosa[47] and Tjarkshave[48] reported on three patients (two with melanoma, one with renal cell carcinoma) with cutaneous sclerosis induced by pembrolizumab or nivolumab, all of whom were males aged between 61 and 77 years old. The onset of SSc occurred 15 to 32 weeks after ICI initiation. Two of the cases conformed to the 2013 EULAR/ACR SSc classification criteria; one was diffuse cutaneous SSc, one was limited diffuse cutaneous SSc and one was sclerosis of the trunk and bilateral thigh skin. One patient had Raynaud's syndrome, abnormal nailfold capillaries and bilateral ground glass opacity in the lower lobes of the lung. None of the three patients had pulmonary hypertension, renal crisis or gastroesophageal reflux. Anticentromere and anti-Scl-70 antibody tests were negative. Skin biopsy findings were consistent with the diagnosis of scleroderma.[47,48] Accumulation of collagen was seen in the dermis, with entrapment and displacement of adnexal structures and loss of periadnexal fat. In early skin lesions, mild perivascular lymphocytic inflammation was seen with periadnexal infiltrates of lymphocytes and plasma cells between the dermal and subcutaneous junction. Immunohistochemical staining of CD34 was lost throughout the dermis, indicating that dermal fibroblasts had been replaced by collagens. Although treatment of traditional SSc with high-dose corticoids is not recommended, it remains the mainstay treatment for severe SSc irAEs. Barbosa and Tjarks have advocated that high-dose glucocorticoids should be administered if SSc is suspected in ICI-treated cancer patients. The three patients in their studies all received prednisone 1 mg/kg/day, two received mycophenolate mofetil, one received intravenous immunoglobin and one also received hydroxychloroquine. All three patients showed significant improvement in the skin lesions.

3.6 | Sicca syndrome

Sicca syndrome is characterized by abrupt onset of xerostomia, which is usually more prominent than dry eyes and may be accompanied by parotid enlargement. Anti-SSA/B antibodies are absent in most patients.[49] Features of salivary gland ultrasonography are similar to those seen in Sjögren's syndrome.[21,50] Blake et al.[51] analyzed salivary gland biopsies from 19 patients with ICI-induced sicca syndrome and identified three histopathological patterns: mild nonspecific chronic sialadenitis, mild-to-moderate sialadenitis and severe sialadenitis. Lymphocyte infiltration and epithelial injury were prominent. Immunohistochemical staining demonstrated a predominantly CD3+ T-cell infiltrate, with a slight predominance of CD4+ compared with CD8+ T cells, but CD20+ B cells were absent, which contrasts with the immune cell infiltrates seen in Sjögren's syndrome.[52] Subjective symptoms can be improved in most cases by discontinuing ICIs and administering glucocorticoids, but salivary secretion generally remains very low.[51]

3.7 | Systemic lupus erythematosus (SLE)

Fadel et al.[53] reported the first case of ipilimumab-induced lupus nephritis, which was diagnosed 6 weeks after initiation of treatment. In this patient, serum creatinine was elevated and abnormal red blood cells were found in the urine. Autoantibody tests were borderline positive for antinuclear antibodies (1:100) and positive for anti-double-stranded DNA antibodies. The serum complement level was normal. Kidney biopsy findings[53] were suggestive of lupus nephritis in that slight hypertrophy of podocytes and extramembranous deposits were present, and immunofluorescence staining revealed deposits of IgG, IgM, C3 and C1q in the extramembranous and mesangial regions. The patient's symptoms resolved after discontinuation of ipilimumab and initiation of high-dose corticoids. Raschi et al.[54] analyzed the Food and Drug Administration Adverse Event Reporting System for irAEs in ICI-treated cancer patients. Among the 4870 reported rheumatic episodes, there were 18 cases of SLE, two of cutaneous lupus, two of lupus-like syndrome, one of lupus nephritis and one of central nervous system lupus. Eighteen cases of SLE were induced by PD-1/PD-L1 inhibitors, with the anti-PD-1 inhibitor nivolumab being the most common cause. The median age of the patients developing SLE was 61 years, the female-to-male ratio was 1.6, and the median time to onset after initiation of ICI therapy was 196 days. SLE is rare among irAEs, probably reflecting differences in the underlying pathophysiological mechanisms of SLE compared with other AIDs.

3.8 | Other considerations

This review has focused mainly on common rheumatic irAEs and some relatively rare poorly described rheumatic irAEs, such as scleroderma. The frequencies of PMR, sicca syndrome, vasculitis and SSc are unclear. In a single-center retrospective study of 1293 patients who received ICIs, three patients developed symptoms consistent with sicca syndrome, two with vasculitis, three with PMR-like syndrome and three with SSc.[15] Rarer irAEs, such as fasciitis[55] and tenosynovitis,[56] have been reported only as isolated case reports and were not included in this review.

Bertrand et al.[57] performed a systematic review and meta-analysis of ICI-associated irAEs and identified an overall incidence of all-grade irAEs of 72% (95% confidence interval 65–79%) for CTLA-4 inhibitors, which was higher than that observed with PD-1/PD-L1 inhibitors. However, more studies have been published on rheumatic irAEs induced by PD-1/PD-L1 inhibitors, possibly because they are more commonly prescribed than CTLA-4 inhibitors.[9,58–60] The incidence and prevalence of rheumatic irAEs varies widely across studies,[8,9,58–61] due in large part to the different definitions of rheumatic irAEs built into the study designs. Thus, it is difficult to directly compare the incidence or prevalence of rheumatic irAEs induced by PD-1/PD-L1-targeting versus CTLA-4-targeting drugs. A prospective clinical trial

of patients with melanoma[9] showed higher incidences of arthralgia and myositis in patients with PD-1/PD-L1 inhibitors than with CTLA-4 inhibitors, and published reports suggest that vasculitis is also most frequently caused by PD-1/PD-L1 inhibitors.[37] Nevertheless, the total number of patients treated with each ICI in these studies is unclear, making it difficult to determine which ICIs are associated specifically with vasculitis.

Other common drug toxicities of which manifestations are similar to rheumatic irAEs can also be induced by ICIs, such as arthralgia and myalgia. It might be difficult to distinguish whether they are rheumatic irAEs or not. Common drug toxicities are seldom accompanied by multiple organ involvement and can often be resolved by suspending treatment; in contrast, rheumatic irAEs often involve multiple organs (e.g., articular destruction, myocardial involvement) and are not generally resolved simply by interrupting ICI therapy. Moreover, rheumatic irAEs can occur concomitantly with common drug toxicities. When this does occur, discontinuation of treatment may be helpful in making a differential diagnosis.

Rheumatic irAEs should be taken into consideration when patients treated with ICIs develop rheumatic manifestations, such as arthralgia, arthritis, myalgia, myositis, dry eyes and dry mouth, that cannot be explained by malignancies. The diagnostic work-up should include and/or take into consideration the following: (1) complete rheumatologic history and physical examination of joints, muscle, vessels, skin and other involved organs; (2) tissue-appropriate imaging modalities such as ultrasound, CT and MRI to evaluate tissue damage and (3) autoimmune blood panels, including antinuclear, anti-extractable nuclear antigen and anti-CCP antibodies, rheumatoid factor, CK levels and inflammatory markers (e.g., erythrocyte sedimentation rate, C-reactive protein). Referral to a rheumatologist should be considered if early symptoms are severe or persist. For patients with mild suspected rheumatic irAEs, symptomatic treatment is appropriate. If no improvement is achieved or the irAE is severe, ICIs should be discontinued immediately and the patient referred to a rheumatologist.

In the experience of nonrheumatic irAE treatment, it is safe to resume ICIs. In a retrospective analysis of 482 patients with non–small cell lung cancer who were treated with ICIs,[62] 14% of patients had serious irAEs requiring ICI discontinuation and 56% of those resumed ICI treatment. In the retreatment group, 48% of the patients did not experience irAE recurrence and the remaining 52% had recurrent or new irAEs. Among the latter group, most irAEs were mild and manageable. ASCO has provided guidelines for the resumption of ICI therapy after irAEs of arthritis, myositis and PMR-like syndrome, but not other rheumatic irAEs. Weighing the potential benefit of ICIs and harm of rheumatic irAEs in cancer patients, it is reasonable that patients with grade 1 irAEs could continue with ICIs and patients with grade 2–4 irAEs should be discontinued and treatment for the irAE should be started immediately. After symptoms have improved, the decision to resume ICIs should be made in consultation with rheumatologists. However, ICIs should be discontinued permanently in the event of potentially lethal rheumatic irAEs, such as myocardial involvement.[26]

4 | CONCLUSIONS

Rheumatic irAEs are relatively common in cancer patients receiving ICIs. Musculoskeletal manifestations (arthralgia, arthritis, myalgia, myositis, PMR-like syndrome) are the most common irAEs, but vasculitis, sicca syndrome, systemic sclerosis and SLE have also been reported. Patients with preexisting autoantibodies and AIDs are particularly prone to developing irAEs, and rheumatic irAEs (arthralgia and myositis) are more frequently seen in patients receiving PD-1/PD-L1 inhibitors compared with CTLA-4 inhibitors. When patients treated with ICIs develop rheumatic manifestations that cannot be explained by the malignancy, rheumatic irAEs should be considered and a diagnostic work-up should be carried out. Differentiating between rheumatic irAEs and common toxicities is an important factor in deciding on further treatment. Instruments to assess the severity of AEs, such as CTCAE and RCTC, should be used with full awareness of their limitations for rheumatic irAEs. Temporary or permanent discontinuation of ICIs and administration of corticoids are the cornerstones of rheumatic irAE management, but immunosuppressive agents, biological agents, intravenous immunoglobin and plasma exchange may also be needed in severe or refractory cases. The decision to resume ICIs after resolution of rheumatic irAEs, especially of grade 3 or 4, should be made in consultation with rheumatologists.

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ORCID

Hui Zhong https://orcid.org/0000-0002-8996-0774

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