CLINICAL GUIDELINE

Management of immune checkpoint inhibitor-related rheumatic adverse events

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Abstract
Immune checkpoint inhibitors (ICIs), which target the programmed cell death receptor-1 and cytotoxic T lymphocyte-associated antigen-4 signaling pathways, represent remarkable breakthroughs in cancer treatment and have improved survival among patients with a variety of malignancies. However, the wide use of ICIs is associated with a spectrum of immune-related adverse events (irAEs) that can affect any organ system, and may sometimes be life threatening. Rheumatic irAEs are not an infrequent type of irAE. In this systematic review, we consider the clinical characteristics of rheumatic irAEs, including patients with pre-existing rheumatic diseases, and focus on the management of rheumatic irAEs.

Introduction
Immune checkpoint inhibitors (ICIs) have recently been responsible for remarkable breakthroughs in cancer treatment. ICIs can induce T cell activation by blocking negative costimulation of T cells resulting in enhanced anti-tumor effects, and can ultimately improve survival
among patients with a variety of malignancies. Several ICIs targeting the programmed death receptor-1 (PD-1) and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) pathways have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency. However, ICIs can also affect the immune tolerance of human tissues, potentially leading to a new spectrum of adverse events, termed immune-related adverse events (irAEs). irAEs can occur in almost every human organ system, and the clinical management of, and research into, irAEs thus involves oncologists and other medical specialists.

The major underlying mechanism of classical rheumatic autoimmune diseases involves abnormal activation of the immune system, leading to autoantibody formation or enhanced inflammatory responses. PD-1 expression is increased in synovial tissues in patients with rheumatoid arthritis (RA), but the PD-1 pathway is downregulated during RA disease progression, suggesting that this pathway might be involved in the development of RA. The CTLA-4 pathway also plays an important role in the pathogenesis of RA, and abatacept, a fusion protein composed of CTLA-4 and the Fc region of human immunoglobulin, has already been approved by the FDA for the treatment of RA. Furthermore, the PD-1 pathway has also been shown to be involved in preventing lupus-like symptoms in mouse models.

Rheumatic irAEs are not uncommon irAEs and can generally be classified into two subgroups: new-onset musculoskeletal symptoms or connective tissue disease, and disease flares in patients with pre-existing rheumatic conditions. In a large prospective French study of 524 patients who received ICIs, 35 patients (6.6%) developed rheumatic irAEs, including noninflammatory musculoskeletal symptoms, polymyalgia rheumatica (PMR), and RA. The median period between ICI exposure and the occurrence of rheumatic irAEs was 70 days. Arthralgia and myalgia were the most common symptoms of rheumatic irAEs. However, these symptoms may be overlooked in research and clinical practice if their symptoms are mild, and it is therefore necessary to remind clinicians about the possibility and importance of rheumatic irAEs.

**Polymyalgia rheumatica (PMR)/giant cell arteritis (GCA)**

Polymyalgia rheumatica (PMR) is an inflammatory disease commonly seen in individuals older than 50 years. It is characterized by shoulder and/or pelvic girdle muscle myalgia and stiffness, with increased acute phase reactants and negative rheumatoid factors or anti-citrullinated protein antibody (ACPA). This disorder always responds well to low-dose glucocorticoids. Giant cell arthritis (GCA) is a type of systemic vasculitis that is relatively rare in Chinese patients, but which has a very close relationship with PMR. GCA is characterized by large-vessel involvement with inflammation of the arterial wall, and involvement of the internal elastic lamina and multinucleated giant cell infiltration.

The median period from ICI exposure to PMR occurrence varies from 10 days to one year, with similar clinical and radiological manifestations compared with classical PMR. However, patients with ICI-induced PMR do not always have increased acute phase reactants and may not respond well to low-dose glucocorticoids. A few patients may develop GCA after ICI treatment, with clinical symptoms including headache, temporal artery tenderness, jaw claudication, and vision loss, and pathological manifestations similar to classical GCA.

**Inflammatory arthritis**

ICI-induced inflammatory arthritis is one of the most common rheumatic irAEs and has been previously reported in several studies. The median period from ICI treatment to inflammatory arthritis onset ranges from two months to two years. Moreover, ICI-related inflammatory arthritis varies in severity from mild disease, which responds well to nonsteroidal anti-inflammatory drugs (NSAIDs) or low-dose glucocorticoids, to severe cases that may require tumor necrosis factor (TNF) inhibitors or interleukin-6 (IL-6) receptor antibodies to ameliorate the symptoms. ICI-related inflammatory arthritis can be further classified into two subgroups. The first type of IA is similar to RA, involving the small joints (proximal interphalangeal joints, metacarpophalangeal joints, and wrists) and bone erosions. However unlike RA, these patients do not show a female predominance and are usually seronegative for rheumatoid factor and ACPA, with earlier bone erosions; however, a few patients with ACPA-positive RA after ICI treatment were also found to be seropositive for ACPA before treatment with ICIs. The second group of patients had clinical manifestations similar to spondyloarthritis, including inflammatory back pain, enthesitis, dactylitis, and oligoarthritis with predominantly large-joint involvement. A small subset of patients may manifest as reactive arthritis or psoriatic arthritis. However, HLA-B27 positivity was rarely seen in the second group of patients.

**Inflammatory myopathy**

ICI-induced inflammatory myopathy is relatively less common than inflammatory arthritis and always occurs in the first two months after ICI treatment, with sudden onset. Inflammatory myopathy is characterized by myalgia, muscle weakness, and elevated serum creatinine kinase (CK) levels. Severe cases may include rhabdomyolysis,
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respiratory muscle weakness, or myocardial involvement, and the condition can sometimes be life-threatening. Muscle biopsies show focal necrotizing myopathy with extensive macrophage and T lymphocyte infiltration. Perifascicular atrophy of muscle fibers, which is a classic pathological finding of dermatomyositis, has not been found in ICI-induced inflammatory myopathy. ICI-related inflammatory myopathy also rarely presents with a classical dermatomyositis-related rash, and patients are seronegative for myositis-specific antibodies and may also have involvement of the axial part of the facial muscle.17-22 Concomitant inflammatory fasciitis or myasthenia gravis can also occasionally occur in patients with ICI-induced inflammatory myopathy.23,24 In our clinic, we have experienced several patients with markedly elevated serum CK levels but no obvious clinical symptoms such as myalgia or muscle weakness. This highlights the need to routinely monitor serum CK levels in patients taking ICIs, even if they have no complaints of myalgia or muscle weakness.

Other connective tissue diseases

New-onset connective tissue disease after ICI treatment is rare. A study at Johns Hopkins Hospital of patients with solid tumors who received ipilimumab and/or nivolumab treatment from 2012 to 2016 included four patients who developed sicca syndrome with relatively abrupt onset of severe dry mouth symptoms, one patient with bilateral parotid gland enlargement, and two with other irAEs. None of these patients had anti-Ro/SSA antibody.14 In the report by Ghosn et al., a patient with melanoma treated with pembrolizumab developed typical Sjögren syndrome with subacute ataxic sensory neuropathy with only a partial response to glucocorticoids, but demonstrated remarkable improvement after treatment with intravenous immunoglobulins and rituximab.25

Barbosa et al. reported on two patients with melanoma and newly developed systemic sclerosis after pembrolizumab treatment.26 There have also been occasional reports of GCA, single-organ vasculitis, and granulomatosis with polyangiitis.27-29

Patients with pre-existing rheumatic diseases

There is limited information about flares of pre-existing rheumatic diseases in patients treated with ICIs because such patients have tended to be excluded from clinical trials. However, we managed a patient with gastric cancer who was also diagnosed with connective tissue disease associated interstitial lung disease. They received three cycles of nivolumab therapy and had a high fever and rapid progression of interstitial lung disease, which failed to respond to medium-dose glucocorticoids but was well-controlled by high-dose glucocorticoids and tacrolimus. A retrospective study conducted at Massachusetts General Hospital reported six patients with rheumatic disease flares after ICI treatment,15 including one case of RA, two of PMR, two of RA with PMR, and one of psoriatic arthritis. The median time from ICI exposure to rheumatic disease flare was 4.6 weeks, and one severe case was finally controlled using tocilizumab. Mitchell et al.20 reported an Australian study including 12 patients with underlying rheumatic diseases, of whom 10 experienced disease flares after ICI therapy, including four cases of inflammatory arthritis and six of PMR. However, patients with rheumatic diseases can also develop new-onset irAEs after ICI treatment. Among 700 patients treated with ICIs and reviewed in a study by the Mayo Clinic,30 16 had a past history of rheumatic diseases. Six patients with rheumatic diseases developed irAEs after ICI treatment, but only one patient with GCA had a disease flare, while the other five patients all had newly occurring irAEs, such as colitis and hypophysitis. It is therefore important to be aware of the possibility of disease flares after ICI treatment in patients with pre-existing rheumatic diseases, and for clinicians to make a differential diagnosis between rheumatic disease flares and new-onset irAEs.

Management of ICI-induced rheumatic irAEs

It is important for rheumatologists to collaborate with oncologists to manage patients with rheumatic irAEs, including the decision on whether or not to continue ICI treatment. Considering that patients with rheumatic irAEs tended to have better cancer-treatment outcomes,8 ICIs should generally be continued if they show positive results. However, ICIs should be temporally or even permanently stopped in the event of severe irAEs.10 In addition, more large prospective studies are needed to determine if glucocorticoids or immunosuppressants affect the anti-tumor effects of ICIs.

NSAIDs are the first line of therapy in patients with inflammatory arthritis with mild symptoms, and low-dose glucocorticoids (prednisone 10–20 mg/day or equivalent dose) can be considered, while NSAIDs are less effective. For patients with moderately severe inflammatory arthritis, prednisone >20 mg/day or equivalent dose plus disease-modifying anti-rheumatic drug (DMARDs) therapy is recommended, while the dose of glucocorticoids can be further increased in cases of severe inflammatory arthritis, and biological agents such as TNF inhibitors can also be used in glucocorticoid-dependent patients.31,32 The use of TNF inhibitors is generally contraindicated in patients with malignancies; however, considering the risks and urgency of tumor patients complicated with irAEs, TNF inhibitors are still an option for managing severe inflammatory arthritis.
Perez-Ruiz et al. recently reported that the prophylactic use of TNF inhibitors concomitant with combined anti-CTLA-4 and anti-PD-1 therapy in mouse models ameliorated irAEs and also improved anti-tumor efficacy. It is therefore important to understand the role of TNF inhibitors in tumor immunotherapy. Moreover, one report described a patient with severe arthritis after ICI treatment that was controlled by IL-6 receptor antibody (tocilizumab) treatment. However, the effectiveness of other biological agents such as IL-17 and IL-12/23 antagonists are still under investigation.

ICI treatment can be continued in patients with mild myalgia, while serum CK levels should be monitored closely and NSAIDs can be used to control the myalgia. Serum CK levels usually decrease gradually after cessation of immunotherapy in patients with mild to moderate elevation of serum CK levels, but without myalgia or muscle weakness. However, in patients with moderate to severe myositis, electromyograms, muscle magnetic resonance imaging, myositis-specific autoantibody testing, and muscle biopsy should be performed to differentiate between irAE and classical myositis. Glucocorticoids are the first-line therapy for ICI-induced myositis, with an initial dose of 0.5–1.0 mg/kg/day prednisone according to the severity of muscle involvement. Intravenous methylprednisolone pulse therapy should be considered and possibly combined with intravenous immunoglobulins in patients with myocardial involvement or life-threatening conditions, and DAMRDs should be used in glucocorticoid-dependent patients. Salem et al. recently reported a case in which the CTLA-4 agonist abatacept was successfully used to treat severe and glucocorticoid-refractory ICI-induced myocarditis, offering a new approach for the treatment of patients with severe ICI-induced myocarditis. However, further studies are needed to evaluate the risks and benefits of abatacept more thoroughly in these patients.

ICI should be stopped in patients with pre-existing rheumatic diseases who experience flare-ups after ICI treatment. Subsequent treatment should then follow the management recommendations for classical rheumatic diseases which usually base the glucocorticoid and immunosuppressant doses on the type and severity of organ involvement.

Conclusions

ICIs represent a new era in the treatment of malignancies, although the concomitant irAEs, including rheumatic irAEs, also bring new challenges and research areas for clinicians. Rheumatologists must engage more in the management and basic research of irAEs.

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Disclosure

The authors have no potential conflicts of interest to disclose.

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