Rheumatic Manifestations for ICIs

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Immune checkpoint inhibitors (ICI) are monoclonal antibodies that activate the immune system aiming at enhancing antitumor immunity. Their clinical efficacy is well documented but the side effects associated with their use are still under investigation. These drugs cause several immune related adverse events (ir-AE) some of which stand within the field of Rheumatology. Herein, we performed a literature review in an effort to evaluate all publicly available clinical data regarding rheumatic manifestations associated with ICI. The most common musculoskeletal ir-AEs are inflammatory arthritis, polymyalgia rheumatica and myositis. Non musculoskeletal rheumatic manifestations are less frequent with the most prominent being sicca, vasculitides and sarcoidosis. Cases of systemic lupus erythematosus or scleroderma are extremely rare. The majority of musculoskeletal ir-AE are of mild/moderate severity and can be managed with steroids with no need for ICI discontinuation. In severe cases, more intense immunosuppressive therapy and permanent ICI discontinuation may be employed. Oncologists should periodically screen patients receiving ICI for new onset inflammatory musculoskeletal complaints and seek a rheumatology consultation in cases of persisting symptoms.

Keywords: immune checkpoint inhibitors ; cancer immunotherapy ; rheumatic ; musculoskeletal ; arthritis ; myositis ; polymyalgia rheumatica ; systemic lupus erythematosus ; sicca ; scleroderma

1. Introduction

The notion of immune system manipulation to achieve antitumor effect entails decades of basic research effort, but it has only recently achieved broad clinical implementation in the field of oncology. Better understanding of tumor genetics and immune surveillance mechanisms is necessary to fight cancer in a more efficient and effective way [1]. While our immune system recognizes cancer cells, it is restrained by various “checkpoints”; molecules such as cytotoxic T lymphocyte antigen 4 (CTLA4), programmed death 1 (PD-1) and its ligand PD-L1 act as brakes restricting T cell effector functions. This process is important for homeostasis and autoimmunity prevention in healthy organisms, but on the other hand it dampens critical T cell cytotoxic functions against tumor cells in cancer patients. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies which target checkpoint molecules and have significant clinical efficacy, rendering immune checkpoint blockade an emerging therapeutic approach in cancer [2]. There is a major expansion in the number of clinical trials involving multiple immunotherapy agents in a variety of cancer types, with lung cancer, melanoma, breast cancer, lymphoma and head and neck cancer being the most studied ones [3].

The widespread implementation of ICIs over the last decade has provided important data on their toxicity profile [4]. The attenuation of T cell inhibitory mechanisms by ICIs leads to hyperactivation of the immune system; as probably expected, this associates with a variety of adverse events characterized by inflammation. Target sites of these adverse events, usually termed as immune-related adverse events (ir-AEs) can include every tissue in the human body, including the gastrointestinal tract, endocrine glands, liver and skin, while cardiovascular, pulmonary and rheumatic ir-AEs are also reported [5].

In this review, rheumatic manifestations in the context of ICI therapy will be discussed. Musculoskeletal and non-musculoskeletal clinical manifestations will be separately analyzed, along with current data concerning imaging and treatment.

2. Discussion

Rheumatic ir-AEs are relatively common and are increasingly recognized. Even though in most cases they are mild/moderate and not life-threatening, they should be diagnosed and managed early since they are associated with pain and functional impairment. Moreover, in light of newer evidence that musculoskeletal ir-AEs may correlate with a favorable tumor response, the appropriate management of these patients by a multidisciplinary team comprised of oncologists and rheumatologists appears to be of critical significance; in this way, patients may be treated effectively and immunotherapy could be maintained.

Rheumatic ir-AEs can be classified as musculoskeletal and non-musculoskeletal. Overall, musculoskeletal manifestations induced by ICI therapy are relatively common, developing in approximately 5%–7.7% of patients according to the prospective studies reported so far. The clinical syndromes most often described are inflammatory arthritis, PMR and myositis. A rheumatology referral is needed in all cases of new-onset inflammatory arthralgia or joint swelling. In most cases of inflammatory arthritis and PMR, ICI therapy may be continued; the majority of patients respond to steroids of less than 20 mg of prednisolone. ICI-induced myositis may have atypical features such as muscle pain or even normal CPK levels. Usually it is the most severe musculoskeletal manifestation induced by ICIs and frequently requires permanent immunotherapy cessation and treatment with high-dose steroids.

The most common forms of non-musculoskeletal rheumatic ir-AEs are sicca, vasculitides and sarcoidosis/sarcoid-like reactions. Cases of SLE and SSc are extremely rare. Of note, ICI-induced rheumatic syndromes appear to have significant differences from their idiopathic counterparts. For example, in most cases, ICI-induced inflammatory arthritis does not have the typical features of RA. Table 1 summarizes all major differences between ICI-induced syndromes and idiopathic counterparts. These data point to the direction that rheumatic ir-AEs are indeed novel clinical entities that should be thoroughly investigated and may not share common pathogenetic mechanisms with idiopathic rheumatic diseases.

In conclusion, the management of ir-AEs in oncologic patients ideally requires a multidisciplinary team with the participation of a rheumatologist. Rheumatic ir-AEs are relatively common; these manifestations should be managed effectively in order to preserve the quality of life of patients with cancer. Large-scale, prospective studies are needed to better delineate the prevalence and clinical characteristics of ICI-induced rheumatic syndromes and to develop relevant therapeutic guidelines.

Table 1. Main differences between ICI-induced rheumatic syndromes and their idiopathic counterparts.

RA	**ICI-Induced Arthritis**
Usually involves small joints of the hands in a symmetrical fashion	May manifest as mono, oligo or polyarthritis
Synovium is primarily targeted	Apart from synovitis, myo-fasciitis may be prominent
Responds to steroids but treatment with DMARDs is always needed	Good response to steroids DMARD needed when relapse occurs during steroid tapering
PMR	**ICI-Induced PMR**
Aching and stiffness in the shoulder and pelvic girdles are typical symptoms	Joint involvement, including knees and hands, may occur
High inflammatory markers are a diagnostic criterion	Absence of increased inflammatory markers is reported in several cases
Responds to low dose of steroids (prednisolone, 20 mg/daily)	Aggressive treatment with higher doses of steroids may be needed
Polymyositis/Dermatomyositis	**ICI-Induced Myositis**
Typical clinical presentation involves proximal muscle weakness, without associated muscle pain, sparing facial muscles Dermatomyositis exhibits typical rash	May present with myalgia and oculomotor symptoms, while typical rash is usually absent

Increase in muscle enzymes and autoantibodies against nuclear or cytoplasmic antigens aid diagnosis	May exhibit significant increase in muscle enzymes, albeit normal in a subset of patients Autoantibodies are usually absent
High-dose steroids are the mainstay of treatment	High-dose steroids are usually required, even though milder clinical phenotypes respond well to moderate doses
Additional immunosuppression is needed in resistant disease and extramuscular features such as ILD	Increased frequency of concurrent myasthenia and/or cardiac involvement is reported and may warrant additional immunosuppression
Systemic Vasculitides	**ICI-Induced Vasculitis**
High inflammatory burden is typical Autoantibodies, such as ANCA, can aid diagnosis in subsets of the disease	Inflammatory markers are commonly increased, but autoantibody positivity is rare
Sjogren Syndrome	**ICI-Induced Sicca**
Striking female preponderance	Male predominance in some case series
Specific autoantibodies are typically positive	Absence of autoantibodies is reported in most cases
Dry eyes and dry mouth are the most frequent complaints	Dry mouth is the most prominent symptom
SLE	**ICI-Induced Lupus**
Typically affects females of childbearing age Antinuclear antibodies are almost always positive	Older age, lack of striking female predominance and absence of autoantibodies are reported

ICI = immune checkpoint inhibitor, RA = rheumatoid arthritis, PMR = polymyalgia rheumatica, ILD = interstitial lung disease, ANCA = antineutrophil cytoplasmic antibodies, DMARDs = disease-modifying antirheumatic drugs, SLE = systemic lupus erythematosus.

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