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RHEUMATOLOGICAL COMPLICATIONS IN PATIENTS UNDERGOING CANCER IMMUNOTHERAPY: A NARRATIVE REVIEW

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ABSTRACT Rheumatological complications from cancer immunotherapy, particularly immune checkpoint inhibitors, are increasingly recognized in clinical practice, affecting approximately 5-10% of patients. These complications include inflammatory arthritis, myositis, Sjögren's syndrome, vasculitis, and lupus-like syndromes. The pathophysiology involves enhanced T-cell activation leading to autoimmunity. Clinical manifestations vary widely and require thorough evaluation. Diagnosis relies on patient history, physical examination, laboratory tests, imaging, and biopsy. Treatment involves NSAIDs, corticosteroids, and DMARDs, tailored to severity. Multidisciplinary collaboration is crucial for optimal management.

KEYWORDS : Immune Checkpoint Inhibitors; Rheumatological Complications; Inflammatory Arthritis; Myositis; Sjögren's Syndrome.

INTRODUCTION

Immunotherapy has revolutionized cancer treatment, significantly improving patient survival rates. However, this therapeutic advancement has also led to an increase in the incidence of immune-related adverse events (irAEs), among which rheumatological complications are prominent. These complications include inflammatory arthritis, myositis, and Sjögren's syndrome, among others. Often, these side effects are not promptly recognized, resulting in suboptimal patient management. This narrative review aims to provide a comprehensive overview of rheumatological complications associated with immunotherapy, addressing their pathophysiology, diagnosis, management, and future research areas (1).

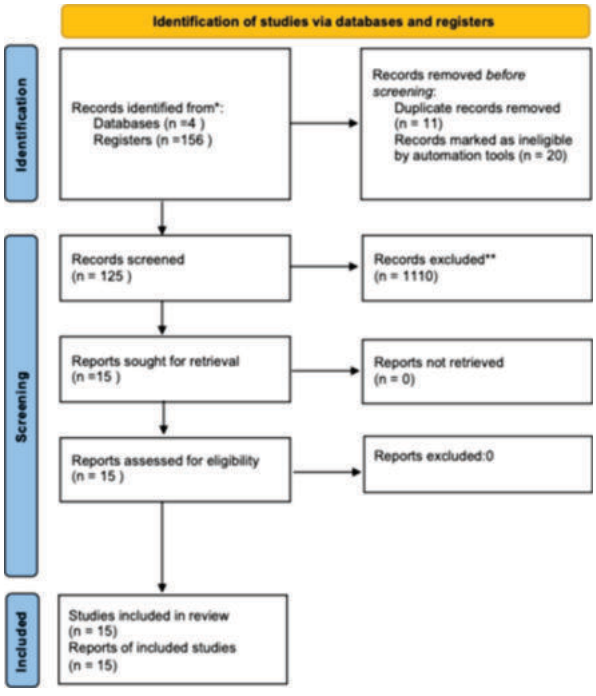

Figure 1. PRISMA.

METHODS

For this narrative review, exhaustive searches were conducted in four databases: PubMed, Scopus, Web of Science, and Embase. The following keywords were used: "rheumatological complications," "immunotherapy," "immune-related adverse events," and "cancer." Articles were selected based on their relevance and methodological quality, including case studies, clinical trials, and systematic reviews. Studies with insufficient data or duplicates were excluded. The final selection included 15 references that provided a comprehensive and up-to-date overview of rheumatological complications associated with immunotherapy in cancer patients.

Epidemiology

Rheumatological complications from cancer immunotherapy, such as checkpoint inhibitors, are increasingly recognized in clinical practice. These immune-related adverse events (irAEs) occur in approximately 5-10% of patients receiving immune checkpoint inhibitors. The incidence varies based on the specific type of immunotherapy and the underlying cancer being treated. Patients with pre-existing autoimmune conditions may be at higher risk, although these complications can also arise in those without any prior autoimmune history (2).

Types Of Complications And Pathophysiology

Rheumatological complications arising from cancer immunotherapy are diverse, including inflammatory arthritis, myositis, Sjögren's syndrome, vasculitis, and lupus-like syndromes. Inflammatory arthritis presents as joint pain and swelling, often resembling rheumatoid arthritis. Myositis involves muscle inflammation, leading to weakness and discomfort. Sjögren's syndrome manifests with dry eyes and mouth due to gland inflammation. Vasculitis and lupus-like syndromes involve blood vessel inflammation and systemic symptoms, respectively (3).

The pathophysiology of these complications is linked to the mechanisms of immune checkpoint inhibitors, which enhance T-cell activation to target cancer cells. However, this heightened immune response can lead to aberrant activation of T-cells against normal tissues, disrupting immune homeostasis. CTLA-4 and PD-1/PD-L1 inhibitors, the main classes of checkpoint inhibitors, have distinct mechanisms of action that contribute to these adverse events. CTLA-4 inhibitors block early T-cell activation checkpoints, while PD-1/PD-L1 inhibitors prevent T-cell exhaustion, both potentially triggering autoimmunity (3,4)

Clinical Manifestations

Rheumatological complications from cancer immunotherapy can present with a wide range of clinical manifestations. Inflammatory arthritis is one of the most common, characterized by joint pain, swelling, and stiffness, often resembling rheumatoid arthritis. This can affect both small

and large joints, including the hands, wrists, knees, and shoulders. Patients may report morning stiffness lasting for over an hour and symmetrical joint involvement (5).

Myositis presents with muscle weakness and pain, typically affecting the proximal muscles, such as those in the hips and shoulders. Patients might have difficulty climbing stairs, rising from a seated position, or lifting objects. In severe cases, myositis can lead to significant muscle damage and elevated levels of muscle enzymes like creatine kinase (5).

Sjogren's syndrome, another common manifestation, presents with dry eyes (xerophthalmia) and dry mouth (xerostomia) due to inflammation of the exocrine glands. Patients may experience a gritty sensation in the eyes, difficulty swallowing dry foods, and an increased risk of dental cavities and oral infections (5,6).

Vasculitis can present with a variety of symptoms depending on the blood vessels involved. Common signs include skin rashes, purpura, and systemic symptoms such as fever, weight loss, and fatigue. Organ-specific manifestations can include renal impairment, neurological symptoms, and gastrointestinal disturbances (6).

Lupus-like syndromes can present with symptoms similar to systemic lupus erythematosus (SLE), such as a butterfly-shaped rash on the face, photosensitivity, and multi-organ involvement including renal, cardiac, and pulmonary systems (6,7).

Diagnosis

The diagnosis of rheumatological complications arising from cancer immunotherapy requires a high index of suspicion and a comprehensive clinical evaluation. Given the overlap of symptoms with other conditions, a detailed patient history and thorough physical examination are essential first steps.

Patient History And Physical Examination

Patient History:

A detailed history should include the onset, duration, and pattern of symptoms, along with any associated systemic features such as fever, weight loss, or fatigue. It is also important to review the patient's cancer treatment regimen, including the type and duration of immunotherapy, as well as any previous history of autoimmune disease or pre-existing rheumatological conditions (7).

Physical Examination:

The physical exam should focus on identifying signs of joint inflammation, muscle weakness, dry mucous membranes, and any cutaneous manifestations such as rashes or vasculitis (7).

Laboratory Tests

Blood Tests:

Routine blood tests including complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are useful to detect inflammation. Specific tests for muscle enzymes (e.g., creatine kinase) are important in suspected cases of myositis (8).

Autoantibodies:

Testing for autoantibodies, such as antinuclear antibodies (ANA), rheumatoid factor (RF), and specific antibodies like anti-Ro/SSA and anti-La/SSB for Sjogren's syndrome, can provide diagnostic clues. However, the presence of autoantibodies alone is not diagnostic and should be interpreted in the context of clinical findings (8).

Imaging Studies

Joint Imaging:

Radiographs, ultrasound, or magnetic resonance imaging (MRI) of affected joints can help assess the extent of inflammation, joint damage, and synovitis(8).

Muscle Imaging:

MRI is particularly useful in diagnosing myositis, revealing muscle edema and inflammation(8).

Functional Tests

Pulmonary Function Tests:

In cases where there is suspected lung involvement, such as interstitial lung disease associated with autoimmune syndromes, pulmonary function tests and high-resolution CT scans may be indicated (9).

Biopsy

Tissue Biopsy:

In certain cases, a biopsy of affected tissue (e.g., skin, muscle, or minor salivary gland) can provide definitive evidence of autoimmune or inflammatory processes (9).

Differential Diagnosis

Exclusion Of Metastatic Disease And Paraneoplastic Syndromes:

It is crucial to differentiate between rheumatological irAEs and symptoms arising from metastatic disease or paraneoplastic syndromes, which can present similarly (9).

Assessment of Other Causes:

Other potential causes of symptoms, such as infections or drug-related side effects, should also be considered (9).

Collaboration And Referral

Multidisciplinary Approach:

A collaborative approach involving oncologists, rheumatologists, and other specialists is essential for accurate diagnosis and management. Early referral to a rheumatologist is recommended when rheumatological irAEs are suspected (10).

Diagnostic Criteria And Guidelines

Use Of Established Criteria:

Applying established diagnostic criteria for rheumatological diseases, adapted to the context of immunotherapy, helps in standardizing the diagnosis. Guidelines from rheumatology societies can provide a framework for managing these complex cases (11).

Treatment

The treatment of rheumatological complications arising from cancer immunotherapy requires a balanced approach to manage symptoms while allowing the continuation of cancer therapy whenever possible. The main goals are to control inflammation, relieve symptoms, and prevent long-term damage. Treatment strategies often involve the use of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs), tailored to the severity of the complications (12).

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

First-Line Treatment:

For mild to moderate symptoms, NSAIDs are typically the first-line treatment. They can effectively reduce pain and inflammation in conditions such as arthralgia and mild inflammatory arthritis. Patients are monitored for potential side effects, including gastrointestinal and renal issues (12).

Corticosteroids

Moderate to Severe Cases:

Corticosteroids are often used when NSAIDs are insufficient. Prednisone, administered at a dose of 10-20 mg per day, is common. For severe manifestations, higher doses may be necessary, followed by a gradual tapering once symptoms are

controlled (13).

Immune Suppression:
Corticosteroids help suppress the immune system, reducing the aberrant immune response causing the rheumatological symptoms. However, long-term use is associated with significant side effects, necessitating careful management (13).

Disease-Modifying Antirheumatic Drugs (DMARDs)
Persistent or Severe Inflammation:
DMARDs, such as methotrexate or sulfasalazine, are considered for patients with persistent or severe inflammatory arthritis who do not respond adequately to NSAIDs or corticosteroids. These drugs can help control chronic inflammation and prevent joint damage (13).

Biologic DMARDs:
In cases where conventional DMARDs are ineffective, biologic DMARDs like TNF inhibitors may be considered, although their use must be carefully weighed against the potential impact on the patient's immune system and cancer therapy (13).

Management of Specific Complications
Myositis:
For myositis, treatment may include high-dose corticosteroids and DMARDs like methotrexate or azathioprine. Physical therapy is also important to maintain muscle function (14).

Sjogren's Syndrome:
Management includes symptomatic treatment with artificial tears and saliva substitutes, along with systemic therapies like hydroxychloroquine for more severe cases (14).

Vasculitis And Lupus-like Syndromes:
These conditions often require a combination of corticosteroids and DMARDs, tailored to the specific manifestations and severity (14).

Collaboration And Monitoring
Multidisciplinary Approach:
A collaborative approach involving oncologists, rheumatologists, and other specialists ensures comprehensive care. Regular monitoring for side effects and treatment efficacy is essential (15).

Adjusting Cancer Therapy:
In some cases, temporary discontinuation or dose adjustment of immunotherapy may be necessary to manage severe rheumatological complications. The decision should be made collaboratively, prioritizing both cancer control and the patient's overall well-being (15).

Future Perspectives And Research Needs
Future research should focus on better understanding the pathogenic mechanisms of rheumatological complications associated with immunotherapy to identify predictive biomarkers and develop preventive strategies. Clinical trials and observational studies with larger patient cohorts are necessary to evaluate the efficacy and safety of specific treatments (15).

CONCLUSIONS
Rheumatological complications of immunotherapy present significant diagnostic and therapeutic challenges. A multidisciplinary approach, along with early identification and appropriate treatment, is essential to improve outcomes and quality of life for patients.

REFERENCES

1. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. 2012;30:2691-2697.
2. Cappelli LC, Gutierrez AK, Bingham CO 3rd, Shah AA. Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: A systematic review of the literature. Arthritis Care Res (Hoboken). 2017;69:1751-1763.
3. Benfaremo D, Manfredi L, Luchetti MM, Gabrielli A. Musculoskeletal and rheumatic diseases induced by immune checkpoint inhibitors: A review of the literature. Curr Drug Saf. 2018;13:150-164.
4. Lidar M, Giat E, Garelick D, et al. Rheumatic manifestations among cancer patients treated with immune checkpoint inhibitors. Autoimmun Rev. 2018;17:284-289.
5. Micaily I, Chernoff M. An unknown reaction to pembrolizumab: Giant cell arteritis. Ann Oncol. 2017;28:2621.
6. Antoun J, Titah C, Cochereau I. Ocular and orbital side-effects of checkpoint inhibitors: A review article. Curr Opin Oncol. 2016;28:288-294.
7. Calabrese C, Cappelli LC, Kostine M, et al. Polymyalgia rheumatica-like syndrome from checkpoint inhibitor therapy: Case series and systematic review of the literature. RMD Open. 2019;5.
8. Chen JH, Lee KY, Hu CJ, Chung CC. Coexisting myasthenia gravis, myositis, and polyneuropathy induced by ipilimumab and nivolumab in a patient with lung adenocarcinoma. J Clin Oncol. 2017;35:97-99.
9. John S, Antonia SJ, Rose TA, et al. Progressive hypoventilation due to mixed CD8+ and CD4+ lymphocytic polymyositis following tremelimumab-durvalumab treatment. J Immunother Cancer. 2017;5:54.
10. Raptopoulou AP, Bertsias G, Makrygiannakis D, et al. The programmed death 1/programmed death ligand 1 inhibitory pathway is up-regulated in rheumatoid synovium and regulates peripheral T cell responses in human and murine arthritis. Arthritis Rheum. 2010;62:1870-1880.
11. Liu C, Jiang J, Gao L, et al. Soluble PD-1 aggravates progression of collagen-induced arthritis through Th1 and Th17 pathways. Arthritis Res Ther. 2015;17:340.
12. Lord JD, et al. Refractory colitis following anti-CTLA4 antibody therapy: Analysis of mucosal FOXP3+ T cells. Dig Dis Sci. 2010;55:1396-1405.
13. Ceeraz S, et al. Immune checkpoint receptors in regulating immune reactivity in rheumatic disease. Arthritis Res Ther. 2014;16:469.
14. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12:252-264.
15. Cappelli LC, Shah AA, Bingham CO 3rd. Immune-related adverse effects of cancer immunotherapy – implications for rheumatology. Rheum Dis Clin North Am. 2017;43:65-78.