Review

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Uncommon but Significant: Onset, Characteristics and Management of Vasculitis and Connective Tissue Diseases Induced by Immunomodulators during Cancer Treatment

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The introduction of immunomodulators as adjuvant therapies in cancer treatment has represented a significant advancement in oncology, improving therapeutic response and patient survival. Emerging targets and molecules could provide new therapeutic opportunities for cancer patients. However, these agents can induce immunological side effects, including vasculitis and connective tissue diseases, which, while uncommon, present significant clinical challenges. This review analyzes the prevalence, clinical characteristics, therapeutic strategies, and management difficulties of vasculitis and connective tissue disorders triggered by immunomodulators in the context of cancer treatment. Although rare, these conditions significantly impact patients, demanding thorough management. Common rheumatological immune-related adverse events include inflammatory arthritis, Sjogren's disease, systemic lupus erythematosus, and systemic sclerosis, all of which require prompt recognition and appropriate intervention. Treatment frequently includes corticosteroids and immunosuppressive drugs, with new alternatives currently accessible. Efficient coordination between oncologists and rheumatologists enhances patient outcomes, highlighting the necessity for organized multidisciplinary strategies. Future research initiatives emphasize the identification of biomarkers for early diagnosis and the development of preventive methods to reduce immune-related adverse events in cancer therapy.

Keywords: immune checkpoint inhibitors; immune-related adverse events; rheumatological complications; cancer immunotherapy; autoimmune diseases; immunosuppressive therapy

Introduction

The introduction of immunomodulatory therapies, particularly immune checkpoint inhibitors (ICIs), has significantly transformed the therapeutic landscape of oncology, offering notable improvements in survival and clinical outcomes for patients across various cancer types. By harnessing and amplifying the patient's immune response, these therapies enable T-cells to recognize and target cancer cells that previously evaded immune detection [1,2]. The most common ICIs target immune-regulatory proteins, including programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Approved drugs such as nivolumab, pembrolizumab, and ipilimumab have shown efficacy in treating a broad range of malignancies, including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, and Hodgkin's lymphoma [1,3].

Despite these groundbreaking advancements, ICIs are not without drawbacks. They are associated with a unique spectrum of immune-related adverse events (irAEs) due to their disruption of immune homeostasis. These adverse events can impact nearly any organ system, with common manifestations in the skin, gastrointestinal tract, lungs, and endocrine organs [4]. Of particular concern, however, are the rheumatological complications associated with ICIs. Although less frequently reported than other organ-specific

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irAEs, rheumatological issues are emerging as significant clinical challenges, with an estimated incidence ranging from 5% to 20% in patients receiving these therapies [5–7]. Such manifestations include inflammatory arthritis, polymyalgia rheumatica (PMR)-like syndromes, vasculitis, and connective tissue diseases, each presenting unique management challenges for clinicians [8,9].

The underlying mechanisms of ICIs further explain these complications. ICIs primarily function by modulating immune checkpoint pathways, which are natural regulators of immune responses. PD-1/PD-L1 inhibitors, including nivolumab and pembrolizumab, work by blocking the interaction between PD-1 on T-cells and PD-L1 expressed on tumor cells, thereby preventing immune evasion and allowing T-cells to effectively target cancer cells [2,9]. CTLA-4 inhibitors, such as ipilimumab, act differently by inhibiting the interaction between CTLA-4 and its ligands (CD80/CD86), which results in enhanced T-cell activation [3]. Moreover, ICIs demonstrate remarkable efficacy in oncology by activating the immune system against cancer cells; however, this can also lead to immune tolerance breakdown, causing the immune system to attack healthy tissues and increasing the risk of irAEs [10].

For instance, the PD-1/PD-L1 and CTLA-4 pathways are pivotal in modulating T-cell activity, serving as critical immune checkpoints that maintain self-tolerance and prevent autoimmunity. PD-1, expressed on activated T cells, binds to its ligands PD-L1 or PD-L2 on antigen-presenting cells or tumor cells, leading to the inhibition of T-cell proliferation and cytokine production, thereby attenuating the immune response [11]. Similarly, CTLA-4, upregulated on T cells post-activation, competes with the costimulatory receptor CD28 for binding to B7 molecules (CD80/CD86) on antigen-presenting cells, resulting in the suppression of T-cell activation during the priming phase [12]. B cells also contribute to immune regulation through antibody production and cytokine secretion, influencing T-cell responses. Cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) play significant roles in immune modulation; IL-6 can promote T-cell survival and differentiation, while TNF-α is involved in the activation and proliferation of T cells, as well as the induction of inflammatory responses [13]. The intricate interplay among these pathways and cellular components is crucial for maintaining immune homeostasis and has significant implications in the context of immunomodulatory therapies for cancer.

In summary, the processes driving irAEs encompass various pathways of immune control, especially with checkpoint inhibition. PD-1 and PD-L1 inhibitors interfere with the PD-1/PD-L1 axis, a mechanism that sustains immunological tolerance by preventing T-cell hyperactivation. By obstructing this mechanism, immunomodulators unintentionally stimulate autoreactive T-cells, resulting in systemic inflammation. Likewise, CTLA-4 inhibitors eliminate one other vital checkpoint, hence augmenting T-cell activity and heightening vulnerability to autoimmune reactions. Cytokines such as IL-6 and TNF-α are released in elevated quantities in response to immunological stimulation, exacerbating tissue inflammation and injury. Increased B-cell activity may lead to heightened generation of autoantibodies typically observed in autoimmune disorders. These pathways collectively establish an environment that diminishes self-tolerance, rendering normal tissues susceptible to immune-mediated assault.

Furthermore, current literature identifies T cell immunoreceptor with Ig and ITIM domains (TIGIT) and Lymphocyte-activation gene 3 (LAG-3) as emerging immune checkpoints with unique irAEs that diverge from those observed with traditional PD-1 and CTLA-4 inhibitors. Research indicates that TIGIT and LAG-3 pathways contribute to the modulation of T-cell exhaustion and immune evasion mechanisms, influencing antitumor immunity in distinct ways [14]. For instance, dual blockade therapies targeting both TIGIT and LAG-3, combined with PD-1 or PD-L1 inhibition, are associated with more complex irAEs, particularly affecting cardiovascular and gastrointestinal systems, differing in scope and severity from those typically induced by PD-1/CTLA-4 inhibitors [15].

Studies also show that LAG-3 and TIGIT engagement in immunotherapy may lead to unique autoimmune reactions due to enhanced activation of effector T-cells and modified regulatory T-cell responses. For example, immune checkpoint therapies involving LAG-3 have shown higher instances of myocarditis and gastrointestinal inflammation, underscoring the need for new monitoring strategies for patients receiving these inhibitors [16]. These novel irAEs emphasize the evolving complexity of immune checkpoint therapy, suggesting that as the field moves beyond PD-1 and CTLA-4, both the therapeutic benefits and risks will require refined management approaches [17,18].

In addition to these established immunotherapies, emerging strategies, such as Chimeric Antigens Receptor Cells-T (CAR-T) cell therapy and personalized cancer vaccines, are also gaining traction in oncology. CAR-T cells are genetically engineered T-cells that specifically target cancer antigens, generating a highly targeted immune response [19]. Cancer vaccines, conversely, aim to stimulate the patient's immune system to recognize and attack tumor-associated antigens [20]. Although these novel therapies hold promise for treating challenging cancers, they also carry a risk of irAEs, underscoring the need for vigilant patient monitoring [5].

Rheumatological irAEs specifically present a diverse range of clinical presentations that can closely resemble traditional autoimmune diseases. Inflammatory arthritis, for instance, is the most frequently reported rheumatological irAE, with an incidence reaching up to 43% in affected patients in some studies [6,8]. Myositis, reported in 2% to 20% of cases, and PMR-like syndromes, typically manifesting as shoulder and pelvic girdle pain, are also common [9].

In rarer cases, vasculitis has been reported in forms ranging from small-vessel vasculitis to giant cell arteritis, impacting multiple organ systems such as the skin, lungs, kidneys, and central nervous system [4,6]. Less common yet clinically relevant are connective tissue diseases like Sjogren's syndrome and systemic sclerosis [7,10].

The onset of rheumatological irAEs varies, often appearing from a few days to several months following the initiation of immunotherapy. For example, inflammatory arthritis typically arises around 120 days after starting treatment [9], while connective tissue diseases and vasculitis may present later. Notably, some autoimmune manifestations can persist even after the discontinuation of ICIs, highlighting the chronic and potentially irreversible nature of these adverse events [6]. Clinically, patients frequently present with elevated inflammatory markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), though they are generally negative for autoantibodies like rheumatoid factor (RF) or anti-citrullinated peptide antibodies (ACPAs), which are typically associated with classic autoimmune diseases [4,9].

Although the exact pathophysiology of rheumatological irAEs is still under investigation, several mechanisms have been proposed. One hypothesis suggests that increased T-cell activity in response to tumor antigens may inadvertently damage normal tissues that express similar antigens, a phenomenon known as molecular mimicry [2,5]. B-cell activation may also contribute, as ICIs can stimulate autoantibody production, thereby exacerbating autoimmune responses [7]. Additionally, cytokines, particularly pro-inflammatory mediators such as IL-6 and TNF-α, have been implicated in the pathogenesis of irAEs [19,20].

Furthermore, these immune processes are often multisystemic, with conditions like colitis, pneumonitis, and hepatitis frequently co-occurring with rheumatological irAEs [10]. Interestingly, the development of one type of irAE appears to increase the likelihood of subsequent rheumatological complications [5,20]. For example, colitis is often seen alongside inflammatory arthritis, while pneumonitis has been associated with both myositis and Sjogren's syndrome [6,9].

Managing rheumatological irAEs presents unique challenges that require balancing continued cancer treatment with controlling autoimmune symptoms. Early detection and intervention are crucial, as untreated irAEs may lead to permanent damage and functional impairment [8]. Initial management typically involves glucocorticoids to reduce inflammation; however, severe or refractory cases may necessitate the use of disease-modifying antirheumatic drugs (DMARDs) like methotrexate or hydroxychloroquine [4,10]. In severe inflammatory cases, particularly with myositis or vasculitis, biologic therapies, including TNF-α inhibitors and IL-6 inhibitors, may also be required [7,19].

Finally, a multidisciplinary approach is essential in managing these complications. Close collaboration between oncologists, rheumatologists, and other specialists is critical to optimizing treatment outcomes. Oncologists prioritize the continuity of cancer therapy, while rheumatologists manage autoimmune complications, helping to prevent long-term damage [9]. In some severe cases, temporary discontinuation of immunotherapy may be necessary, particularly for life-threatening conditions such as severe myositis or vasculitis [8]. However, resuming cancer treatment as soon as possible remains a priority to maintain overall therapeutic efficacy [6].

Recent comprehensive reviews and meta-analyses have shed new light on the prevalence, characteristics, and long-term management needs of irAEs induced by ICIs, especially in patients with coexisting rheumatologic conditions. Indeed, emerging evidence indicates a unique spectrum of irAEs, especially impacting patients with preexisting rheumatologic autoimmune diseases [21,22]. These patients, notably those with rheumatoid arthritis, exhibit elevated risks of both disease flares and new irAEs, with a 41% flare rate and a 33% incidence of new onset irAEs. This underscores the critical need for rigorous monitoring, as the interplay between autoimmune and oncologic conditions demands careful management to balance therapeutic benefits and adverse effects [21]. Long-term or chronic irAEs are increasingly recognized as a significant issue, with conditions such as arthritis, dermatitis, and endocrinopathies persisting well beyond the cessation of ICI therapy. These chronic irAEs, affecting up to 43% of patients, present substantial challenges, as endocrine-related events like thyroiditis and adrenal insufficiency often lead to irreversible hormonal deficiencies requiring lifelong replacement therapy [22].

Among rheumatologic irAEs, manifestations such as arthritis, vasculitis, and myositis demand an interdisciplinary approach for effective management, integrating oncology and rheumatology expertise. Traditional treatments like corticosteroids are frequently insufficient, prompting the use of TNF-α and IL-6 inhibitors to control inflammation more precisely. The clinical presentation of these irAEs often mirrors but is distinct from primary rheumatic diseases, complicating diagnosis and requiring tailored intervention strategies [23]. Additionally, ICI-induced inflammatory arthritis and PMR present unique clinical patterns, such as increased tenosynovitis and seronegative profiles, challenging standard rheumatologic frameworks. This variability in symptoms highlights the need for specialized outcome measures, as traditional rheumatic disease management guidelines may not be fully applicable to ICI-induced conditions [24].

The persistence of rheumatologic complications, further emphasizes the need for long-term care strategies. Many patients continue to experience these symptoms for over six months after ICI discontinuation, with 52% requiring ongoing immunosuppressive therapy to manage their condition. Such prolonged treatment not only complicates

quality of life but also raises concerns about the impact of ongoing cancer therapy. This underscores a pressing need for refined management protocols to optimize both the control of irAEs and the efficacy of cancer treatment [25].

The increasing prevalence of immune-related adverse events underscores the necessity of a multidisciplinary approach to patient management. Collaborative strategies, such as multidisciplinary tumor boards and specialist immune-related adverse event management clinics, can significantly improve treatment results. Joint consultations with oncologists, rheumatologists, and other physicians enable prompt modifications to cancer treatment and irAE management, enabling comprehensive care that tackles both malignancy and autoimmune consequences.

Indeed, early intervention is crucial in the management of irAEs. Suggested treatments encompass regular baseline and subsequent testing of inflammatory markers, including CRP, ESR, and serum cytokines (e.g., IL-6). In high-risk patients, advanced imaging techniques like Magnetic Resonance Imaging (MRI) can identify subclinical inflammation. Regular interdisciplinary meetings with oncologists, rheumatologists, and laboratory specialists enable prompt modifications to immunotherapy, while the swift administration of corticosteroids helps mitigate disease progression.

Future research directions should focus on identifying biomarkers predictive of irAE risk, such as human leukocyte antigen (*HLA*) genotypes or cytokine profiles, to enable personalized risk assessment. Additionally, developing genetic risk score systems could allow clinicians to tailor treatment strategies based on individual immune response profiles.

This review aims to provide a comprehensive overview of the onset, characteristics, and management of vasculitis and connective tissue diseases induced by immunomodulatory therapies in cancer patients.

Onset and Characteristics of Vasculitis and Connective Tissue Diseases

Sjogren's Syndrome

Sjogren's syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic infiltration of exocrine glands, leading to sicca syndrome with symptoms of dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). SS affects primarily women (9:1 ratio), and the most severe complications include an increased risk of lymphoma, systemic infections, and renal, pulmonary, and neurological diseases [26].

A study demonstrated that SS can be triggered by PD-1/PD-L1 checkpoint inhibitors in cancer patients [27]. Data from the International ImmunoCancer Registry (ICIR), which included 26 patients treated with nivolumab, pembrolizumab, or durvalumab, revealed that 96% of patients developed dry mouth, and 65% developed dry eyes. Minor salivary gland biopsies showed chronic sialadenitis in many patients. The study noted a predominance of immunonegative profiles, with lower rates of autoantibodies (52% positive anti-nuclear antibodies (ANA), 20% positive Ro/anti-Sjogren's syndrome-related antigen A autoantibodies (SS-A)), compared to idiopathic SS. Additionally, the study highlighted that PD-1 blockade is strongly associated with the development of SS.

Another study demonstrated that SS can emerge as a rare but significant rheumatological complication following treatment with PD-1 and PD-L1 checkpoint inhibitors. In the cohort studied, one patient fulfilled the 2017 American Congress of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for SS, while others exhibited sicca symptoms without the typical autoantibodies such as anti-Ro [28].

Moreover, a case report showed that a patient developed xerostomia after two cycles of nivolumab, which persisted and led to a diagnosis of SS after three months [29]. Salivary gland hypofunction was confirmed through tests, and a biopsy revealed lymphocytic infiltration, predominantly CD8+ T cells. This case highlights the risk of SS with nivolumab and the need for early detection and management of salivary gland dysfunction.

In summary, SS can be triggered as an irAE in patients undergoing ICI therapy, particularly with PD-1/PD-L1 inhibitors. These cases overall highlight the need for close monitoring, as SS can occur without typical autoimmune markers, and early detection is essential for managing salivary gland dysfunction and preventing further complications.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by the immune system's attack on self-antigens, leading to widespread inflammation and tissue damage. Clinical manifestations vary but commonly include malar rash, photosensitivity, arthritis, serositis, renal involvement (lupus nephritis), and hematologic abnormalities. Treatment typically involves immunosuppressive agents, including corticosteroids, antimalarials like hydroxychloroquine, and biologic therapies such as belimumab or rituximab, aimed at controlling disease activity and preventing organ damage [30].

A recent study showed that SLE may present as an irAE in patients treated with ICIs for solid-organ tumors [31]. In the study, which evaluated 102 patients, one individual with pre-existing SLE developed non-specific colitis during ICI therapy, but no severe flare-ups of SLE were noted, and autoantibody levels remained stable. The study also highlighted the occurrence of various irAEs such as colitis, dermatitis, and pneumonitis, reflecting the need for careful monitoring of irAEs, especially in patients with autoimmune backgrounds.

Moreover, a case reported a 52-year-old female who developed SLE after several cycles of pembrolizumab for lung cancer [32]. She presented with polyarthritis and a subacute annular cutaneous rash. Skin biopsy and serological findings (ANA positivity) led to a diagnosis of SLE. Treatment with hydroxychloroquine and corticosteroids resulted in improvement of both cutaneous and joint symptoms. This case emphasizes the potential for SLE onset as an immune-related adverse event in patients undergoing anti-PD-1 therapy.

In summary, SLE can appear as a rare irAE in patients receiving ICI therapy, particularly with anti-PD-1 treatments like pembrolizumab. While SLE is usually a chronic autoimmune condition, recent evidence suggests that it can be induced or worsened by ICIs, with symptoms ranging from mild to severe. Alongside onset patterns, individuals with SLE as an immune-related adverse event exhibit symptoms including cutaneous lupus erythematosus, arthritis, and serositis. These cases highlight the importance of careful monitoring, especially in patients with pre-existing autoimmune conditions, to ensure prompt identification and management of serious irAEs.

Giant Cell Arteritis

Giant cell arteritis (GCA) is a granulomatous vasculitis that primarily affects medium and large arteries, most commonly the temporal arteries. It typically presents in elderly individuals with symptoms such as headache, scalp tenderness, jaw claudication, and visual disturbances, including sudden vision loss. If untreated, GCA can lead to serious complications such as blindness or, in rare cases, scalp necrosis. Treatment usually involves high-dose corticosteroids to control inflammation and prevent irreversible tissue damage [33].

A recent study showed that GCA can be triggered as an immune-related adverse event by nivolumab treatment in cancer patients [34]. In this case, a woman in her 60s receiving nivolumab for stage IV lung adenocarcinoma developed GCA with scalp necrosis, a rare but severe complication. Symptoms, including headache, scalp tenderness, and visual impairment, appeared after the first nivolumab infusion. A temporal artery biopsy confirmed GCA, and treatment with high-dose intravenous prednisone led to improvement of scalp necrosis, although visual deterioration persisted. This case emphasizes the potential for GCA as an adverse event in patients undergoing immunotherapy.

Moreover, a recent case report showed that a 65-year-old man receiving pembrolizumab for urothelial carcinoma presented with painless vision loss in the right eye [35]. Ophthalmological exams, coupled with a temporal artery biopsy, confirmed the diagnosis of GCA. Despite treatment with intravenous corticosteroids, the patient experienced no improvement in visual acuity. This case, along with other reports in the literature, underscores the potential for pembrolizumab to trigger GCA and highlights the need for prompt recognition and management of this serious side effect [36–38].

In summary, GCA can be triggered as an irAE in patients undergoing ICI therapy, particularly with PD-1 inhibitors like nivolumab and pembrolizumab. As shown in the analyzed cases, GCA may develop in cancer patients receiving these treatments, presenting with symptoms such as headache, scalp tenderness, and vision loss. Temporal artery biopsy often confirms the diagnosis. These cases highlight the importance of early detection and treatment with high-dose corticosteroids to manage inflammation, although visual outcomes may remain poor. Prompt recognition and management are crucial to prevent serious complications.

ANCA Associated Vasculitis

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis is a group of autoimmune disorders characterized by inflammation and damage to small blood vessels, typically associated with the presence of ANCA [39]. It primarily affects organs such as the kidneys, lungs, and skin, leading to symptoms like glomerulonephritis, pulmonary hemorrhage, and purpura. Treatment typically includes immunosuppressive agents such as corticosteroids and cyclophosphamide or rituximab to control inflammation and prevent organ damage [40].

Bacillus Calmette-Guérin (BCG) immunotherapy, commonly used for non-invasive bladder cancer, can induce perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) associated vasculitis as an immune-related adverse event [41]. In this case, a 68-year-old man developed nephritic syndrome and renal failure after receiving BCG for bladder cancer. High titers of p-ANCA and a renal biopsy revealed necrotizing glomerulonephritis. The patient was treated successfully with immunosuppressive therapy, including steroids and mycophenolate mofetil, which resulted in clinical improvement. This case highlights the potential for systemic immune-mediated complications following BCG instillation.

Moreover, a recent case report revealed that ANCA-associated vasculitic neuropathy can occur as a rare irAE during treatment with ipilimumab, an immune checkpoint inhibitor used in oncology [42]. In this instance, a 37-year-old woman receiving ipilimumab for melanoma developed neuropathy, confirmed by nerve biopsy, which demonstrated vasculitis of the vasa nervorum along with positive ANCA (anti-myeloperoxidase (MPO) and anti-proteinase 3 (PR3)). The condition was successfully managed with high-dose corticosteroids and mycophenolate mofetil, leading to clinical remission. This case, along with others reported in the literature, underscores the potential for vasculitic neuropathy in patients undergoing ICI therapy.

In addition, it has been described that ANCA-associated pauci-immune necrotizing glomerulonephritis

can be a rare irAE during treatment with pembrolizumab, a PD-1 inhibitor [43]. The patient, a 65-year-old man with squamous cell carcinoma, developed acute renal failure after several months of therapy. A kidney biopsy revealed necrotizing glomerulonephritis without immune complex deposits, and the patient tested positive for p-ANCA and MPO antibodies. Treatment with high-dose corticosteroids and rituximab led to partial improvement. This case highlights the potential for pembrolizumab to cause severe renal complications and underscores the importance of early diagnosis and treatment in managing these irAEs.

In summary, ANCA-associated vasculitis refers to a group of autoimmune disorders characterized by small vessel inflammation and damage, typically associated with the presence of ANCA. These conditions can affect organs such as the kidneys, lungs, and skin, leading to symptoms like glomerulonephritis and pulmonary hemorrhage. Treatment generally involves immunosuppressive therapies, such as corticosteroids and rituximab, to control inflammation and prevent organ damage. These cases analyzed have highlighted that ANCA-associated vasculitis can emerge as an irAE during ICI therapy. BCG immunotherapy, commonly used for bladder cancer, has been shown to trigger p-ANCA vasculitis, while checkpoint inhibitors like ipilimumab and pembrolizumab have been linked to cases of vasculitic neuropathy and pauci-immune necrotizing glomerulonephritis. These cases emphasize the importance of monitoring for vasculitic irAEs in patients receiving ICIs, as early diagnosis and treatment are critical to preventing severe outcomes.

Autoimmune Myositis

Autoimmune myositis is a group of inflammatory muscle diseases characterized by chronic muscle weakness, inflammation, and elevated muscle enzymes, often involving proximal muscles [44]. Treatment typically includes immunosuppressive agents like corticosteroids and disease-modifying drugs to reduce inflammation and restore muscle function [45].

In this case, a 62-year-old female with metastatic ocular melanoma developed autoimmune myositis and myasthenia gravis after receiving combination therapy with nivolumab and ipilimumab [46]. The patient experienced generalized body weakness, fatigue, and ptosis, symptoms that appeared two weeks after the initiation of immunotherapy. Elevated creatinine kinase levels and the presence of acetylcholine receptor antibodies confirmed the diagnosis. Treatment with high-dose corticosteroids and intravenous immunoglobulin (IVIG) led to improvement in both muscle strength and ocular symptoms. This case underscores the potential for severe neuromuscular irAEs in patients undergoing combined immune checkpoint inhibitor therapy.

Another case report describes a 79-year-old patient with lung adenocarcinoma who developed nivolumab-induced myositis after receiving the immune checkpoint inhibitor [47]. Symptoms such as ptosis, muscle weakness, and dysphagia appeared one week after the second infusion. Blood tests revealed elevated creatine kinase levels, and a muscle biopsy confirmed necrotizing myositis with CD8+ T-cell infiltrates. The patient was treated with intravenous immunoglobulins and corticosteroids, leading to gradual clinical improvement. This case highlights the potential for severe neuromuscular irAEs with nivolumab and emphasizes the importance of early recognition and treatment to prevent further complications.

In conclusion, autoimmune myositis can occur as a serious irAE during cancer immunotherapy, particularly with drugs like nivolumab and ipilimumab. In a notable case, a 62-year-old woman with metastatic ocular melanoma developed both myositis and myasthenia gravis after receiving combination therapy [46]. She presented with significant muscle weakness and ptosis two weeks after treatment began, and lab tests confirmed elevated creatinine kinase and acetylcholine receptor antibodies. Aggressive treatment with corticosteroids and IVIG led to improvement in her symptoms. Similarly, a 79-year-old patient with lung adenocarcinoma developed nivolumab-induced myositis just one week after his second infusion. Muscle biopsy revealed necrotizing myositis with CD8+ T-cell infiltrates [47]. Early intervention with corticosteroids and immunoglobulins resulted in gradual recovery. These cases illustrate the importance of recognizing neuromuscular complications early in patients undergoing immune checkpoint inhibitor therapy, as prompt treatment is critical in preventing long-term damage or severe complications.

Systemic Sclerosis

Systemic sclerosis (SSc) is a complex autoimmune disease characterized by vasculopathy and tissue fibrosis affecting the skin and internal organs. Genetic and environmental factors influence susceptibility, severity, and onset. The peak incidence occurs between 30 and 60 years, predominantly in females (6:1 ratio), though males exhibit more severe forms and higher mortality [48]. There are two main subsets: diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc). DcSSc involves skin damage proximal to elbows and knees or affecting the thorax/abdomen, with a higher risk of internal organ involvement and a worse prognosis. LcSSc involves skin damage distal to elbows and knees, is more associated with pulmonary arterial hypertension, and has a better prognosis [49]. Moreover, recent studies suggest that SSc could present ocular involvement such as dry eye and retinal vascular abnormalities [50,51].

The treatment of SSc primarily involves immunosuppressive therapies aimed at managing inflammation and preventing disease progression. Recent approaches include mycophenolate mofetil, which has shown efficacy in reducing skin thickening and stabilizing lung function in systemic sclerosis-associated interstitial lung disease. Additionally, rituximab, a B-cell depleting agent, and newer therapies

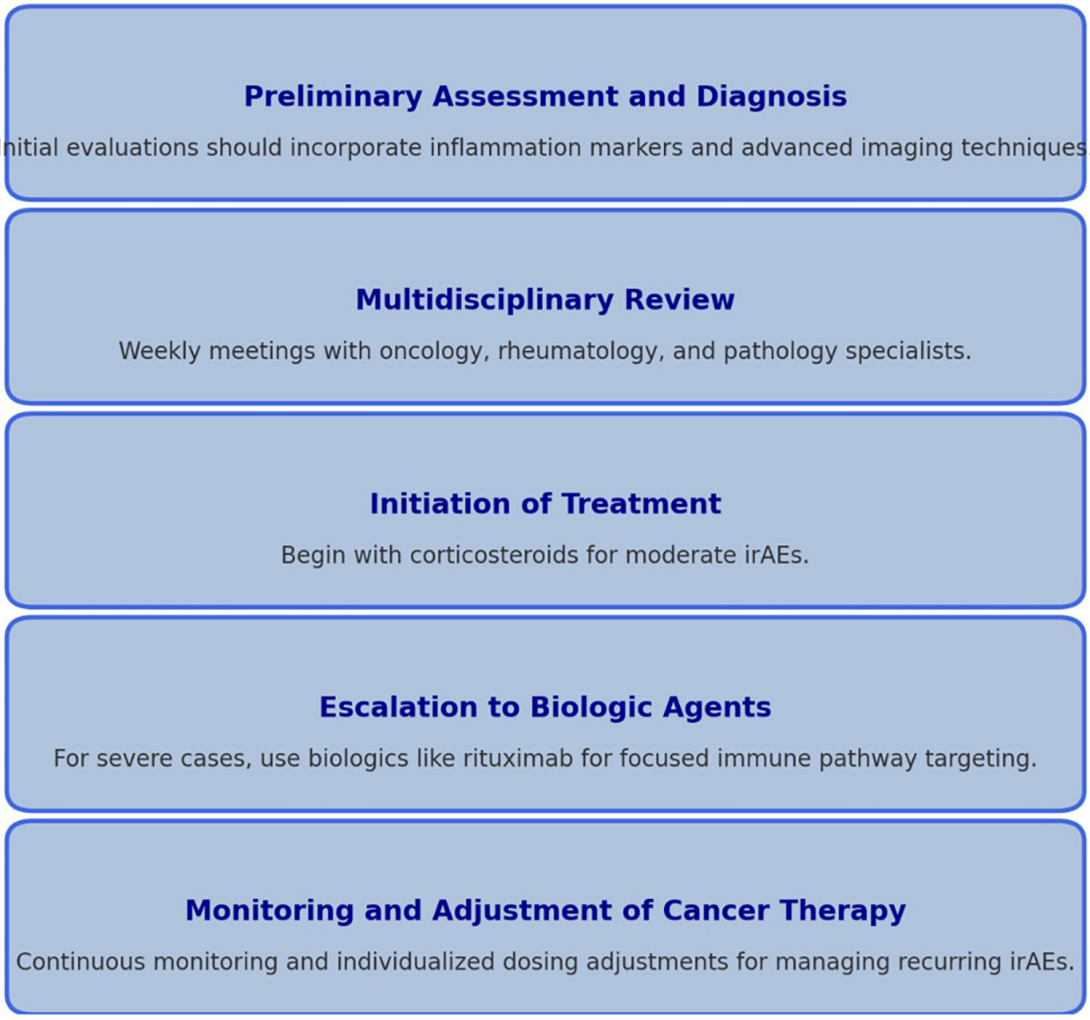

Fig. 1. Workflow for assessment and management of immune-related adverse events (irAEs). The figure created using Inkscape version 1.3, developed by the Inkscape Project. Manufacturer: Inkscape.org, located in Boston, MA, USA.

like tocilizumab, an IL-6 receptor inhibitor, are being used to target specific immune pathways involved in the disease. High-dose corticosteroids may be used in cases with severe inflammatory symptoms, although their use is generally limited due to the risk of renal crisis [52].

A recent case report details a 47-year-old woman with metastatic melanoma who developed SSc after initiating nivolumab therapy [53]. The patient exhibited symptoms such as inflammatory arthralgias, morning stiffness, and cutaneous sclerosis, accompanied by carpal tunnel syndrome and cardiac involvement. Laboratory findings revealed positive RNA-Polymerase III antibodies. Treatment with corticosteroids resulted in partial improvement of her symptoms. This case underscores the potential for immune checkpoint inhibitors like nivolumab to induce systemic scleroderma as an immune-related adverse event and emphasizes the importance of early recognition and management in patients receiving immunotherapy.

Moreover, another case report discusses a 75-year-old man with urothelial carcinoma who developed scleroderma-like syndrome after receiving pembrolizumab [54]. The patient initially experienced cyanosis and digital ulcers during chemotherapy, which worsened after starting pembrolizumab, leading to thickening of the skin on his hands and the development of digital scars. Laboratory tests showed positive anti-Ro52 antibodies but negative scleroderma-specific antibodies. Pembrolizumab was discontinued, and the patient was treated with corticosteroids, resulting in clinical improvement. This case highlights the potential for immune checkpoint inhibitors like pembrolizumab to induce scleroderma-like syndromes as an immune-related adverse event.

Prompt recognition of SSc biomarkers, including anti-RNA polymerase III and anti-topoisomerase antibodies, can enable timely management. Treatments aimed at specific pathways, such as tocilizumab (IL-6 suppression) and abatacept (T-cell modulation), demonstrate potential in the management of progressive SSc. Subsequent investigations may improve individualized therapeutic approaches, especially for high-risk patients susceptible to severe irAEs.

Moreover, tocilizumab demonstrates effectiveness in mitigating disease development and alleviating fibrotic symptoms.

SSc has been identified as a potential irAE in patients receiving ICIs like nivolumab and pembrolizumab. These case reports highlight instances where patients developed SSc or scleroderma-like syndromes, manifesting with skin thickening, arthralgias, and other systemic symptoms. Treatment with corticosteroids often results in symptom improvement, emphasizing the need for early diagnosis and intervention in managing these autoimmune complications in cancer patients undergoing immunotherapy.

Management

For the comprehensive management of immunomodulator-induced vasculitis and connective tissue diseases, recent studies underscore a structured and multi-phase approach to ensure both precise diagnostics and effective therapeutic responses [55,56].

Preliminary Assessment and Diagnosis—initial evaluations should incorporate specific markers of inflammation (e.g., C-reactive protein, erythrocyte sedimentation rate) alongside advanced imaging techniques.

Multidisciplinary Review—weekly interdisciplinary meetings involving specialists from oncology, rheumatology, and pathology are recommended for optimal decision-making in complex cases. Recent findings emphasize that multidisciplinary engagement is critical for detecting rare adverse effects of immunotherapies and for tailoring treatment protocols to patient-specific immune profiles, reducing risks of long-term adverse events [56].

Initiation of Treatment—initial therapeutic interventions often begin with corticosteroids to address moderate irAEs. The rationale is that corticosteroids can mitigate symptoms effectively without compromising immune surveillance against malignancies. This strategy, however, requires careful balancing to avoid exacerbating immune-related symptoms. For severe rAEs, an initial corticosteroid dosage of 1–2 mg/kg/day is advised, with a gradual decreasing as symptoms ameliorate. Treatment should focus on harmonizing irAE care with the ongoing cancer therapy to reduce the likelihood of recurrence.

Escalation to Biologic Agents—for severe cases, especially where conventional immunosuppression is insufficient, biologic agents such as rituximab are increasingly employed. Biologics target specific immune pathways implicated in vasculitis and connective tissue damage, offering a more focused approach with fewer systemic side effects. Data from recent studies suggest rituximab and other biologics as viable alternatives for managing resistant or recurrent irAEs in patients undergoing immunotherapy [57].

Monitoring and Adjustment of Cancer Therapy—continuous monitoring is essential to balance cancer control with autoimmune management. Recent guidelines advocate for individualized dosing adjustments of cancer therapy, especially for patients with recurring irAEs, to maximize oncological benefits while minimizing immune-related toxicity (Fig. 1) [57,58].

This updated approach, grounded in current studies, reflects a nuanced understanding of immunotherapy-related complications, stressing the importance of personalized, multidisciplinary care to optimize patient outcomes [56–58].

Conclusions

In conclusion, ICIs have transformed cancer treatment, offering improved survival outcomes for many patients. However, they are also associated with a wide range of immune-related adverse events, including rheumatological complications such as Sjogren's syndrome, systemic lupus erythematosus, giant cell arteritis, ANCA-associated vasculitis, autoimmune myositis, and systemic sclerosis. These conditions, though rare, can present significant clinical challenges, requiring early diagnosis and prompt intervention. Corticosteroids and immunosuppressive therapies are commonly used to manage these irAEs, but the approach must be individualized based on the severity of the autoimmune response and the need to continue cancer treatment. Collaboration between oncologists and rheumatologists is essential to ensure that irAEs are effectively treated while minimizing disruption to cancer therapy. Effective options for multidisciplinary therapy encompass routinely convened tumor board meetings and collaborative clinics where oncologists and rheumatologists work together to modify immunomodulatory therapies according to the severity of irAEs. Weekly joint examinations provide a prompt response in instances of severe autoimmune symptoms, hence enhancing cancer treatment and mitigating irAE progression. Further research is needed to better understand the mechanisms underlying these adverse events and to develop strategies for prevention and management.

Availability of Data and Materials

Not applicable.

Author Contributions

CG, RobF, RosF, MZ designed the research study. EV, RobF, RicF performed the research. ED, AM, RicF, CG, DI analyzed the data, provided help and advice on each section, provided modifications with each draft, visualized and edited all versions. RobF, CG, MZ, RosF, and RicF wrote the manuscript. All authors contributed significantly to editorial changes of important content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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