Review article

Immune checkpoint inhibitor-associated myocarditis: current insights into pathogenesis, diagnosis, and treatment

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy by enhancing T-cell-mediated antitumor immunity through blockade of cytotoxic T-lymphocyte-associated antigen 4 and programmed cell death protein 1 pathways. Despite their clinical efficacy across multiple solid tumors and select hematologic malignancies, ICIs can disrupt peripheral immune tolerance, triggering immune-related adverse events, among which myocarditis is rare but potentially fatal.

Immune checkpoint inhibitor-associated myocarditis (ICI-M) typically emerges early after therapy initiation and is characterized by dense myocardial infiltration of activated T lymphocytes, particularly clonally expanded $CD8^+$ cells. Mechanisms involve autoreactive responses against cardiac antigens, such as α-myosin heavy chain, and molecular mimicry with tumor or skeletal muscle proteins. Clinical presentations are highly heterogeneous, ranging from isolated biomarker elevation to fulminant myocarditis with cardiogenic shock, malignant arrhythmias, or conduction disturbances. Concomitant myositis or myasthenia gravis-like syndromes are common, reflecting shared antigenic targets.

Diagnosis requires integrated evaluation using clinical assessment, cardiac biomarkers, electrocardiography, echocardiography, and cardiac magnetic resonance, with endomyocardial biopsy remaining definitive. Early recognition and prompt initiation of high-dose corticosteroids are critical to mitigate morbidity and mortality, while second-line immunosuppressive strategies are increasingly explored in refractory cases. Despite its low incidence, ICI-M carries substantial risk, underscoring the need for vigilance and multidisciplinary management.

Key words: immune checkpoint inhibitors, ICI-associated myocarditis, cardiotoxicity, cardio-oncology, immune-related adverse events

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INTRODUCTION

Effective antitumor immunity requires precise T-cell activation, which depends on antigen recognition via the T-cell receptor (TCR)–major histocompatibility complex (MHC) interaction and concomitant co-stimulatory signals. Immune checkpoints, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1), normally restrain T-cell responses to maintain peripheral tolerance and prevent autoimmunity. ICIs are monoclonal antibodies designed to disrupt these inhibitory pathways, thereby enhancing T-cell-mediated antitumor activity. CTLA-4 blockade primarily affects early T-cell priming in secondary lymphoid organs, whereas PD-1 and its ligand (PD-L1) inhibition restores effector function within peripheral tissues and the tumor microenvironment. Clinically, ICIs have demonstrated efficacy across a wide range of solid tumors and select hematologic malignancies, either as monotherapy or in combination regimens. Combination therapy can provide synergistic immune activation but is associated with an increased risk of immune-related adverse events, including myocarditis [1–6].

MATERIALS AND METHODS

This narrative review was conducted to summarize current evidence regarding immune checkpoint inhibitor–associated myocarditis. A literature search was performed using major biomedical databases, including PubMed and Scopus, to identify relevant publications addressing the epidemiology, immunopathogenesis, clinical presentation, diagnostic strategies, management, and outcomes of this condition. Peer-reviewed articles, clinical studies, registry analyses, and guideline documents published in English were considered. The selected literature was critically analyzed and synthesized to provide an updated overview of the current understanding of this cardio-oncologic complication.

IMMUNOPATHOGENESIS OF ICI-ASSOCIATED MYOCARDITIS

Immune checkpoint inhibitor-associated myocarditis (ICI-M) arises from a breakdown of peripheral immune tolerance within the myocardium [7]. The condition typically manifests early after treatment initiation, with a median onset of approximately 21 days and nearly ⅓ of cases occurring after the first dose, underscoring the rapidity with which immune dysregulation may develop under checkpoint blockade [8]. The myocardium is normally protected by tightly regulated immune mechanisms, including limited baseline T-cell residency and inhibitory signaling pathways such as PD-L1 expression on endothelial and parenchymal cells [9]. Pharmacologic inhibition of PD-1/PD-L1 or CTLA-4 disrupts these cardioprotective pathways, facilitating excessive activation and tissue infiltration of effector T lymphocytes [9].

Histopathological analyses consistently reveal dense infiltration of $CD4^+$ and $CD8^+$ T lymphocytes within the myocardium and conduction system, frequently accompanied by macrophages, supporting a predominantly cell-mediated mechanism of injury [9]. Single-cell transcriptomic and TCR sequencing studies identify clonally expanded cytotoxic $CD8^+$ T cells as the dominant immune population in affected cardiac tissue. Experimental depletion of $CD8^+$ T cells markedly improves survival in murine models, confirming their central pathogenic role [10].

The cardiac-restricted protein α-myosin heavy chain has emerged as a clinically relevant autoantigen, in part because it is not expressed in medullary thymic epithelial cells and therefore escapes complete negative selection during T-cell development. Peripheral T cells from patients with ICI-M exhibit antigen-specific expansion in response to α-myosin peptides, with shared TCR clonotypes detected in cardiac tissue, skeletal muscle, and circulating lymphocytes [10]. This clonal overlap supports a model of antigenic cross-recognition and provides a mechanistic basis for the frequent coexistence of myocarditis with myositis and myasthenia-like syndromes [7]. Molecular mimicry between tumor antigens and structurally related muscle proteins may further amplify autoreactive T-cell responses in the context of checkpoint blockade [9].

At the effector level, myocardial injury is mediated through perforin- and granzyme-dependent cytotoxicity, engagement of death receptor pathways, and cytokine-induced cardiomyocyte dysfunction [11]. Immune-mediated involvement of the cardiac conduction system contributes to the high incidence of malignant arrhythmias and sudden cardiac death observed in severe cases [11]. Collectively, these data support a mechanistic framework in which immune checkpoint blockade unmasks latent autoreactivity against incompletely tolerized cardiac antigens, culminating in $CD8^+$ T cell-driven myocardial inflammation and injury [9, 11].

PATIENT- AND TREATMENT-RELATED RISK FACTORS FOR ICI-ASSOCIATED CARDIOTOXICITY

Advanced age has consistently been associated with an increased risk of ICI-M, particularly among patients aged ≥65–75 years. Age-related immune dysregulation and diminished myocardial reserve may further increase susceptibility to immune-mediated cardiac injury [12]. Regarding sex, broader observational and pharmacovigilance data indicate a higher proportion of myocarditis cases among men; however, these analyses have not consistently demonstrated a statistically significant independent sex-specific risk after adjustment for confounders, suggesting

that the apparent male predominance may partially reflect differences in cancer epidemiology and treatment exposure rather than definitive biological susceptibility [12]. In contrast, in a retrospective cohort of patients with esophageal cancer, male sex was identified as a significant risk factor, with a more than twofold higher incidence of myocarditis compared with females, and was incorporated – together with age and baseline cardiac biomarker levels – into a predictive model that improved early diagnostic accuracy in this specific population [13]. Elevated body-mass index has also been linked to increased ICI-M risk, potentially reflecting metabolic inflammation and heightened cardiovascular vulnerability [12]. Furthermore, in a multicenter lung cancer cohort, earlier onset of myocarditis – defined as within 132 days of ICI initiation – was associated with significantly worse overall survival, indicating that rapid development of cardiotoxicity identifies a high-risk phenotype in patients with lung cancer [14]. Collectively, these data indicate that age, sex in tumor-specific contexts, metabolic burden, cardiovascular comorbidity, baseline biomarkers, and early temporal onset collectively shape the risk profile and clinical trajectory of ICI-related myocarditis [12–14].

CLINICAL SPECTRUM AND PHENOTYPIC VARIABILITY OF ICI-MYOCARDITIS

The clinical spectrum of ICI-M encompasses subclinical presentations to fulminant, life-threatening disease. Mild cases may manifest solely as isolated elevations in cardiac biomarkers in the absence of overt clinical symptoms [9], and approximately 10.1% of cases are initially asymptomatic, with diagnosis dependent upon laboratory abnormalities, electrocardiographic changes, or cardiac magnetic resonance imaging, emphasizing the necessity for heightened vigilance even in the absence of clinical findings [8]. Intermediate presentations frequently mimic classical viral myocarditis, with acute coronary syndrome-like symptoms, de novo heart failure, or progression to chronic heart failure, often accompanied by nonspecific complaints such as chest discomfort, dyspnea, palpitations, orthopnea, or fatigue. Severe disease may present with cardiogenic shock or malignant arrhythmias, including high-grade atrioventricular block and ventricular tachyarrhythmias. Pericardial involvement, with or without overt pericarditis, and recurrent pericardial or pleural effusions have also been reported [9]. Data from the International ICI-Myocarditis Registry indicate that approximately ⅓ of patients present with left ventricular ejection fraction (LVEF) <50%, which correlates with more pronounced symptoms, including dyspnea and elevated natriuretic peptides, as well as an increased incidence of in-hospital complications. Conversely, patients with preserved LVEF more frequently exhibit concomitant myositis or myasthenia gravis-like syndromes, suggesting distinct clinical subphenotypes [15]. Overlap syndromes are common, with myocarditis co-occurring with myositis in 30–40% of cases and myasthenia gravis-like manifestations in approximately 10% [16]. Neuromuscular manifestations may include generalized muscle weakness, diplopia, or ptosis, whereas systemic manifestations such as fever, rash, or diarrhea are comparatively uncommon [8].

MULTIMODAL DIAGNOSTIC STRATEGIES IN ICI-ASSOCIATED MYOCARDITIS

The diagnosis of ICI-M requires an integrated approach, incorporating clinical assessment, cardiac biomarkers, electrocardiography, and multimodal imaging, with cases classified as definite, probable, or possible based on these findings and the exclusion of alternative etiologies [9]. Serum troponin elevation is the most frequently observed laboratory abnormality and is present in the majority of patients; however, it is nonspecific and may be elevated in conditions including acute coronary syndromes, demand ischemia, or concomitant immune-mediated myositis [8, 17]. High-sensitivity troponin I (hs-TnI) appears more cardiac-specific than hs-TnT and has been associated with early left ventricular dysfunction [17]. Natriuretic peptides are often elevated but lack specificity for myocarditis and primarily reflect heart failure severity. Electrocardiographic abnormalities are highly prevalent, with 85.1% of patients demonstrating new changes after ICI initiation; conduction disturbances are most common, including complete atrioventricular block in 35.4% of cases, along with bundle branch blocks, supraventricular arrhythmias, and ventricular tachyarrhythmias. ST-segment and T-wave changes frequently necessitate differentiation from acute coronary syndromes, though coronary angiography typically excludes obstructive disease [8].

Echocardiography is widely used for structural and functional assessment, detecting left ventricular enlargement, systolic dysfunction, regional wall motion abnormalities, strain changes, and pericardial effusion, though preserved LVEF is common and does not exclude significant myocarditis. Advanced echocardiographic measures, such as global longitudinal strain, provide prognostic information independent of LVEF. Cardiac magnetic resonance (CMR) allows noninvasive tissue characterization, identifying late gadolinium enhancement, increased T1/T2 mapping values, myocardial edema, and strain abnormalities; however, normal findings do not exclude disease. Molecular imaging techniques, including ^{68}Ga-FAPI and PD-1/PD-L1-targeted PET, may detect early myocardial inflammation and immune activation prior to structural injury, offering potential for risk stratification and monitoring [18]. Endomyocardial biopsy remains the diagnostic gold standard, demonstrating lymphocytic myocarditis with a predominance of

$CD8^+$ T cells and macrophage infiltration, and providing mechanistic confirmation of immune-mediated myocardial injury, despite limitations related to sampling variability [8]. Pericardial effusions, while supportive, lack diagnostic specificity. The coexistence of myocarditis with extracardiac immune-related toxicities, particularly myositis or myasthenia gravis-like syndromes, should further heighten clinical suspicion and may reflect immune cross-reactivity against shared muscle antigens [9]. Collectively, diagnostic strategies must be individualized, balancing the need for diagnostic certainty with procedural risk, and integrating biomarker trends, imaging findings, and clinical context to guide timely identification and management.

THERAPEUTIC APPROACHES AND IMMUNOSUPPRESSIVE MANAGEMENT

Management of ICI-M requires prompt recognition and immediate discontinuation of immune checkpoint inhibitor therapy in all suspected cases [9, 19, 20]. Patients should be hospitalized for close clinical observation and continuous electrocardiographic monitoring, ideally in centers with cardio-oncology expertise, while individuals with fulminant disease or hemodynamic instability may require intensive care and consideration of temporary mechanical circulatory support [19, 20]. Early initiation of high-dose systemic glucocorticoids represents the cornerstone of treatment and has been associated with lower troponin levels and reduced incidence of major adverse cardiovascular events [9]. Current recommendations support prompt administration of intravenous methylprednisolone at doses of 500–1000 mg daily for 3–5 days once myocarditis is considered probable. Clinical improvement – reflected by a >50% reduction in troponin concentration and resolution of ventricular dysfunction, atrioventricular conduction disturbances, or arrhythmias – permits transition to oral prednisone at approximately 1 mg/kg daily followed by gradual tapering guided by clinical status, electrocardiography findings, and biomarker trends [19].

Despite corticosteroid therapy, a substantial proportion of patients may exhibit steroid-refractory disease, defined by persistent biomarker elevation, ongoing arrhythmias, or ventricular dysfunction after several days of high-dose treatment [19, 20]. In such cases, escalation to additional immunosuppressive therapies may be required [9, 20]. Reported second-line options include mycophenolate mofetil, antithymocyte globulin, intravenous immunoglobulin, plasmapheresis, and targeted immunomodulatory agents [9, 19, 20]. Abatacept, a CTLA-4 fusion protein that induces T-cell anergy, is currently under prospective clinical evaluation as a potential therapeutic strategy [20]. Other agents, including tocilizumab, alemtuzumab, and JAK-STAT inhibitors such as tofacitinib or ruxolitinib, have been used in selected refractory cases, although evidence remains limited [19, 20]. In contrast, infliximab is generally discouraged in patients with concomitant heart failure [19]. Supportive cardiovascular management should follow established heart failure and arrhythmia guidelines and may include diuretics, inotropes, temporary pacing, or mechanical circulatory support when clinically indicated. Long-term cardiologic therapy may be necessary in patients with persistent ventricular dysfunction following the acute phase [9]. Decisions regarding potential re-initiation of immune checkpoint inhibitor therapy after recovery should be made by a multidisciplinary team, considering myocarditis severity and available oncologic treatment alternatives [19].

CLINICAL OUTCOMES AND PROGNOSTIC DETERMINANTS IN ICI-MYOCARDITIS

ICI-M is associated with substantial morbidity and mortality, although clinical outcomes vary considerably among affected patients. In a real-world cohort, 16.7% of patients died during hospitalization and 55.6% were deceased at follow-up, with cancer progression representing the most common cause of death (55.6%), followed by non-cardiac immune-related adverse events and respiratory failure, while death directly attributable to myocarditis occurred less frequently (16.7%) [21]. Reduced LVEF (<50%) identifies a high-risk phenotype and is independently associated with increased 30-day all-cause and myocarditis-related mortality. However, adverse outcomes may also occur in patients with preserved LVEF, indicating that the absence of overt systolic dysfunction does not exclude clinically significant disease [22]. Factors associated with more severe clinical presentation include pre-existing cardiovascular disease, prior exposure to cardiotoxic oncologic therapies, dyspnea at presentation, and a longer interval between initiation of immune checkpoint inhibitor therapy and myocarditis onset [22]. Patients experiencing major adverse cardiac events (MACE) more frequently exhibit male sex, larger left ventricular end-diastolic diameter, elevated creatinine and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, prolonged dyspnea prior to presentation, and a higher prevalence of heart failure or arrhythmias. Nevertheless, multivariable analyses have not consistently identified reliable predictors of mortality, underscoring the unpredictable clinical course of ICI-M [21].

CONCLUSION

Immune checkpoint inhibitors have fundamentally reshaped contemporary oncologic therapy but have also introduced a spectrum of immune-related toxicities affecting multiple or-

gan systems, including the heart. ICI-associated myocarditis represents one of the most serious of these complications, requiring a high index of clinical suspicion due to its variable and often non-specific presentation. Early recognition is crucial, as timely discontinuation of immunotherapy and prompt initiation of immunosuppressive treatment significantly influence clinical outcomes. Increased awareness of the risk factors, clinical manifestations, and diagnostic strategies summarized in this review may facilitate earlier detection and more effective management. Consequently, improved vigilance among clinicians may enable faster therapeutic intervention and potentially reduce morbidity and mortality associated with this condition.

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Anna Jastrzębska: research concept and design, collection of data, data curation, formal analysis, writing the article, critical revision of the article, final approval of the article.
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