ISSN: 2584-0355
DOI: doi.org/10.51219/MCCRJ/Marco-Aurélio-de-Souza-Costa/337

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Medical & Clinical Case Reports Journal

https://urfpublishers.com/journal/case-reports

Vol: 3 & Iss: 3

Review

Diagnosis of Myocarditis Related to Cancer Immunotherapy - A Brief Review

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Citation: Costa MAS, Silva MM, Estival LB, et al. Diagnosis of Myocarditis Related to Cancer Immunotherapy - A Brief Review. *Medi Clin Case Rep J* 2025;3(3):1229-1231. DOI: doi.org/10.51219/MCCRJ/Marco-Aurélio-de-Souza-Costa/337

Received: 17 August, 2025; **Accepted:** 19 August, 2025; **Published:** 21 August, 2025

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ABSTRACT

Myocarditis associated with cancer immunotherapy has emerged as a serious complication of immune checkpoint inhibitors, particularly anti–PD-1, anti–PD-L1 and anti–CTLA-4 antibodies. Although its incidence is low (<1%), mortality may exceed 50% when diagnosis is delayed or management is inadequate. Clinically, presentations range from mild symptoms such as fatigue and chest discomfort to acute heart failure and potentially fatal arrhythmias. This clinical variability reflects the complex interplay between antitumor immune response and autoimmune cardiac activation. Diagnosis requires a high index of suspicion in patients who initiated immunotherapy within the previous three months and present with atypical cardiovascular symptoms. Biochemical testing reveals elevated cardiac troponin and natriuretic peptides, though these markers lack specificity for myocarditis versus other cardiac injuries. Electrocardiography often shows nonspecific changes such as bundle branch blocks, PR-interval prolongation or supraventricular arrhythmias. Cardiac magnetic resonance imaging (CMR) is the noninvasive gold standard, demonstrating myocardial edema and gadolinium late enhancement consistent with inflammatory syndrome. However, limited availability and contraindications may hinder its use. Endomyocardial biopsy remains the reference for definitive diagnosis, showing lymphocytic inflammatory infiltrate and myocyte necrosis, but carries procedural risks and sampling error. Diagnostic protocols combine clinical criteria (immunotherapy context, cardiac symptoms), laboratory markers and imaging findings to stratify suspicion as probable or confirmed. Initial management includes discontinuation of immunotherapy and early high-dose glucocorticoids (prednisone 1–2 mg/kg/day), followed by immunosuppressants such as methotrexate, azathioprine or mycophenolate in refractory cases. In critical scenarios, intravenous immunoglobulin, plasmapheresis or biologic agents (e.g., rituximab) may be employed. Despite advances, gaps remain regarding optimal steroid tapering schedules, criteria for immunotherapy rechallenge and predictors of treatment response. Prospective studies and multicenter registries are essential to identify risk biomarkers and continuous cardiac monitoring protocols such as strain echocardiography and serial troponin measurement to reduce morbidity and mortality, optimize antitumor therapy and ensure patient safety.

Keywords: Myocarditis; Cancer immunotherapy; Immune checkpoints; Cardiac magnetic resonance; Glucocorticoids

Introduction

Cancer immunotherapy has revolutionized the treatment of diverse malignancies, yielding prolonged responses and significant survival benefits even in poor-prognosis tumors. Immune checkpoint inhibitors namely anti–PD-1 (programmed cell death protein 1), anti–PD-L1 (programmed death-ligand 1) and anti–CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) antibodies block inhibitory pathways and enhance cytotoxic T-cell activity against tumor cells[1]. Despite these therapeutic successes, immune dysregulation can trigger immune-related adverse events (irAEs) affecting the skin, gastrointestinal tract, liver, endothelium and, less commonly, the heart[2]. Myocarditis due to immunotherapy is rare but highly lethal, with early reports estimating mortality between 25% and 50%. Multicenter registries reported incidence rates from 0.06% to 1.14%, peaking within 6 to 12 weeks of treatment initiation. The pathophysiology involves recruitment of autoreactive T cells to the myocardium, likely due to molecular mimicry between tumor and cardiac antigens. Histopathology shows CD4+ and CD8+ lymphocytic infiltrates, focal myocyte necrosis and early fibrosis.

Clinically, immunotherapy-related myocarditis may mimic acute coronary syndromes, acute heart failure or arrhythmic disorders. Chest pain, dyspnea, unexplained fatigue and syncope should raise suspicion in patients receiving checkpoint inhibitors. Cardiac biomarkers chiefly troponin I or T and B-type natriuretic peptide are valuable for screening but lack specificity. Electrocardiograms demonstrate abnormalities in up to 80% of cases, including bundle branch blocks, QT prolongation or atrial arrhythmias. CMR enables noninvasive evaluation of inflammation and fibrosis via gadolinium late enhancement and T2 mapping for edema, achieving >75% sensitivity and ~90% specificity by Lake Louise criteria[3]. Nonetheless, contraindications (e.g., metal implants, renal insufficiency) and resource scarcity limit its universal application. Endomyocardial biopsy remains the diagnostic gold standard but is invasive and prone to false negatives due to sampling error.

Objectives

The primary objective of this study is to systematically review the literature on myocarditis associated with cancer immunotherapy.

Materials and Methods

A systematic literature review was conducted in PubMed, Embase and Scopus through May 2025 using the keywords “myocarditis,” “immune checkpoint inhibitors,” “cancer immunotherapy,” “diagnosis,” and related terms.

Discussion

Checkpoint inhibitor-induced myocarditis poses significant diagnostic challenges given its rarity, variable clinical manifestations and symptom overlap with other cardiac conditions. Troponin elevation serves as an early warning but requires careful interpretation, as it may reflect myocardial infarction or chemotherapy-related injury. A multimodal diagnostic strategy integrates biochemical markers, electrocardiography, echocardiography and CMR. Global longitudinal strain on echocardiography can detect subclinical systolic dysfunction before ejection fraction decline, permitting earlier diagnosis. CMR, guided by Lake Louise criteria, excels at characterizing myocardial edema and fibrosis, yet limited access and contraindications restrict widespread use. Endomyocardial biopsy, while definitive, carries risks of ventricular perforation and false negatives. Emerging guided techniques such as electroanatomic mapping or CMR-guided biopsy may improve diagnostic yield but await large-scale validation. International guidelines recommend troponin and echocardiographic surveillance before each immunotherapy cycle during the first three months, the period of highest risk. Immediate immunosuppression with high-dose glucocorticoids improves survival, although relapse rates remain substantial during rapid tapering. Adjunctive immunosuppressants (e.g., mycophenolate, azathioprine) demonstrate benefit in refractory cases. Intravenous immunoglobulin and plasmapheresis target autoantibodies and cytokines in fulminant myocarditis, but randomized trials are lacking.

Decisions regarding immunotherapy rechallenge after myocarditis resolution remain controversial. Some studies report high relapse rates, limiting reinitiation to carefully selected patients under strict monitoring[4]. Novel biomarkers such as circulating cytokine profiles and microRNA signatures may enable risk stratification and guide therapeutic decisions in the future[5-9]. Prospective randomized trials and multicentre registries are critical to establish standardized monitoring protocols and management algorithms. Collaboration between cardiologists and oncologists in dedicated cardio-oncology units is essential to minimize morbidity and mortality while preserving antitumor efficacy through multidisciplinary, patient-centred care[10-15].

Conclusion

Immunotherapy-related myocarditis is an uncommon but potentially fatal complication if not diagnosed and treated promptly. Its heterogeneous presentation necessitates vigilant monitoring protocols that include cardiac biomarkers, strain echocardiography and CMR. Immediate high-dose glucocorticoid therapy, supplemented by additional immunosuppressants in refractory cases, improves patient outcomes. However, uncertainties persist regarding optimal immunosuppressive tapering, criteria for immunotherapy reintroduction and reliable risk predictors. Prospective studies, national registries and multidisciplinary cardio-oncology collaborations are imperative to develop robust guidelines, refine diagnostic and therapeutic strategies and balance antitumor efficacy with cardiac safety.

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