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Review Article

Immune Checkpoint Inhibitor-Induced Myocarditis: A Review of Published Cases

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Abstract

Background: Immune checkpoint inhibitors (ICIs) targeting CTLA-4, PD-1 and PD-L1 have transformed treatment of metastatic melanoma and other cancers, but the same mechanism that unleashes anti-tumour immunity can also attack the myocardium.

Objective: To review the published case reports, series, registries and mechanistic literature on ICI myocarditis, drawing on melanoma-specific reports where the literature specifies them.

Methods: Narrative review of case reports, case series, pharmacovigilance analyses, registry cohorts, mechanistic studies and guideline documents.

Findings: Reported incidence ranges from roughly 0.06% to 1.3% of ICI-treated patients, rising toward 2% with combination therapy. Onset is typically early (median 34 days, one registry of 35 patients), and historical fatality has reached 25-50%. Published cases document fulminant presentations with conduction abnormalities, cardiogenic shock and myositis; refractory cases have been treated with anti-thymocyte globulin, abatacept and ruxolitinib, the latter combination linked in one cohort to a marked fatality reduction.

Conclusions: The published record supports early biomarker-based suspicion, prompt ICI discontinuation, and stepwise escalation of immunosuppression in refractory disease, with still-limited evidence for targeted second-line agents.

Keywords: Immune checkpoint inhibitor; Myocarditis; Melanoma; Cardiotoxicity; Immune-related adverse event

Abstract

Background: Immune checkpoint inhibitors (ICIs) targeting CTLA-4, PD-1 and PD-L1 have transformed treatment of metastatic melanoma and many other cancers, but the same mechanism that unleashes anti-tumour immunity can also unleash autoimmune attack on the myocardium. ICI-associated myocarditis is uncommon but disproportionately lethal among immune-related adverse events. **Objective:** To review the published case reports, case series, registries and mechanistic literature on ICI myocarditis, with attention to melanoma where the literature specifies it. **Methods:** Narrative review of case reports, case series, pharmacovigilance analyses, registry cohorts, mechanistic studies and guideline documents. **Findings:** Reported incidence ranges from roughly 0.06% to 1.3% of ICI-treated patients, rising toward 2% with combination CTLA-4 plus PD-1 blockade. Onset is typically early, with a median of about 34 days in a multicentre registry of 35 patients, and historical fatality has reached 25-50%. Published cases, several in melanoma, document fulminant presentations with conduction abnormalities, cardiogenic shock and concurrent myositis, alongside milder disease recognised only through biomarker surveillance. Management centres on ICI discontinuation and high-dose corticosteroids; refractory cases have been treated with anti-thymocyte globulin, abatacept and ruxolitinib, the latter combination associated in one cohort with a marked reduction in fatality. **Conclusions:** The published record supports early biomarker-based suspicion, prompt ICI discontinuation, and stepwise escalation of immunosuppression in refractory disease, with emerging but still limited evidence for targeted second-line agents.

Keywords: immune checkpoint inhibitor; myocarditis; melanoma; cardiotoxicity; immune-related adverse event

Introduction

Immune checkpoint inhibitors have reshaped treatment of metastatic melanoma and expanded into lung, renal, urothelial, lymphoma and other cancers by blocking the inhibitory receptors CTLA-4, PD-1 and PD-L1 that tumours exploit to evade T-cell attack. Removing these brakes restores anti-tumour cytotoxicity but also removes a check on autoreactive T cells, producing immune-related adverse events (irAEs) that can affect skin, gut, endocrine organs, lungs, joints, nerves and heart [1].

Cardiac irAEs are uncommon but disproportionately dangerous. Myocarditis, the best-characterised and most feared, was first drawn to wide attention by two fatal cases of fulminant myocarditis in melanoma patients on combination ipilimumab and nivolumab, reported in the New England Journal of Medicine in 2016 [2]. That report, alongside a contemporaneous series describing cardiac, neurological, respiratory, musculoskeletal and ocular toxicity of anti-PD-1 therapy [3] and a further series across CTLA-4- and PD-1-blocking regimens [4], established that ICI myocarditis was real, could be fulminant, and could kill otherwise-responding patients.

This is a narrative review, not a case report of the authors' own patients, surveying published case reports, registries, mechanistic studies and society guidance on the epidemiology, pathophysiology, presentation, diagnosis, management and prognosis of ICI myocarditis, drawing on melanoma-specific reports where available.

Epidemiology and Incidence

Reported incidence varies with ascertainment method. A widely cited synthesis places it between roughly 0.06% and 1% of ICI-treated patients [5], while a pharmacovigilance analysis of the WHO's VigiBase found rising reports of fatal ICI myocarditis over time, with fatality substantially higher for combination CTLA-4 plus PD-1 therapy than either agent alone [6]. A systematic review of fatal ICI toxicities estimated 0.3% to 1.3% of treated patients, with fatal events developing early — a

median of 40 days after monotherapy and 14.5 days after combination therapy [7]. A more recent meta-analysis focused on cardiotoxicity found cardiovascular adverse events and/or myocarditis in 1.07% of trial patients [8].

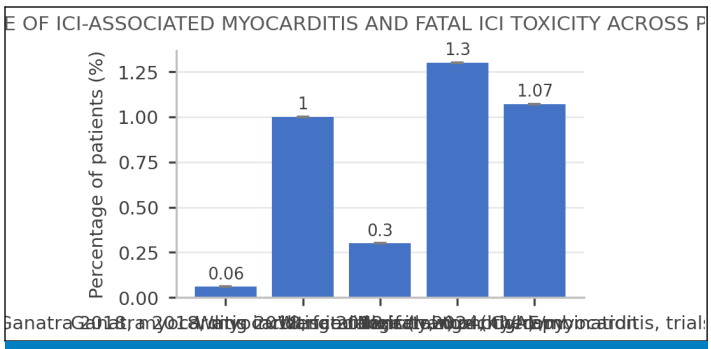

Figure 1: Reported incidence of ICI-associated myocarditis and fatal ICI toxicity: 0.06%-1% [5]; 0.3% (monotherapy) to 1.3% (combination) fatal toxicity [7]; 1.07% cardiovascular/myocarditis events across trials [8].

A multicentre registry of 35 patients found a median onset of 34 days (IQR 21-75), confirmed a higher rate of major adverse cardiac events with combination therapy, and found myocarditis often accompanied other irAEs, particularly myositis [9]. A pooled analysis of published case reports found pembrolizumab (30.2%), nivolumab (23.6%) and nivolumab-plus-ipilimumab (19.8%) the most frequently implicated regimens, spanning malignancies with melanoma and non-small cell lung cancer most common [10]. Biomarker surveillance shows troponin and other cardiac/skeletal-muscle markers are markedly more likely abnormal in confirmed myocarditis: in one cohort 95% of confirmed cases had elevation in at least three biomarkers, versus 5% of ICI-treated patients without myocarditis [11].

Pathophysiology and Mechanism

The leading hypothesis is that ICI myocarditis reflects loss of the restraint PD-1/PD-L1 and CTLA-4 signalling ordinarily place on autoreactive T cells, unmasking latent autoimmunity against cardiac antigens [1]. Biopsy typically shows lymphocytic infiltration with CD4+/CD8+ T cells and macrophages, resembling acute transplant rejection rather than viral myocarditis, informing the immunosuppressants later trialled in refractory disease.

A mouse model combining monoallelic Ctla4 loss with complete Pdcd1 absence produced premature death from myocardial T-cell/macrophage infiltration, recapitulating human disease; abatacept ameliorated it, providing preclinical rationale for the abatacept cases below [12]. Concurrent skeletal/ocular muscle involvement (myositis, myasthenia-like syndromes) recurs across the case literature, consistent with shared T-cell clones recognising cardiac and skeletal antigens [13].

Clinical Presentation

The case record spans indolent, biomarker-detected disease to fulminant cardiogenic shock, often within the same regimen class. In the sentinel report, two melanoma patients on combination ipilimumab and nivolumab developed myocarditis with progressive conduction abnormalities and myositis within the first cycle, and both died despite intensive immunosuppression [2]. In the Heinzerling series, a 72-year-old man on combination therapy then nivolumab monotherapy developed myocarditis with cardiomyopathy, thyroiditis and hypophysitis after his third cycle, illustrating clustering with other irAEs; he survived with defibrillator monitoring, diuresis and oral corticosteroids [4]. In the Zimmer series, three melanoma patients ranged from cardiomyopathy after one pembrolizumab cycle, to asystole at 17 weeks on nivolumab, to stable angina at 10 weeks on pembrolizumab resolving on discontinuation alone [3] — showing onset can extend well beyond the first weeks.

Fulminant, rapidly fatal courses recur throughout the literature. Fatal myocarditis with rhabdomyositis was reported in stage IV melanoma on combined ipilimumab and nivolumab, refractory to corticosteroids [14]. An early case of acute heart failure from autoimmune myocarditis occurred in a 73-year-old woman with metastatic uveal melanoma on third-line pembrolizumab, showing the

disease is not restricted to cutaneous melanoma or first-line therapy [15]. A case specifically reported for survival after a fulminant presentation stood out because such outcomes were, at the time, unusual [16].

Table 1: Published cases and case series of immune checkpoint inhibitor-associated myocarditis reviewed here [2,4,3,24,15,16,14,25,13,26,27]; N = 11 reports.

Report	Age/sex	Cancer type	ICI regimen	Presentation	Outcome
Johnson 2016, n=2	65/F; not stated	Melanoma	Ipi + nivo	Conduction block, myositis, cycle 1	Fatal (both)
Heinzerling 2016	72/M	Melanoma	Ipi+nivo then nivo	Cardiomyopathy, thyroiditis, hypophysitis, cycle 3	Survived
Zimmer 2016, n=3	73/M; 87/M; 77/M	Melanoma	Pembro or nivo	Cardiomyopathy; asystole (17wk); angina (10wk)	Survived
Tay 2017	Not stated	Not stated	Nivolumab	Fulminant, steroid-refractory	Survived (ATGAM)
Läubli 2015	73/F	Uveal melanoma	Pembro, 3rd line	Acute heart failure	Survived
Arangalage 2017	Not stated	Not stated	Not stated	Fulminant myocarditis	Survived
Saibil 2019	Not stated	Melanoma, stage IV	Ipi + nivo	Fatal, steroid-refractory + rh abdomyositis	Fatal
Salem 2019	Not stated	Not stated	Not stated	Glucocorticoid-refractory	Survived (abatacept)
Byer 2024	Not stated	Not stated	Not stated	Steroid-refractory, myasthenia/myositis overlap	Survived (abata+ruxo)
Wadden 2025	Not stated	Not stated	Not stated	Fulminant myocarditis	Recovered (abata+ruxo)
Vockenhuber 2025	Not stated	Not stated	Not stated	Steroid-refractory	Survived (ruxolitinib)

Overlap with myositis and myasthenia-like syndromes is clinically important because respiratory muscle involvement can cause ventilatory failure independent of cardiac pump failure, a distinction emphasised in cohort studies of severe presentations [17]. Concurrent troponin/creatine kinase elevation alongside ECG abnormalities ranging from nonspecific repolarisation change to complete heart block is a consistent theme; case definitions for cancer-therapy-associated myocarditis were designed explicitly to standardise recognition of this heterogeneous spectrum [18].

Diagnostic Approach

Because ICI myocarditis can progress rapidly to shock or fatal arrhythmia, guidance favours a low threshold for suspicion and rapid evaluation. SITC guidance recommends baseline troponin in at-risk patients, repeat testing with new cardiopulmonary or neuromuscular symptoms, ECG, and multidisciplinary evaluation given the overlap with myositis and neurological irAEs [19]. ASCO similarly recommends admission for suspected any-grade myocarditis, with biomarkers, ECG and echocardiography first-line and a low threshold for MRI or biopsy [20]. ESMO likewise recommends prompt corticosteroids once myocarditis is confirmed or suspected, with imaging to exclude alternatives such as pulmonary embolism or pneumonitis [21]. The 2022 ESC cardio-oncology guidelines recommend triage within 24 hours and immediate ICI discontinuation with high-dose corticosteroids pending work-up [22].

A retrospective cohort found cardiotoxic event rates higher after the first and third infusions, reinforcing surveillance around those time points [23]. Proposed case definitions distinguish probable from confirmed disease using presentation, biomarkers, imaging and histopathology together [18]; a multi-marker profile discriminates myocarditis far better than troponin alone [11].

Management and Treatment, Including Refractory Cases

Table 2: Society guideline recommendations for diagnosis and initial management of immune checkpoint inhibitor-associated myocarditis [19,20,21,22].

Society (year)	Surveillance	Work-up if suspected	First-line treatment	Source
SITC (2021)	Baseline troponin, at-risk	ECG, multidisciplinary review	ICI hold, corticosteroids	brahmer2021
ASCO (2021)	Biomarkers as indicated	ECG, echo; MRI/biopsy if unclear	Admission, high-dose steroids	schneider2021
ESMO (2022)	Symptom-triggered biomarkers	Imaging to exclude PE/pneumonitis	Prompt corticosteroids	haanen2022
ESC cardio-oncology (2022)	Risk-stratified	Triage within 24h	Immediate ICI stop, steroids	lyon2022

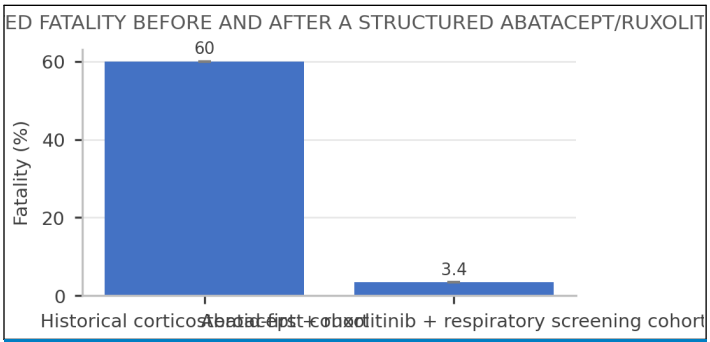

Figure 2: Myotoxicity-related fatality in a 40-patient cohort: historical corticosteroid-first strategy (60%) versus abatacept plus ruxolitinib with respiratory screening (3.4%, P<0.0001) [17].

First-line management across guidelines is immediate, permanent ICI discontinuation with high-dose corticosteroids (typically IV methylprednisolone), started as soon as diagnosis is suspected [20,21,19]. Both fatal cases in the sentinel report received ICU admission and high-dose methylprednisolone yet still died, showing corticosteroids alone are often insufficient in fulminant disease [2].

For corticosteroid-refractory disease, the literature documents an expanding second-line armamentarium: equine anti-thymocyte globulin (ATGAM) for fulminant, steroid-unresponsive myocarditis after nivolumab [24]; the first published abatacept case for severe glucocorticoid-refractory disease, supported by mouse-model data showing CTLA-4/PD-1 interaction [25,12]; abatacept combined with the JAK inhibitor ruxolitinib, including a myasthenia-myositis overlap case successfully salvaged [13] and a fulminant case with sustained recovery [26]; and ruxolitinib monotherapy in at least one further steroid-refractory case [27].

The strongest evidence for a structured second-line strategy comes from a single-centre cohort of 40 patients, where early respiratory screening, ventilation when indicated, receptor-occupancy-guided abatacept, and ruxolitinib together were associated with 3.4% myotoxicity-related fatality versus 60% under earlier corticosteroid-first management (P<0.0001) [17]. The investigators call this hypothesis-generating given the single-centre design, but it is the strongest published signal that early second-line immunosuppression may improve survival in severe disease.

Outcomes and Prognosis

Mortality estimates vary with severity, era and definition, but historical figures cluster around 25-50%, with combination therapy consistently more fatal than monotherapy [6,9]. Two melanoma patients on combination therapy died despite maximal intensive care [2], while a case reported specifically for survival after fulminant presentation stood out because such outcomes were then unusual [16]. Later reports of second-line immunosuppression — anti-thymocyte globulin [24], abatacept [25], abatacept plus ruxolitinib [13,26], and ruxolitinib alone [27] — describe survival in previously refractory disease, and cohort data from the same group suggest this shift corresponds to a substantial fatality reduction when applied systematically [17].

Longer-term prognosis, including durability of recovery and safety of rechallenge, remains less characterised than the acute presentation; guidelines generally counsel against rechallenge after confirmed myocarditis, reflecting the severity and unpredictable recurrence risk documented here [19,21,20].

Conclusion

The published record — from the sentinel fatal melanoma

cases that defined the syndrome, through series describing overlap with neuromuscular and endocrine toxicity, to registry, pharmacovigilance and mechanistic studies, and an expanding set of case reports and one substantial cohort of targeted second-line immunosuppression — describes an uncommon but disproportionately dangerous complication of a therapy class that has transformed outcomes in melanoma and other cancers. Incidence clusters below 1.5% but rises with combination therapy; onset is typically within one to three months; presentation ranges from asymptomatic biomarker elevation to fulminant shock, often with myositis or myasthenia. Guidelines converge on immediate ICI discontinuation and high-dose corticosteroids first-line, with a still largely case-report-level evidence base now supporting early escalation to targeted second-line agents such as abatacept and ruxolitinib in refractory disease. Prospective confirmation of this strategy, and better characterisation of long-term outcomes and rechallenge safety, remain the most pressing gaps.

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