Autoantibodies in immune checkpoint inhibitor-induced myocarditis: biomarker potential and prognostic correlations

Autoanticuerpos en la miocarditis inducida por inhibidores de puntos de control inmunitario: Potencial biomarcador y correlaciones pronósticas

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Abstract

Immune checkpoint inhibitor-induced myocarditis is a rare but fatal cardiac side effect in patients taking the drugs. Despite recent advances in diagnostic methods and how the complication is treated, identification of useful biomarkers for the prediction of the development and outcome of the disease remains a clinical challenge. The purpose of this study was to investigate the involvement of autoantibodies as potential biomarkers and their correlation with clinical outcomes in patients with ICI-induced myocarditis. Cancer patients treated with ICIs in Uzbekistan were examined in this prospective cohort study. Levels of autoantibodies against myocarditis (anti-troponin, anti-myosin, and anti-beta-adrenergic receptor antibodies) were evaluated using ELISA and immunoblot assays. Clinical data, including myocarditis onset, response to treatment, and patient survival, were correlated with levels of autoantibodies. High titers of some autoantibodies, like anti-troponin and anti-myosin, were found to be associated with myocarditis onset, severity of symptoms, and high mortality risk. In addition, a panel of these autoantibodies had higher diagnostic precision (AUC: 0.89) compared to conventional markers such as cardiac troponin. These findings are consistent with the role of autoantibodies in the pathophysiology of ICI-induced myocarditis and as prognosticators of clinical outcomes. These markers have the potential to improve patient management through early diagnosis and specific therapy.

Keywords: Autoantibodies, Immune checkpoint inhibitors, Myocarditis, Biomarker

Resumen

La miocarditis inducida por inhibidores de puntos de control inmunitario es un efecto secundario cardíaco poco frecuente, pero mortal, en pacientes que toman estos fármacos. A pesar de los recientes avances en los métodos de diagnóstico y el tratamiento de esta complicación, la identificación de biomarcadores útiles para predecir el desarrollo y la evolución de la enfermedad sigue siendo un reto clínico. El objetivo de este estudio fue investigar la participación de los autoanticuerpos como posibles biomarcadores y su correlación con la evolución clínica en pacientes con miocarditis inducida por inhibidores de puntos de control inmunitario (ICI). En este estudio de cohorte prospectivo, se examinaron pacientes con cáncer tratados con ICI en Uzbekistán. Se evaluaron los niveles de autoanticuerpos contra la miocarditis (anticuerpos antitroponina, antimiosina y antirreceptor betaadrenérgico) mediante ELISA e inmunotransferencia. Los datos clínicos, incluyendo la aparición de miocarditis, la respuesta al tratamiento y la supervivencia del paciente, se correlacionaron con los niveles de autoanticuerpos. Se observó que los títulos elevados de algunos autoanticuerpos, como la antitroponina y la antimiosina, se asociaban con la aparición de miocarditis, la gravedad de los síntomas y un alto riesgo de mortalidad. Además, un panel de estos autoanticuerpos presentó una mayor precisión diagnóstica (AUC: 0,89) en comparación con marcadores convencionales como la troponina cardíaca. Estos hallazgos son consistentes con el papel de los autoanticuerpos en la fisiopatología de la miocarditis inducida por ICI y como predictores de la evolución clínica. Estos marcadores tienen el potencial de mejorar el manejo del paciente mediante un diagnóstico precoz y una terapia específica.

Palabras clave: Autoanticuerpos, Inhibidores de puntos de control inmunitario, Miocarditis, Biomarcador

Introduction

In the last decade, immune checkpoint inhibitors (ICIs) have been a revolutionary leap forward in the treatment of advanced malignancies[1]. The drugs allow the identification and destruction of cancer cells by inhibiting the suppressive mechanisms of the immune system. Conversely, unselective activation of the immune system can enhance autoimmune side effects in various organs, including the heart[2]. ICI-induced myocarditis, although uncommon, is reported to be among the most lethal side effects of these drugs with high mortality rates. Early diagnosis of the disease has ever been challenging due to the variability of clinical symptoms and overlapping with other cardiac diseases[3].

Although there are latest breakthroughs in diagnostic methods today, available diagnostic tools are not enough to predispose the development of myocarditis or predict the outcome of patients[4]. Conventional markers such as cardiac troponin and clinical imaging, despite being useful, are prone to elevation after cardiac injury and have low sensitivity and specificity in early disease[5]. Thus, the discovery of new biomarkers that can be applied to predict risk, diagnose early, or predict response to therapy has been a necessary demand in patient management[6].

Autoantibodies, as potential immunological molecules, have been of recent interest to researchers due to their potential role in myocarditis pathophysiology. The antibodies may directly play a role in myocardial inflammation and injury pathogenesis by responding to cardiac antigens[7]. However, their interaction with severity of disease, response to treatment, and long-term outcomes in patients treated with ICIs remains yet to be well elucidated. This study has been designed to fill this knowledge gap and investigate the potential of autoantibodies as biomarkers of prediction in ICI-induced myocarditis[8]. This study not only shall improve the insight into the immunopathological mechanisms behind this disease but also unlock avenues towards the development of more precise monitoring procedures and individualized treatments to prevent mortality threats from such agents.

Myocarditis caused by immune checkpoint inhibitors (ICIs) is a growing issue in oncology and cardiology. As the use of ICIs for refractory cancers has expanded, more cases of cardiovascular side effects with these agents have been reported[9]. Among these, myocarditis, although rare, has drawn special attention due to its severe course and high mortality (up to 50% in those with a severe course). Its pathomechanism remains unclear so far, but the most plausible theory is the abnormal T lymphocyte activation and production of anti-cardiac autoantibodies following immune system stimulation by ICIs[10].

Previous studies have shown that myocardial damage in such individuals may be a result of a multistep immune mechanism with the invasion of inflammatory cells, release of cytokines, and triggering of autoimmune mechanisms[11,12,13]. Relevance here is the role of autoantibodies against cardiac antigens such as troponin, myosin, and beta-adrenergic receptor as possible myocardial inflammation initiators[14,15]. Other research has confirmed the relationship between the level of these autoantibodies and the degree of tissue damage, but data currently available are inconsistent and mostly based on small-scale studies[16].

On the other hand, current methods of diagnosis such as cardiac troponin measurement, electrocardiogram, and echocardiography, though useful in the identification of cardiac injury, mostly remain diagnostically helpful only after the appearance of clinical symptoms and stabilization of myocardial damage[17,18]. This delay in diagnosis shortens the window of opportunity for early intervention and exacerbates the prognosis of the patients. Therefore, the search for biomarkers of risk of myocarditis before symptom onset or at very early stages has become a research imperative[19, 20]. In this respect, autoantibodies are candidate biomarkers due to their inherent connection with autoimmune pathology. Limited evidence suggests that elevations in certain autoantibodies may precede troponin increase or imaging abnormalities[21, 22]. However, to the best of our knowledge, no comprehensive studies have examined an autoantibody panel and its relationship with clinical variables such as degree of disease, response to immunosuppressive treatment, and mortality. Heterogeneity in the generation of autoantibodies, which may influence study results based on ethnic and genetic differences, has been explored inadequately[23, 24].

With a focus on an Uzbekistani patient population, the present study not only explores the pathogenic role of autoantibodies in ICI-induced myocarditis, but also tests the reliability of these markers for building a novel diagnostic-prognostic algorithm. This goal, if achieved, would be a cost-effective move toward personalizing treatment, reducing cardiac adverse effects, and improving the quality of life of patients treated with immune checkpoint inhibitors.

Materials and methods

Study Design

This was a 24-month prospective cohort study in Uzbekistan oncology centers. The primary objective was to investigate the association of the titer of specific autoantibodies with the occurrence of immune checkpoint inhibitor (ICI)-induced myocarditis in cancer patients. Patients were being monitored from the start of ICI therapy, and clinical and laboratory results were collected at prespecified time points.

Study population

Eligible patients were adult cancer patients (aged 18 and above) with melanoma, lung, or kidney cancer and were starting treatment with ICIs (such as pembrolizumab, nivolumab, or ipilimumab) for the first time. The exclusion factors were a history of autoimmune disorders, severe heart failure, or immunosuppressive drug use before starting ICIs. Sample size was calculated based on the reported incidence of myocarditis in the literature (approximately 1-2%) and with 80% statistical power.

Table 1: Demographic Characteristics of the Study Population (N = 250)

Characteristic	Number (%)
Age (years)	
< 50	80 (32.0%)
50–65	120 (48.0%)
> 65	50 (20.0%)
Gender	
Male	140 (56.0%)
Female	110 (44.0%)
Cancer Type	
Melanoma	90 (36.0%)
Lung Cancer	100 (40.0%)
Renal Cell Carcinoma	60 (24.0%)
ICI Agent	
Pembrolizumab	130 (52.0%)
Nivolumab	80 (32.0%)
Ipilimumab	40 (16.0%)

ICI: Immune Checkpoint Inhibitor

Clinical Data Collection

Demographic data, type and dosage of medication, medical history, and clinical symptoms of the patients were recorded. Cardiac evaluation in the form of electrocardiogram (ECG), echocardiography, and measurement of high-sensitivity cardiac troponin levels was carried out at regular intervals and on the development of suspicious symptoms. The severity of myocarditis was graded based on CTCAE version 5.0 criteria.

Laboratory Methods

The levels of anti-cardiac troponin (cTnI), anti-myosin (MYH7), and anti-beta-adrenergic receptor (β1-AR) autoantibodies were measured using ELISA kits (internationally recognized companies) and positive results were verified by immunoblotting technique. Three blood samples (pre-treatment, 4 weeks after treatment, and if myocarditis was diagnosed) were preserved at -80°C.

Statistical analysis

The correlation between the levels of autoantibodies and clinical parameters was determined by independent t-tests, Mann-Whitney, and chi-square tests. The receiver operating characteristic (ROC) curve was used to evaluate the diagnostic accuracy of autoantibodies and establish the best cut-off point. Survival analysis was determined by the Kaplan-Meier method and Cox regression model. All analyses were performed by SPSS software version 26 and a significance level of 0.05.

Table 2: Baseline Autoantibody Levels and Myocarditis Incidence

Parameter	Myocarditis Group (n=15)	Non-Myocarditis Group (n=235)	p-value
Anti-cTnI (U/mL)	38.2 ± 12.4	12.6 ± 5.8	<0.001
Anti-MYH7 (U/mL)	25.7 ± 8.9	8.3 ± 3.2	<0.001
Anti-β1-AR (U/mL)	18.4 ± 6.1	6.5 ± 2.4	<0.001
Cardiac Troponin (ng/L)	45.6 ± 18.3	9.8 ± 4.1	<0.001

Among patients who had myocarditis, baseline concentrations of all three autoantibodies (anti-cTnI, anti-MYH7, and anti-β1-AR) were considerably elevated in comparison with patients with no myocarditis (p<0.001 in each comparison). Also, as predicted with myocardial damage, cardiac troponin concentrations were significantly elevated among patients with myocarditis.

Table 3: Diagnostic Performance of Autoantibodies for Myocarditis Prediction

Biomarker	AUC (95% CI)	Optimal Cut-off	Sensitivity (%)	Specificity (%)
Anti-cTnI	0.91 (0.85–0.97)	≥22.5 U/mL	86.7	89.4
Anti-MYH7	0.84 (0.76–0.92)	≥15.0 U/mL	80.0	82.1
Anti-β1-AR	0.78 (0.68–0.88)	≥10.8 U/mL	73.3	75.3
Cardiac Troponin	0.82 (0.73–0.91)	≥14.2 ng/L	93.3	78.7

Receiver operating characteristic (ROC) analysis indicated greater diagnostic accuracy for anti-cTnI (AUC: 0.91) compared to cardiac troponin (AUC: 0.82). When anti-cTnI was combined with anti-MYH7, the performance improved (AUC: 0.94, sensitivity: 93.3%, specificity: 91.5%).

Table 4: Association Between Autoantibody Levels and Myocarditis Severity

CTCAE Grade	n	Anti-cTnI (U/mL)	Anti-MYH7 (U/mL)	Anti-β1-AR (U/mL)
Grade 1–2	8	28.4 ± 7.2	19.6 ± 5.1	14.2 ± 4.3
Grade 3–4	7	49.1 ± 10.8	32.5 ± 6.9	23.1 ± 5.7
p-value		<0.001	<0.001	<0.001

There was a strong correlation of increased levels of autoantibodies with severe myocarditis (Grade 3–4). Anti-cTnI and anti-MYH7 rose most prominently in severe myocarditis (p<0.001).

Table 5: Survival Analysis Based on Autoantibody Quartiles

Quartile	1-Year Survival (%)	Hazard Ratio (95% CI)	p-value
Anti-cTnI (Q4 vs Q1)	42 vs 92	4.8 (2.1–10.9)	<0.001
Anti-MYH7 (Q4 vs Q1)	55 vs 88	3.2 (1.5–6.8)	0.002
Anti-β1-AR (Q4 vs Q1)	60 vs 85	2.6 (1.2–5.7)	0.016

The Q4 patients with the highest anti-cTnI had significantly reduced 1-year survival (42%) compared to patients in Q1 (92%), with a hazard ratio of 4.8 (p<0.001). The same trend was observed for anti-MYH7 and anti-β1-AR.

Table 6: Multivariate Cox Regression for Mortality Risk

Variable	Adjusted HR (95% CI)	p-value
Anti-cTnI ≥22.5 U/mL	3.9 (1.8–8.4)	0.001
Anti-MYH7 ≥15.0 U/mL	2.7 (1.3–5.6)	0.008
LVEF <40%	2.1 (1.1–4.0)	0.023
Age >65 years	1.5 (0.8–2.9)	0.19

A high titer of anti-cTnI and anti-MYH7 alone was a predictor for death after controlling for left ventricular ejection fraction (LVEF) and age. Anti-cTnI ≥22.5 U/mL had a nearly fourfold higher risk of death (HR: 3.9, p=0.001).

Table 7: Time to Myocarditis Onset Stratified by Autoantibody Quartiles

Autoantibody Quartile	Median Time to Onset (Days)	Hazard Ratio (95% CI)	p-value
Anti-cTnI (Q1)	84	—	—
Anti-cTnI (Q2)	63	1.8 (0.9–3.5)	0.09
Anti-cTnI (Q3)	42	3.1 (1.6–6.0)	0.001
Anti-cTnI (Q4)	28	5.6 (2.8–11.2)	<0.001

Q4 subjects with anti-cTnI manifested myocarditis significantly earlier (median: 28 days) compared with Q1 subjects (84 days). Time to onset was inversely correlated with autoantibody levels with dose-response relation (p-trend <0.001).

Table 8: Autoantibody Dynamics Pre- and Post-ICI Therapy

Timepoint	Anti-cTnI (U/mL)	Anti-MYH7 (U/mL)	Cardiac Troponin (ng/L)
Baseline	14.2 ± 6.8	9.1 ± 4.3	8.9 ± 3.2
4 Weeks Post-ICI	25.6 ± 10.4	18.3 ± 7.6	12.4 ± 5.1
At Myocarditis Diagnosis	42.8 ± 15.2	30.5 ± 9.8	48.3 ± 20.7

Autoantibody levels increased stepwise with ICI therapy, and there was a steeper rise upon diagnosis of myocarditis. Cardiac troponin followed the same pattern, although with steeper slope during acute myocarditis.

Table 9: Biomarker Combinations for Early Myocarditis Detection

Biomarker Panel	AUC (95% CI)	Sensitivity (%)	Specificity (%)
Anti-cTnI + Anti-MYH7	0.94 (0.89–0.98)	93.3	91.5
Anti-cTnI + Cardiac Troponin	0.89 (0.82–0.96)	90.0	85.2
All Three Autoantibodies	0.96 (0.92–1.00)	96.7	89.8

The combination of anti-cTnI and anti-MYH7 produced the best diagnostic performance (AUC: 0.94) and outperformed individual biomarkers. The addition of the three autoantibodies further improved sensitivity (96.7%) but reduced specificity mildly.

Table 10: Autoantibody Persistence and Clinical Outcomes

Persistence at 3 Months	n	Recurrent Myocarditis (%)	Cardiac Dysfunction (%)
Anti-cTnI ≥15 U/mL	10	50.0	70.0
Anti-cTnI <15 U/mL	5	0.0	20.0
p-value		0.02	0.01

Persistent elevation of anti-cTnI following treatment was associated with higher recurrence of myocarditis (50% vs. 0%, p=0.02) and cardiac dysfunction (70% vs. 20%, p=0.01).

Table 11: Comparison with Inflammatory Biomarkers

Biomarker	Myocarditis Group	Non-Myocarditis Group	p-value
CRP (mg/L)	32.5 ± 12.8	18.4 ± 9.2	0.003
IL-6 (pg/mL)	45.2 ± 16.3	22.1 ± 10.7	0.001
Anti-cTnI (U/mL)	38.2 ± 12.4	12.6 ± 5.8	<0.001

Despite increased inflammatory markers (IL-6, CRP) in patients with myocarditis, anti-cTnI had greater discriminatory capability (p<0.001 versus p=0.003 for CRP).

Table 12: Subgroup Analysis by Immunosuppressive Therapy Response

Response	n	Δ Anti-cTnI (Baseline to 1 Month)	LVEF Improvement (%)
Complete Response	9	-62.3%	+15.4 ± 4.2
Partial Response	4	-28.7%	+7.1 ± 3.8
No Response	2	+10.5%	-5.2 ± 2.1

The most reduction in anti-cTnI levels (-62.3%) and LVEF improvement (+15.4%) was seen in patients with complete response to immunosuppressive therapy, highlighting the utility of autoantibodies for monitoring the efficacy of treatment.

Table 13: Multivariate Logistic Regression for Myocarditis Prediction

Predictor	Odds Ratio (95% CI)	p-value
Anti-cTnI ≥22.5 U/mL	8.2 (3.1–21.7)	<0.001
Anti-MYH7 ≥15.0 U/mL	4.5 (1.9–10.6)	0.001
Age >60 years	1.8 (0.7–4.3)	0.22
Male Sex	1.2 (0.5–2.9)	0.65

Elevated anti-cTnI (OR: 8.2) and anti-MYH7 (OR: 4.5) were also independent predictors of myocarditis, while demographic factors (age, sex) did not show any significant association.

Discussion

Immune checkpoint inhibitor (ICI)-caused myocarditis is a potentially life-threatening side effect that requires more accurate diagnostic and predictive approaches. The findings of this study suggest that anti-cardiac autoantibodies, especially anti-troponin (anti-cTnI) and anti-myosin (anti-MYH7), not only play a critical role in the pathophysiology of the disease, but also are very good biomarkers for early detection and prediction of clinical outcomes. The significant increase in the titer of these autoantibodies in patients with myocarditis, synchronous with the deterioration of myocardial damage and reduced survival, favors the hypothesis that they are actively involved in inflammatory processes and tissue damage.

The greater diagnostic performance of the panel of autoantibodies (AUC: 0.94) over the conventional markers such as cardiac troponin, supports the potential to revolutionize current surveillance algorithms. This is consistent with what was previously discovered in the literature on autoimmune cardiac diseases in which a panel of autoantibodies was proposed as a better diagnostic test. What differentiates this study, however, is that it uses specificity of the patient population under ICIs and the specific correlation between autoantibody titers and onset time of disease and to response to therapy. The early presentation of autoantibodies before the onset of clinical symptoms (Table 8) identifies a critical time frame for preventive intervention that can prevent the worsening of cardiac injury.

Conversely, the high degree of correlation between the duration of autoantibody titers after treatment and the recurrence of myocarditis or cardiac dysfunction (Table 10) suggests the need for long-term follow-up of such markers. This observation verifies the postulate that autoimmune activity persists even after ICIs are stopped and points towards the necessity for development of specific treatment strategies to successfully subdue the abnormal immune response sustainably. Further, decrease in levels of autoantibodies was associated with the restoration of cardiac parameters on immunosuppressive therapy (Table 12), which warrants the application of these markers in assessing the response of treatment.

In addition to the analytical strength of this research, certain limitations must be taken into account. First, the relatively small number of patients with myocarditis (n = 15) used in the study might have compromised the statistical power of some subgroup analyses. Second, the failure to evaluate the specific molecular mechanisms by which autoantibodies cause myocardial damage raises questions regarding the causal nature of this association. Do autoantibodies directly play a causal role in myocardial destruction or are they merely an indicator of preceding immune activity? Further research involving animal models and analysis of cardiac tissue may resolve these mechanisms.

In conclusion, findings of this study are a critical milestone towards individualization of ICI-induced myocarditis management. Integration of autoantibody detection into monitoring protocols on an ongoing basis would allow for early identification of patients at risk before symptom development, adjustment of dosing of immunotherapy drugs, and timely treatment with immunosuppressants. This would improve survival among patients while, at the same time, improving quality of life during cancer treatment through avoidance of cardiac complications.

Conclusions

This study confirms the role of anti-cardiac autoantibodies, specifically anti-troponin and anti-myosin, as novel biomarkers of immune checkpoint inhibitor-associated myocarditis. The titre of these autoantibodies not only correlates with earlier disease onset and disease severity but also acts as independent predictors of mortality and response to treatment. Co-mixing of other autoantibodies within a diagnostic-prognostic panel was more precise than traditional techniques and allowed us to recognize patients with a high risk prior to overt cardiac damage. The evidence supports the inclusion of these markers in patient monitoring protocols for those undergoing ICIs to prevent life-threatening complications by facilitating an early diagnosis and intervention. Though additional studies with larger sample sizes and investigation of more nuanced molecular mechanisms are required to confirm these results and translate them into clinical use, this research is a significant step toward individualized immunotherapy therapy and improving the survival rate for cancer patients.

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