Electrocardiographic Manifestations of Immune Checkpoint Inhibitor Myocarditis

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Immune checkpoint inhibitors (ICI) have transformed oncology care by unleashing T-cells to achieve anti-tumor effects but can cause inflammatory adverse events including myocarditis.[1] ICI-myocarditis is highly arrhythmogenic but specific electrocardiographic manifestations and their prognostic significance are poorly understood.[2]

A retrospective multicenter registry (IRB#181337; *NCT04294771*) including 49 institutions and 11 countries was built with a REDCap web-based platform to collect 147 cases of ICI-myocarditis through January 2020. ECG were available in 125 cases for independent analysis by two cardiologists (blinded to each case) who interpreted 24 pre-specified ECG features. Presenting ECG was defined as ECG obtained within 3 days of admission. To allow for complete ECG measurement, patients were excluded from quantitative analysis if presenting ECG were only showing paced rhythms or sustained ventricular arrhythmias. Baseline ECG was defined as the most recent ECG obtained before ICI exposure and was available for independent interpretation in 52 cases. Paired t-test and McNemar's test were used to compare features of presenting ECG to baseline ECG. A Cox proportional-hazards model adjusted for age and sex determined association of ECG features with all-cause mortality within 30 days of presentation. The proportional hazard assumption was verified using the score test based on the Schoenfeld residuals and was met for each predictor.

Median (IQR) age was 67 years (58-77) and 92/147 (62.6%) were male. Median time from first ICI dose to myocarditis presentation was 38 days (21-83). Presenting ECG showed elevated heart rate (93.9 vs 80.4 bpm;p=0.009), prolonged QRS (95.3 vs. 93.2ms;p=0.02) and prolonged QT corrected for heart rate (441.8 vs 421.0ms;p=0.03; Fridericia's) compared with baseline ECG (n=52). Sokolow-Lyon Index (sum of S wave in V1 and R wave in V5 or V6) showed a significant decrease in voltage from baseline (1.39 vs 1.69mV;p=0.006). The incidence of left bundle branch block (10/52 [19%] vs. 3/52 [6%];p=0.046) and sinus tachycardia (25/52 [48%] vs 15/52 [29%];p=0.02) were increased versus baseline. In aggregate, conduction

disorders (35/52 [67%] vs. 23/52 [44%];p=0.01) and repolarization abnormalities (27/52 [52%] vs 13/52 [25%],p=0.008) were significantly increased (Table).

Throughout hospitalization (median: 11 days, IQR:7-24), 101/147 (68.7%) patients experienced conduction disorders defined as fascicular, bundle, and/or heart blocks with second-degree heart block in 11/147 (7.5%) and complete heart block in 25/147 (17.0%). Supraventricular arrhythmias including atrial fibrillation, atrial flutter, and multifocal atrial tachycardia had a cumulative incidence of 35/147 (23.8%), 31/147 (21.1%), 2/147 (1.4%), 2/147 (2.1%), respectively. A total of 22/147 (15.0%) patients experienced one or more life-threatening ventricular arrhythmia episodes, including 16/147 (10.9%) sustained ventricular tachycardia, 4/147 (2.7%) ventricular fibrillation, and 2/147 (1.4%) torsade de pointes. Complete heart block and life-threatening ventricular arrhythmia co-occurred in 11/147 (7.5%) patients.

Immunomodulating treatments were given to 121/147 (82.3%) patients of which 118/121 (97.5%) received corticosteroids and 51/121 (42.1%) received plasmapheresis or non-steroidal immunomodulators. Electrophysiology devices were placed in 21/146 (14.4%) patients within 30 days of presentation including 20/21 (95%) pacemakers for high-grade atrioventricular block and 3/21 (14%) defibrillators for secondary prevention of ventricular arrhythmia. In 146 patients with 30-day surveillance, 39/146 (26.7%) died within 30 days of presentation of which 24/39 (62%) were attributable to myocarditis. Other causes of death included cancer progression 6/39 (15%), sepsis 6/39 (15%), and non-cardiac IrAE 7/39 (18%), of which 6 were attributable to non-cardiac myotoxicities (e.g., myositis).

Patients with ICI-myocarditis were more likely to experience all-cause mortality within 30 days if they developed complete heart block (12/25 [48%] vs. 27/122 [22.1%]; HR=2.62, 95% confidence interval=[1.33-5.18],p=0.01) or life-threatening ventricular arrhythmias (12/22 [55%] vs. 27/125 [21.6%]; HR=3.10[1.57-6.12],p=0.001).

All-cause mortality was associated with pathological Q-waves (12/19 [63%] vs 18/106 [17.0%]; HR=5.98 [2.8-12.79],p<.001, adjusted for age and sex) and inversely associated with

Sokolow-Lyon Index (HR/mV=0.57 [0.34-0.94],p=.03). Other ECG features were not associated with mortality (Table). Both low-voltage and pathological Q-waves signify a loss of electromotive force and are intuitive markers for the extent of inflammatory infiltrate and cardiomyocyte damage. ICI-myocarditis is histologically characterized by lymphocyte and macrophage infiltrates that affect both the myocardium and the conduction system.[3,4] The finding that low-voltage and pathological Q-waves predict mortality suggests that suppressing the underlying inflammatory infiltrate may be a greater priority than antiarrhythmic drugs or devices.[5]

This study's multicenter approach introduced variability in data collection and interpretation. To mitigate this effect, clear adjudication criteria were provided and each submission was subjected to a bi-institutional review process. Self-reporting allowed for assembly of an ICI-myocarditis cohort of this size but likely selected for more clinically severe cases. The comparison to baseline ECG was limited by availability of baseline ECG which likely enriched for patients with pre-existing cardiac disease thereby underestimating ECG changes caused by ICI-myocarditis.

This study shows that ICI-myocarditis is highly arrhythmogenic, presenting with new conduction blocks, decreased voltage, and repolarization abnormalities which frequently degenerate to malignant arrhythmias. Further studies are needed to evaluate how these ECG changes can facilitate screening, prognostication, and monitoring strategies in ICI-myocarditis.

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Table: Presenting ECG of ICI-myocarditis as compared with baseline and as predictors of All-cause mortality using survival analyses adjusting for age and sex*

	ICI-Myocarditis, Presenting ECG	ICI-Myocarditis, Baseline ECG	p-value	Cox Proportional Hazards Model For 30 day All-Cause Mortality
	Median (IQR) N; n/N (%)	**Median (IQR) N; n/N (%)**	**paired t-test**	adjusted HR (95%CI) p-value
Heart Rate (bpm)	93.9 [72.6-114.7] N=52	80.4 [68.1-94.8] N=52	0.009	1.01 [0.99-1.02], p=.40 N=125
PR Length (ms)†	162.8 [136.0-186.0] N=42	154.1 [136.0-187.6] N=46	0.10	1.00 [0.99-1.01], p=.55 N=107
QTcF Length (ms)‡	441.8 [414.9-462.6] N=49	421.0 [399.2-440.4] N=51	0.03	1.00 [1.00-1.01], p=.36 N=122
QRS Length (ms)	95.3 [85.7-118.2] N=52	93.2 [82.7-102.5] N=52	0.02	1.00 [0.99-1.01], p=.90 N=125
Sokolow-Lyon Index (mV)§	1.39 [0.85-2.03] N=52	1.69 [1.28-2.26] N=52	0.006	0.57 [0.34-0.94], p=.03 N=124
			McNemar's test	
CONDUCTION DISORDERS**	35/52 (67%)	23/52 (44%)	0.01	1.56 [0.69-3.53], p=.29 N=125
- Bundle Branch Block, Left Bundle	10/52 (19%)	3/52 (6%)	0.05	1.00 [0.38-2.62], p=.99 N=125
- Bundle Branch Block, Right Bundle	14/52 (27%)	9/52 (17%)	0.18	1.48 [0.71-3.06], p=.29 N=125
- Fascicular Block, Left Anterior	10/52 (19%)	5/52 (10%)	0.23	0.85 0.32-2.25], p=.75 N=125
- Fascicular Block, Left Posterior	6/52 (12%)	2/52 (4%)	0.22	0.47-3.85], p=.59 N=125
- Heart Block, First Degree	9/52 (17%)	7/52 (13%)	0.72	0.83 [0.28-2.40], p=.72 N=125
ECG Findings of Pericarditis	4/52 (8%)	1/52 (2%)	0.25	0.75 0.22-2.51], p=.64 N=125
- ST Segment Elevation, Diffuse	3/52 (6%)	1/52 (2%)	0.62	0.83 [0.25-2.81], p=.76 N=125
PREMATURE VENTRICULAR COMPLEX (ALL TYPES)	9/52 (17%)	3/52 (6%)	0.08	1.01 [0.37-2.75], p=.99 N=125
- Premature Ventricular Complex	9/52 (17%)	3/52 (6%)	0.08	0.77 [0.26-2.30], p=.64 N=125
SINUS MECHANISM	42/52 (81%)	46/52 (88%)	0.29	0.76 0.31-1.89], p=.56 N=125

* Only arrhythmia subgroups with at least n>2 are shown

† PR intervals are unmeasurable in supraventricular arrhythmia

‡ QT intervals are unmeasurable in paced ventricular complexes, QT was corrected for heart rate by Fridericia's method (QTcF)

§ Sokolow-Lyon Index are unmeasurable without precordial leads

** When multiple eligible ECG were available, ECG without complete heart block or supraventricular arrhythmias were preferentially selected for this analysis focusing on PR, QRS and QTc measurements

- Normal Sinus Rhythm	17/52 (33%)	31/52 (60%)	0.002	0.50 [0.23-1.09], p=.08 N=125
- Sinus Tachycardia	25/52 (48%)	15/52 (29%)	0.02	1.67 [0.80-3.49], p=.17 N=125
REPOLARIZATION ABNORMALITIES	27/52 (52%)	13/52 (25%)	0.008	1.52 0.74-3.12], p=.26 N=125
- ST Segment Depression, Diffuse	5/52 (10%)	1/52 (2%)	0.22	1.60 [0.48-5.30], p=.44 N=125
- ST Segment Depression, Regional	4/52 (8%)	0/52 (0%)	NA	0.53 0.07-3.90], p=.53 N=125
- T Wave Inversions	21/52 (40%)	12/52 (23%)	0.07	1.49 [0.71-3.12], p=.29 N=125
SUPRAVENTRICULAR ARRHYTHMIA**	7/52 (13%)	6/52 (12%)	1.00	2.21 0.84-5.79], p=.11 N=125
- Atrial Fibrillation**	6/52 (12%)	5/52 (10%)	1.00	1.83 [0.63-5.27], p=.27 N=125
UNCATEGORIZED				
- Premature Atrial Complex	5/52 (10%)	3/52 (6%)	0.68	1.59 [0.47-5.38], p=.46 N=125
- Left Ventricular Hypertrophy	12/52 (23%)	16/52 (31%)	0.34	0.49 [0.15-1.61], p=.24 N=125
- Low QRS Voltage	4/52 (8%)	1/52 (2%)	0.37	3.27 [0.95-11.23], p=.06 N=125
- P Wave Abnormality Suggestive of Left Atrial Enlargement	11/52 (21%)	9/52 (17%)	0.75	1.10 [0.46-2.63], p=.83 N=125
- Q Waves, Pathological	8/52 (15%)	4/52 (8%)	0.22	5.98 [2.8-12.79], p<.001 N=125

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