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1 ***Electrocardiographic Manifestations of Immune Checkpoint Inhibitor Myocarditis***

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

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

55 Median (IQR) age was 67 years (58-77) and 92/147 (62.6%) were male. Median time
56 from first ICI dose to myocarditis presentation was 38 days (21-83). Presenting ECG showed
57 elevated heart rate (93.9 vs 80.4 bpm;p=0.009), prolonged QRS (95.3 vs. 93.2ms;p=0.02) and
58 prolonged QT corrected for heart rate (441.8 vs 421.0ms;p=0.03; Fridericia's) compared with
59 baseline ECG (n=52). Sokolow-Lyon Index (sum of S wave in V1 and R wave in V5 or V6)
60 showed a significant decrease in voltage from baseline (1.39 vs 1.69mV;p=0.006). The incidence
61 of left bundle branch block (10/52 [19%] vs. 3/52 [6%];p=0.046) and sinus tachycardia (25/52
62 [48%] vs 15/52 [29%];p=0.02) were increased versus baseline. In aggregate, conduction

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

65 Throughout hospitalization (median: 11 days, IQR:7-24), 101/147 (68.7%) patients
66 experienced conduction disorders defined as fascicular, bundle, and/or heart blocks with second-
67 degree heart block in 11/147 (7.5%) and complete heart block in 25/147 (17.0%).
68 Supraventricular arrhythmias including atrial fibrillation, atrial flutter, and multifocal atrial
69 tachycardia had a cumulative incidence of 35/147 (23.8%), 31/147 (21.1%), 2/147 (1.4%), 2/147
70 (2.1%), respectively. A total of 22/147 (15.0%) patients experienced one or more life-threatening
71 ventricular arrhythmia episodes, including 16/147 (10.9%) sustained ventricular tachycardia,
72 4/147 (2.7%) ventricular fibrillation, and 2/147 (1.4%) torsade de pointes. Complete heart block
73 and life-threatening ventricular arrhythmia co-occurred in 11/147 (7.5%) patients.

74 Immunomodulating treatments were given to 121/147 (82.3%) patients of which 118/121
75 (97.5%) received corticosteroids and 51/121 (42.1%) received plasmapheresis or non-steroidal
76 immunomodulators. Electrophysiology devices were placed in 21/146 (14.4%) patients within 30
77 days of presentation including 20/21 (95%) pacemakers for high-grade atrioventricular block and
78 3/21 (14%) defibrillators for secondary prevention of ventricular arrhythmia. In 146 patients with
79 30-day surveillance, 39/146 (26.7%) died within 30 days of presentation of which 24/39 (62%)
80 were attributable to myocarditis. Other causes of death included cancer progression 6/39 (15%),
81 sepsis 6/39 (15%), and non-cardiac IrAE 7/39 (18%), of which 6 were attributable to non-cardiac
82 myotoxicities (e.g., myositis).

83 Patients with ICI-myocarditis were more likely to experience all-cause mortality within
84 30 days if they developed complete heart block (12/25 [48%] vs. 27/122 [22.1%]; HR=2.62, 95%
85 confidence interval=[1.33-5.18], $p=0.01$) or life-threatening ventricular arrhythmias (12/22 [55%]
86 vs. 27/125 [21.6%]; HR=3.10[1.57-6.12], $p=0.001$).

87 All-cause mortality was associated with pathological Q-waves (12/19 [63%] vs 18/106
88 [17.0%]; HR=5.98 [2.8-12.79], $p<.001$, adjusted for age and sex) and inversely associated with

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

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

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

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- 128

129 Table: Presenting ECG of ICI-myocarditis as compared with baseline and as predictors of All-cause mortality using survival analyses adjusting for
 130 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