to CRT was associated with a significant reduction in total LV area (183.5 ± 49.9 cm^2 vs. 125.7 ± 44.4 cm^2) and total LV area with WT <6 mm (35.2 ± 27.8 cm^2 vs. 8.4 ± 9.3 cm^2) between baseline and 6 months, respectively. Although for both reductions, the proportion of LVWT <6 mm area also decreased from 17.6% (range 11.1% to 21.2) at baseline to 3.6% (range 2.1% to 7.5%) at 6 months (average decrease of 11.6 ± 8.3% per patient). In other words, responders had 96.4% (range 92.5% to 97.9%) of normal LVWT at 6 months. In addition, responders had fewer LVWT segments of <6 mm at 6 months compared with baseline (1.0 [range 0.0 to 1.5] vs. 3.0 [range 2.0 to 4.5], respectively; p = 0.021). Basal and/or midsegments were sites of higher WT normalization compared with the apex (**Table 1**). **Figure 1** illustrates the WT remodeling in a CRT responder.

This work is the first prospective CT-guided study that evaluated the impact of CRT on WT change in a responder. The primary finding was that response to CRT was associated with WT normalization (especially in basal and/or midsegments). The mechanism underlying this association remains elusive. Previous work showed that the correction of dyssynchrony led to regression in WT inhomogeneity (3). In addition, improvements in molecular function and calcium regulation, which lead to enhanced LV contraction, was seen in CRT responders. Notably, the apical WT remained unchanged after 6 months. This observation was supported by recent work that demonstrated that the apical region was thinner at baseline and even after resynchronization (3).

The limited sample size made our pilot study hypothesis-generating, which will require validation in larger studies. In addition, only 2 nonresponders had CT at 6 months and that limited our ability to compare change in WT between responders and nonresponders. Further CT-guided studies are needed to investigate the impact of CRT on WT normalization.

In summary, response to CRT is associated with WT normalization, as assessed by CT. This remodeling was particularly notable in the basal and/or midsegments.

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All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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RESEARCH CORRESPONDENCE

Case Series of Ventricular Tachycardia and Myocarditis From Programmed Cell-Death Protein-1 Inhibitor Treated With Infliximab

Regulation of T-cell signaling through immune checkpoint inhibition, including programmed cell-death protein (PD)-1, creates a remarkable anti-malignancy response.

Immune-related adverse events result from immune system over-activation. Mahmood et al. (1) found a multicenter prevalence of 1.14% of checkpoint inhibitor myocarditis, with a 46% incidence of complete heart block (CHB), cardiovascular death, cardiogenic shock, or cardiac arrest in these patients. Patients with myocarditis experienced an 8.6% incidence of CHB and a 26% incidence of atrial arrhythmias that required intervention (1).

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We present 2 cases of anti-PD1 immune myocarditis and steroid-refractory ventricular tachycardia (VT) successfully treated with steroids and infliximab.

Case 1 was a 53-year-old woman with metastatic ovarian adenocarcinoma who was treated with carboplatin, paclitaxel, and surgical debulking, and who was started on pembrolizumab. Four days later, she presented locally with neurological immunopathology and troponin T elevation (0.659 ng/ml; normal: 0 to 0.03 ng/ml). Her electrocardiogram showed normal sinus rhythm (NSR) and the echocardiogram showed a left ventricular ejection fraction (LVEF) of 50%. She was discharged on 50 mg of prednisone for her neurological symptoms, and pembrolizumab was discontinued.

She presented to our hospital 1 month later with exertional chest pressure during her steroid taper. She had accelerated idioventricular rhythm (AIVR) alternating with NSR (**Figure 1**). Her laboratory values were notable for elevated troponin T (0.754 ng/ml), N-terminal pro-B-type natriuretic peptide (815 pg/ml), and mild transaminitis. The echocardiogram showed LVEF of 35% and right ventricular dysfunction. Catheterization showed nonobstructive disease. Cardiac magnetic resonance (CMR) imaging exhibited patchy delayed gadolinium enhancement consistent with myocarditis. She declined endomyocardial biopsy. She was started on prednisone 1 mg/kg, but AIVR and VT continued. These arrhythmias improved with 1 g of methylprednisolone for 3 days but recurred upon steroid taper. She was given infliximab (5 mg/kg), and her arrhythmias terminated. She was discharged on a steroid taper guided by troponin, which took 9 months to normalize. LVEF normalized after pulse dose steroids and remained normal despite continued troponin elevation.

Case 2 was a 62-year-old woman with metastatic renal cell carcinoma status post-nephrectomy who received tyrosine kinase inhibitor chemotherapy and who started nivolumab. Five weeks after initiation, she presented locally with sudden dyspnea on exertion and chest tightness. Laboratory values included troponin T of 36.2 ng/ml, elevated transaminases (peak aspartate aminotransferase: 4,112 U/l; alanine aminotransferase: 2,830 U/l), and lactate (peak 7.3 mmol/l). Her electrocardiogram showed diffuse ST elevations, and catheterization showed nonobstructive disease. She was initiated on intravenous methylprednisolone (1 mg/kg). She then developed episodic VT and CHB (**Figure 1**), and was transferred to our institution.

The echocardiogram showed severe right ventricular dysfunction, LVEF of 25%, and a small pericardial effusion. Right heart catheterization hemodynamics were consistent with cardiogenic shock. An endomyocardial biopsy was nondiagnostic and showed fibrosis and absent myocardium. CMR showed patchy delayed gadolinium enhancement. Her constellation of symptoms and findings were believed to be most consistent with perimyocarditis. She had a temporary pacing wire placed. Cardiothoracic surgery declined mechanical circulatory support due to her metastatic cancer.

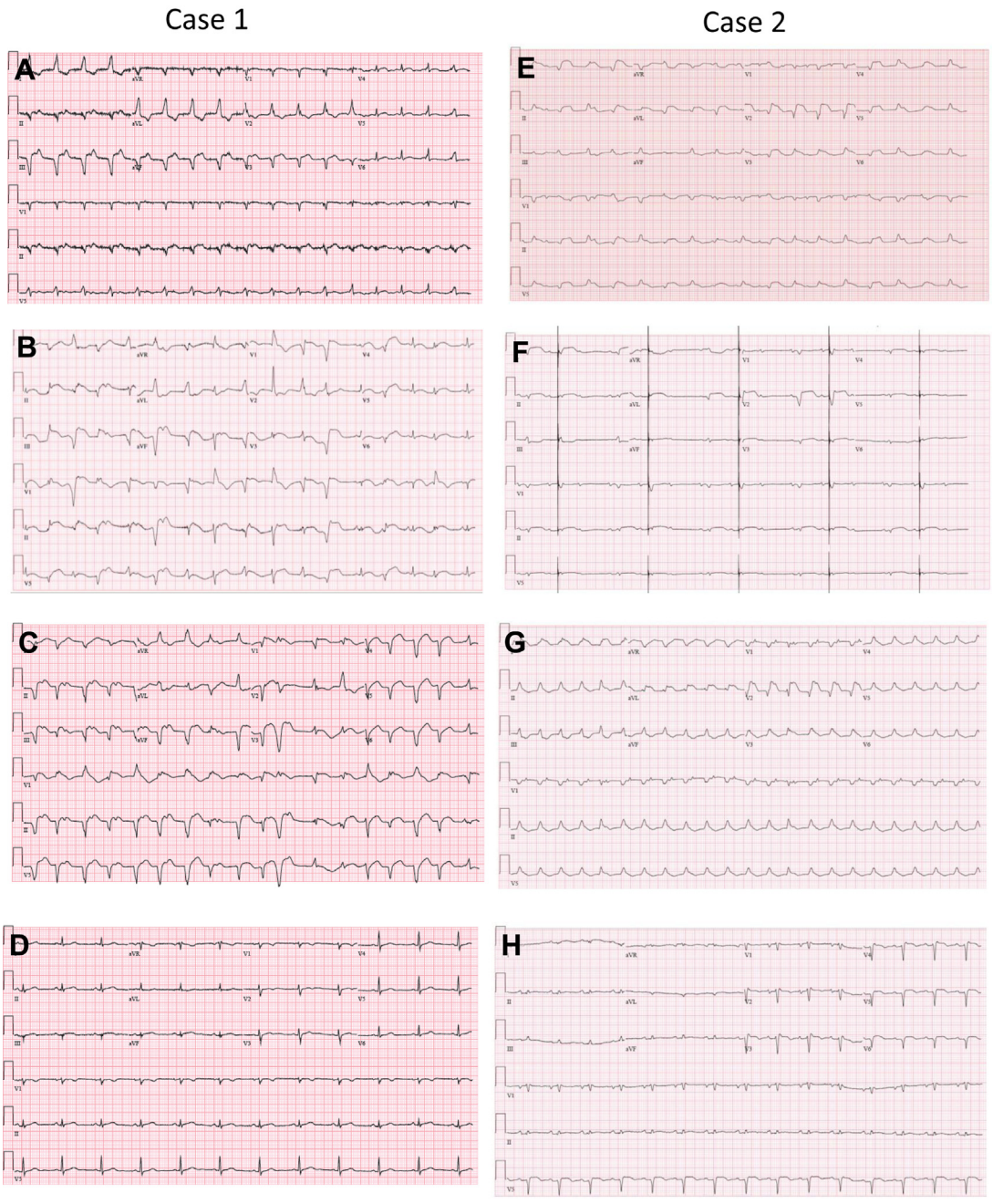
She was given 2 g methylprednisolone for 3 days and 1 dose of infliximab (5 mg/kg). Her conduction block resolved, and she underwent single-chamber implantable cardioverter-defibrillator placement. After temporary inotropic support, she recovered from cardiogenic shock. Follow-up echocardiogram 17 days post-infliximab administration showed a LVEF of 55%. She presented 2 months later with fatal bacteremia and pulmonary embolism.

The mechanism of checkpoint inhibitor myocarditis appears to be T-cell–mediated. Endomyocardial biopsy results from multiple series identified CD4+, CD8+, and PD1-lymphocytic infiltration. Mouse models showed that these T-cells required PD1 to maintain self-tolerance to myocardial components (2). This mechanism provided a rationale for infliximab, which reduces lymphocytic infiltration through tumor necrosis factor-alpha inhibition.

When treating any immune-related adverse event, we advocate for exclusion of cardiac involvement. Screening may be done with troponin and electrocardiographic testing, which Mahmood et al. (1) found to be abnormal in 94% and 89% of patients with checkpoint inhibitor myocarditis, respectively. Aggressive treatment should be initiated early with involvement of a multidisciplinary team. The American Society of Clinical Oncology recommends treatment with high-dose steroids, with treatment similar to cellular cardiac allograft rejection if refractory (methylprednisolone, mycophenolate, thymoglobulin, infliximab) (3).

Physicians must be vigilant in monitoring for rare but often fatal checkpoint inhibitor myocarditis and associated arrhythmias. In steroid-refractory cases, use of infliximab should be considered, despite its contraindication in severe heart failure. Analysis in a larger series of patients may further define the role of infliximab in anti-PD1 antibody-mediated myocarditis.

FIGURE 1 **ECGs for Cases 1 and 2**



(A) Presenting electrocardiogram (ECG) showing accelerated idioventricular rhythm with competing normal sinus rhythm (NSR). **(B)** ECG after high-potency steroid administration showing sinus rhythm with multifocal premature ventricular complexes. **(C)** Irregular ventricular tachycardia with occasional fusion and capture beats. **(D)** ECG 2 weeks after infliximab administration showing return of NSR with narrow QRS conduction. **(E)** Presenting ECG showing high-grade heart block and diffuse ST elevations. **(F)** ECG after temporary pacing wire placement showing intermittent native conduction with occasional block competing with pacing. **(G)** ECG 24 h after infliximab administration showing regular wide complex tachycardia with native conduction and prolonged first-degree block. **(H)** ECG 8 days after infliximab administration showing return of NSR with narrow QRS conduction.

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