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EDITORIAL COMMENT

Episodic Myocarditis in Arrhythmogenic Cardiomyopathy

A Novel Treatment Target?*

Eric D. Smith, MD, Adam Helms, MD, MS

In this issue of *JACC: Case Reports*, Ghawanmeh et al[1] present a case of arrhythmogenic cardiomyopathy (ACM) caused by a pathogenic variant in desmoplakin (*DSP*). The case demonstrates the increasingly recognized presentation of *DSP* cardiomyopathy as acute myocarditis, highlighting both the importance of considering genetic causes of myocarditis and the current knowledge gap in our understanding of how to best treat this form of ACM.

Patients with *DSP* cardiomyopathy typically present with the left ventricular predominant form of ACM, marked by subepicardial left ventricular fibrosis, left ventricular dysfunction, arrythmias, and discrete episodes of chest pain/myocarditis.[2,3] Initially described in 2005, the left dominant form of ACM is distinct from the more common right dominant form of ACM.[4] To further define the characteristics of these patients, we previously compared patients with *DSP* and *PKP2* variants to demonstrate the importance of genotype-based diagnosis and risk stratification.[3] Despite the difference in left or right ventricular involvement, most cases of ACM are due to variants in desmosomal genes, indicating a common molecular basis.[5] However, some subsets of ACM are caused by variants in genes outside of the desmosome, such as *LMNA* or *RBM20*, and exhibit unique features that emphasize the importance of genotype-driven clinical management.[6,7]

Despite an improvement in the clinical characterization of patients with ACM, the pathogenesis of ACM, including *DSP* cardiomyopathy, remains incompletely understood. No disease-modifying treatments for ACM have been proved to date. As this case highlights, inflammation may be present during acute episodes of myocarditis in *DSP* cardiomyopathy and has been suggested to be associated with worse clinical outcomes.[8] The presence of inflammatory infiltrates of ACM hearts was described in early reports and was thought to contribute to the fibrofatty replacement often described at autopsy.[9] The association of genetic cardiomyopathies with acute myocarditis has garnered increasing attention, indicating that this clinical entity may be more common than previously realized.[10]

Given that the primary abnormality in *DSP* cardiomyopathy occurs in the desmosome, it is not yet clear whether the apparent inflammation evolves from transient myocardial injury in the predisposed ACM heart or whether inflammation occurs as a direct molecular consequence of desmosomal disruption. Supporting the former, the desmosome is critical for structural linkage between cells, and disruption of the desmosome leads to failure of normal intercellular adhesion.[11] Supporting a primary inflammatory pathway, both abnormal Wnt/β-catenin and NFκB signaling dysregulation have been described in model systems of ACM.[12,13]

Interestingly, in the case presented here, the patient also carries a pathogenic missense variant in fukutin-related protein (FKRP), a known cause of limb-girdle muscular dystrophy. FKRP functions in normal glycosylation of the dystroglycan complex, which is responsible for tethering myofilaments to

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From the Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA.

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cell membranes and adjacent extracellular matrix. Pathogenic variants in *FKRP* alone have been reported to be associated with cardiomyopathy only when present as compound heterozygous or homozygous variants.[14] Thus, this patient carried a *DSP* pathogenic variant in addition to a potentially sensitizing variant in FKRP; together, these variants may have led to the markedly increased susceptibility to myocardial injury evident by her young age at presentation. Cases such as this give a glimpse of the potential oligogenic contributors to disease variability in ACM.

Although the presence of inflammation has been clearly demonstrated and likely contributes to pathogenesis in ACM, data on the role of systemic anti-inflammatory treatments to modify the disease course are lacking. Recently, modulation of NFκB signaling in mice and induced pluripotent stem cell cardiomyocyte deficient models of desmoglein-2 was shown to reverse inflammatory phenotypes in these model systems, leading to the suggestion that medications targeting the centrally mediating cytokine, IL-1β, might be an effective treatment strategy.[12] However, data supporting this hypothesis in patients are not yet available, and clinical trials have been hindered by the rarity of this condition. Case reports such as the one here offer some optimism about this type of approach. However, this optimism must be tempered by the many limitations of isolated clinical reports. In our experience, inflammatory/myocarditis episodes in DSP cardiomyopathy are self limited, with troponin levels falling to an unmeasurable level within a few days of initial presentations without any intervention. An interesting corollary to inflammation in ACM is the inflammatory cascade after myocardial infarction. Postinfarction inflammation is a well-described phenomenon directly caused by myocardial injury, and numerous studies have failed to show significant benefit from anti-inflammatory therapies.[15] This apparent lack of benefit may stem from the role of inflammation in regulation of the fibrotic repair response and a potentially narrow therapeutic window for both dose and timing of treatment.[16] Thus, careful consideration of dose, timing, and specificity for the myocardium will be needed when anti-inflammatory treatment for ACM is considered.

Although anti-inflammatory medications are potentially an exciting new therapeutic avenue for ACM, we advocate that more work needs to be done before this approach can be used in patients. ACM is a chronic condition without clear endpoints for treatments, and all current anti-inflammatory agents carry risk. Future work is critically needed to investigate the specific role of inflammation and fibrosis in preclinical model systems representative of the full genetic spectrum of ACM. Meanwhile, multicenter studies are needed to improve our understanding of the natural history of episodic myocarditis episodes in patients with ACM to inform future randomized clinical studies.

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ADDRESS FOR CORRESPONDENCE: Dr. Eric D. Smith, University of Michigan, Division of Cardiovascular Medicine, Department of Internal Medicine, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109, USA. E-mail: ersm@umich.edu. Twitter: @EricSmithMD.

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