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Myocarditis: Entering the Mainstream

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Recent media attention on myocarditis during the SARS-CoV-2 pandemic led the medical community to reexamine the longstanding classifications of myocarditis that are rooted in more than a century of clinical and experimental medicine. From the first description of myocarditis in 1837 through the discovery of the Coxsackie enteroviruses in 1948, the understanding of myocarditis consisted of histological patterns (eg, granulomatous, lymphocytic, eosinophilic, or giant cell myocarditis) associated with various pathogens (famously Group A streptococcus and *Trypanosoma cruzi*) within a clinical syndrome of heart failure or arrhythmia. Daldorf's isolation and characterization of Coxsackie viruses in rat cardiomyocytes led to enteroviral and later autoimmune murine models with prominent lymphocytic infiltrates. Experimental studies in these systems led to a 3-phase model of (1) injury followed by (2) innate and adaptive immune response and, last, (3) dilated cardiomyopathy.

In the 1960s heart biopsy (endomyocardial biopsy) for unexplained cardiomyopathy introduced the antemortem diagnosis of myocarditis and ushered in an era in which myocarditis was identified in patients with advanced heart failure at tertiary medical centers capable of heart transplantation.[1] Histological criteria with high specificity but low sensitivity were codified in 1986 in what would become known as the "Dallas Criteria." In Europe and to variable degrees elsewhere, antigen-specific immunostains with greater accuracy in predicting the risk of cardiac adverse events are now used to define myocarditis.[2]

Beginning in the 1990s, the innovations of cardiac magnetic resonance imaging (CMR), cardiac troponin testing, and searchable databases with hundreds of millions of medical records dramatically changed the landscape of clinical myocarditis. CMR widened the diagnostic lens, revealing epicardial and mid-myocardial regions most affected in acute myocarditis that were not amenable to endomyocardial biopsy. CMR studies demonstrated that the prognosis of mild myocarditis is much better than acute myocarditis presenting with heart failure. With this broader view of myocarditis enabled by CMR and sensitive troponin assays, chest pain emerged as the most common presenting symptom in mild myocarditis. In low-risk clinical scenarios CMR replaced endometrial biopsy as the diagnostic test of choice. Coincident with the growth of CMR, epidemiological estimates of the global burden of myocarditis derived from multinational datasets helped to inform clinical trial designs.

The original 3-phase pathogenesis model has been modified through the discovery that pathogenic or likely pathogenic variants of cardiomyopathic genes are common in myocarditis. Variants in sarcomeric genes commonly seen in dilated and hypertrophic cardiomyopathy are more prevalent in severe cases, whereas desmosomal genes typically seen in right ventricular cardiomyopathy are more prevalent in nonsevere cases. Children with more severe myocarditis have an especially high rate of cardiomyopathic gene variants.[3] Myocardial stromal cells that initiate and sustain myocarditis have joined lymphocytes and anticardiac antibodies as candidate therapeutic targets in an expanded disease model.[4] Last, the clinical effect of estrogen and testosterone on cardiac inflammation received considerable attention after reports that young adult men were

Key Words: databases, factual ■ heart failure ■ magnetic resonance imaging ■ myocarditis ■ troponin

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disproportionately affected by mRNA vaccine–associated myocarditis.

The recognition of mild myocarditis cases created gaps in our understanding of the prognosis and management of patients with a nonsevere clinical presentations. Because major cardiac adverse event rates are low in this population, longer duration studies in large cohorts are needed to define the best approach to exercise restriction and management of chest pain. Persons with a genetic predisposition and specific causes such as immune checkpoint inhibitor therapy may be at greater risk of recurrence. In immune checkpoint inhibitor–associated myocarditis a greater understanding of the prognostic implications of an isolated rise in troponin is needed to guide management recommendations in asymptomatic people. In mild cases, the psychological and social burden in patients with a diagnosis of acute myocarditis can exceed the physical effect of the disease. On the horizon, diagnostic tests such as regulatory miRNA in the blood and positron emission tomography with pathway-specific imaging agents may refine testing algorithms with greater diagnostic accuracy.[5]

Treatments have lagged the advances in mechanistic understanding of myocarditis. However, positive trials with colchicine and anti–interleukin-1 antibodies for atherosclerosis have generated interest in the next generation of myocarditis treatments. Randomized clinical trials are now underway for specific forms of myocarditis, including fulminant, cardiac sarcoidosis, and immune checkpoint inhibitor–related myocarditis. The stage has been set with new cellular targets and diagnostic tools for the next generation of clinical and experimental studies to advance our knowledge and refine management practices across the spectrum from preclinical to end-stage myocarditis.

ARTICLE INFORMATION

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Sources of Funding

None.

Disclosures

Dr Cooper receives consulting fees from Bristol Meyers Squibb, CardiolRx, Moderna, and the Chan Zuckerberg Rare as One Foundation and has equity ownership in Stromal Therapeutics, LLC.

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