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Acute myocarditis: An overview on emerging evidence

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Myocarditis is an inflammatory disease of the heart that may present with a wide spectrum of clinical manifestations, ranging from an asymptomatic state to infarct-like chest pain, severe heart failure, and life-threatening ventricular arrhythmias [1]. Although endomyocardial biopsy still represents the gold standard, the diagnosis of acute myocarditis currently relies on several clinical and imaging criteria. At the present time, several aspects of this complex disease need to be clarified: Which patients need a biopsy? What is the role of the cardiac magnetic resonance (CMR) regarding myocarditis assessment? What is the workflow that can drive to a correct diagnosis and treatment?

The variability of clinical manifestation and the risks of a sudden hemodynamic deterioration make the delineation of this process extremely challenging. As previously reported, myocarditis can evolve toward three main different scenarios with different long-term implications: a benign self-limited form, a form characterized by an arrhythmic expressivity and a form characterized by heart failure (acute/chronic) [1].

In this issue of Trends in Cardiovascular Medicine, Ammirati et al. systematically review all the available evidence from observational registries on acute myocarditis with special attention to the areas in which we have a substantial lack of knowledge [2].

Combining retrospective data from multiple studies is gaining importance to create risk stratification models able to identify those patients at higher risk who may benefit from further investigation, close medical follow-up and evaluation for an implantable cardioverter defibrillator (ICD). The authors have reported data from a large Italian multicenter registry including 220 patients with acute myocarditis confirmed by EBM. The authors found that a pool of variables including presentation with hemodynamic decompensation, left ventricular ejection fraction (LVEF) <50% and a QRS duration >120 msec characterize a subgroup of patients with "complicated" acute myocarditis whom may benefit from mechanical hemodynamic support. In this scenario, physicians need to be trained to quickly identify patients with hemodynamic instability and to promptly refer them to tertiary centers where mechanical support and cardiac surgery are available [3].

Interestingly, similar findings have been reported in the pediatric population. According to a German registry including children and young adults (median age 13-years) admitted to the hospital for acute myocarditis presenting with decompensated heart failure, the need for mechanical hemodynamic support was as high as 14% while in-hospital death/heart transplant rate was 8%, and the overall mortality rate was 5% [4]. Unfortunately, all these data come from relatively small retrospective studies with a substantial lack of large randomized trials.

The pathophysiologic process behind acute myocarditis typically involves an abnormal immune-mediated response to various viral agents. Recently, the Covid-19 outbreak renewed attention to viral myocarditis. In the present work, the authors describe the viral role in different settings: passive bystander, causative agent able to directly damage myocytes or trigger of immune response against the myocytes. In a large European Study of Epidemiology and Treatment of Inflammatory Heart Disease, presence of viral genome was found in only 12% of 3055 symptomatic cases [5]. In this setting, the European Society of Cardiology position statement recommends against the use of immunosuppressant agents in the presence of viral genome. Some cases have been described where the use of immunosuppression did not increase Parvovirus B-19 viral replication. In this review, the authors suggest that the risk to benefit ratio may be in favor of immediate use of steroids in the setting of myocarditis with life threatening presentation. However, this statement needs further endorsement by large scale clinical trials.

Based on the available evidence, Ammirati et al. suggest a risk-based approach to patients with suspected myocarditis. Transthoracic Echocardiography is the first line test to assess cardiac function and pericardial involvement because it is easily accessible and available at bedside.

When acute myocarditis is highly suspected based on a clinical evaluation, CMR is recommended to confirm the diagnosis thanks to its tissue-characterization capabilities. In particular, CMR has demonstrated an accuracy of 79% in identifying acute myocarditis when at least two out of three of the following criteria are present: (1) edema visualized asT2 enhancement, (2) scar or active inflammation visualized by late gadolinium enhancement (LGE) imaging, usually in a regional subepicardial distribution [6].

The use of EBM remains indicated to guide therapy in patients with high risks features while in uncomplicated cases CMR together with biomarkers like cardiac Troponin may be sufficient. The 2007 AHA/ACC statement and the ESC recommendations for EMB were more strict regarding the use of EBM, recommending it only in unexplained, new-onset heart failure of <2 weeks du-

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ration associated with hemodynamic compromise, and in the setting of unexplained new-onset heart failure between 2 weeks and 3 months duration associated with a dilated LV and new bradyarrhythmia or new ventricular arrhythmias, or a failure to respond to standard care within 1 to 2 weeks of diagnosis. The 2013 statement expanded the indications relying more on the physician choice in every patient with suspected myocarditis [7]. This position has been confirmed in 2016 since EMB may be considered in patients with heart failure that is rapidly progressing. Biopsy is also indicated in association with biomarkers and cardiac imaging in a new emerging entity: myocarditis associated with use of immune checkpoint inhibitors (ICI) [8]. ICI are antibodies that induce an immune-mediated attack on cancer cells by blocking tumor-driven inhibition of T-cell activation. Their use is significantly increased and represents a new frontier for their disseminated use despite unpredictable side effects including myocarditis, colitis, dermatitis, pneumonitis and endocrinopathies. Because of substantial lack of prospective data, treatment of ICI-associated myocarditis remains empirical [8].

In the oncoming years a substantial effort in determining accurate risk stratification tools is warranted. Emerging CMR studies regarding scar assessment in term of extension and localization seem to help the clinician identify patients that need to be protected from life-threatening arrhythmias. Moreover, recent studies have highlighted that myocarditis can be the first signs of an underlying cardiomyopathy [9,10].

In conclusion, nowadays, despite great improvements in the diagnosis and treatment of myocarditis, its morbidity and mortality are still significant and further efforts are required for identification of short and long term prognosis predictors.

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