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Editorial

Fighting the "Lernaean Hydra" of systemic immune-mediated diseases

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Systemic immune-mediated diseases (SIDs) affect 8% of the population with 78% of patients being female. Although great progress has been achieved in the treatment of systemic symptoms in SIDs, cardiovascular disease (CVD) still remains the main cause of death. Myocarditis is an important contributor constituent of CVD in SID patients [1]. In this paper, Peretto et al. [2] compared patients with biopsy-proven acute myocarditis secondary to SIDs to controls with isolated myocarditis, matched 1:1 by age, gender, ethnicity and clinical presentation. The authors demonstrate that SID patients with acute myocarditis had a higher prevalence of elevated plasma levels of inflammatory biomarkers, signs of associated pericarditis, and replacement fibrosis at histology compared to controls. However, the cardiovascular magnetic resonance (CMR) Lake Louise criteria for myocarditis were negative in 19/27 (76%) SID patients vs. 10/25 (40%) controls. Although baseline clinical characteristics were not significantly different between groups, at 12-month follow-up the incidence of the composite major endpoint of cardiac death, end-stage heart failure or malignant ventricular arrhythmias was significantly higher in SID patients compared to controls. Therefore, myocarditis in the presence of underlying SIDs is associated with a significantly worse prognosis at 1-year follow-up [2].

SIDs are characterized by immune system dysregulation, activation of immune cells and inappropriate inflammation leading to organ damage and eventually death. Consequently, life expectancy in SIDs remains lower compared to the general population and CVD represents the main contributor to premature mortality. The European league against rheumatism (EULAR) recommends tight disease control accompanied by regular assessment of traditional CVD risk factors in combination with lifestyle changes [3]. Although this recommendation is important for coronary artery disease (CAD) prevention, it does not guarantee prevention of myocardial inflammation in this context. Therefore, a careful clinical and imaging evaluation is necessary in cases with acute myocardial inflammation that can be either the first manifestation or a flare of the underlying SID.

According to the study by Peretto et al., myocardial inflammation in SIDs merits more intensive clinical management, due to increased risk of unfavorable outcomes at follow-up [2]. The need for this becomes clear when we consider that the suppression of systemic inflammation does not necessarily eliminate inflammation in the myocardial microenvironment, which very often follows its "revolutionary" way in contrast to the underlying SID which may seem quiescent [4]. Furthermore, as mentioned in the supplementary materials file, the adopted therapeutic regimen of choice in virus-negative isolated myocarditis (group L) was: azathioprine 2 mg/kg + prednisolone 1 mg/kg, with treatment duration 12 ± 1 months, while SID (group S) patients underwent different therapeutic regimens, chosen by an ad-hoc team of immunologists based on the specific underlying SID with various degrees of complexity (range 1 to 4 drugs) and an overall longer treatment duration (> 12 months).

Unfortunately, myocardial inflammation is not always acute. Low-grade inflammation can also be present in SID patients, run silently and finally lead to diffuse microfibrosis and development of heart failure. In these oligo-asymptomatic cases, the role of CMR is of great value since it is the only noninvasive diagnostic tool that does not utilize ionizing radiation and can perform tissue characterization. CMR has the potential to prompt early cardiac and anti-rheumatic treatment even in silent cases of myocardial edema by detecting acute phase phenomena in the myocardium [5]. However, long term multicenter studies examining the clinical benefit of silent myocarditis treatment in SID patients are still missing and therefore definite conclusions cannot be drawn.

Another important issue is the mismatch between CMR (negative T2 STIR sequences) and EMB (positive for active inflammation), particularly in SIDs. This can be potentially explained by various factors such as: a) limitations of T2STIR techniques due to artifacts b) low grade chronic inflammation that does not allow the detection of any increase in T2STIR values and c) the lack of advanced CMR imaging evaluation including T1, T2 mapping and extracellular volume fraction quantification (ECV) that can precisely quantify any change occurring at the molecular level. The Lake Louise criteria play an

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important role in the evaluation of acute myocardial inflammation. However, the introduction of T1, T2 mapping and ECV allowed the quantification of diffuse fibrosis, missed by older late gadolinium enhanced sequences for fibrosis detection, as well as the assessment of diffuse myocardial oedema, both commonly encountered in SID patients with myocardial inflammation. As a result, these novel CMR indices can play a complementary role to the Lake Louise criteria for the diagnosis of myocardial inflammation in SID patients [6].

To conclude, just like the Lernaean Hydra, the beast of legend from Greek mythology that spawned two new heads for every one that was cut off, SIDs similarly pose a challenge to currently employed diagnosis and treatment methods for myocardial inflammation. The mythical hero Hercules eventually defeated the beast by cutting off all its heads and burning the remainder of the neck using sword and fire. To extend this analogy, the challenge for treating physicians handling SID patients at the moment is to invent their own “sword and fire” in the form of early diagnosis and effective treatment for suppressing both the systemic and myocardial inflammatory components. It is only then that the “beast” we see in premature death in SID patients can truly be dealt with decisively.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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