Editorial

Myocarditis with very high troponins: risk stratification by cardiac magnetic resonance

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Myocarditis is an inflammation of the myocardium that can be caused by a variety of etiologies, commonly viral, but also toxins, drugs, and autoimmune processes (1). The usual patterns of clinical presentation include chest pain, arrhythmias, and heart failure. The disease severity may vary greatly, ranging from asymptomatic or mild flu-like symptoms to cardiogenic shock and sudden death (2). Patients presenting with chest pain with preserved left ventricular (LV) function typically have an excellent prognosis. Conversely, patients presenting with heart failure and/or life-threatening arrhythmias, in particular when associated with severe LV dysfunction, have a greater risk of adverse events during follow-up. An integrated approach with clinical evaluation (i.e., history, physical exam, electrocardiography) and noninvasive imaging [i.e., echocardiography, cardiac magnetic resonance (CMR) imaging] is fundamental for the identification of cases of suspected myocarditis. In patients with myocarditis presenting with chest pain, an acute coronary syndrome (ACS) often needs to be ruled out appropriately with an angiogram.

The gold standard for a definite diagnosis and therapy of myocarditis is an endomyocardial biopsy (EMB). However, this is an invasive test with risk of complications and carries the limitation of sampling error, since myocarditis is often a patchy process. EMB and specific therapies, like immunosuppression, should be reserved for patients presenting with major clinical syndromes (such as a strong suspicion of giant cell myocarditis with severe heart failure and/or life-threatening arrhythmias) that are refractory to conventional therapies.

We now have newer, non-invasive imaging modalities such as CMR, which can help aid the diagnosis and guide therapy in acute myocarditis. T2-Weighted imaging (T2-W) is indicative of tissue free water and is increased during an inflammatory process, such as observed in acute myocarditis (3). T2-W edema imaging on CMR can accurately and non-invasively establish a diagnosis of acute myocarditis. High sensitivity and specificity of T2-W compared to EMB has been reported (4). Studies have shown that contrast-enhanced CMR identified areas of myocardial inflammation in up to 70% of patients with biopsy-proven myocarditis (5). Mahrholdt *et al*. (6) has validated these findings against histopathology. Late gadolinium enhancement (LGE) in myocarditis is usually patchy, and involves the subepicardial regions (7). CMR may also be critical in the diagnosis of acute myocarditis in a patient with prior known CAD (8).

Fan *et al*. (9) report an interesting case of acute myocarditis in a 16-year old boy presenting as ACS with sudden onset chest pain, ST segment elevation and significantly high cTnI levels, but preserved LV function. He had an episode of likely acute myocarditis in the past. He had a viral prodrome prior to both these presentations. CMR findings were consistent with acute myocarditis with good resolution of inflammation on follow up imaging.

ACS and stress-induced cardiomyopathy are two important differential diagnoses that need to be considered and ruled out in patients presenting with chest pain, EKG changes and positive troponins. The patient described had no obstructive coronaries on angiography. The transthoracic echo and cardiac MRI did not reveal any

typical wall motion abnormalities to suggest stress-induced cardiomyopathy.

There are several interesting aspects to this case report. This was a case of recurrent acute myocarditis. The fact that the overall LV function was preserved during both episodes (especially in the presence of significantly elevated troponin levels during the second episode), is quite intriguing. Preserved LV function in patients with myocarditis places them in the "low-risk syndrome" category. The authors have repeated the cardiac MRI in 3 months to document continued preservation of LV function and demonstrate resolution of myocardial edema and reduction of the extent of LGE. Since edema, and not fibrosis, is the cause for LGE in the acute phase of myocarditis, the area of LGE usually decreases with time (1).

Cardiac troponins are well established as sensitive and specific markers of myocardial injury. Increased cTnI levels can be detected in just over one-third of patients with myocarditis (10). However, a normal EKG, a negative troponin and/or creatine kinase does not exclude the diagnosis of myocarditis (11). The preservation of LV function during an episode of acute myocarditis with high levels of troponins is typically not common, but has been reported (12). Although a rise in troponin level seems logical and anticipated in acute myocarditis, the troponin levels do not seem to have the same prognostic value in acute myocarditis when compared to ACS (13). Thus, elevated troponin levels should not itself be a reason for a prolonged follow-up or additional investigations (14). The patient presented in the article had a very high level of troponin, but eventually had an excellent outcome. It seems reasonable to assume that troponin release in myocarditis results from increased permeability of cardiomyocyte cell membrane and does not exclusively reflect cell necrosis. Troponin level in acute myocarditis may be more influenced by the timing of measurement than by the severity of myocardial damage and dysfunction (12).

It may be worth pointing out that the authors have utilized a "qualitative" assessment of myocardial edema on T2-W. They have not used the newer T2 mapping sequences to "quantitate" myocardial edema (15). Kellman *et al*. (16) found that T2-mapping sequences are superior to T2-W in identifying tissues with interstitial edema, because T2-W sequences do not offer quantitative T2 measurements that would allow for comparisons between different studies (17).

Additionally, T1 mapping post-contrast agent has been recently used to detect diffuse fibrosis in heart failure and showed promising results for the detection of diffuse fibrosis in myocarditis (18). Native T1 values (without contrast) were significantly increased in patients with myocarditis, their values were higher in acute compared with convalescent phase of myocarditis and this index was an independent discriminator between health and disease, as well as, a discriminator between acute and convalescent phase of myocarditis. Additionally, acute myocarditis can be independently identified by native T1 of >5 SD higher than the mean of the normal range, whereas convalescence is best defined by either abnormal native T1 (>2 SD) or presence of LGE (19). Finally, native T1-mapping in acute myocarditis displays the typical non-ischemic patterns, similar to LGE, but without the need for gadolinium, providing significant incremental value by diagnosing additional areas of myocardial inflammation beyond T2W and LGE and identifies extra cases, where the routine applied techniques failed (20). It would have been interesting and intriguing to know the native T1 values in this patient during the acute event and later on follow up.

There is also no mention of the patient getting a cardiac MRI during his first hospitalization in January 2014. Hence the presence and extent of increased T2 signal (i.e., myocardial edema) and LGE from that event is unknown. The presence of any residual, persistent delayed enhancement from the initial event therefore will remain unknown. Based on the much lower increase in cardiac troponin and a good clinical recovery with preserved LV function, one could speculate that the initial event was probably a mild episode of acute myocarditis with good resolution in subsequent months.

In conclusion, acute myocarditis is an important differential diagnosis in patients presenting with ACS-like symptoms, elevated cardiac enzymes and non-obstructive coronaries on angiography. Those patients with a normal LV function without wall motion abnormalities, stable arrhythmic profile, and complete resolution of EKG abnormalities have excellent long-term prognosis. Troponin levels are not prognostically relevant in acute myocarditis, and long-term outcomes are often independent of cardiac enzyme release (21).

Currently, the key diagnostic approach, if there is a clinical suspicion for myocarditis, is to perform a CMR evaluation (using T2, early and late gadolinium-enhanced images), since this technique is the most reliable noninvasive way to establish diagnosis. The application of T1 and T2 mapping improves the diagnostic capability of the technique. The presence of subepicardial late gadolinium

enhancement, typically present in this condition, does not seem convincingly related to a worse prognosis when associated with preserved ventricular wall motion and a stable arrhythmic profile (14). Further studies in this setting are needed to confirm these findings. There has also been a proposal to consider a noninvasive follow-up prolonged up to 2 years in the presence of LGE, even if the LV function is preserved (22).

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Footnote

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