Clinically suspected myocarditis with pseudo-infarct presentation: the role of endomyocardial biopsy

Alida L. P. Caforio[1], Giacomo Malipiero[2], Renzo Marcolongo[2], Sabino Iliceto[1]

[1]Department of Cardiological, Thoracic and Vascular Sciences, University of Padova, Padova, Italy; [2]Department of Medicine, Hematology and Clinical Immunology, University of Padova, Padova, Italy

Correspondence to: Alida L. P. Caforio, MD, PhD, FESC. Department of Cardiological, Thoracic and Vascular Sciences, University of Padova, via N Giustiniani, 2, 35128 Padova, Italy. Email: alida.caforio@unipd.it.

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Myocarditis can have heterogeneous clinical presentations, ranging from paucisymptomatic disease to life-threatening ventricular dysfunction or malignant arrhythmia (1). The acute infarct-like scenario with chest pain, ischemic-like electrocardiographic changes, troponin release and unobstructed coronary arteries (with or without a recurrent evolution), reported in the case by Fan *et al.* (2), represents one of the most common presenting modalities (1-5). Myocardial necrosis in this context is thought to result from microvascular ischemic damage induced by direct endothelial viral infection and/or by the myocardial inflammatory *milieu per se* (6). Parvovirus B19 directly infects cardiac and extra-cardiac endothelial cells; in addition, by infecting bone-marrow derived angiogenic cells, it may impair endothelial regeneration, leading to endothelial dysfunction and angina-like symptoms (e.g., microvascular angina) (7). In virus-negative myocarditis, other mechanisms have been advocated, as exemplified by pathophysiological studies in rheumatologic or dysmetabolic patients with microvascular angina (8).

Fan *et al.* (2) suggest that the infarct-like presentation is associated with spontaneous resolution and a benign clinical course. Regarding the prognostic significance of a specific clinical pattern of disease onset, heart failure presentation (with or without dilated cardiomyopathy) notably carries a dismal prognosis in a high percentage of patients (3,9) and detailed histological analysis of

endomyocardial biopsy (EMB), including viral genome search and immunohistochemistry, is nowadays considered a key diagnostic and prognostic tool with undeniable therapeutic consequences, even in acute onset disease (10,11). On the other hand, infarct-like presentation has predominantly been associated with a favorable outcome, mainly in association with preserved pump function (3,9). However, a significant incidence of myocarditis recurrence and/or chronic myocardial damage, resulting in dilated cardiomyopathy and worsening myocardial dysfunction, ranging from 12.5% to 29% of patients, has also been reported in some series (12-15), casting doubts about its presumed benign prognosis. The discrepancy may relate to the use of different diagnostic, stratification and outcome criteria in distinct cohorts. For instance, Youn *et al.* considered as "acute" patients those with symptom onset within 3 months from EMB confirmation, without specifying presentation patterns or the presence of viral genome (12). Kindermann *et al.* (13) included only biopsy-proven patients with a viral prodrome in the 6 months prior to clinical onset and did not distinguish patients according to presentation patterns, e.g., pseudo-infarct *vs.* heart failure. Chopra *et al.* (14) stratified patients according to clinical presentation patterns, but did not confirm the diagnosis histologically and did not rule out coronary artery disease by coronary angiography. Therefore viral etiology was only presumed and non-inflammatory causes

(e.g., coronary artery disease) or rare myocarditis forms with a recognized unfavourable evolution (e.g., giant cell or eosinophilic myocarditis, which often may have a pseudo-infarct presentation) were not excluded. Similar considerations may be applicable to the work of Sanguineti *et al.* (15) who found a rate of 10.8% of major adverse clinical events (MACE) during a 18 months follow up of 203 "acute" clinically suspected myocarditis patients, 89% of whom with chest pain at disease onset. In addition, the authors did not provide data regarding the incidence of MACE according to clinical presentation patterns. Finally, in biopsy proven myocarditis case series, microbiological agents detection in tissue specimen was not always performed and, when available, different viral agents were investigated; for example, HCV infection, a presumed cause of chronic myocardial damage, was frequently overlooked or unreported. Last but not least, there may be cases with both "pseudo-ischemia" presentation and heart failure or arrhythmia so these patterns cannot be considered mutually exclusive (1,4,5). Thus, at present there are insufficient prospective biopsy-proven data to confirm or rule out that the pseudo-infarct presentation of myocarditis is *per se* associated with benign prognosis.

Obviously, the type and load of microbiological triggers of myocarditis as well as the dominating mechanisms of myocardial damage, i.e., direct viral myocytopathic effects *versus* immune-mediated mechanisms, are likely to impact on both short- and long-term prognosis. Mahrholdt *et al.* described an additive effect of the presence of parvovirus B19 (PVB19), human herpesvirus 6 (HHV6) or both on the clinical presentation pattern and outcome of a cohort of 257 patients with biopsy proven myocarditis (6). Some authors suggested a negative prognostic role for high PVB19 genomic load, as well as its value to distinguish acute from chronic PVB19–associated myocarditis (16). However, in another series of 108 biopsy-proven patients affected by PVB19-associated myocarditis, genomic viral load failed to be an independent marker of poor prognosis, casting a shadow on the real biologic and prognostic significance of this virus, at least in the acute phase of the disease (17). In several patients' cohorts, anti-heart autoantibodies to various autoantigen specificities were reported as negative prognostic markers of progressive immune-mediated disease (reviewed by Caforio *et al.*) (4) but these markers were not searched for in many short- and long-term prognostic studies. Finally, global burden of myocardial tissue involvement, defined not only by clinical and ultrasound signs of myocardial dysfunction but

also by late gadolinium enhancement (LGE) extension on contrast cardiac magnetic resonance (CMR), is not available in some cohorts and different quantification algorithms were used for its estimation. Again, long-term prospective data in biopsy-proven disease are needed to validate by multivariable analysis any newly proposed non-invasive or invasive biomarker (3,4,6).

The controversy regarding the prognostic value of clinical and histological markers of disease activity and severity is nourished by a perceived lack of therapeutic consequences of achieving an aetiological diagnosis. This point deserves special attention. It is well known that aggressive immunosuppressive therapy is mandatory in giant cell myocarditis and eosinophilic or hypersensitivity myocarditis to preserve patients' life and promote myocardial recovery (1,3,4). In addition, in acute onset myocarditis associated with systemic immune-mediated disease a prompt clinical management is life-saving (1,3,4). Moreover, even when remission spontaneously ensues and ventricular function is apparently restored, the acute inflammatory event, regardless of its infectious or immune-mediated etiology, may still lead to long-term ventricular dysfunction or arrhythmogenicity (e.g., non-ischemic ventricular scars) (18). This raises the question whether an aetiology-directed therapy in the acute phase may promote "*restitutio ad integrum*", preventing formation and maintenance of irreversible arrhythmia and heart failure myocardial tissue substrates.

When considering chronic myocarditis patients, good evidence is available regarding specific treatments. Thanks to the pioneering work of Frustaci and others (19), patients affected by active lymphocytic virus-negative myocarditis and systolic ventricular dysfunction refractory to conventional cardiologic therapy, can now undergo an immunosuppressive treatment with a high probability of obtaining a complete or at least partial recovery of myocardial contractility. Unfortunately, only sporadic therapeutic experience has been collected in the subset of acute patients and with contrasting results. Once more, patients with different diseases and different disease phenotypes have been grouped together making synthetic systematic review almost impossible. Most trials included patients with decreased ventricular function, irrespective of the clinical presentation pattern. The Myocarditis Treatment Trial (20), to cite the most historically relevant, did not observe significant difference between treated and placebo patients, however significant limitations of this study were the lack of viral genome search as well as of

current sensitive immunohistochemical EMB markers and the wide variability in symptoms duration from clinical onset to the beginning of immunosuppressive therapy (from few weeks up to 2 years). In addition, the study was underpowered to detect efficacy of immunosuppression on outcome. A recent meta-analysis discouraged the use of corticosteroids in acute pediatric and adult myocarditis, but again studies were pooled together and most of them lacked enrollment of patients based upon an etiology-specific diagnosis, thus making the results of the meta-analysis uninterpretable (21). It is worth noting that in a recent European Society of Cardiology (ESC) expert consensus document it is recommended to use immunosuppression, including steroids, only in EMB-proven virus-negative myocarditis, since this treatment is generally contraindicated and may be harmful in patients with cardiac or extra-cardiac infection (4). More recently a therapeutic attempt using IL1-inhibitors in clinically-suspected acute fulminant myocarditis patient has been attempted with surprising results (22). Although histologic confirmation was lacking, this case report might pave the way to revolutionary changes in acute myocarditis treatment and a randomized clinical trial is strongly advisable to confirm or reject this cytokine-targeted approach.

Altogether, the lack of biopsy confirmation and of detailed etiological definition of acute infarct-like clinically suspected myocarditis (as the disease is felt to be self-limiting despite controversial results in the long-term prognostic studies) and the consequent lack of controlled etiology-directed trials have led to the current *wait and see* strategy, aimed at ensuring the best symptomatic cardio-active treatment and documenting the complete recovery of signs and symptoms of heart dysfunction and damage by physical examination and ultrasound/CMR. This approach carries the risk of underdiagnosing and undertreating patients with severe, progressive or recurrent disease. To break down this self-feeding diagnostic-therapeutic vicious cycle and promote a real knowledge of biological and clinical events in acute infarct-like myocarditis as well as support the existence of progressing patients and identify new therapeutic windows, the ESC expert consensus document recommends a uniform approach to the diagnosis of myocarditis (4). This document offers a clear definition of clinically suspected myocarditis and suggests that the execution of an EMB should be considered in every patient with clinically suspected myocarditis, with or without a pseudo-infarct presentation, and regardless of the degree of systolic dysfunction at presentations. Such document may

be useful not only for the management of individual patients with acute myocarditis, but also to improve the uniformity of practices across academic centers for the purpose of collaborative studies. The same etiology-directed approach has been proposed in a recent ESC expert consensus document on myocardial infarction with normal coronary arteries (MINOCA), which underlines the role of CMR and of EMB in the etiological diagnosis of the MINOCA syndrome (23).

Fan *et al.* (2) based their diagnosis mainly on CMR. The usefulness of CRM is undoubtful in strengthening the diagnostic hypothesis of myocarditis and defining its anatomical extension, although the diagnosis of certainty as well as the etiological diagnosis of infectious (mainly viral) versus non-infectious immune-mediated myocarditis is based upon EMB (4). It is worth noting that the sensitivity of CMR to detect myocarditis varies with the clinical presentation, and it is higher in EMB-proven myocarditis presenting as myocardial infarction (80%) than in biopsy verified myocarditis presenting as a cardiomyopathic or arrhythmic event (57% and 40%, respectively) (24). It has been shown that in this context the combination of CMR and EMB gives diagnostic synergy with a substantial reduction in the rate of unexplained MINOCA cases, particularly in relation to myocarditis. With the combined approach comprising CMR and EMB, a final diagnosis could be established applying the 'Believe-The-Positive-Rule' in 95% of MINOCA patients (25).

In relation to the clinical case report, only etiological hypotheses could be generated since an EMB was not performed. What is really going on in this young patient? Recurrent infections with different agents? Recurring autoimmune disease triggered by distant infectious events? Is the myocardium infected by one or more agents? What is the risk of subsequent evolution to chronic cardiomyopathy and the risk of further recurrences? What is the risk of sudden arrhythmic death, particularly should the conductive myocardium turn out to be affected? Since recurrence of clinically acute myocarditis might be a risk factor for further recurrences, as exemplified by many other disease states (e.g., ischemic cardiomyopathy, autoinflammatory or autoimmune diseases, neoplastic disease, sarcoidosis etc.), careful etiologic research with EMB would be mandatory in this particular case.

From the available literature, recurrent infarct-like presenting myocarditis seems to be a rare clinical entity, mostly associated with recurrent post-streptococcal disease, toxics or other substances abuse and autoinflammatory

diseases. An autoimmune mechanism seems to be operative in post-streptococcal disease by molecular mimicry. Organ specific autoimmunity may be also triggered by recurrent mucosal inflammatory events or via superantigenic stimulation of anergic autoreactive clones. Moreover, direct viral reinfection of the myocardial muscle and subsequent immune clearance may also be possible, especially in immune-suppressed HIV individuals. Whatever the dominating mechanism, a genetically predisposition seems to be necessary for multiple episodes of myocarditis to result and may be responsible for the transition from triggered damage to chronic endogenously maintained auto-immune damage. To clarify these key issues the only option at the moment is to perform EMB in consecutive patients with clinically suspected myocarditis with or without a pseudo-infarct presentation and to collect long-term follow-up data (4).

Another point that deserves some consideration is the utility and significance of troponin as a biomarker. The authors suggested that the high troponin peak observed during the acute phase could be related to a transitory cell membrane permeabilization of otherwise morphologically and functionally preserved myocardial cells. Since cardiomyocyte necrosis was not excluded by EMB, this hypothesis seems at best unlikely. First, at CMR follow-up LGE and oedema were still present. At the best of current CMR interpretation, these findings indicate irreversible post-inflammatory necrotic changes as well as ongoing myocarditis. Myocarditis is defined as histologically proven myocardial inflammation and non-ischemic myocardial necrosis (4). Biopsy-proven myocarditis is frequently diagnosed in patients with negative troponin and CMR studies (4,5,24). Therefore, lack of troponin release or a negative CMR does not rule out ongoing myocarditis, even in this patient. Obviously, since biopsy-proven myocarditis may occur with or without troponin release, troponin does not correlate with long-term prognosis. On the other hand, it is undisputable that troponin release should always be interpreted as a biomarker of cardiomyocyte necrosis and irreversible damage, although, in the scenario of inflammatory necrosis, less sensitive than EMB.

To conclude, prospective biopsy-proven long-term data from large clinical cohorts are needed to define predictors of outcome and of recurrence in clinically suspected myocarditis with pseudo-infarct presentation.

Acknowledgements

Footnote

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