REVIEW

The fate of acute myocarditis between spontaneous improvement and evolution to dilated cardiomyopathy: a review

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The World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) task force on the definition and classification of cardiomyopathies recently updated and reclassified heart muscle diseases.¹ Myocarditis was defined as “an inflammatory disease of the myocardium . . . diagnosed by established histological, immunological, and immunohistochemical criteria.” Three distinct forms of inflammatory cardiomyopathy (that is, myocarditis associated with cardiac dysfunction) are recognised: idiopathic, autoimmune, and infectious. Various infectious factors may cause myocarditis, but viral agents, especially coxsackie group B viruses, are most commonly associated with this disease.²

Myocarditis has been recognised for almost two centuries, since Corvisart first described this disease in clinical terms in 1812,³ but in the last three decades there has been renewed interest in the inflammatory process in the myocardium. The reasons for this are multiple: the introduction of endomyocardial biopsy for in vivo diagnosis (the disease was often overdiagnosed in the past on purely clinical grounds);⁴ related efforts to produce standardised criteria for histological diagnosis (the Dallas criteria; fig 1)⁵; better understanding of cardiotropic viruses, studied in animal models of myocarditis,⁶ leading to new insights into the immunological mechanisms of the disease (fig 2)⁷ and potential treatments in humans⁸; and lastly—and perhaps most interestingly—the finding of a possible causal relation between viral myocarditis and dilated cardiomyopathy,⁹

a major cause of congestive heart failure in western countries.

Despite numerous published reports on this disease, the natural history of acute myocarditis is still poorly understood, despite the development of immunological and molecular tools for investigating viral diseases which have improved our understanding of their long term course, and in some cases have identified persistence of viruses in the myocardium.¹⁰

In this review we describe our personal experience on the natural history of biopsy proven acute myocarditis of viral or unknown origin, and we review current reports.

Natural history of acute myocarditis

The natural history of acute myocarditis is largely unknown. There have been few studies on its short and long term evolution, reflecting the difficulties in diagnosing and following up the disease. Lately, the contribution of endomyocardial biopsy has been invaluable, making early diagnosis of the disease possible, with histological identification of the time course of the inflammatory process.

Nevertheless, several questions remain unsolved. First, as acute myocarditis is rarely symptomatic, it is difficult to identify subclinical episodes¹¹ and their possible evolution to disease indistinguishable from idiopathic dilated cardiomyopathy.^{12–13} Furthermore, among symptomatic patients, even after the wide acceptance of the standard Dallas pathological criteria,⁵ possible interobserver variability in the interpretation of biopsy specimens,¹⁴ different selection criteria, and the intrinsic limitations of the procedure (number of biopsy

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Figure 1 Histological section of active lymphocytic myocarditis according to the Dallas criteria. A dense infiltrate of lymphocytes in close contact with damaged and necrotic myocytes is evident (haematoxylin and eosin × 100).

Figure 2 CD4RO positive T lymphocytic cellular infiltrates in a diffuse pattern (× 40).

Figure 3 Clinical presentation and evolution of acute viral myocarditis (dotted lines indicate potential evolution). DCM, dilated cardiomyopathy.

specimens, sampling error, reduced sensitivity^{14,15} have led to high variability in the reported incidence of myocarditis in different series (ranging from 0–67%).^{13,16} Finally, the time interval between symptom presentation and endomyocardial biopsy is crucial: histological signs of inflammation usually recover relatively soon after the onset, so that later morphological diagnosis may be difficult in clinical practice.¹⁷

In order to predict the natural history of biopsy proven acute myocarditis, we have differentiated patients according to their clinical presentation.¹⁸ Patients with acute myocardial infarction-like presentation usually have a good prognosis, with a complete or partial recovery of cardiac function,^{18–20} although in a minority cases (12.5% in our series) progressive left ventricular dysfunction may occur. Patients with bradyarrhythmias may follow a similar course. Fulminant myocarditis, particularly in paediatric patients, is characterised by dramatically high early mortality (more than 75%),^{18,21} generally from multisystem failure.^{18,22} Acute myocarditis with supraventricular arrhythmias at the onset usually follows a

favourable course, whereas ventricular arrhythmias may cause cardiopulmonary arrest which is fatal if not promptly diagnosed and treated.²³ Patients with aborted sudden cardiac death are at risk of recurrent life threatening arrhythmias even after resolution of the inflammatory process, because of the persistence of the arrhythmogenic substrate (that is, reparative fibrosis).²³ In the large subset of patients presenting with congestive heart failure there is a different potential evolution, ranging from partial or complete recovery to progressive evidence of dilated cardiomyopathy (left ventricular systolic dysfunction, eventually with right ventricular involvement, generally associated with ventricular dilatation) (fig 3). Thus the natural history of acute myocarditis may include either “spontaneous” improvement or deterioration to dilated cardiomyopathy.

Spontaneous improvement

In past reports, spontaneous improvement has been described in up to 70% of suspected cases of endemic viral myocarditis diagnosed entirely on clinical grounds.²⁴ After the introduction of endomyocardial biopsy, the real incidence remains uncertain. Both Dec and colleagues and Olsen and associates reported spontaneous improvement in 40–50% of patients with histologically confirmed acute myocarditis.^{13,25} More recently, Maisch and colleagues performed a meta-analysis of data currently available in a mixed cohort of patients with or without biopsy (pool of 12 studies, 388 patients followed up for 3–60 months).²⁶ This analysis showed variability in spontaneous resolution, with an average of 57% of patients improving with medical treatment and restriction of physical activity alone. These data are in agreement with those observed in the recent myocarditis treatment trial²⁷ performed in patients with a histological diagnosis of acute myocarditis. In our experience of 54 patients with biopsy proven acute myocarditis, the overall incidence of spontaneous improvement was 50%, and improvement was more common among patients with chest pain or arrhythmias at the onset.¹⁸ Thus spontaneous improvement seems to be relatively frequent in acute myocarditis, which should be borne in mind when deciding whether to start immunosuppressive or antiviral treatment in the acute phase of the disease.

Evolution to dilated cardiomyopathy

Approximately 36 years ago acute viral myocarditis was suggested as a potential cause of dilated cardiomyopathy.²⁸ This hypothesis has been supported by several studies, but definitive proof of the link is still lacking. Studies in animal models show progressive ventricular dysfunction and dilatation in the presence of chronic viral myocarditis.²⁹ Long term follow up studies on patients with acute myocarditis have shown a variable incidence of dilated cardiomyopathy, ranging from 0–52%, over a mean period of three years (range three months to 13 years) (table 1). However, studies based on clinical diagnosis alone^{24,30–35,38,39,41} should be differentiated from those based on endomyocardial

Table 1 Evolution to dilated cardiomyopathy in patients with acute myocarditis

Reference	Number of patients	Diagnosis	Evolution to DCM (%)	Mean follow up or range
Bengtsson 1966 ³⁰	90	Clinical	15	60 months
Helin 1968 ³¹	12	Clinical	0	7 months
Sainani 1968 ³²	19	Clinical	0	3 months
Smith 1970 ³³	42	Clinical	7	84 months
Gerzen 1972 ³⁴	18	Clinical	28	12 months
Levi 1977 ³⁵	10	Clinical	0	42–68 months
Kitaura 1979 ³⁶	11	Histology	27	18–156 months
Edwards 1982 ³⁷	5	Histology	20	6–12 months
Kayakawa 1983 ³⁸	20	Clinical	30	49 months
Fenoglio 1983 ²¹	18	Histology	17	12 months
Kayakawa 1984 ³⁹	10	Clinical	30	55 months
Daly 1984 ⁴⁰	9 (IS 9)	Histology	22	6 months
Dec 1985 ¹³	18	Histology	11	6–12 months
Das 1985 ⁴¹	18	Clinical	11	54 months
Billingham 1986 ⁴²	20 (IS 15)	Histology	40	5 months
Giesecke 1987 ²⁴	45	Clinical	11	3 months
Quigley 1987 ¹²	23	Histology	52	43 months
Weiss 1987 ⁴³	13 (IS 1)	Histology	46	36 months
Anderson 1987 ⁴⁴	10	Histology	20	6–12 months
Sekiguchi 1988 ¹⁷	20	Histology	10	49 months
Salvi 1990 ⁴⁵	38 (IS 28)	Histology	29	49 months
Davidoff 1991 ⁴⁶	36 (IS 20)	Histology	19	30 months
Sekiguchi 1994 ⁴⁷	90	Histology	14	45 months
Maisch 1994 ⁴⁸	21	Histology	28	6 months
Mason 1995 ²⁷	47	Histology	17	52 months
Sinagra 1997 ¹⁸	56 (IS 36)	Histology	39	48 months
Total	719		Mean 21%	Mean f/u 33 months

Published data on the incidence of progression to dilated cardiomyopathy in patients with clinical or histological diagnosis of acute myocarditis of viral or unknown origin.

DCM, dilated cardiomyopathy; f/u, follow up; IS, number of patients treated with immunosuppressive drugs (no placebo controlled data).

biopsy findings,^{12 13 17 18 21 27 36 37 40 42–48} as well as from studies investigating patients treated with or without immunosuppressive drugs.

Among the histological studies, the incidence of dilated cardiomyopathy varies from 14% in the ISFC survey⁴⁷ to 40% in the study by Billingham and Tazelaar⁴² and 52% in the series of Quigley and colleagues.¹² These data, however, reflect differences in diagnosis and patient selection. In particular, Quigley and colleagues described evolution to dilated cardiomyopathy in a group of 23 patients with biopsy proven acute myocarditis during a five year follow up.¹² In the ISFC survey,⁴⁷ a multi-centre and retrospective study performed between 1990 and 1992 on 90 cases of acute viral myocarditis (nine of them postmortem), evolution to dilated cardiomyopathy during a mean 45 months of follow up was observed in 14%. Similar data were reported in previous studies from Japan.^{49 50} However, the above mentioned studies predominantly investigated advanced stages of heart failure, characterised by a high early mortality (up to 32%). While we observed evolution to dilated cardiomyopathy in 62% of patients with heart failure symptoms at presentation, the incidence was significantly lower in those with clinical presentation other than congestive heart failure (5%, $p < 0.05$).⁵¹ According to some investigators,^{27 52} endomyocardial biopsy in patients with idiopathic dilated cardiomyopathy may identify a relatively high incidence (4–10%) of Dallas histological criteria for active myocarditis. On the other hand, the finding of high or rising enterovirus specific antibody titres in some patients with dilated cardiomyopathy is an indication of a previous enteroviral infection.⁵³ More recently, the application of molecular technology to the clinical diagnosis of infectious disease has shown genomic viral persistence in myocardial samples in a widely variable percentage of patients with dilated cardiomyopathy (ranging from 0–76%).^{10 54–56} This variability could be explained by the different molecular biological techniques used (increasing sensitivity and specificity with nested polymerase chain reaction compared with slot-blot hybridisation), the different number of biopsy samples (influencing the probability of sampling error), and different types of sample processing (better sensitivity and reproducibility with frozen samples than with fixed ones). In addition, there is potential for contamination in the processing of samples with enteroviral pathogens, especially if tissue is collected by the cardiologist and processed through the pathology laboratory. This possibility needs to be taken into account.

Long term prognosis

The long term prognosis of acute myocarditis of suspected viral origin was usually good in initial reports of small groups of patients diagnosed on clinical grounds alone.^{57 58} This observation has subsequently been confirmed by Dec and colleagues in a series of 18 patients with biopsy proven lymphocytic myocarditis followed up for three years (15 survived (83%)).⁵⁹ More recently, however, Grogan and

associates found no difference in survival between patients with biopsy proven acute myocarditis (56%) and idiopathic dilated cardiomyopathy with negative biopsy findings (54%) during a five year follow up of 27 patients.⁶⁰ We found a similar four year transplant-free survival (54%) in a group of patients with acute myocarditis and heart failure symptoms, compared with 87% in patients with other types of clinical presentation (arrhythmias and chest pain) ($p < 0.05$).⁵¹ In agreement with Grogan and associates, we observed increased morbidity and long term mortality in the subset of patients with congestive heart failure at presentation.

Factors in prognosis

Definitive data on predictors of long term prognosis in patients with acute myocarditis are lacking. As we have already suggested, knowledge of the type of clinical presentation may be helpful in establishing an early and often correct clinical prognosis. In a preliminary analysis we observed that patients with chest pain or advanced atrioventricular block at onset had a good prognosis on long term follow up and none developed dilated cardiomyopathy.⁴⁵ There was a strong suggestion that the shorter clinical history and the better left ventricular function at onset in this subset of patients might explain their favourable course in comparison with patients who already had congestive heart failure at presentation. More recently,⁵¹ in a series of 60 patients (34 male, 26 female; mean (SD) age, 35 (15) years) with biopsy proven acute myocarditis followed up for 48 (46) months, we observed a reduced four year transplant-free survival in those with congestive heart failure ($p < 0.05$) (fig 4); moreover, left ventricular end diastolic diameter at diagnosis and lack of improvement on short term follow up (9 (3) months) predicted long term evolution to dilated cardiomyopathy ($p < 0.05$) and death or heart transplantation ($p < 0.05$) in patients with heart failure at presentation. Goldberg and colleagues, in a similar series of 109 patients with acute histologically diagnosed myocarditis (median follow up 98

Figure 4 Four year transplant-free survival curves in patients with arrhythmic or acute myocardial infarction-like presentation (group 1) v patients with heart failure presentation (group 2). Mean (SD) follow up, 48 (46) months. Modified from Sinagra et al. *G Ital Cardiol* 1997;27:758–74.

months), confirmed the predictive value of ventricular function and ECG abnormalities (presence of bundle branch block), and emphasised that syncope was a particularly unfavourable presenting symptom.⁶¹ Recently, McCarthy and colleagues, in a 13 year experience at the Johns Hopkins Hospital, observed that patients with fulminant myocarditis who survive from the acute phase with aggressive haemodynamic support are most likely to have a complete recovery of left ventricular function, with an excellent long term prognosis, compared with patients with acute non-fulminant myocarditis ($p = 0.05$).⁶²

Among other variables, reduced left ventricular ejection fraction at onset is clearly the main predictor of decreased survival in patients with acute myocarditis.⁵⁹ Quigley and colleagues identified the positive prognostic value of preserved left ventricular systolic function or of its early normalisation (within 6–8 months) in the natural history of myocarditis.¹² As only a subgroup of patients with acute myocarditis appears to develop dilated cardiomyopathy, the prognostic value of left ventricular dysfunction may depend on the exact time when it is observed in the natural history of the disease. However, Weiss and associates emphasised that the clinical status during follow up (based on radionuclide assessment of left ventricular function), even after 12–15 months from onset, did not necessarily predict long term outcome owing to the potential recurrence of autoimmune inflammatory process.⁴³

ECG abnormalities such as QRS alterations, atrial fibrillation, or low voltages may predict an unfavourable clinical course of acute myocarditis, reflecting more extensive myocardial injury.⁶³ Positive serology for coxsackievirus B was also an unfavourable predictive factor for acute myocarditis in a 15 year follow up study,⁵⁷ although this observation was not confirmed in a successive series of patients with coxsackievirus myopericarditis observed for 23 years.⁵⁸ This apparent discordance may be explained by the low incidence of congestive heart failure at onset in the latter group of patients. Histological findings in endomyocardial biopsy samples obtained in the acute phase of myocarditis have been evaluated as a predictive marker of subsequent haemodynamic and clinical status. The conclusions are conflicting at present. Quigley and colleagues did not identify any histological pattern that could predict the long term outcome,¹² contrary to a previous report from the same group.⁶⁴ More recently, Sakai and associates observed that Azan Mallory staining of myocytes may be useful in predicting haemodynamic improvement in patients with acute myocarditis.⁶⁵

Molecular biological predictors

The recent development and wide application of molecular biological techniques for the detection of viral genome in the myocardium (slot-blot hybridisation, in situ hybridisation, and polymerase chain reaction) have made a fresh contribution to our understanding of the natural history of myocarditis. Bowles and colleagues have identified enteroviral genome by slot-blot hybridisation from biopsy samples of

patients with acute myocarditis,¹⁰ dilated cardiomyopathy,¹⁰ and end stage dilated cardiomyopathy (explanted hearts),⁶⁶ concluding that persistence of virus after enteroviral myocarditis might predispose to the later development of dilated cardiomyopathy, and that virus might persist in the myocardium until the end stage of the disease.⁶⁶ A study by Archard and associates confirmed the importance of viral persistence: they observed that enteroviral persistence in the myocardium (coxsackievirus B) was the strongest predictive factor of mortality in patients with dilated cardiomyopathy or acute myocarditis ($p = 0.02$; length of follow up 24 months).⁶⁷ Subsequently, Why and colleagues prospectively evaluated 120 patients with heart muscle disease (43 with histological diagnosis of myocarditis, 77 with dilated cardiomyopathy), dividing them into two groups on the basis of the presence or absence of enteroviral RNA sequences in the first endomyocardial biopsy specimens (slot-blot hybridisation).⁶⁸ Mortality and progression to cardiac transplantation during the follow up (mean length 25 months) was greater in the enterovirus positive group than in the enterovirus negative group (25% *v* 4%, $p = 0.02$); the detection of enterovirus RNA in the myocardium has been shown by multivariate regression analysis to be an independent predictor of clinical outcome. More recently, Figulla and colleagues found that enterovirus positive patients (in situ hybridisation) with left ventricular dysfunction had a better prognosis than enterovirus negative patients,⁶⁹ and speculated that myocardial enterovirus infection with associated left ventricular dysfunction is a distinct disease entity with a benign course. At present, the precise correlation between persistence of viral infection and prognosis has still to be determined. Preliminary reports show that enterovirus may persist in a defective form,^{66–70} thus causing a lack of inflammatory response in the myocardium and at the same time modulating cardiac gene expression (a process already observed in the failing heart).⁷¹ Moreover, virus persistence may provoke an immune mediated process with further deterioration of cardiac function.

Conclusions

Acute myocarditis may be asymptomatic and present with a benign subclinical course. The natural history of symptomatic myocarditis varies from early death from multisystem failure (fulminant myocarditis) or ventricular arrhythmias, to complete recovery or long term evolution to dilated cardiomyopathy. The type of clinical presentation plays an important role in the prognosis—cardiac death and the need for heart transplantation is significantly more likely in patients with heart failure symptoms at onset.¹⁸ Some non-invasive variables evaluated at clinical presentation show good predictive accuracy in this subset of patients with acute myocarditis. These include left ventricular systolic function and end diastolic diameter, ECG alterations, and the improvement occurring during short term follow up.

In our opinion, these clinical and non-invasive variables may help cardiologists to

identify early those patients with acute myocarditis of viral or unknown origin who need more aggressive treatment. Such patients need close follow up to evaluate the timing of possible heart transplantation.

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IMAGES IN CARDIOLOGY

Double orifice mitral valve associated with non-compaction of left ventricle

A 45 year old man was admitted because of dyspnoea on effort and palpitations. He had no familial history of heart disease. An ECG showed left ventricular hypertrophy. Radiographs of the chest revealed mild cardiomegaly. Short axis transthoracic echocardiography

indicated the existence of two orifices in the mitral valve. With the apical four chamber view, double left ventricular inflow jets were obtained by colour Doppler at the diastolic phase. Colour Doppler echocardiography also showed mild mitral regurgitation from both orifices. To define double orifice mitral valve and evaluate the subvalvar apparatus in detail, a transoesophageal echocardiograph was performed. Double orifices were clearly visible from the ring of the valve, and each orifice had its own subvalvar apparatus separately at the free part of each leaflet.

An abnormality of the left ventricle was also detected. The left ventricle was dilated and diffusely hypokinetic (end diastolic/end systolic dimension 58/48 mm, ejection fraction 30%). The left ventricular wall was thickened, especially at the apex, and appeared sponge-like. There were numerous, excessively prominent trabeculations associated with deep intertrabecular recesses. The contrast entered into the intertrabecular recesses. We diagnosed non-compaction of left ventricular myocardium. Treatment with an angiotensin converting enzyme inhibitor and diuretics proved effective. After the patient's symptoms disappeared, β blocker treatment with metoprolol was initiated; six months later, the patient's left ventricular dimension was reduced and left ventricular wall motion was improved (end diastolic/end systolic dimension 53/32 mm, ejection fraction 52%).

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