Clinicopathological correlates can predict acute myocarditis in patients with recent-onset heart failure: preliminary data

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Endomyocardial biopsy; Heart failure; Myocarditis.

Background. **The aim of this study was to verify whether or not the clinical profile could be helpful in diagnosing myocarditis in patients with recent-onset (< 6 months) heart failure, suspected myocarditis and a biopsy-proven diagnosis.**

Methods. **From March 1998 to December 2000, 118 patients underwent a complete clinical, hemodynamic, echocardiographic and laboratory examination and a diagnostic endomyocardial biopsy in our Department; among them, 28 patients were admitted with clinically suspected myocarditis; in 9, the diagnosis was confirmed by the histopathologic findings.**

Results. **At the time of presentation, patients with biopsy-proven myocarditis showed early in-hospital admission (median 6 vs 69 days) with fever, a higher sinus rate and a significantly lower systolic blood pressure. Left ventricular dilation was observed in the non-myocarditis group only (left ventricular end-diastolic diameter 65.0 ± 8.9 vs 52.6 ± 5.8 mm); right ventricular function, as assessed by evaluation of the tricuspid annulus plane systolic excursion (TAPSE) and the right ventricular ejection fraction (RVEF) were found to be significantly lower in the myocarditis group (TAPSE 14.2 ± 3.6 vs 20.3 ± 7.0 mm; RVEF 21.3 ± 11.1 vs 30.3 ± 11.5%). Only patients with biopsy-proven myocarditis had an increase in serum creatine kinase and inflammatory markers (erythrocyte sedimentation rate and white blood cell count). Three cases had a clinical presentation of fulminant myocarditis showing marked increases in the serum levels of creatine kinase and inflammatory markers, and severely compromised right ventricular function and cardiac index.**

Conclusions. **At univariate analysis, an early onset, fever, tachycardia, hypotension, a reduced right ventricular function, increased creatine kinase, erythrocyte sedimentation rate and white blood cell count were predictive of myocarditis. In patients with recent-onset heart failure, the clinical, laboratory and echocardiographic profiles can suggest, but not prove, a diagnosis of myocarditis.**

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Introduction

Acute myocarditis is an inflammatory disease of the myocardium, in which the underlying triggering and perpetuating mechanisms are still incompletely known: infectious agents and immunological disorders go hand in hand in this elusive clinical entity, creating, in spite of more than three decades of study, an extremely difficult task for the clinician in his attempts to formulate a diagnosis and a prognosis and to establish the most adequate therapy[1]. Currently, no specific clinical criteria exist that can reliably confirm a diagnosis of acute myocarditis, and endomyocardial biopsy still represents the most predictive diagnostic tool.

The clinical course of acute myocarditis varies from asymptomatic cases to severe and refractory cardiac failure. Lieberman et al.[2] proposed a clinical and pathological classification of acute myocarditis, including four different subgroups: fulminant, acute, chronic active, and chronic persistent. Fulminant myocarditis has been characterized by the presence of flu-like illness, sudden worsening of the clinical and hemodynamic profiles, histologic evidence of multiple foci of myocardial necrosis and lymphocytic infiltrates. The final outcome may be death or complete recovery.

Recently McCarthy et al.[3] prospectively evaluated the long-term outcome and they observed a significantly better prognosis in fulminant myocarditis than in acute myocarditis.

The aim of this study was to describe the characteristics of a series of consecutive patients hospitalized for recent-onset heart failure and clinically suspected myocarditis and to verify whether or not the clinical and pathological profile could be helpful in establishing the diagnosis.

Methods

Study population. From March 1998 to December 2000, 118 patients with recent-onset heart failure (< 6 months, range 2-150 days) were referred to our Institution and underwent a complete diagnostic evaluation comprehensive of endomyocardial biopsy. Acute myocarditis was clinically suspected on the basis of a recent flu-like syndrome or of a sudden onset of heart failure in 28 of them. Endomyocardial biopsy was performed as soon as possible after in-hospital admission.

In no case was there a history of previous cardiac diseases. Two patients (in the acute myocarditis group) were affected by systemic immunological disorders (Table I). In no case was a human immunodeficiency virus infection detected.

Laboratory. Blood samples were collected at the time of in-hospital admission and subsequently for routine determination and immunological and virological assessment.

Endomyocardial biopsy. *Biopsy sample collection.* All patients underwent endomyocardial biopsy using the right internal jugular or femoral venous approach and a Caves-Schultz or disposable (Cordis Inc., Miami, FL, USA) 7F or 8F bioptome. At least four specimens were taken from the right ventricular septum during an echo-monitored procedure, and then referred to the Department of Pathology for light and electron microscopy and immunohistochemical studies. In 10 cases a single specimen was sent to the Department of Virology in order to evaluate for the presence of RNA enteroviruses using polymerase chain reaction analysis.

Histopathological and immunohistochemical studies. Samples were fixed by immersion in buffered 10% formalin, rapidly dehydrated and embedded in paraffin. The blocks were serially cut to obtain 45 sections which were then stained with hematoxylin-eosin, with Movat pentachrome or with Masson trichrome. Special stains were performed with Congo red in order to determine the presence or otherwise of amyloid deposits, and with the periodic acid-Schiff method. With regard to immunohistochemical analysis the slides were incubated with antisera specific for the characterization of inflammatory infiltrates.

Electron microscopy study. One sample was fixed with Karnovsky's fixative, postfixed with 1.5% osmium tetroxide in 0.2 M cacodylate buffer, dehydrated and embedded in Epon-Araldite resin. The ultrastructural study allows for the evaluation of the presence and the characteristics of myocardial damage.

Diagnostic criteria. Myocarditis was diagnosed only in patients fulfilling the Dallas criteria[4], on the basis of the presence of both inflammatory cells and myocardial

Table I. Characteristics of patients with biopsy-proven acute myocarditis.

Patient	Age (years)	Sex	Associated pathology	Flu-like illness	Presentation	Inotropic support	Histologic diagnosis	Outcome
1. LF	24	F	Systemic lupus erythematosus	Yes	Chest pain, CHF	Amine infusion	Acute myocarditis	Alive (steroids)
2. PE	44	F	None	No	AV block, chest pain	Pacemaker + amine infusion	Acute myocarditis	Alive
3. SF	41	M	Churg-Strauss syndrome	No	Chest pain	Amine infusion	Acute myocarditis	Alive (steroids)
4. CG	39	F	None	Yes	CHF	Amine infusion	Acute myocarditis	Alive
5. ZL	63	F	None	No	Chest pain	IABP	Acute myocarditis	Alive
6. GE	22	M	None	Sore throat	Chest pain	Amine infusion	Acute myocarditis	Alive
7. FE	47	F	None	Yes (dysentery)	Cardiogenic shock	IABP	Fulminant myocarditis	In-hospital death
8. IS	43	F	None	Yes (abdominal pain, nausea)	Cardiogenic shock	Novacor	Fulminant myocarditis	In-hospital death
9. MM	39	M	None	Yes	Cardiogenic shock	DC-shock, IABP	Fulminant myocarditis	In-hospital death

AV = atrioventricular; CHF = congestive heart failure; IABP = intra-aortic balloon pump.

necrosis; fulminant acute myocarditis was retrospectively diagnosed in accordance with the criteria proposed by Lieberman et al.[2].

Cardiac catheterization. All patients underwent right heart catheterization using a Swan-Ganz modified catheter which permits the determination of the right ventricular ejection fraction (REF-1® Baxter-Edwards Inc., Santa Ana, CA, USA). Hemodynamic evaluation included pulmonary pressures, right atrial and pulmonary wedge pressures, cardiac output, systemic vascular resistance, pulmonary artery and arteriolar vascular resistances, and the right ventricular ejection fraction.

Echocardiographic assessment. Two-dimensional color-Doppler evaluation was performed at the time of presentation, and of endomyocardial biopsy. The left ventricular diastolic and systolic diameters and the septal thickness were evaluated using the M-mode parasternal approach. The left ventricular volumes and ejection fraction were studied in the 4-chamber apical view. The right ventricular performance was determined using a tricuspid annular plane systolic excursion (TAPSE) recording.

Electrocardiographic evaluation. ECG study was performed at the time of admission and then daily during the period of hospitalization. We only analyzed the ECG recorded during the first day of hospitalization.

Statistical analysis. Descriptive statistics were computed as the mean and SD for continuous variables, or as the median and interquartile range (IQR) for skewed distributions, and as absolute and relative frequencies for categorical variables. The association of a series of clinical, hemodynamic, echocardiographic and laboratory characteristics in case of a biopsy-proven diagnosis of myocarditis was assessed by means of univariate logistic models. The odds ratios and their 95% confidence intervals that approximate the relative risk of myocarditis with respect to the reference category for categorical variables or for a 1-unit increase of the measurement for continuous variables were calculated. Due to the low number of events, no multivariate model was fitted.

The Stata 7 program (StataCorp, College Station, TX, USA) was used for computation. A two-sided p value < 0.05 was retained for statistical significance.

Results

Clinical profile of patients with myocarditis. On the basis of the histopathologic diagnosis, 9 patients were classified as having myocarditis (6 acute myocarditis and 3 fulminant myocarditis), whereas in 19 patients there was no evidence of inflammatory involvement of the myocardium. In view of a clinical picture which was very suggestive of viral infection, 5 of the 9 patients with myocarditis underwent peripheral muscle (quadriceps) biopsy as well. The latter however failed to show any sign of viral activity.

The clinical characteristics and descriptive data of the patients with confirmed myocarditis are reported in tables I and II. Patients with biopsy-confirmed myocarditis (n = 9) had a mean age of 40 ± 12 years and 6 were female. Symptom onset was more frequent in the winter season (75% between November and March) and the median time from symptom onset to hospital admission was 6 days (IQR 2-24). Patients with fulminant myocarditis had fever (mean 38.8°C), while patients with acute myocarditis presented with only a slight increase in body temperature (mean 37.4°C).

The clinical presentation was variable, but the main cardiac symptom at the time of hospital admission was chest pain. Three patients presented with cardiogenic shock at the time of hospitalization: 2 patients required an intra-aortic balloon pump, and in 1 patient a left ventricular assist device (Novacor® LVAS, Baxter Novacor Division, Oakland, CA, USA) was implanted; 2 subjects were refractory to amine infusion and they died of multiorgan failure, while the LVAS patient died of intracranial hemorrhage, during the phase of weaning

Table II. Descriptive data of patients with biopsy-proven fulminant and acute myocarditis.

	Fulminant myocarditis (n=3)	Acute myocarditis (n=6)
Days from onset	6 ± 13	7 ± 27
Age (years)	47	38.8
Female sex (%)	66	66
Heart rate (b/min)	126.7	96.2
Temperature (°C)	38.8	37.4
Systolic blood pressure (mmHg)	81.7	90.2
LVEF (%)	18.3	26.7
LVEDV (ml)	133.3	125.8
LVEDD (mm)	55	52
TAPSE (mm)	12.3	15.2
ESR (mm, 1st hour)	37	34.3
AST (mU/ml)	618.3	207.8
Creatinine (mg/dl)	3	0.9
BUN (mg/dl)	175	42.5
CK (mU/ml)	2897	340.2
WBC ($\times$ 1000/μl)	17 600	12 803
Neutrophils (%)	86.1	74.8
mPAP (mmHg)	24.7	17.5
PCWP (mmHg)	21.7	11.3
Cardiac index (l/min/m^2)	1.2	2.5
RVEF (%)	16.7	23.7

AST = aspartate transaminase; BUN = blood urea nitrogen; CK = creatine kinase; ESR = erythrocyte sedimentation rate; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RVEF = right ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion; WBC = white blood cells.

from the device; in these 3 cases the clinical and pathological features were ascribed to fulminant myocarditis.

ECG, performed in all patients at admission and then daily during hospitalization, showed in all cases low voltages in the peripheral (R or S wave in limb leads < 7 mm) and precordial leads. The rhythm was a high sinus rate (mean 96.2 b/min) in patients with acute myocarditis whereas a marked tachycardia (mean 126.7 b/min) was found in those with fulminant myocarditis; in 1 patient with acute myocarditis an advanced-degree atrioventricular block requiring temporary pacing was diagnosed. No patient showed left bundle branch block; interestingly, in the subgroup of patients with fulminant myocarditis, right bundle branch block (in 1 case associated with left anterior hemiblock) had been observed in 2 patients. Ventricular arrhythmias had been observed in many subjects and mainly consisted of recurrent episodes of non-sustained ventricular tachycardia.

At presentation, in acute myocarditis patients the mean left ventricular ejection fraction as assessed at echocardiography was 23.8% (range 15-37%), with a slight left ventricular dilation (left ventricular end-diastolic diameter 52 mm, left ventricular end-systolic diameter 42 mm) and a slight increase in ventricular diastolic volumes (left ventricular end-diastolic volume 128 ml). Right ventricular function, as deduced from the TAPSE evaluated by M-mode analysis on the tricuspid plane in the apical 4-chamber view, was significantly reduced in acute myocarditis patients (mean value 14.2 ± 3.6 mm). Some patients showed localized wall motion abnormalities. However, this characteristic was also common in the non-myocarditis group, hampering a significant association with the diagnosis of myocarditis.

The hemodynamic assessment, performed early after hospital admission, was significantly different between the acute myocarditis and the fulminant myocarditis groups: in patients with acute myocarditis we observed a very slight impairment of the cardiac index (mean 2.5 l/min/m^2), normal pulmonary artery (mean 17.5 mmHg) and wedge pressures (mean 11.3 mmHg) and a moderately reduced right ventricular ejection fraction (mean 23.7%).

Patients with fulminant myocarditis were characterized by a low cardiac output (mean cardiac index 1.2 l/min/m^2) and increased pulmonary artery (mean 24.7 mmHg) and wedge pressures (mean 21.7 mmHg); the mean right ventricular ejection fraction was 16.7%. This value was in agreement with the reduced values of the TAPSE at echocardiography.

Laboratory findings showed increased values of the erythrocyte sedimentation rate and of the serum levels of C-reactive protein in the acute myocarditis group; similarly the white cell count was characterized by leukocytosis and neutrophilia; increased serum levels of the markers of myocardial necrosis were also observed (mean creatine kinase 403 mU/l, with a high degree of variability: SD 282-2188).

Clinical profile of patients without biopsy-proven myocarditis. The mean age of these patients was 41 ± 13 years and 5 were female; no seasonal distribution was observed and the median time to admission was 69 days (IQR 24-150). In subjects without acute myocarditis, the onset of the disease was characterized by dyspnea in 80%, palpitations in 15% (3/19), and in 1 case by syncope. Five of them had a flu-like syndrome and only one developed a fever in the days before hospitalization.

ECG showed atrial fibrillation in 1 patient, whereas the remaining 18 were in sinus rhythm; in 1 patient a sustained ventricular tachycardia was recorded; 3 had a transient first-degree atrioventricular block but none required pacing. Only 5 patients presented low voltages in the peripheral leads.

At echocardiographic evaluation they showed a depressed left ventricular ejection fraction (mean 27.0 ± 6.51%) and increased left ventricular diameters (end-diastolic 65.0 ± 8.9 mm, end-systolic 52.5 ± 8.8 mm) and volumes (end-diastolic 228.5 ± 65.9 mm, end-systolic 167.8 ± 58.4 mm); the TAPSE was normal (20.3 ± 7.0 mm).

The hemodynamic data of patients in this group were consistent with a lower hemodynamic impairment than that observed in patients with acute and fulminant myocarditis: blood pressure (114/74 mmHg), pulmonary pressure (15.9 ± 6.8 mmHg), pulmonary wedge pressure (9.38 ± 5.96 mmHg), cardiac index (2.9 ± 0.7 l/min/m^2), and the right ventricular function (ejection fraction 30.3 ± 11%) were substantially in the normal range.

In patients without myocarditis, laboratory analysis did not reveal any significant elevation of the serum levels of the markers of inflammation or cardiac damage.

Discussion

The diagnostic approach to acute myocarditis remains difficult and uncertain; the role of the patients' clinical characteristics, and of the echocardiographic, hemodynamic and laboratory findings is controversial. In fact, the clinical features of acute myocarditis vary from the absence of symptoms to symptoms and signs of moderate or severe cardiac failure[5]. In our case series a striking difference was observed in both the clinical and functional characteristics of patients with and without confirmed myocarditis (Table III). In particular, general symptoms such as a flu-like onset and fever, tachycardia and chest pain were more likely in the former group, with an increase in laboratory inflammatory indices; cardiac function, measured both at hemodynamic analysis and echocardiography, was impaired to a higher degree in these patients, especially in patients with fulminant myocarditis. Data from several previous studies are consistent with our findings: Pinamonti et

Table III. Association of clinical, laboratory and functional findings with confirmed diagnosis of myocarditis.

	Confirmed (n = 9)	No myocarditis (n = 19)	p	OR	95% CI
Age (years)	40 ± 12	41 ± 13	0.924	0.99	0.93-1.06
Female sex	6 (67%)	5 (26%)	0.041	5.60	1.00-31.25
Flu-like onset	6 (67%)	5 (26%)	0.041	5.60	1.00-31.32
NYHA III-IV	7 (77%)	4 (21%)	0.004	13.12	1.92-89.51
Days from onset	6 (2-24)*	69 (24-150)*	0.002**	0.42**	0.21-0.84**
Heart rate (b/min)	106 ± 22.2	86 ± 19.2	0.018	1.05	1.00-1.10
Temperature (°C)	37.6 ± 1.1	36.6 ± 0.3	0.001	11.07	1.37-89.31
SBP (mmHg)	87.3 ± 12.9	114.8 ± 16.1	< 0.001	0.88	0.81-0.96
DBP (mmHg)	54.1 ± 15.9	74.2 ± 10.6	< 0.001	0.85	0.75-0.96
LVEDD (mm)	52.6 ± 5.8	65.0 ± 8.9	< 0.001	0.79	0.65-0.95
LVESD (mm)	42.3 ± 8.4	52.5 ± 8.8	0.011	0.87	0.76-0.99
LVEDV (ml)	128.3 ± 25.9	228.5 ± 65.9	< 0.001	0.95	0.92-0.99
LVESV (ml)	93.8 ± 34.8	167.8 ± 58.4	< 0.001	0.97	0.94-0.99
TAPSE (mm)	14.2 ± 3.6	20.3 ± 7.0	< 0.001	0.72	0.53-0.96
ESR (mm, 1st hour)	35.2 ± 32.8	5.4 ± 3.3	0.001	1.13	0.96-1.31
CK (mU/ml)	403 (282-2188)*	54 (45-442)*	0.012**	2.55**	1.05-6.18**
WBC (× 1000/μl)	14 402 ± 5150	7944 ± 2310	< 0.001	1.59	1.06-2.39
Neutrophils (%)	79.6 ± 8.5	62.5 ± 5.4	< 0.001	1.31	1.05-1.65
Cardiac index (l/min/m^2)	2.1 ± 0.8	2.9 ± 0.7	0.008	0.18	0.04-0.84
RVEF (%)	21.3 ± 11.1	30.3 ± 11.5	0.075	0.93	0.86-1.01
dPAP (mmHg)	16.8 ± 7.0	11.1 ± 6.1	0.041	1.15	0.99-1.32
mPAP (mmHg)	19.9 ± 6.9	15.9 ± 6.8	0.160	1.09	0.96-1.24
PCWP (mmHg)	11 (8-20)*	6 (5-13)*	0.084**	3.65**	0.77-17.18**

DBP = diastolic blood pressure; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; dPAP = diastolic pulmonary artery pressure; SBP = systolic blood pressure. Other abbreviations as in table II. * = interquartile range; ** = after log transformation.

al.[6] described 41 patients with histologically proven myocarditis and found a non-dilatory left ventricular dysfunction in about 70% of cases. A significant reduction in left ventricular ejection fraction without any significant cavity dilation was observed by Felker et al.[7] in acute myocarditis described as fulminant in view of its clinical onset, whereas acute myocarditis was characterized by increased left ventricular diastolic dimensions.

The presence of right ventricular dysfunction as assessed at two-dimensional echocardiography has been considered a useful independent prognostic marker in patients with symptomatic cardiomyopathy related to active myocarditis[8,9]. We confirm that the biopsy-proven myocarditis group had reduced indices of right ventricular function: these features were represented by the analysis of the TAPSE, as evaluated at echocardiography, which was significantly lower in the acute myocarditis group and by a lower (even if of borderline statistical significance) right ventricular ejection fraction.

The absence of any significant dilation of the left ventricle could explain the lack of left bundle branch block in the myocarditis group; on the other hand, further observations are probably needed to explain the evidence of right bundle branch block recorded in patients with fulminant myocarditis. The presence of ST-segment and T-wave changes was similar in both groups, while ventricular arrhythmias were more frequently recorded in the myocarditis group.

Recently, McCarthy et al.[3] prospectively evaluated the long-term outcome of patients with fulminant myocarditis; they observed that the long-term prognosis in fulminant myocarditis is significantly better than in acute myocarditis (survival at 11 years 93 vs 45%), and they concluded that fulminant myocarditis can be considered an independent predictor of survival. Our data, though less consistent, do not confirm these findings: patients with fulminant myocarditis performed worse and died within 1 month of in-hospital admission; in a single case report of our experience, endomyocardial biopsy documented an acute and early healing phase of the inflammatory disease during left ventricular assist device support[10].

To date, despite its limited sensitivity and specificity, endomyocardial biopsy represents the gold standard for the diagnosis of myocarditis[10-12]; the Dallas criteria[4], introduced in 1986, constitute the standard rules for a histologic diagnosis; at light microscopy, active myocarditis is defined by the presence of infiltrating lymphocytes and myocytolysis. In the presence of lymphocytic infiltration without myocardial necrosis, borderline myocarditis should be taken into consideration. Nonetheless, there are still many unresolved issues on the significant discrepancies about the prevalence of myocarditis in large cohorts of patients (4-26%) and on the discordance between the clinical and histologic features[13,14]. In a previous experience, our group reported a low frequency of myocarditis (4.3%) in a consecutive

series of 601 patients with idiopathic congestive heart failure[14]. Thirty eight patients had a clinical history and signs suggestive of myocarditis: a very recent onset of congestive heart failure and/or arrhythmias and/or conduction disturbances and of a close-to-recent history of flu-like febrile illness; biopsy-proven myocarditis has been found in 16/38 patients. In this experience of a university hospital, a referral center for heart transplantation, the prevalence of myocarditis in a consecutive series of subjects with recent-onset heart failure was found to be low (7.6%); among the subgroup of patients with clinically suspected myocarditis, the prevalence of biopsy-proven disease was 32%.

The clinical presentation together with the laboratory profile and echocardiographic images can suggest a diagnosis of myocarditis. Our analysis confirms that an accurate evaluation of patients with recent-onset heart failure cannot be achieved without the support of endomyocardial biopsy. This type of approach would also allow a better prognostic and therapeutic evaluation. Various recent studies including patients with acute myocarditis complicated by hemodynamic instability[15-18] suggest that left ventricular assist devices may be a life-saving strategy. They may either allow a progressive restoration of left ventricular function or "bridge" the patients to heart transplant in case weaning is not possible.

In conclusion, our data suggest that a careful evaluation of clinical symptoms, including the time of onset, can provide useful diagnostic information; the presence of fever and of a worsening hemodynamic picture, as deduced from a decreased systemic blood pressure, have a clinically significant role; laboratory signs of inflammation complete the clinical picture. Finally a reduction in right ventricular performance, as evaluated on the basis of the echocardiographically determined TAPSE, can be of particular relevance in defining the diagnosis.

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