Fatal myocarditis: morphologic and clinical features

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Autopsy; Epidemiology; Myocarditis.

Background. **Autopsy studies report a frequency of myocarditis ranging from 0.11 to 5.5% in the general population, reaching almost 50% in selected groups. Myocarditis is often undiagnosed and the incidence of fatal course myocarditis has never been evaluated. The aim of our study was to assess the frequency of fatal course myocarditis in a consecutive series of autopsies and to describe the clinical, histological and morphologic features of the disease.**

Methods. **From January 1, 1995 to January 31, 1996, 2560 autopsies were performed, and 143 cases of active myocarditis were diagnosed (5.6%).**

Results. **In 39 cases (1.5%; 12 males; 4/39 aged ≤ 35 years) active myocarditis was identified as the final cause of death. Only in 1 case was myocarditis suspected *ante-mortem*. The histological pattern was lymphocytic in 64% of cases. A mixed inflammatory infiltration was found in 33% and a granulomatous infiltration in 3%. In 49% of cases myocarditis was localized in both ventricles and the interventricular septum. The clinical presentation of myocarditis was heart failure in 18/39 patients (46%), cardiac arrest in 4/39 patients (10%) and syncope and chest pain in 1/39 patient (3%). The mean creatine phosphokinase levels were 890 ± 2742 IU/l (assessed in 11/39 patients, 28%) but they were increased only in 7/39 (18%). ECG (performed in 29/39 patients, 74%) showed sinus rhythm in 16/39 patients (55%, > 100 b/min in 41%), atrioventricular or interventricular conduction defects in 10/39 patients (34%) and a pathological Q wave in 4/39 patients (14%). At echocardiography (performed in 7/39 patients, 18%), right and/or left ventricular dysfunction was found to be present in 5 cases (71%) and a pericardial effusion in 4 cases (57%).**

Conclusions. **Myocarditis is underdiagnosed *ante-mortem*. A high index of clinical suspicion is mandatory for prompt diagnosis and treatment of this fatal disease seen also in the young.**

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Introduction

The incidence of myocarditis varies widely in the general population[1] and most cases are not diagnosed because the disease is either only mildly symptomatic or asymptomatic. Endomyocardial biopsy, performed with a standardized method, is very useful to diagnose the disease in the acute clinical setting[2-4], but its use is not justified in asymptomatic subjects.

Only autopsy studies could provide a realistic estimate of the real frequency of myocarditis in the general population[5]. Previous autopsy studies reported an incidence of myocarditis ranging from 0.11 to 5.5% in unselected groups[1]. Higher rates were observed in infectious disease hospitals or among patients with AIDS[6-8]. This wide variability also reflects the absence of standardized histological criteria for the diagnosis of myocarditis. In a study conducted in Sweden, the application of the Dallas criteria led to an autopsy frequency of myocarditis of 1.06%[5]. Two studies conducted in Turin, Italy, showed the importance of systematic myocardial sampling during autopsy to avoid underestimating the frequency of myocarditis[1,9]. In the first, a prospective study in which a standardized method of myocardial sampling was followed, the incidence of myocarditis was found to be 5.1%[9]. In the other study, which was retrospective and in which the Dallas criteria were applied, the incidence was found to be 0.53%[1]. In none of the previous autopsy studies was the incidence of fatal course myocarditis investigated.

In the present study, we assess the frequency of fatal course myocarditis in a consecutive series of autopsies and describe the clinical, histological and morphologic features of the disease.

Methods

Data from 2560 consecutive autopsies, performed between January 1, 1995 and January 31, 1996, were reviewed at the De-

partment of Pathology of the University of Trieste, Italy.

Myocardial samples were systematically taken from different sites, with a mean of 5 samples per subject. During autopsy, the number of myocardial samples was increased when myocarditis was macroscopically suspected. Pathology samples were properly labeled.

Myocarditis was diagnosed using the Dallas criteria[4,10]. Borderline myocarditis cases were excluded from the present study.

The excised myocardial samples were fixed in 10% formalin and embedded in paraffin. Paraffin sections were cut to a thickness of 5 µ and stained with hematoxylin and eosin, as well as with Azan-Mallory and Weigert-van Gieson stains to detect fibrosis. In selected cases, modified Giemsa staining was used to identify eosinophils and the von Kossa stain for interstitial and myocyte calcifications.

If the cause of death was not myocarditis, we reviewed the autopsy and clinical records from the last hospital admission. On the other hand, when myocarditis was considered the final cause of death, we reviewed both the autopsy records as well as all the clinical records from the year preceding the patient's death. We evaluated each case for the presence of cardiac disease, hypertension, alcohol abuse, hypersensitivity, chemo- or radiotherapy in the year preceding the death or a family history of sudden death. Major and systemic non-cardiac diseases were also evaluated. We noted the symptoms reported at the time of the last hospital admission as well as the tests performed, with particular attention to the white blood cell count, C-reactive protein and erythrocyte sedimentation rate.

Electrocardiograms and echocardiograms, performed during the year preceding death, were also reviewed.

Finally, we recorded morphologic data such as heart weight, wall thickness, cardiac chamber dimensions, and coronary artery gross anatomy.

Results

The Department of Pathology of the University of Trieste, Italy, performed 2560 consecutive autopsies between January, 1, 1995 and January 31, 1996. Twelve thousand eighteen hundred histological samples, 143 autopsy records, and 169 clinical records were reviewed.

The frequency of active myocarditis was 5.6% (143 patients, 44 males, 99 females). In 1.5% of cases (39 subjects) active myocarditis was identified as the final cause of death, while in the remaining 4.1% of cases (104 subjects), death was due to other causes, mostly disseminated tumors, with secondary cardiac involvement in some, pulmonary embolism, non-cardiogenic shock or respiratory insufficiency.

We will focus on the 39 subjects with fatal course myocarditis, in the absence of other major clinical conditions.

There were 12 males (mean age 55 ± 40 years) and 27 females (mean age 76 ± 34 years). Fatal course myocarditis was found more frequently in subjects ≥ 75 years of age (54%) (Table I).

Active myocarditis, defined according to the Dallas criteria[4], was found in all cases. Fibrosis was present in 48% of cases. Borderline myocarditis was excluded from the present study. The prevalent inflammatory infiltrate was lymphocytic (64%) (Figs. 1 and 2). Only 3 cases (8%) of giant cell myocarditis were identified (Table II, Fig. 3). An 87-year-old woman died of left ventricular rupture due to biventricular mixed inflammatory cell myocarditis. The cardiac location of myocarditis differed among age groups (Table II). The prevalent location was biventricular and septal (49%). In most cases, the coronary arteries were patent.

A review of the clinical records showed that some of the most frequent causes of myocarditis were present in our population: 44% of subjects had an infection, mostly pneumonia, 1.3% had a history of alcohol abuse, and 0.8% had a chronic inflammatory disease.

Table I. Frequency of fatal course myocarditis according to age group.

Age (years)	No. patients	%	% out of 2560 autopsies
< 50	5	13	0.2
50-64	6	15	0.2
65-74	7	18	0.3
≥ 75	21	54	0.8

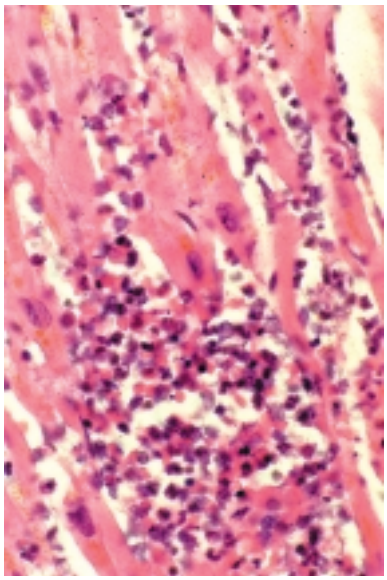

Figure 1. *Lymphocytic myocarditis that fulfills the Dallas criteria. Significant interstitial lymphocytic infiltrate with associated myocyte damage (hematoxylin-eosin, 150×).*

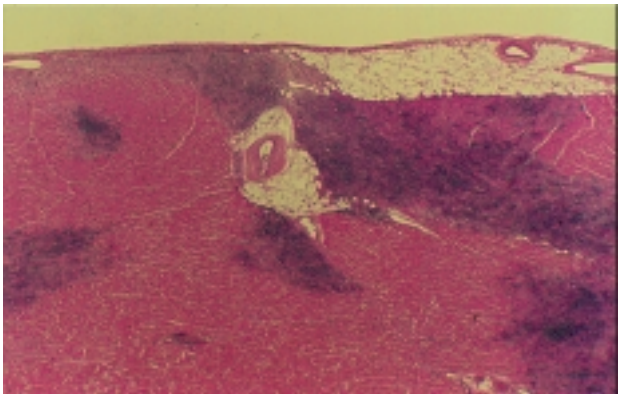

Figure 2. *Severe lymphocytic myocarditis in a 14-year-old girl (hematoxylin-eosin, 40×).*

The clinical manifestations at the time of presentation included congestive heart failure in 46% of cases and cardiac arrest in 10%. A viral syndrome characterized by fever, myalgias and fatigue, was found in 23% of patients (Table III). In 5 patients (12%) it was not possible to identify any symptoms at the time of presentation. A preexisting cardiac disease was present in 72% of subjects. It was mostly coronary atherosclerosis or hypertensive cardiomyopathy that was judged not to be relevant for the prognosis.

Thirteen subjects (33%) had an increased white blood cell count, erythrocyte sedimentation rate and C-reactive protein levels, not attributable to other concomitant inflammatory conditions. In 1 patient with lymphocytic cell myocarditis, the white blood cell count was increased with lymphocytes representing 51% of the total. Creatine phosphokinase was checked only in 28% of cases (Table III), and the mean value was 890 ± 2742 IU/l.

ECG was performed in 74% of patients (Table III). Forty-one percent of patients had sinus tachycardia and 34% atrial fibrillation. Conduction defects were present in 34% of cases. Left and right atrial dilation as well as repolarization defects were noted in 21% of cases. An echocardiogram was performed in only 18% of patients. Left and right ventricular dysfunction, as well as a pericardial effusion, was found (Table III). *Antemortem*, a cardiac cause of death was suspected in 77% of cases (Table III). Myocarditis was suspected in 1 case only (3%).

Table II. Histological and morphologic findings in 39 cases of fatal course myocarditis.

Parameter	No. pts	Frequency (%)
Infiltrate		
Lymphocytic	25	64
Mixed inflammatory cell	13	33
Granulomatous	1	3
Giant cell infiltrate	3	8
Location in all pts (n=39)		
LV, RV, septum	19	49
LV and RV, or LV or RV and septum	14	36
LV or RV or septum	6	15
Location in pts aged < 50 years (n=5)		
LV, RV, septum	5	100
Location in pts aged 50-64 years (n=6)		
LV, RV, septum	3	50
LV and RV, or LV or RV and septum	2	33
LV or RV or septum	1	17
Location in pts aged 65-74 years (n=7)		
LV, RV, septum	5	72
LV and RV, or LV or RV and septum	1	14
LV or RV or septum	1	14
Location in pts aged ≥ 75 years (n=21)		
LV, RV, septum	6	29
LV and RV, or LV or RV and septum	11	52
LV or RV or septum	4	19
Heart weight (g)		
Mean	448 ± 305	
250-350	12	31
350-500	16	41
> 500	11	28
Traverse heart diameter (cm)		
Mean	12.5 ± 3	
11-12	17	44
> 12	22	56
Vertical heart diameter (cm)		
Mean	9.5 ± 2.7	
8-10	24	61
> 10	10	26
< 8	5	13
LV wall thickness (mm)		
Mean	15.2 ± 6.8	
10-11	4	10
> 11	35	90
RV wall thickness (mm)		
Mean	4 ± 2.4	
3-4	19	49
> 4	14	36
< 3	6	15
Coronary arteries		
Patent	31	80
Stenosis < 50%	6	15
Stenosis > 50%	2	5

LV = left ventricle; pts = patients; RV = right ventricle.

Discussion

The real incidence of myocarditis in the general population is difficult to estimate because of the clinical characteristics of the disease[1]. Most cases have nonspecific symptoms or are asymptomatic. The wide variability in the reported incidence in biopsy and autopsy series is due to the absence of standardized diagnostic criteria, the variability among pathologists reviewing the histological samples, different patient populations and the periodicity of viral infections.

The clinical presentation varies widely in the general population[11] and it is not possible to predict the progression of the disease. An interesting study on fulminant myocarditis[12] showed that this condition is characterized by clinical features which are distinct from

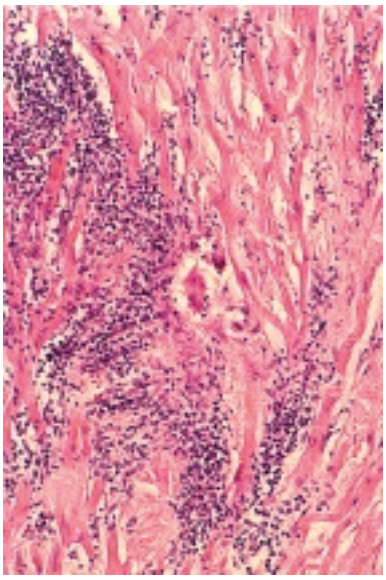

Figure 3. *Idiopathic type giant cell myocarditis. Extensive, mixed inflammatory infiltrate, multinucleated giant cells and severe myocyte damage (hematoxylin-eosin, 40×).*

Table III. Clinical correlation in fatal course myocarditis.

Parameter	No. patients
Clinical presentation	
Heart failure	18 (46%)
Cardiac arrest	4 (10%)
Fulminant myocarditis	1 (3%)
Syncope	1 (3%)
Chest pain	1 (3%)
Non-specific	9 (23%)
Missing data	5 (12%)
Laboratory data	
↑ White blood cell count	7 (18%)
↑ Erythrocyte sedimentation rate	5 (13%)
↑ C-reactive protein	3 (8%)
↑ Creatine phosphokinase	7 (18%)
Electrocardiogram	
Sinus rhythm	4 (14%)
Sinus tachycardia	12 (41%)
Atrial fibrillation	10 (34%)
Conduction defects	10 (34%)
Q waves	4 (14%)
ST-segment elevation	4 (14%)
LA and RA dilation	6 (21%)
Repolarization defects	6 (21%)
Echocardiogram	
Wall motion abnormality	4 (57%)
LV dysfunction	5 (71%)
RV dysfunction	4 (57%)
Pericardial effusion	4 (57%)
Suspected cause of death	
Not better specified cardiac disease	15 (38%)
Pulmonary embolism	6 (15%)
Acute myocardial infarction	4 (10%)
Electromechanical dissociation	2 (5%)
Endocarditis	1 (3%)
Refractory heart failure	1 (3%)
Myocarditis	1 (3%)
None	9 (23%)

LA = left atrial; LV= left ventricular; RA = right atrial; RV= right ventricular.

those of acute myocarditis. The former is characterized by a severe clinical presentation but a good long-term prognosis. On the other hand, acute myocarditis has less severe symptoms and clinical findings at the time of presentation, but a more frequent evolution toward progressive ventricular dysfunction, death or cardiac transplantation.

The presence of myocarditis in young people and its possible evolution toward refractory heart failure or sudden death has to be emphasized. Our study represents the first attempt to retrospectively study fatal course myocarditis and correlate its clinical and histological features.

The 5.6% frequency of active myocarditis found in our study is one of the highest reported in the literature[1]. A higher frequency has been reported in selected populations[6-8]. In our study, women were more often affected than men, confirming a previous finding[9]. This higher prevalence in female subjects could be related to specific immunologic and endocrine mechanisms, as reported for *peripartum* myocarditis[13]. The more frequent occurrence of fatal course myocarditis among patients > 75 years could reflect a bias in the population studied being older than the national average. Our data are different from those previously reported in other respects[1,9,14].

In our patients, the inflammatory process involved most of the myocardial tissue. The heart was only mildly dilated. The moderate hypertrophy found in our population could be explained by the pressure overload due to hypertension in some subjects, but also by tissue edema and inflammatory cell infiltration.

The laboratory and ECG findings were not specific for myocarditis. The echocardiogram was altered in all subjects.

Conditions known to be commonly associated with myocarditis were present in almost 50% of cases. Except in 1 case, the clinical picture at the time of presentation was not critical. Our data support previously reported data regarding the presentation and outcome of acute myocarditis[12]. Considering the absence of specific signs and symptoms of myocarditis, it is not surprising that the diagnosis was rarely suspected before autopsy. In 10% of cases, fatal course myocarditis manifested with sudden death.

These data emphasize the importance of a prompt diagnosis of myocarditis: a disease that may occur even in young patients, is potentially treatable but has nonspecific clinical manifestations. In patients presenting with symptoms of heart failure, cardiac arrest, syncope or chest pain, clinicians should consider myocarditis in the differential diagnosis, especially if potential causes of myocarditis are present. In this clinical setting, an echocardiogram is a very useful tool.

The Myocarditis Treatment Trial[15] opened a big discussion regarding the utility of immunosuppressive therapy and subsequently of endomyocardial biopsy. The criteria adopted by different Centers for performing an endomyocardial biopsy vary. In general, we rec-

ommend an endomyocardial biopsy for patients with recent-onset heart failure (< 6 months) in NYHA class II-IV or with severe left ventricular systolic dysfunction (ejection fraction < 35-30%), and for patients with hemodynamically significant supraventricular or ventricular arrhythmias, or with advanced atrioventricular conduction defects.

A note should be made regarding myocarditis in patients dying of cancer and not included in this analysis. It is possible that inflammatory infiltration of the heart represents a hypersensitivity reaction due to cytokine-mediated activation of the immune system.

Study limitations. In our study, the diagnosis of active myocarditis was made using the Dallas criteria. The diagnostic sensitivity could have been increased by using immunohistochemistry, as demonstrated by numerous works published in recent years[16-18]. It would have been useful to evaluate viral persistence in the myocardium with polymerase chain reaction or with reverse transcription polymerase chain reaction. There is evidence that virus-positive myocarditis is associated with more severe histological damage and a worse systolic function and prognosis, and that it evolves toward death or cardiac transplantation[19].

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