Fulminant myocarditis: Characteristics, treatment, and outcomes

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Abstract

Myocarditis is an inflammatory disease of the myocardium with a broad spectrum of clinical presentations, ranging from mild symptoms to severe heart failure. The course of patients with myocarditis is heterogeneous, varying from partial or full clinical recovery in few days to advanced low cardiac output syndrome requiring mechanical circulatory support or heart transplantation. Fulminant myocarditis (FM) is a peculiar clinical condition and is an acute form of myocarditis, whose main characteristic is a rapidly progressive clinical course with the need for hemodynamic support. Despite the common medical belief of the past decades, recent comprehensive data, including a recent registry that compared FM with acute non-FM, highlighted that FM has a poor inhospital outcome, often requires advanced hemodynamic support, and may result in residual left ventricular dysfunction in survivors. This review aimed to provide an updated practical definition of FM, including essentials in the diagnosis and management of the disease. Finally, the outcome of FM was critically revised according to the current published registries focusing on the topic. *(Anatol J Cardiol 2018; 19: 00-00)*

Keywords: fulminant myocarditis, mechanical circulatory support, heart transplantation, outcome, registries

Introduction

Myocarditis is an inflammatory disease of the myocardium (1, 2). It often results from common viral infections, through either direct myocyte damage or postviral immune-mediated responses. Myocarditis can also be triggered by nonviral infections and numerous medications, including new immune checkpoint inhibitors (3), and has been associated with several systemic autoimmune disorders (4). Myocarditis has a broad spectrum of clinical presentations, ranging from mild symptoms, such as chest pain associated with minimal ventricular dysfunction, to life-threatening arrhythmia and severe heart failure (HF) (5). Similarly, the course of patients with myocarditis is heterogeneous, varying from partial or full clinical recovery in few days to advanced HF requiring mechanical circulatory support (MCS) or heart transplantation (HTx) (6). The present review was focused on fulminant myocarditis (FM), an acute-onset clinical presentation, whose dramatic presenting scenarios include rapidly progressive hemodynamic compromise, cardiogenic shock, and fatal arrhythmia (7, 8). The main objective of the current review was to provide updated evidence on FM, including a new practical definition, key elements for its diagnosis, controversies in its management, and new insights on its short and long-term course according to recently published series. Particular attention was focused on our recently published registry comparing FM with acute non-FM (6).

Moving toward a modern and practical definition of FM

In 1991, Lieberman et al. (9) defined the clinicopathological scenario of myocarditis. Using clinical and pathological elements, they described FM as follows: acute illness within 2 weeks of the onset of symptoms after a distinct viral prodrome with severe cardiovascular compromise, ventricular dysfunction, and extensive inflammatory infiltrates of lymphocytes and macrophages on histological examination, thus excluding eosinophilic myocarditis and giant cell myocarditis (GCM) that often present with a fulminant course and are clinically undifferentiable. This definition was adopted by McCarthy et al. (10) in their retrospective series of 15 cases with FM, again excluding patients with other inflammatory infiltrates. In a more recent review by Ginsberg et al. (7), FM was defined as the distinct onset of symptoms in the first 2 weeks, followed by severe symptoms of HF and hypotension or overt cardiogenic shock needing inotropes, vasopressors, and/or MCS, thus moving from a clinicopathological entity toward a peculiar clinical scenario for physicians. In our recent study, which included the largest group of patients with FM, key enrollment criteria for FM were the onset of cardiovascular symptoms within 30 days prior to

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Table 1. Proposed criteria for fulminant myocarditis: a historical perspective

Lieberman et al. 1991 (9)	
1	Distinct onset of cardiac symptoms
2	Multiple foci of active myocarditis at initial endomyocardial biopsy
3	Complete recovery or death
4	Complete resolution of active histological myocarditis
5	No benefit from immunosuppressive treatment
Ginsberg et al. 2013 (7)	
1	Distinct onset of symptoms in preceding 1-2 weeks
2	Class IV heart failure symptoms
3	Hypotension with need for inotropes and vasopressors
4	Need for hemodynamic support (IABP, VAD, or ECMO)
Ammirati et al. 2017 (6)	
1	Acute illness (history of <2–4 weeks since the onset of symptoms)
2	Hemodynamic instability due to cardiogenic shock or arrhythmia, including sudden death
3	Need for hemodynamic support (inotrope and/or MCS)
4	Multiple foci of active myocarditis, regardless of the type of inflammatory infiltrate, on histological examination

ECMO - extracorporeal membrane oxygenation; IABP - intra-aortic balloon pump; MCS - mechanical circulatory support; VAD - ventricular assist device

admission and low cardiac output syndrome requiring inotropes and/or MCS (6). A suggested practical definition of FM may thus be summarized as follows (Table 1): (1) Acute illness (<2–4-week history from the onset of symptoms); (2) Hemodynamic instability due to cardiogenic shock or arrhythmia (including sudden death); (3) Need for hemodynamic support (inotrope/MCS); and (4) Multiple foci of active myocarditis, regardless of the type of inflammatory infiltrate (i.e., giant cells, granuloma, lymphocytic, or eosinophilic) on histological examination. In summary, FM is not an etiological disease entity, but is a peculiar clinical condition within the acute forms of myocarditis, whose main characteristic is a dramatic and rapidly progressive clinical course.

Key elements for diagnosis

FM may affect individuals of all ages, although it is most frequent in the young and pediatric populations. Precise data on the true prevalence or incidence of FM in the general population do not exist. Although defined as an uncommon illness, recent studies have reported myocarditis in up to 12% of cases of sudden death in patients aged <40 years. It is the third leading cause of sudden cardiac death in young competitive athletes (11). In our series of 187 patients with acute myocarditis, FM was diagnosed in 55 (29%) (6). Notably, as the study was carried out in two Italian referral centers for myocarditis and HTx (Niguarda Hospital, Milano and San Matteo Hospital, Pavia), up to 75% of patients with FM were transferred from other hospitals. Early recognition of patients at the risk of progression to fulminant forms is essential. Acute myocarditis evolving into FM generally presents with evidence of systolic dysfunction on echocardiogram, ST-T segment abnormalities on electrocardiogram (ECG), high release of troponins, hypotension, and frequent arrhythmia. A comprehensive approach integrating clinical, imaging, and histological information is pivotal for diagnosis.

Clinical presentation and initial diagnostic assessment

Rapidly progressive severe HF symptoms (e.g., dyspnea, peripheral edema, chest discomfort, and worsening fatigue) resulting in hemodynamic compromise and cardiogenic shock and requiring treatment with inotropes or MCS represent the most common clinical presentation (7). Patients are often able to recall a distinct time of the onset of symptoms, usually within the preceding 2–4 weeks. Life-threatening arrhythmia and aborted sudden cardiac death represent the most dramatic clinical presentations. Viral prodromal symptoms (e.g., respiratory or gastrointestinal symptoms) may be found, frequently suggesting postviral etiology, although they can also be present in eosinophilic myocarditis. ECG signs are neither specific nor sensitive. Abnormalities include nonspecific ST segment changes and ST-T elevation mimicking acute coronary syndromes and conduction disturbances. Serum cardiac biomarker levels, specifically for troponin I or T, are usually elevated in myocarditis. Serum inflammatory marker, including leukocyte count, erythrocyte sedimentation rate, and C-reactive protein level, may be elevated, but they lack specificity and sensitivity. Laboratory findings consistent with multi organ failure due to low cardiac output syndrome (e.g., elevated levels of creatinine and liver transaminases) may vary according to the severity of presentation. In our series, dyspnea and syncope, female sex, left bundle-branch block, and life-threatening arrhythmia at presentation were more frequent in FM than in non-FM (6). ECG abnormalities and increase inflammatory and cardiac injury marker levels were common in both the groups.

Imaging

Coronary angiography is often performed early to exclude acute coronary artery disease. Echocardiography is essential to rule out noninflammatory cardiac diseases and assess global biventricular size and function (12). FM is frequently characterized by severe biventricular dysfunction, a normal-to-mildly increased left ventricle (LV) end-diastolic diameter, increased septal wall thickness reflecting myocardial inflammatory interstitial edema, and presence of pericardial effusion. Regional wall motion abnormalities might be present due to the focal nature of the initial inflammatory process. Cardiac magnetic resonance (CMR) is a useful noninvasive imaging technique as it can detect inflammation, edema, necrosis, and fibrosis within the myocardial tissue (13, 14). However, due to the critical condition of patients with FM in the acute phase, it is often less feasible and frequently delayed and endomyocardial biopsy (EMB) is often performed without CMR. In our series, CMR was performed in 45% of patients with FM within a median time of 15 days since admission. CMR sequences suggestive of edema and late gadolinium enhancement (LGE) were found in all patients with myocarditis. A diffuse LGE pattern was observed more frequently in patients with FM than in those with non-FM patients (80% vs. 20%) (6). LGE is a dynamic time-dependent (inverse correlation with time to first CMR) process in acute myocarditis, mostly reflecting tissue edema in the acute phase (15). A prognostic role of LGE has been described in patients with myocarditis, and variations in guiding treatment and predicting long-term recovery have been highlighted (15).

EMB

EMB is the reference standard for the diagnosis of myocarditis. EMB, when performed in centers with a high-volume experience, has a low complication rate (0%–0.8%) and should thus be practiced in referral centers. Dallas criteria, which are standardized histopathological criteria, are applied to define active myocarditis: an inflammatory infiltration of the myocardium with necrosis of myocytes or borderline myocarditis without myocyte necrosis. Limitations of the Dallas criteria include a high degree of interobserver variability and low sensitivity. Immunohistochemical criteria were introduced to improve its accuracy. Active myocarditis was defined as immunoistochemical detection of mononuclear infiltrates (T lymphocytes and macrophages) using a cutoff of >14 cells/mm^2, in addition to increased expression of HLA class II molecules. Besides the pivotal role in confirming diagnosis, EMB is essential to distinguish specific histologies, such as GCM, eosinophilic myocarditis, and sarcoidosis, from lymphocytic myocarditis, because in the former conditions, early immunosuppressive therapy is recommended, whereas the role of immunosuppressive agents in lymphocytic myocarditis remains controversial (1, 2). Recent scientific statements highly recommend EMB in patients with FM, severe ventricular arrhythmia, or advanced heart block (16-18). EMB should be performed early in the course of the disease, and multiple specimens should be examined to increase the diagnostic accuracy (19). In our series, EMB was performed more frequently in patients with FM than in those with non-FM (71% vs. 8%); 28 patients underwent EMB without CMR, of which 26 had FM (6). Lymphocytic myocarditis was the most frequent form of biopsy-proven myocarditis among FM (72%), followed by GCM (14%), and eosinophilic myocarditis (12%).

Management

Supportive measures and HF medical treatment

Supportive measures play a key role in the management of FM. Initial treatment often requires mechanical ventilation, inotropic agents, and vasopressors to correct hypotension, respiratory failure, and overt cardiogenic shock. In patients with low cardiac output not responding to maximal pharmacological therapy, MCS can be used. Intra-aortic balloon counterpulsation (IABP) has been the most widely used technique to optimize the hemodynamic profile in adults by reducing the afterload and myocardial oxygen demand. When IABP alone is not effective in maintaining adequate cardiac output, several temporary MCS devices can be employed (20). Among MCS devices, venoarterial extracorporeal membrane oxygenator (va-ECMO) has been the most extensively used advanced temporary MCS device in recent years for providing cardiorespiratory support in seriously ill patients and often represents the unique MCS suitable for pediatric patients. Indeed, in 2005, Asaumi et al. (21) described one of the first series of patients (n=14) with FM treated with percutaneous va-ECMO in Japan from 1996 and 2001. They found that va-ECMO could be useful to increase survival in patients with FM, observing a 71% inhospital survival, thus demonstrating the advantage of using va-ECMO in refractory FM. The published va-ECMO weaning rates due to cardiac recovery in FM ranged from 66% to 100%, with a survival to hospital discharge ranging from 56% to 87.5%, including data from Extracorporeal Life Support Organization (ELSO) (21-35). In our series, MCS was used in 65% of patients (70% of adults and 25% of pediatric patients); IABP was the most commonly used MCS device, alone or in combination with va-ECMO. The overall inhospital survival was 74.5%, which was consistent with previous similar registries. Long-term implantable left ventricle assist devices (LVADs) are rarely used to provide adequate circulation for a more extended time period to allow the resolution of myocarditis and bridge a patient from emergent temporary MCS to HTx, which is the final option for treating critically ill patients affected by myocarditis. HTx survival is comparable to that of patients with other types of HF as shown in a recent series, although higher rates of relapses have been demonstrated, especially in patients with GCM undergoing HTx (36, 37). Once patients with FM recover from cardiogenic shock, pharmacological treatment for HF, including beta-blockers, diuretics, angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers, should be initiated according to current consensus (38).

Immunosuppressive treatment

Immunosuppressive therapy is the mainstay of treatment for eosinophilic myocarditis, GCM, cardiac sarcoidosis, and FM forms

associated with systemic autoimmune diseases (39-41). Since the first report of the Multicenter GCM Study Group, recommended treatment has been the triple combination of antithymocyte globulins, prednisone, and cyclosporine (42). Other available immunosuppressants, such as intravenous immunoglobulins (mostly used in pediatric patients), mycophenolate mofetil, methotrexate, rituximab, or azathioprine, can be included or used as second-line treatments (43). In our center, GCM is treated with initial high-dose steroids whose dose is gradually tapered (e.g., methylprednisolone 1000 mg once a day for 3 days, followed by prednisone 60 mg once a day for 15 days and finally tapered to 10 mg once a day for 6–10 weeks), plus thymoglobulin (1 mg/kg, generally as a single dose), and cyclosporine (5 mg/kg a day, continued long-term). In case of eosinophilic myocarditis, steroids (e.g., methylprednisolone 1000 mg once a day for 3 days, followed by oral prednisone 1 mg/kg once a day with gradual tapering) are advocated (41, 44). Use of other immunosuppressants has also been reported (e.g., azathioprine 2 mg/kg or intravenous cyclophosphamide) (41). Withdrawal of possible etiologically relevant drugs is mandatory in case of suspected hypersensitivity or evidence of hypereosinophilia. First-line treatment of cardiac sarcoidosis includes either intravenous administration of corticosteroid alone or in combination with azathioprine or methotrexate (45), whereas cyclophosphamide or rituximab can be used in unresponsive forms. Immunosuppressants are also recommended in myocarditis associated with systemic immune diseases (18). Currently, there is a complete lack of standardized immunosuppressive management for lymphocytic postviral FM, and its role remains controversial (16, 46). Current evidence mostly obtained from a cohort of patients with myocarditis and chronic HF(>6 months) suggested that in patients with lymphocytic myocarditis, immunosuppressive treatment should be administered only in the presence of elevated levels of tissue inflammatory markers and absence of a viral genome on PCR analyses of myocardial samples (40). However, the importance of the presence of viral genome in guiding the treatment for acute-phase FM is currently unknown. Current recommendations of our center include intravenous gammaglobulin administration in pediatric patients (single-infusion regimen of 0.5–2 g/kg) and steroid administration in adults (e.g., methylprednisolone 1000 mg once a day for 3 days, followed by oral prednisone 1 mg/kg once a day with gradual tapering). In our series, a large proportion of patients with FM were treated with immunosuppressive therapy (overall 64%, regimens including the use of intravenous steroids in 43% and steroids alone in 30%); when considering only adults with postviral myocarditis, overall 55% of

Table 2. Registries including cases of fulminant myocarditis

Authors	Years	Patients	Age	LVEF at admission	Histology[a]	Treatment	Duration of follow-up	Events
Lieberman et al. 1991 (9)	12/1983-07/1988	4	-	-	All lymphocytic	-	4.7 y	1 death 0 HTx
McCarthy et al. 2000 (10)	7/1984-6/1997	15	35±16 y	-	All lymphocytic	2 MCS 13 vasopressors	5.3 y (15 d-11 y)	1 death 0 HTx
Amabile et al. 2006 (47)[b]	1998-2003	11	1 y (0-9)	22±9%	Available in 3 patients Histology ns	0 MCS 0 9 inotropes	58.7 m (33.8-83)	1 death
Teele et al. 2011 (48)[b]	1996- 2008	20	12.7 y (6 d-17.4 y)	27.8% (8-55)	Available in 18 patients Histology ns	10 MCS 20 inotropes	0.7 y (13 d-6.4 y)	3 deaths 1 HTx
Matsuura et al. 2016 (49)[b]	01/2006-12/2011	74	6.5±5.3 y	-	-	51 MCS Inotropes ns	-	38 death
Anzini et al. 2013 (50)	1981-2009	10	28±18 y	22% (18-24)	9 lymphocytic 1 eosinophilic	MCS ns 9 inotropes	147 m±107	5 deaths or HTx
Ammirati et al. 2017 (6)	05/2001-11/2016	55	33 y (17-42)	22% (18-30)	Available in 43 patients 32 lymphocytic 7 GCM 5 eosinophilic	55 inotropes 35 MCS	59 m (29-83)	10 deaths 5 HTx
Inaba et al. 2017 (35)	2007-2009	42	-	31±16%	-	37 MCS	-	20 deaths

GCM - giant cell myocarditis; HTx - heart transplantation; LVEF - left ventricle ejection fraction; MCS - mechanical circulatory support; ns - not specified
[a]Histological data available either from endomyocardial biopsy or autopsy specimen
[b]Pediatric patients only

Table 3. Studies including 10 or more patients with fulminant myocarditis managed by extracorporeal circulatory support

Authors	Years	Patients	Age	Histology[a]	Survival to hospital discharge
Aoyama et al. 2002 (22)	05/1989-03/2000	52	47.9±16 y	Available in 43 patients Lymphocytic ns 2 eosinophilic 2 GCM	59.6%
Chen et al. 2005 (25)	1994-2001	15	27.1±19.3 y	Available in 11 patients 10 lymphocytic 1 GCM	73%
Asaumi et al. 2005 (21)	1/1993-12/2001	14	17±2 y	Available in 9 patients Histology ns	71.4%
Thiagarajan et al. 2009 (26)	1992-2007	16	-	-	56%
Gariboldi et al. 2010 (27)	03/2006-06/2008	10	-	-	70%
Hsu et al. 2011 (24)	1994-2009	75	29.7±18.7 y	Available in 50 patients Histology ns	64%
Ishida et al. 2013 (28)	01/1995-03/2010	20	45.1±19.2 y	-	60%
Mirabel et al. 2011 (30)	01/2002-03/2009	35	-	Available in 25 patients 20 lymphocytic 2 GCM 2 eosinophilic	68.6%
Beurtheret et al. 2013 (31)	01/2005-12/2009	14	-	-	65%
Wu et al. 2012 (33)	01/2003-06/2010	16	-	-	87.5%
Diddle et al. 2015 (32)	1995-2011	147	31 y (21-47)	-	61%
Nakamura et al. 2015 (29)	1999-2013	22	Survivor g: 36.5±4.1 y Non survivor g: 60.2±5 y	-	59%
Lorusso et al. 2016 (34)	01/2008-12/2013	57	37.6±11.8 y	Available in 15 patients Histology ns	71.9%
Inaba et al. 2017 (35)	2007-2009	37	-	-	59%

GCM - giant cell myocarditis; ns - not specified
[a]Histological data available either from endomyocardial biopsy or autopsy specimen

patients were treated with immunosuppressive therapy, including intravenous steroids in 45% and steroids alone in 39% (6) .

Favorable or unfavorable outcomes?

Careful evaluation of the patient population and study inclusion criteria used to define FM series is essential when studying short- and long-term FM outcomes (Table 2). In 1991, Lieberman et al. (9) were the first to describe four cases of FM. Full recovery of LV function (in three patients) or death from the disease (one of four) within 1 month was considered one of the five characteristics distinguishing FM from non-FM. Limitations of their series were the small number of cases and the fact that only patients with lymphocytic myocarditis were included. McCarthy et al. (10) subsequently published a retrospective series of 15 FM cases and compared them with patients with acute non-FM with reduced LV function. All patients with FM were defined as having fever, distinct onset of HF symptoms, history consistent with the presence of a viral illness within 2 weeks before hospitalization, histopathologically borderline or active myocarditis on EMB, and severe hemodynamic compromise requiring high doses of vasopressors or LVAD. In this series, two patients with FM required MCS; the remaining received high-dose vasopressors. Among the patients with FM, only one died during index hospitalization, and 93 percent were alive without having received HTx at 1 year and at the end of 11 years, showing that patients with FM, despite the critical illness at presentation, have excellent long-term survival, which is distinct from that of patients with acute myocarditis. Study limitations include the low number of FM cases, exclusion of GCM or eosinophilic myocarditis, absence of autopsy cases, and longer time frame between symptom onset and study inclusion, possibly contributing to a selection bias. Besides, patients with FM could have been underrepresented, because in the study period (1984–1997), temporary MCS was less extensively used, possibly leading to exclusion of severe FM cases dying prior to study enrollment due to rapid unfavorable disease course. With the advent of MCS, the chance of survival for severe FM presenting with refractory cardiogenic shock has increased, and several studies enrolling FM cases aggressively treated with MCS have highlighted their poor inhospital survival, better reflecting the life-threatening course of the disease (47-50). Anzini et al. (50) studied 10 biopsy-proven FM cases; of these, four (40%) were aged <13 years. Histopathological analysis identified lymphocytic myocarditis in nine patients and eosinophilic myocardi-

tis in one. Five of the 10 patients with FM died or underwent HTx soon after the disease onset. After 6 months, 50% of patients surviving the acute phase presented with LVEF of <50% and demonstrated an excellent long-term HTx-free survival. In the series of 14 patients with FM treated with percutaneous ECMO described by Asaumi et al. (21), FM was defined as requiring percutaneous ECMO or LVAD for cardiogenic shock not responding to intensive medical treatments or for refractory ventricular tachyarrhythmia. The acute inhospital survival rate for FM was 71%. Following the acute phase, none of the survivors died or received HTx, as in the non-FM group. Recent registries including patients with FM treated with ECMO provide additional evidence on FM outcomes (Table 3) (21-35). In a large retrospective review based on data from the Extracorporeal Life Support Organization (230 ECMO centers) registry that analyzed 147 patients with a diagnosis of acute myocarditis treated with ECMO from 1995 to 2011 (HF was the indication in 74% of patients and extracorporeal resuscitation in 21%), survival to hospital discharge was 61% and HTx-free survival to discharge was 56%, confirming ECMO as a useful MCS device in adults with myocarditis with cardiogenic shock and highlighting the high inhospital mortality of this disease (32). In this study, as histological data were not available, viral myocarditis was defined by ICD-9 code or reported positive viral test result (7% of cases); 17 patients (12%) had a documented infection prior to the initiation of ECMO (viral, bacterial, or fungal). Interestingly, by demonstrating that a history of arrest prior to cannulation to ECMO was associated with a two-fold increase in mortality, this study focused the attention toward an early deployment of ECMO prior to cardiac arrest to prevent end-organ perfusion and reduce mortality. Similar inhospital mortality rates were found by Nakamura et al. (29) in a cohort of 22 consecutive patients with FM managed by peripheral va-ECMO between 1999 and 2013 and by Inaba et al. (35) in a cohort of 37 patients with FM requiring MCS between 2007 and 2009 (survival to discharge was 59% and inhospital mortality was 41% in both the studies). Lorusso et al. (34) retrospectively reviewed 57 adult patients with FM treated with ECMO. Acute myocarditis was clinically defined as the presence of the following three primary criteria: (1) sudden and refractory cardiogenic shock, cardiac arrest, or severe hemodynamic instability despite the administration of aggressive inotropic drugs with or without IABP; (2) demonstration of normal coronary artery anatomy on an angiogram; and (3) echocardiographic signs of myocardial tissue swelling and biventricular involvement. Hospital death was observed in 16 patients (28.1%), and three eventually underwent HTx. Actual survival rates were 77% at 1 year, 76% at 2 years, and 65% at 5 years. Common limitations of most of the above-mentioned studies focusing on patients with FM managed with MCS encompass their retrospective nature, differences in the definition of FM, mainly based on clinical parameters, clinical course and exclusion of other causes of cardiogenic shock, as well as low availability of histological information (EMB data provided in <50% of the studies), eventually leading to heterogeneous cohorts of selected patients. Additionally, few data on long-term survival have been provided. In our recent study, inhospital mortality was 18.2% (10 deaths) in patients with FM compared with 0% in those with non-FM (6). Death or HTx occurred in 25.5% (10 deaths and 4 HTx) and 0%, respectively. HTx-free survival was significantly reduced in FM compared with non-FM at the 9-year follow-up (64.5% vs. 100%). In the FM group, most adverse events occurred during hospitalization: 10 deaths (all from cardiac causes), four HTxs, and one LVAD implantation who underwent HTx within 1 year. Among the 10 inhospital deaths, one had GCM, two had eosinophilic myocarditis, and seven had lymphocytic myocarditis. Four transplanted patients had GCM, and one patient discharged on LVAD had lymphocytic myocarditis. When only verified cardiac deaths were considered, worse survival for FM compared with non-FM at the 9-year follow-up (74.9% vs. 100%) was still present. Moreover, when children were excluded, HTx-free survival was significantly reduced in FM compared with that in non-FM (63.8% vs. 100%). Similar findings were obtained in subanalysis that focused on adult patients with acute postviral myocarditis. Confirming the significantly higher mortality and need for HTx previously observed in pediatric patients with FM (49), we had three inhospital deaths among the eight pediatric patients with FM (all lymphocytic myocarditis). Consistent with previous reports, no cardiac deaths occurred in our patients with FM and non-FM after the acute phase. LVEF improved in both FM and non-FM groups during hospitalization, although LVEF at discharge was significantly lower in patients with FM than in those with non-FM. The proportion of patients with LVEF of <55% at discharge was larger in the FM than in the non-FM group (53% vs. 19%). Considering the last available LVEF after discharge with a median follow-up of 22 months, the proportion of patients with LVEF of <55% was still higher in the FM group than in the non-FM group (29% vs. 9%). Most LVEF recovery was observed during hospitalization, with a median increase in LVEF of 32% in patients with FM. Thus, if a specific treatment (e.g., steroids) is initiated, the greatest benefit should be expected in the initial weeks from onset, when the greatest recovery has been observed. In conclusion, at odds with initial findings, recent evidence underline that FM is associated with high inhospital mortality and need for HTx, mostly in the acute phase of the disease, and is characterized by partial long-term LV functional recovery in a significant group of patients.

Conclusion

FM is a severe inflammatory disease of the myocardium presenting with dramatic clinical scenarios, including fatal ventricular arrhythmia and rapidly progressive severe HF resulting in hemodynamic compromise that often requires treatment with inotropes or MCS. Despite the common medical belief of the past decades, recent strong and comprehensive data highlight that FM has poor inhospital outcome and often requires proper monitoring in intensive care unit and prolonged hemodynamic support with inotropes and temporary MCS. Especially in the acute phase of the disease, death or need for HTx is more common in FM, both

for relatively rare forms with high mortality (i.e., GCM or eosinophilic myocarditis) as well as for less lethal forms (e.g., lymphocytic myocarditis), than in non-FM. Moreover, patients with FM have more severely impaired LVEF at admission, which despite steep improvements during hospitalization, remains lower than that in patients with non-FM at long-term follow-up, suggesting partial LV healing. To reduce inhospital mortality rates, rapid referral to hub centers for aggressive supportive treatment and early EMB should be the standard of care for FM in the modern era. Although in specific forms of FM (i.e., eosinophilic myocarditis, GCM, cardiac sarcoidosis), immunosuppressive therapy represents the mainstay of medical treatment, there is a complete lack of standardized medical management for lymphocytic FM despite the increasing evidence of its poor outcome. A critical re-evaluation of the role of immunosuppressive treatment in the acute phase of lymphocytic FM is warranted in order to further improve inhospital survival and prevent irreversible myocardial injury.

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