Fulminant Myocarditis: Epidemiology, Pathogenesis, Diagnosis, and Management

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Fulminant myocarditis (FM) is a rare, distinct form of myocarditis that has been difficult to classify. Since 1991, the definition of FM has evolved, and it is currently considered an acute illness with hemodynamic derangement and arrhythmias due to a severe inflammatory process requiring support of cardiac pump function and/or urgent management of serious arrhythmias. Diagnosis is aided through use of biomarkers and cardiac imaging, but endocardial biopsy remains the gold standard. Recent evidence has revealed that patients with FM are significantly more likely to die or require heart transplantation than those with the nonfulminant form, refuting previous studies proposing a paradoxically low mortality in patients with FM. Acute hemodynamic derangement is managed by intensive contemporary pharmacologic and interventional approaches, whereas the role of immunosuppressive therapy has not been clarified. Early recognition and aggressive management are essential for favorable outcomes. In conclusion, FM is an inflammatory process requiring intensive support, and it causes a higher morbidity and mortality than acute nonfulminant myocarditis.   © 2019 Published by Elsevier Inc. (Am J Cardiol 2019;124:1954−1960)

Myocarditis, an inflammatory disease of cardiac muscle, can result from a wide variety of infectious, toxic, and autoimmune causes, although presentation after a recent viral infection is most common. Although the course of the disease is usually self-limiting, acute, nonfulminant myocarditis can progress to fulminant myocarditis (FM) (Figure 1). Nonfulminant myocarditis is typically insidious in presentation and may be unnoticed as it progresses into the chronic phase of the disease. The definition of FM has evolved since its original description in 1991. It involves acute illness with hemodynamic derangement and ventricular arrhythmias due to a severe inflammatory process requiring support of cardiac pump function and/or urgent management of serious arrhythmias. Early recognition and aggressive management are essential for favorable outcomes. Recent evidence has revealed that patients with FM are significantly more likely to die or require heart transplantation than those with the nonfulminant form, refuting previous studies proposing a paradoxically low mortality in patients with FM.[1,2] This review presents a contemporary assessment of the major clinical aspects of FM.

Epidemiology

The annual incidence of acute myocarditis is estimated at approximately 22 cases per 100,000 population, according to data from the Global Burden of Disease Study 2013, with heart failure occurring in 0.5% to 4.0% of these cases.[3] Based on postmortem studies, the incidence of myocarditis is 0.05% to 0.1% in the general population and can develop in 1% to 5% of all patients with acute viral infections.[4] The initial year of the condition is clinically the most precarious, with a mortality rate of 20%, which subsequently declines and stabilizes after approximately 3 years.[5]

In the Marburg Myocarditis Registry, a collection of over 1,000 patients with documented myocarditis, only 2.5% presented with the fulminant phenotype.[6] In studies of patients hospitalized with myocarditis, approximately 30% were considered fulminant and in several series of pediatric patients hospitalized with myocarditis, over one-third were diagnosed with FM.[2] Despite these reports, there are no systematic data on the true prevalence and incidence of FM.

Etiology

The initial pathogenesis of both FM and nonfulminant myocarditis is considered to be similar. The most common causative factors include: myriad infections (coxsackievirus, adenovirus, cytomegalovirus, HIV, parvovirus B19, Epstein-Barr virus, aspergillus, hepatitis C, influenza A and B, streptococcal species, Mycoplasma pneumoniae); toxic substances (cocaine, ethanol, heavy metals); autoimmune conditions (Churg-Strauss syndrome, Kawasaki disease, systemic lupus erythematosus, inflammatory bowel disease); and adverse medication reactions (anthracycline drugs, cephalosporins, diuretics, penicillin, phenytoin, sulfonamides, tetracycline).[7] Although there are no worldwide etiologic studies of FM, reports from this country and Europe identify viral infections—specifically coxsackievirus A and B and adenovirus—as the most common causes of myocarditis.[8,9]
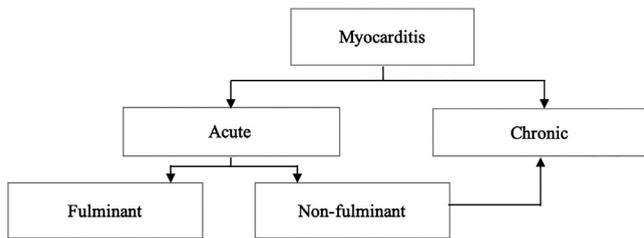
Figure 1. Potential clinical course of myocarditis.

FM can manifest as 3 primary histologic subtypes: lymphocytic, eosinophilic, or giant cell. Given the dominant prevalence of lymphocytic myocarditis, some equate FM with the lymphocytic form and consider the eosinophilic and giant cell subtypes as alternative diagnoses (i.e., types of acute, nonfulminant myocarditis). The pathogenesis of all 3 forms of FM most commonly involves direct, virally mediated myocyte damage and/or immune-mediated cellular injury.[7] Lymphocytic myocarditis is most frequently caused by viruses, but bacterial, fungal, and parasitic infections have also been implicated.[10] Giant cell myocarditis is mediated by T cell-induced inflammation secondary to systemic autoimmune disease.[11] It is pathognomonically associated with multinucleated giant cells on endomyocardial biopsy (EMB), with patients often developing malignant ventricular arrhythmias or atrioventricular block. The pathophysiology of eosinophilic myocarditis is poorly understood but most cases display associations with drug or allergic hypersensitivity reactions.[12]

Presentation

FM can have a heterogeneous presentation, thus, the clinical features that define and differentiate fulminant from acute nonfulminant myocarditis and other cardiomyopathies have evolved while maintaining several unifying mainstays. FM has been characterized by an acute onset of symptoms following a distinct viral prodrome, followed by severe cardiovascular dysfunction, biopsy evidence of active lymphocytic myocarditis, and a clinical course leading either to complete resolution of symptoms or death within 1 month.[13] Although these patterns represented means by which clinicians could identify FM, nonlymphocytic subtypes of myocarditis were excluded. There have also been similar attempts to characterize FM based on clinical features alone. These classifications highlight the key aspects of FM: well-defined and acute onset (≤30 days before presentation) of severe heart failure, commonly preceded by a viral prodrome of fever, lethargy, and myalgias.

In contrast to patients with acute nonfulminant myocarditis who present with New York Heart Association class II-III symptoms of heart failure, patients with the fulminant form most commonly exhibit symptoms of heart failure that meet NYHA class IV criteria. However, patients with FM may suffer from a wide range of cardiovascular and pulmonary symptoms, comprising a heterogeneous presentation. In milder presentations, findings typically include hypotension, fatigue, chest pain and palpitations, dyspnea at rest, and mild to moderate left ventricular (LV) dysfunction. More severe presentations can include aborted sudden cardiac death, sustained ventricular arrhythmias, end-organ dysfunction consequent to inadequate systemic perfusion, respiratory failure, and aborted sudden death.[14]

Given the variability of presentation, it may be difficult to differentiate between FM, acute nonfulminant myocarditis, and other potential etiologies of acute onset severe heart failure. Differentiation is essential, however, due to variations in management and prognosis of these syndromes. According to the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, myocarditis should be suspected when patients present with acute onset heart failure, arrhythmias, and chest pain that are not explained by other disease processes such as noninflammatory cardiomyopathies or coronary heart disease.[15]
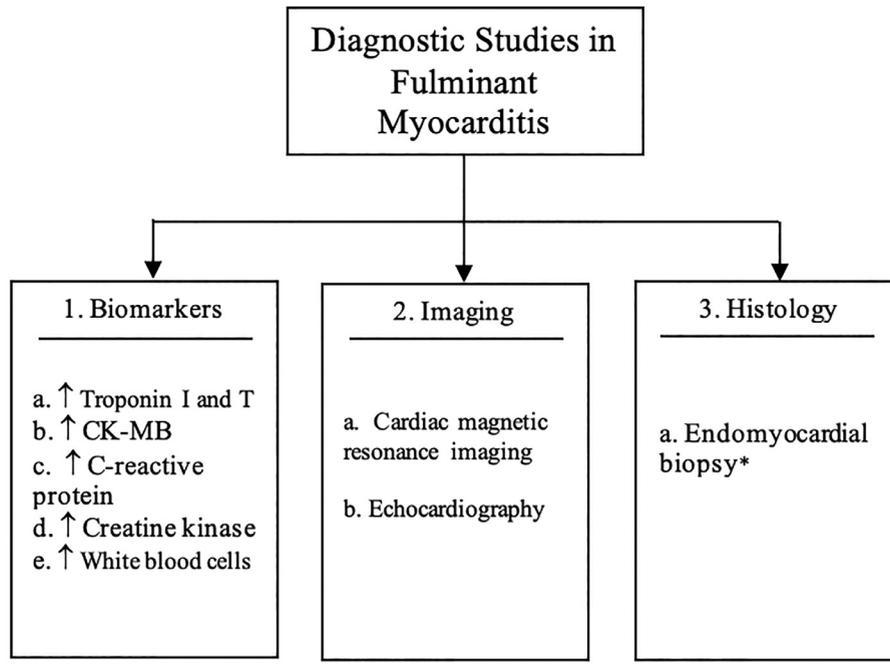
Diagnosis

Studies of diagnosis and evaluation of patients presenting with suspected FM can be considered in several categories. These include: (1) biomarkers, (2) imaging, and (3) histology (Figure 2).

A number of biomarkers can assist both in diagnosing FM and estimating extent of disease. Markedly elevated plasma concentrations of cardiac troponins, creatine kinase MB, and white blood cells, as well as signs of end-organ damage (elevations of blood urea nitrogen, creatinine, liver transaminases), are nonspecific, indirect markers of myocardial dysfunction. It has been reported that FM was associated with significantly higher plasma concentrations of C-reactive protein and creatinine kinase MB than acute nonfulminant myocarditis.[16] Cardiac troponins, while reliable markers of myocardial injury, are not specific for etiology of the insult.

Both cardiac magnetic resonance imaging (CMR) and echocardiography are useful for identifying FM. CMR can provide increased imaging quality for detecting FM in patients with relatively mild cases of myocarditis and the method is especially important in institutions without capacity for endomyocardial biopsy. Diagnosis of myocarditis by CMR in the acute setting is dependent on the presence of 2 of 3 findings, as defined by a set of standardized, CMR-specific diagnostic findings known as the Lake Louise criteria: (1) myocardial edema, (2) myocardial hyperemia or global relative enhancement, and (3) myocardial fibrosis or late gadolinium enhancement.[17,18] These 2 latter criteria can be appreciated in Figure 3. Echocardiography is important for bedside assessment of cardiac anatomy and function as well as for differentiating acute myocarditis from inflammatory cardiomyopathies and other cardiac conditions with overlapping clinical presentations. However, echocardiography has limited capacity to predict a fulminant disease course. Common findings in FM include near normal left ventricular diastolic dimensions, increased septal wall thickness, and impaired left ventricular ejection fraction (LVEF).[14] Decreased LVEF on presentation is an independent predictor of a fulminant disease course.[19]

The gold standard for diagnosis of FM is histologic confirmation of myocarditis by EMB. Myocarditis is defined on histopathologic examination by the Dallas criteria (standardized histopathologic measures), reflecting infiltration

Diagnostic Studies in Fulminant Myocarditis

1. Biomarkers

a. ↑ Troponin I and T
b. ↑ CK-MB
c. ↑ C-reactive protein
d. ↑ Creatine kinase
e. ↑ White blood cells

2. Imaging

a. Cardiac magnetic resonance imaging

b. Echocardiography

3. Histology

a. Endomyocardial biopsy*

*Immunohistochemistry can be applied when biopsy results are equivocal. See text for discussion of these methods.

Figure 2. Fulminant myocarditis: diagnostic studies. CK-MB = creatine kinase MB isoenzyme.

of the myocardium by inflammatory cells causing injury and potential necrosis of myocytes. Immunohistochemistry is applied to bolster the diagnostic capabilities of EMB. Additionally, EMB plays a critical role in differentiating lymphocytic from nonlymphocytic myocarditis. Presence of infiltrating lymphocytes and myocytolysis is diagnostic of the lymphocytic form of myocarditis (Figure 4). Because

of its importance for diagnosis, EMB should be performed early in cases of suspected FM.

Management

Management should be individualized to each patient's presentation and therapeutic requirements. Patients presenting
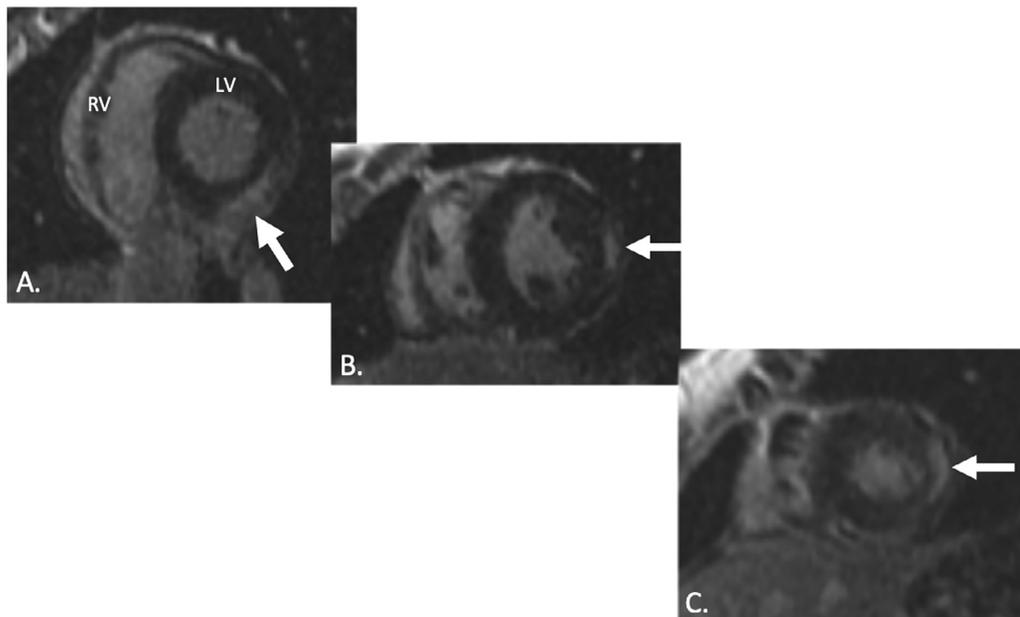

Figure 3. Magnetic resonance images of the heart in a 16-year-old male with fulminant myocarditis. The images were obtained 10 minutes after intravenous administration of gadolinium. Patchy foci of subepicardial delayed enhancement (hyperintense [lighter] areas indicated by arrows) are seen within the basal inferolateral (A), mid-lateral (B), and apical-lateral (C) left ventricular segments, reflecting destruction of myocardial fibrils at these locations. LV = left ventricle; RV = right ventricle.
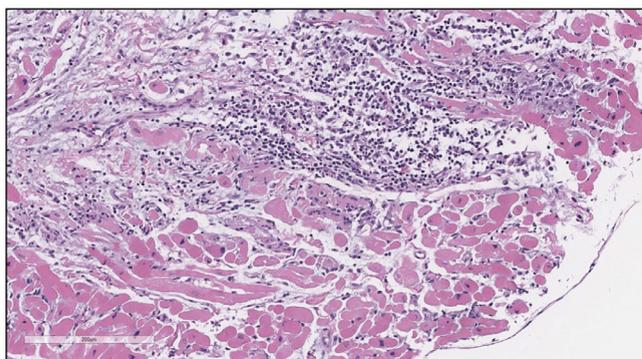
Figure 4. Endomyocardial biopsy diagnostic of lymphocytic myocarditis. Abundant evidence of infiltrative lymphocytes, interstitial edema, and myocytolysis.

with severe hemodynamic instability should undergo EMB early in the clinical course. For management of severe cardiac failure, the guidelines set forth by the American College of Cardiology/American Heart Association/Heart Failure Society of America provide essential recommendations.[20] Initial treatment should focus on stabilizing patients to prevent end-organ damage. Positive inotropic agents are administered to treat hemodynamic instability and vasodilator therapy may be added if blood pressure is adequate. Choice among these drug(s) is based on each patient's specific hemodynamic profile. If this approach is inadequate, mechanical circulatory support (MCS) is recommended.[17] Intra-aortic balloon pumps (IABP) is a commonly used, first-line technique due to its success in reducing afterload and myocardial oxygen demand. When stronger interventions are required, extracorporeal membrane oxygenation (ECMO) should be initiated, which has proved successful in improving refractory FM. Lastly, long-term ventricular assist devices can be implanted to maintain systemic perfusion, prevent end-organ damage, and afford time for recovery or for bridging to cardiac transplantation, if indicated.

The role of immunosuppressive therapy remains uncertain and varies depending on the etiology of the condition. For giant cell and eosinophilic myocarditis, steroids (e.g., methylprednisolone followed by a gradual oral prednisone taper) are the foundation of management, with antithymocyte globulins, and cyclosporine available as adjunctive treatments. Additionally, muromonab-CD3 and sirolimus have been shown to further improve transplant-free survival in patients with giant cell myocarditis.[7,21] In FM secondary to systemic diseases (i.e., sarcoidosis), steroids alone or in combination with azathioprine or methotrexate are considered first line. Intravenous immunoglobulin (IVIG) has been associated with improved LV function and decreased arrhythmias in some adult patients with acute FM, but it is mostly used in pediatric patients.[22] However, this benefit may be short lived, as newer evidence has found no decrease in in-hospital mortality when IVIG was used for FM treatment.[23] Currently, no randomized, prospective trials implementing IVIG in this patient population exist, but several case reports have suggested short- and long-term success with IVIG.[24,25]

Prognosis

Estimation of prognosis in patients with FM is challenging because of a lack of consistent correlation of clinical data with long-term outcomes. However, factors associated with increased mortality or need for cardiac transplantation include the presence of intramyocardial viral genomes, biventricular dysfunction, pulmonary capillary wedge pressure ≥15 mm Hg, echocardiographic evidence of myocardial fibrosis, and histopathology reflecting lymphocytic, giant cell, or granulomatous etiologies of myocarditis.[26] Tables 1 and 2 compiled recent case series of FM with outcomes in adult and pediatric populations, respectively. These cases were associated with diverse treatment regimens and a wide range of survival data. However, they

Table 1

Outcomes of recent adult case series of fulminant myocarditis (2012 to 2019)

First author	PMID	No. of patients	Etiology	Myocardial infiltration	Primary therapy	Survival
Saji 2012	22307381	64	Viruses	Lymphocytic, eosinophilic	-IVIG, CS -MCS	52%
Ning 2013	24349238	5	–	–	-ECMO	80%
Ukimura 2013	23089894	29	Influenza A (H1N1 strain)	–	-Antiviral -MCS	72%
Polito 2015	26127018	6	–	–	-MCS	67%
Lin 2016	27132549	18	–	–	-IVIG, CS -ECMO	78%
Okada 2016	26833577	8	Mumps (1 pt) Unknown (7 pts)	–	-ECMO	63%
Vigneswaran 2016	26613943	11	Parvovirus B19	Lymphocytic	-IVIG -ECMO	54%
Inaba 2017	28255801	42	–	–	–	85%
Chin 2018	28226202	13	Scrub typhus	–	-Antibiotics	84.5%
Hekimian 2018	29929152	4	Influenza B	–	-Antiviral -ECMO	100%
Liao 2018	28900672	33	–	–	-ECMO	79%
Ammirati 2019	31319912	165	Viruses	Lymphocytic, eosinophilic, giant cell	-IVIG, CS -MCS	72%

CS = corticosteroids; ECMO = extracorporeal membrane oxygenation; IVIG = intravenous immunoglobulin; MCS = mechanocirculatory support.

Table 2
Outcomes of recent pediatric case series of fulminant myocarditis (2012 to 2019)

First author	PMID	No. of patients	Mean age	Etiology	Myocardial infiltration	Primary therapy	Survival
Lin 2013	23515152	6	7 yrs	–	–	-ECMO	100%
Lee 2014	25550704	17	4.3 yrs	Viruses (3 pts)	–	-IVIG, CS -ECMO	64.7%
Miyake 2014	24332245	41	10 yrs	–	–	-IVIG, CS	88%
Pei 2015	26575884	24	8 yrs	–	–	–	50%
Jung 2016	27165733	13	25.8 mos	Viruses (7 pts) Unknown (6 pts)	–	-ECMO	92%
Matsuura 2016	27725476	74	6.5 yrs	Viruses (56 pts)	Lymphocytic	-IVIG, CS -MCS	49%
Yang 2016	27351572	7	7 yrs	–	–	-IVIG, CS -ECMO	71%
Ye 2016	27806793	12	8.3 yrs	–	–	-ECMO -ECPR	83%
Yan 2018	30518007	77	–	–	–	-ECMO	70%
Rodriguez-Gonzalez 2019	30863755	12	10 yrs	Viruses (8 pts)	–	-ECMO	59%
Schubert 2019	31297930	28	12.2 yrs	–	–	-IVIG, CS -MCS	79%
Yang 2019	30834480	26	39 mos	–	–	-ECMO	77%

CS = corticosteroids; ECMO = extracorporeal membrane oxygenation; ECPR = extracorporeal cardiopulmonary resuscitation; IVIG = intravenous immunoglobulin; MCS = mechanocirculatory support; mos = months; yrs= years.

were seldomly based on biopsy-proven myocarditis, a major limitation when considering the accuracy of a FM diagnosis.

Until recently, it was reported that the diagnosis of FM was associated with a paradoxically low mortality in contrast to acute nonfulminant myocarditis.[1,14,27] Previous studies suggested that (1) in acute nonfulminant myocarditis, there was impaired recovery of initially depressed LVEF which persisted beyond the acute phase, and (2) patients with FM had greater and more rapid recovery of LVEF with less likelihood of long-term dysfunction and mortality.[1,14,28] However, more recent results differ with this previously accepted view by citing the small study cohorts and absence of rigorous inclusion criteria as the source of the discrepancy regarding clinical course.[2,29] These more recent reports with larger cohorts indicate that FM is associated with overall worse outcomes that include lower LVEF at last follow-up, higher in-hospital mortality, and increased rates of cardiac transplantation.[2,29] When the criteria used in the older studies (those with nonlymphocytic myocarditis preceded by a viral prodrome) that proposed a low mortality rate in FM patients were applied to these more recent studies, the conclusions in the recent studies did not change; FM was still associated with overall worse outcomes.[2,29] Additionally, a newly established registry of 443 patients with acute myocarditis (both fulminant and nonfulminant types) reflected a similar trend: worse course, both short- and long-term, in patients with FM, as indicated by a markedly reduced LVEF, life-threatening arrhythmias, or low cardiac output syndrome.[2,29] These patients had more frequent heart transplantation (11%), increased cardiac mortality (15%), and a markedly higher rate of major cardiac events related to myocarditis at 5-year follow-up (11%) compared with patients without complications in whom these measures were completely absent (0%).[2,29] Consequently, there is a need for larger, long-term studies of mortality and LV

function in rigorously documented patients with fulminant compared with acute non-FM.

Conclusion

FM is a distinct, yet rare, form of myocarditis that has been difficult to classify. Since its initial definition near the end of the last century, the proposed criteria of FM have evolved. The presentation remains that of a characteristic, acute onset of severe heart failure commonly preceded by a viral prodrome of fever, lethargy, and myalgias. Diagnosis is aided through application of biomarkers and cardiac imaging, but endomyocardial biopsy remains the gold standard for documentation. Acute hemodynamic derangement and serious arrhythmias are managed by contemporary pharmacologic and interventional methods, whereas the role of immunosuppressive agents has not been clarified.

Disclosures

The authors have no conflicts of interest to disclose.

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