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MANAGEMENT OF HEART FAILURE (TE MEYER, SECTION EDITOR)

Management of fulminant myocarditis: A diagnosis in search of its etiology but with therapeutic options

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Abstract Fulminant myocarditis is a clinical syndrome with signs of acute heart failure, cardiogenic shock, or life-threating rhythm disturbances in the context of suspected myocarditis. It is not an etiological diagnosis, but may have different underlying causes and pathogenetic processes – viral, bacterial, toxic, and autoreactive. Clinical management of the disease entity at the acute stage involves hemodynamic monitoring in an intensive care unit or similar setting. Rapid routine work-up is mandatory with serial EKGs, echocardiography, cardiac MRI, heart catheterization with endomyocardial biopsy for histology, immunohistology, and molecular analysis for the underlying infection and pathogenesis. Heart failure therapy is warranted in all cases according to current guidelines. For fulminant autoreactive myocarditis, immunosuppressive treatment is beneficial; for viral myocarditis, IVIg can resolve the inflammation, reduce the viral load, and even eradicate the microbial agent. ECMO, IABP, ventricular assist devices, LifeVest, or ICD implantation can bridge to recovery or to heart transplantation.

Keywords Fulminant myocarditis · Acute myocarditis · Inflammatory cardiomyopathy · Etiology · Pericarditis · Histology · Immunohistology · Polymerase chain reaction · Molecular diagnosis · Management · Prognosis · Treatment · IVIg · Immunosuppression · Antiviral treatment · Restraint of physical activity

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Introduction

In its recent position statement, the ESC Working Group on Myocardial and Pericardial Diseases reviewed, in an expert consensus document, our current knowledge on clinical presentation, diagnosis, and treatment of myocarditis [1••]. The current perspective on management of myocarditis aligns with the etiologically based diagnosis and treatment that we have employed for many years [2, 3, 4••, 5••]. Diagnostic criteria proposed by the European consensus document [1••] for clinically suspected myocarditis based on biopsy-proven pathogenetic forms is similar to our previous suggestions [2, 3, 4••, 5••].

Fulminant myocarditis has been defined as a clinical manifestation of cardiac inflammation with rapid onset and severe hemodynamic compromise. However, the diagnosis of fulminant myocarditis as a distinct disease entity was not mentioned in the recent ESC scientific statement [1••]. Fulminant myocarditis was also not specifically noted in the 1996 WHF/ISFC guidelines on cardiomyopathies [6], the 1999 WHF consensus conference [7], or the recent European [8] and American guidelines [9] on cardiomyopathies. This is not without reason. Fulminant myocarditis is per se not a histological or immunohistological diagnosis. It was therefore neither listed in the Dallas criteria [10] nor in the consensus document of the ESC, AHA, and ACC on endomyocardial biopsy [11], the 2009 Japanese guidelines on cardiomyopathies [12], or the 2012 consensus statement of pathologists on endomyocardial biopsy [13]. Fulminant myocarditis is not an etiologically based disease entity; rather, it is a syndrome within the acute forms of myocarditis whose major clinical feature is a

dramatic clinical course with variable, sometimes poor prognosis [4••, 5••, 14, 15].

Fulminant myocarditis may be considered an acute myocarditis in which different etiologies are embedded. In fact, it is a diagnosis in search of an etiology, although some specific histological forms of myocarditis, such as giant-cell myocarditis, cardiac sarcoidosis, and eosinophilic heart disease, may exhibit the fulminant clinical phenotype more frequently than the acute viral or autoreactive forms of myocarditis [16].

And while neither a histological nor an etiological diagnosis, the term fulminant myocarditis has been used increasingly in recent years despite its imprecise nature. A major excuse for use of the term has been physicians' and patients' unwillingness to look at the heart of the matter, namely the underlying etiology and pathology of an "idiopathic" disease, which in reality it is not. The present review on fulminant myocarditis reflects this dilemma.

Current Definitions of Myocarditis, Inflammatory Cardiomyopathy, and Fulminant Myocarditis

The 1996 WHF/ISFC task force on the definition and classification of cardiomyopathies included inflammatory heart muscle diseases (myocarditis, perimyocarditis) in the group of secondary cardiomyopathies [6]. Inflammatory cardiomyopathy was defined as inflamed myocardium assessed histologically (= myocarditis) in association with cardiac dysfunction. The pathohistological criteria at that time were the Dallas criteria [10], which distinguished active, recurrent, healing, and borderline myocarditis. The etiology was assumed to be infectious, toxic, or autoimmune. Non-inflammatory viral cardiomyopathy was defined as viral persistence in a dilated heart without ongoing inflammation. The World Heart Federation consensus meeting in 1999 defined myocardial inflammation by quantitative immunohistological criteria (≥14 infiltrating cells/mm^2) [7]. These infiltrating cells could be T and B lymphocytes, their activated forms, and up to 4 monocytes or macrophages/mm^2. The causative microbial agent in the myocardial tissue was assessed or excluded by polymerase chain reaction (PCR) or in situ hybridization. When applying endomyocardial biopsy and these methods, the following terms are appropriate [4••, 5••]:

- Viral myocarditis, if the inflammation in the endomyocardial biopsy is associated with a positive test for viral RNA or DNA;
- Viral inflammatory cardiomyopathy, if a positive PCR on microbial agents in the biopsy is associated with a dilated and inflamed heart; and
- Viral heart disease, if dilated cardiomyopathy is associated with viral persistence with inflammation.
- Autoreactive myocarditis or autoreactive inflammatory cardiomyopathy describe an inflamed heart with ≥14 infiltrating cells but with no detectable microbial agent.
- Myocarditis with normal ejection fraction (MNEF) describes histologically proven inflammation in a heart with normal ejection fraction and no relevant dilatation (HFNEF).
- Viral or autoimmune etiology can be used as additional criteria, with the abbreviation VMNEF and AMNEF. The inclusion of diastolic heart failure under these conditions would conform to the consensus document of the Heart Failure Association and Echocardiography Association of the ESC [17].

The term "fulminant" myocarditis was initially used in a clinical setting [18]. The last decade, however, has seen an enormous number of case reports describing patients with poor prognosis of different etiologies who underwent various life-saving interventions or suffered a lethal outcome. It is perhaps surprising that an etiological diagnosis was established in many cases. Table 1 incorporates the clinical syndrome of fulminant myocarditis into the systematics of the current WHF criteria [5••, 14, 18] by adding quantitative histology, immunohistology, and PCR on microbial pathogens to clinical manifestation and functional parameters. It also outlines the clinical course and currently available treatment options.

Incidence and Natural History of Fulminant Myocarditis

Fulminant myocarditis is a rare syndrome [5••, 14, 16, 18]. At the time of our Marburg Myocarditis Registry, of the 1,098 patients with more than 14 infiltrating cells in the biopsy samples [19•], only 27 patients (2.5 %) presented with the "fulminant" clinical phenotype. Data on the true prevalence or incidence of fulminant myocarditis in the general population do not exist or are merely speculative. Some autopsy studies report up to 12 % of cases of sudden death in patients less than 40 years of age [20–28]. They may be partly "hidden" in statistics on sudden death in the pediatric [25–27] and young adult [20] populations, or in autopsy studies on military recruits [24] and young athletes [28], or they may even mimic right ventricular cardiomyopathy [29] as recently noted [30].

Pathohistology

Histological and immunohistological specimens from patients with a fulminant clinical phenotype can be derived from Fig. 1. Diagnoses made from the biopsies of these patients included giant-cell myocarditis, cardiac sarcoidosis, acute

Table 1 Phenotypes of myocarditis (modified from [14] with permission from Elsevier)

Clinical phenotype	Fulminant myocarditis	Acute myocarditis	Chronic active myocarditis	Chronic persistent myocarditis
Symptoms	Shock, heart failure, dyspnea, severe rhythm disturbances, sudden death from heart failure or recovery	Heart failure, reduced EF with near normal LV dilatation, pericardial effusion (up to 20 %), angina in PVB19 myocarditis	Heart failure, variable EF with LV dilatation, pericardial effusion (up to 10 %), angina in PVB19 myocarditis	Heart failure, variable EF with LV dilatation, pericardial effusion (up to 10 %), angina in PVB19 myocarditis
Dallas criteria	Infiltrate (active myocarditis or giant cells), necrosis	Active, often focal lymphocytic myocarditis	Borderline myocarditis, focal small infiltrates	Borderline or persistent myocarditis
World Heart Federation criteria*)	$\geq$50 infiltrating cells/mm^2, necrosis, possibly giant cells	$\geq$14 infiltrating cells, mostly lymphocytes, necrosis likely	$\geq$14 infiltrating cells, lymphocytes and macrophages, necrosis and apoptosis not obligatory	$\geq$14 infiltrating cells, lymphocytes and macrophages, necrosis and apoptosis not obligatory
Immuno-histology	Immunoglobulin binding mostly IgM to sarcolemma and fibrils and complement fixation	Immunoglobulin (IgM, IgA and IgG) binding to sarcolemma and fibrils	Immunoglobulin (IgG) binding to sarcolemma and fibrils	Immunoglobulin (IgG) binding to sarcolemma and fibrils
PCR on microbial pathogens	Negative in giant-cell or autoreactive myocarditis, positive in up to one third	Negative in autoreactive lymphocytic myocarditis, positive in up to one-third of cases	Negative in autoreactive lymphocytic myocarditis, positive in up to one-third of cases	Negative in autoreactive lymphocytic myocarditis, positive in up to one-third of cases
Course	Variable, from lethal outcome to spontaneous healing	Variable, from deterioration to defective healing	Chronic heart failure	Chronic heart failure
Treatment	Immunosuppression in PCR-negative cases, IVIg in virus-positive cases, intermittent assists device, ICDs	Immunosuppression in PCR-negative cases, assist device, ICDs; in viral myocarditis, IVIg in trials	Immunosuppression in PCR-negative cases, prophylactic ICDs when EF<35 %; in viral myocarditis, IVIg or IFN in trials	Immunosuppression in PCR-negative cases, prophylactic ICDs when EF <35 %; in viral myocarditis, IVIg or IFN in trials

lymphocytic myocarditis with necrosis of the autoreactive type, acute HHV6-positive myocarditis, and clinically fulminant myocarditis with a minimal infiltrate only, which would histologically fit chronic myocarditis but appeared to be fulminant in the clinical course, as in this case heart failure and severe ventricular arrhythmias dominated the clinical manifestations. It should be noted, however, that histology and quantitative cell count in biopsy specimens are not a de facto equivalent of fulminant myocarditis, as clinical and pathohistological phenotypes do not necessarily match. Therefore, the WHF consensus of $\geq$50 infiltrating cells/mm^2 in biopsy specimens reflects the rough estimate of experts but is not dogma. It is in accordance with the quantitative histological WHF criteria [7] and corresponds well to the ESC status document [1••] and the findings of other European [31•] and American pathologies [32]. Representative histological findings are demonstrated in Fig. 1.

Experimental Models of "Fulminant Myocarditis"

The classic animal model of acute forms of non-viral myocarditis is inflammation as EAM (experimental autoimmune myocarditis) induced by cardiac myosin induced in mice [33, 34] or Lewis rats or by sarcolemmal preparations in mice [35] or rabbits [36]. Their respective histologies may also exhibit giant cells [37]. Remarkably, inhibition of mast cells by cromolyn sodium reduced the number of mast cells in the inflamed myocardium, attenuated consecutive fibrosis, and prevented left ventricular dilatation in rats [38].

Recent reviews of experimental models of viral myocarditis [39••, 40, 41] have included detailed analysis of murine myocarditis models of coxsackievirus B3 [39••, 41], encephalomyocarditis virus (EMCV), reo-, adeno-, parvo-, herpes, and influenzavirus [39••] and pathogenetic and therapeutic interactions with calcium overload, the renin-angiotensin-aldosterone system, gene expression of TGF-ß, and the NF-kB/cytokine pathway [40]. The infection-versus-autoimmunity hypothesis in animal models and with respect to patients was also covered extensively [42, 43•, 44].

Etiology and Pathogenesis of Fulminant Myocarditis

Systematic studies within the last decade on the etiology of acute or fulminant myocarditis are scarce [2, 4••, 5••, 15, 18, 22, 24, 31•, 45–49], while reports during the same period on fulminant myocarditis cases with established microbial etiology are less infrequent [50–95]. In the Marburg Myocarditis registry (1989–2003) 26 adult patients with a fulminant phenotype of acute myocarditis were identified, including 3 patients with giant-cell myocarditis, 8 with cardiac sarcoidosis, 4

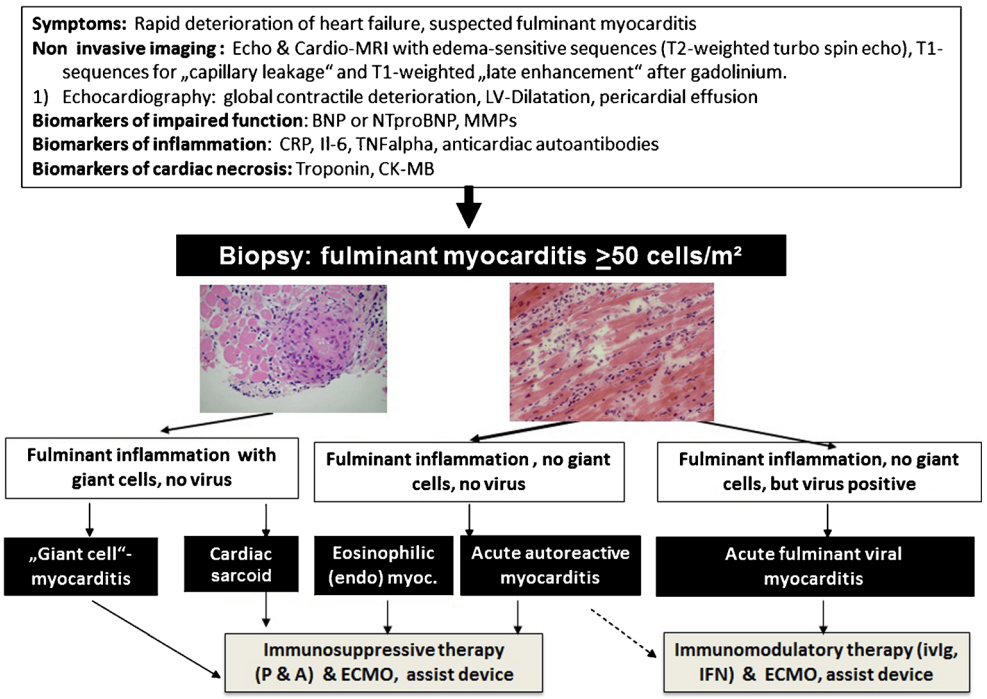

Fig. 1 Diagnostic and treatment algorithm in fulminant myocarditis (modified from [3] and [5••] with permission from Springer)

with autoreactive non-viral, 4 with viral myocarditis, and 7 with eosinophilic myocarditis ([16, 19] and unpublished data) (Table 2). In a South Korean series of 33 patients with biopsy-proven acute myocarditis, 20 patients were ascribed to fulminant myocarditis, 19 were diagnosed as lymphocytic, and 1 as giant-cell myocarditis. Fifteen of the patients had evidence of coxsackie B infection as assessed by either PCR or in situ hybridization or neutralization test [96], and 5 had eosinophilic myocarditis (Table 2). Of note, plasma thioredoxin levels as a marker of oxidative stress and sTNFR-II levels as a proinflammatory marker were higher in the fulminant myocarditis group when compared to a disease control cohort of 13 patients. IL-10, an anti-inflammatory marker that blocks NFKB, was also higher in the fulminant myocarditis group. Increased levels of IL-10 were also found in a similar investigation [97], but without direct correlation to prognosis.

In a U.S. pediatric cohort of 16 children with fulminant clinical phenotype, 12 patients demonstrated myocarditis histologically (Table 2). All underwent either ECMO or ventricular assist devices for bridge to recovery [45]. Seven children had a positive PCR for parvovirus B19 (PVB19) in blood or myocardial tissue, 2 for Epstein-Barr virus, and 1 each for cytomegalovirus and enterovirus (Table 2). The presence of virus and inflammation in the myocardial tissue predicted poor long-term outcome. A Japanese survey of 169 pediatric cases from 1997 to 2002 compared the etiology and outcome of 64 fulminant with 89 acute and 8 chronic myocarditis cases. In the fulminant group, 12 were virus-positive (5 for Coxsackie, 4 for influenza, and 1 each for echo-, adeno-, and cytomegalovirus) (Table 2). In the acute myocarditis group, 22 were virus-positive (9 for Coxsackie, 5 for influenza, 1 each for echo- and parvovirus B19, and 1 each for measles, herpes zoster, and mycoplasma). The incidence of the different viruses was comparable in the fulminant and acute groups [47]. In the 2009 H1N1 epidemic, the etiology was obvious (Table 2) [59–64, 66–68, 70–73]. Table 3 gives an overview of case reports on fulminent myocarditis published recently. The fatal case of HHV6 myocarditis in an immunocompetent adult demonstrates well the diagnostic dilemma between clinical course and histology, which in this case showed only scars with viral glycoprotein in endothelial and mononuclear cells [54].

Studies excluding a viral etiology are rare [106–108] (e.g., the TIMIC [106] and ESETCID [108] trials, which were treatment trials for autoreactive non-viral myocarditis). Unfortunately, despite the fact that methods such as viral PCR for cardiac tissue have been available now for almost two decades, even the most recent publications on fulminant myocarditis are largely devoid of any attempt to define its underlying microbial etiology [98, 109–156]. This disappointing list begins with the 1996 U.S. Myocarditis Treatment Trial [126], which was published before all PCR methods for detection of viral DNA and RNA were available, and ends in 2012 with a Japanese survey [115] and a descriptive Chinese study [156] on fulminant myocarditis.

The association of certain viruses with fulminant myocarditis during the last decade deserve special attention in light of the regional epidemic outbreaks such as the H1N1 swine flu epidemic in Southeast Asia [73] and epidemiologic shifts in Europe from entero- and adenoviruses to PVB19 and HHV6, as well as different susceptibilities in children when their viral spectrum is compared to that of adults (Tables 2 and 3).

Table 2 Etiologies of fulminant myocarditis in registries and small studies

Histological and molecular phenotype	Marburg Myocarditis Registry (adults) 1989–2003 (n=26; % of fm)	South Korea [96] adults (n=20; % of fm)	U.S. [45] pediatric pts. (n=16; % of fm)	Japanese pediatric survey [47] (n=64; (% of fm)	H1N1 epidemic 2009 Japanese survey [72, 73] (n=36; % of fm)
Fulminant viral myocarditis / No patients	4 (15.4 %)	14 (70 %)	11 (69 %)	12 (18.75 %)	36 (100 %)
-Parvo B19	2 (7.7 %)	0	7 (44 %)	0	0
-HHV 6	1 (3.85 %)	0	0	0	0
-Enterovirus	1 (3.85 %)	14 (70 %)	1 (6.25 %)	5 (7.8 %)	0
-Echovirus	0	0	0	1 (1,5 %)	0
-Adenovirus	0	0	0	1 (1.5 %)	0
-Influenza	0	0	0	4 (6.25 %)	0
-H1N1	0	0	0	0	36 (100 %)
Parainfluenza	0	0	0	0	0
-Denguevirus	0	0	0	0	0
-EBV	0	0	2 (12.5 %)	0	0
-CMV	0	0	1 (6.25 %)	1 (1.5 %)	0
-Q-Fever	0	0	0	0	0
Autoreactive /non viral fm	4 (15.4 %)	0	5 (31 %)	52 (81.25 %)	0
Bacterial Meningoccal fm	0	0	0	0	0
Giant cell myocarditis	3 (11.5 %)	1 (5 %)	0	0	0
Sarcoid heart disease	8 (30.8 %)	0	0	0	0
Eosinophilic myocarditis	7 (26.9 %)	5 (25 %)	0	0	0

fm = fulminant myocarditis

Parvovirus B19 From various European studies [19•, 50, 91, 157], overviews, and registries [3, 4••, 5••, 14], as well as the ESC position statement [1••], the association of the PVB19 genome to suspected or biopsy-proven myocarditis is the most frequent finding in endomyocardial biopsies. In cases without inflammation, which is approximately 50 % of the virus-positive biopsies in our registry, the pathological impact on cardiac function is still a matter of debate: is PVB19 the cause of symptoms or heart failure, or is it just a harmless passenger [158–160]?

Human Herpes Virus 6B (HHV-6B) In the last five years, HHV-6B has been found up to 20 % more frequently in adult endomyocardial biopsies, often together with PVB19, and may even be integrated in the chromosome as ciHHV6. HHV-6B, like CMV, EBV, HHV7 and HHV8, is a latent virus and can be both encephalo- and cardiotropic [52–54].

Influenza and H1N1 Influenza accounts for up to 5 million cases of severe illness and up to 300,000 deaths annually [74]. Myocardial involvement after influenza virus infection ranges from asymptomatic (frequent) to rare fulminant myocarditis with cardiogenic shock [74–80]. Influenza B-induced cardiogenic shock is even rarer [81, 82]. The 2009 pandemic of Eurasian swine lineages known as H1N1 influenza was declared a global pandemic by the World Health Organization. Cardiac complications are similar, although an excess of reports has flooded the recent literature [59–73].

Enteroviruses Coxsackie B viruses still play a role in acute and fulminant myocarditis in the pediatric population [41, 44, 45, 47, 57, 58]. In Europe, they have virtually disappeared in the adult population [2, 3, 4••, 19•, 157].

Epidemiology

Tables 2 and 3 indicate different etiologies of fulminant myocarditis in various geographical areas of the world. In Europe and the U.S., acute and chronic enteroviral adult fulminant myocarditis has declined, and PVB19, HHV6 [19•, 45, 157], and double infections have increased. In the South Korean series, lymphocytic enteroviral causes still dominate [96], while the 2009 H1N1 influenza endemic in Southeast Asia prevails in the recent publications of case reports from Japan [72,73].

Symptoms and Non-invasive Clinical Work-up

As illustrated in Table 1, the syndrome of fulminant myocarditis presents with shock, acute heart failure, dyspnea, fever, and severe rhythm disturbances, with the occurrence of sudden death or death from heart failure [3, 4••, 5••, 14, 18, 91, 120, 121, 127, 132]. Some authors contend that fulminant myocarditis is easily distinguishable from acute myocarditis by the

Table 3 Etiologies of fulminant myocarditis in case reports 2003–2013

Histological and molecular phenotype	No. patients	References	Comments
Fulminant viral myocarditis:			
-Parvo B19	12	[50, 51]	Epidemic 2009
-HHV 6	3	[52–54]	
-Herpesvirus	1	[55]	
-Enterovirus(Coxsackie)	3	[56–58]	
-Echovirus	0		
-Adenovirus	0		
-H1N1	13	[59–73],	
-Influenza A or B	A: 7; B: 2	A: [74–80]; B: [81, 82];	
-Parainfluenza	1	[83]	
-Denguevirus	1	[84]	
-EBV	1	[85]	
-CMV	0		
-Q-Fever	3	[86]	
Autoreactive /non viral			
Bacterial (e.g., meningococcal fm)	3	[87–89]	
Giant-cell myocarditis	12	[32, 37, 46, 90, 98, 99]	New atrial giant-cell myocarditis
Sarcoid heart disease	36	[32, 100–102]	
Eosinophilic endomyocarditis; DRESS	4	[103–105]	

presence or absence of cardiogenic shock in the acute phase [1••, 18, 25, 30, 91, 121, 127, 161]. We consider this distinction acceptable but arbitrary, and view fulminant myocarditis etiologically and clinically as part of the acute myocarditis entity. Early on, it may be virtually indistinguishable clinically from giant-cell myocarditis, which is a distinct clinical and histopathological entity, and it may be classified retrospectively by its clinical outcome. Liebermann [18] once defined the prognosis as "complete recovery or death." This is no longer the case, however, due to a better understanding of the underlying microbial and autoimmune etiology and pathogenesis, lifesaving ECMO and LVAD treatment, and CRT and ICD implantation and reported defective healing in survivors.

Routine clinical work-up includes sequential EKGs, which may show low voltage due to an accompanying pericardial effusion [162, 163] or myocardial edema [139, 142, 148]. Echocardiography may show a speckled myocardium, a so-called velvet carpet [135] and reduced hemodynamic parameters and ventricular/atrial enlargement [71], or radial strain dyssynchrony [95, 124]. Cardiac magnetic resonance imaging (CMRI) can exhibit late gadolinium enhancement [98, 148], global enhancement, and features described in the Lake Louise white paper, although negative MRI findings, with the exception of edema formation, were also reported [55]. Increased troponin and CK-MB concentrations are common in the acute stage. BNP and NT-proBNP levels parallel the pump failure of patients in their clinical course.

Heart Failure Treatment and Device Therapy of Fulminant Myocarditis

Restriction of physical activity, heart failure therapy, and antiarrhythmic treatment according to current guidelines (e.g., amiodarone or beta-blocker) are fundamental treatment options. If long-term prevention of sudden cardiac death is imperative, LifeVest in the case of transient or CRT-ICD implantation should be considered. In fulminant myocarditis with cardiogenic shock, most publications within the last five years have demonstrated a beneficial effect of temporary intra-aortic balloon pump (IABP) [95, 128, 142, 148], ECMO (extracorporeal membrane oxygenation) support [80, 114, 118–120, 128, 131–133, 135, 142, 143, 149, 151, 154, 157], implantation of LVAD or BiVAD [121, 122, 129] or Impella device [153], and heart transplantation [155].

Specific Treatment in Fulminant Myocarditis

In biopsy-proven viral etiology of fulminant myocarditis, IVIg treatment is recommended [1••, 3, 4••, 5••, 16]. Although one controlled trial [164] showed no improvement, the majority of studies demonstrated benefit [16, 114], particulary in fulminant myocarditis [164]. For a detailed overview, refer to [16].

In biopsy-proven autoreactive myocarditis, data from the TIMIC study in acute myocarditis [106] and preliminary data from the ESETCID trial [16, 108] indicate benefit from immunosuppression, although the patients in these studies were

not labeled fulminant. Similarly, a recent case report indicated a benefit with cortisone treatment [141, 143, 163]. Whether the initial optimism for phenylpyridazinone is justified [107] will need to be proven in a larger randomized trial.

Specific Diseases Often Associated with a Fulminant Clinical Phenotype

Idiopathic Giant Cell Myocarditis

The histopathological hallmark of giant-cell myocarditis (GCM) is giant cells in addition to a lymphocytic infiltrate. Clinical symptoms are acute heart failure and malignant ventricular arrhythmias. Its incidence is extremely rare, and its etiology is assumed to be autoimmune although influenced by genetic background, as it resembles experimental GCM in Lewis rats. If clinically suspected, GCM is a class I B indication for endomyocardial biopsy [1••, 2, 3, 4••, 5••, 11]. The natural course is lethal if untreated. Immunosuppression or monoclonal anti-CD3 antibodies can be lifesaving. The recommended specific treatment algorithm is shown in Fig. 1. For dosages and duration, refer to [16]. Recent publications underline the poor prognosis [32, 37, 46, 90, 98, 99], which may be better in the newly described atrial GCM [99], which 5 of 6 patients survived without immunosuppression.

Cardiac Sarcoidosis

This granuloma-forming disease is more frequent than GCM. In the context of systemic sarcoidosis, suspicion of cardiac involvement is easily discernible. In isolated cardiac sarcoidosis, MRI and nuclear scans are leading the way diagnostically, as endomyocardial biopsy may miss the characteristic noncaseating granuloma with giant cells [32, 100–102]. Treatment is either corticoid or a combination with azathioprine or cyclosporine.

Eosinophilic Heart Disease and DRESS

Eosinophilic heart disease, which develops in three stages (eosinophilic endomyocarditis, thrombotic endocardial disease, and endomyocardial fibrosis), was indicated in 7 of 26 patients of the Marburg Registry fulminant phenotype [4••] (Table 2). While color-flow Doppler echocardiography and MRI are able to identify the histological stage, endomyocardial biopsy is the standard diagnostic method. The European form is immunologically mediated; the tropical form may be caused by a helminthic or protozoal infection.

DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome can be caused by various drugs [103–105] and is also treated with corticoids, immunosuppressives, or ECMO in refractory cases.

Conclusions

Fulminant myocarditis is not an etiological diagnosis, but rather a clinical syndrome in search of its various etiologies. It can be considered part of the spectrum of acute myocarditis, with particularly severe initial symptoms, acute heart failure, and cardiogenic shock, often accompanied by significant troponin release. The fulminant inflammation may resolve and the patient may recover almost completely, or the patient may die from cardiogenic shock or sudden death, but the outcome cannot be predicted with certainty at the initial stage. Therefore, treatable diagnoses such as giant-cell myocarditis, cardiac sarcoidosis, eosinophilic heart disease or DRESS, and lymphocytic viral or non-viral autoreactive myocarditis must be made rapidly by endomyocardial biopsy, histopathology, immunohistology, and PCR for a possible underlying microbial cause. ECMO, transient or permanent LVAD or BiVAD implantation, together with ICD implantation, have been lifesaving as a bridge to recovery or to heart transplantation.

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Compliance with Ethics Guidelines

Conflict of Interest Bernhard Maisch, Volker Ruppert, and Sabine Pankuweit each declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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