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Review Article

Death and Grief of Viral Myocarditis and Exciting Portrayal of Viruses

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Abstract

Myocarditis is most often due to a viral infection. Viral myocarditis remains a prominent infectious-inflammatory disease for patients throughout the lifespan. Viral infections may cause inflammation of heart muscle (myocarditis) with temporary or potentially permanent damage to heart muscles cells Dealeading to a secondary cardiomyopathy occur when the heart muscle fibers are abnormally stretched when the heart chambers increase in size and volume. The stretched muscles lose their ability to contract strongly, similar to a slinky or an elastic band that has been overstretched and loses its shape and function. As the heart walls continue to stretch, they can also cause damage to the heart valves between the chambers of the heart causing blood to regurgitate or backwash, and as a result there is decreased cardiac output and heart failure. Viral (adenovirus, parvovirus B19, Coxsackievirus, HIV, Enterovirus, rubella virus, polio virus, cytomegalovirus, human herpes virus 6 and possibly hepatitis C.

Keywords: *Adenovirus; Parvovirus B19; Coxsackievirus; HIV; Enterovirus; Rubella Virus; Polio Virus; Cytomegalovirus; Human Herpes Virus 6 Hepatitis C*

Introduction

Every soul shall taste death. Sometimes you will never know the value of a moment until it becomes a memory. In the last few decades, India has emerged as the world capital for heart disease, with more people with heart problems in this country than anywhere else in the world and that's not all; in comparison with the west, Indians are affected by cardiovascular-related problems at a significantly younger age Even in women with breast cancer, dying from heart disease is a leading cause of death. Is there any silver bullet? [1].

Viral heart disease, also known as myocarditis is a heart condition caused by a virus. The virus attacks the heart muscle, causing inflammation and disrupting the electrical pathways that signal the heart to beat properly.

Adenovirus, Coxsackievirus B, Cytomegalovirus, Enteric cytopathic human orphan virus (ECHO Virus), Human parvovirus (B19) and Rubella viruses are responsible for causing Myocarditis and other cardiac problems. Signs and symptoms include chest pain, fatigue, shortness of breath and arrhythmias.

Virus infections of the heart are a significant cause of sudden unexpected death due to cardiovascular reasons in young men and also produce chronic cardiomyopathy which frequently requires heart transplantation [2].

During the first phase, direct destruction of the cardiomyocytes occurs by virus-mediated lysis, causing degradation of cell structures, which in turn facilitates entry of the virus into the cells with consequential myocyte injury and cardiac dilatation [3].

Adenovirus can cause heart muscle damage, left ventricular dysfunction, heart muscle dysfunction, and severe heart transplants.

Coxsackie B virus induces cardiomyopathy and damages heart cells. The immune system continues to damage heart. This virus extensively damages the heart.

Cardiovascular complications constitute a rare manifestation of Cytomegalovirus (CMV) infection; it is a diagnostic challenge in emergency cases [4].

B19 is a common infectious agent, and that resulting myocarditis is currently believed to be a rare event, either the virus is only mildly cardiotropic or other unknown concerted factors are required to cause clinical disease [5].

Echovirus disease occurs disproportionately in males and children. Infection within the first two weeks of birth can cause devastating and potentially fatal disease. In this population, death usually results from overwhelming Liver failure or Myocarditis, rather than infection of the central nervous system. Older children and adults have a better prognosis. Myocarditis is the most frequent complication in adults.

Lorin E Ainger., *et al.* described the clinical course, electrocardiographic, radiological, virological and post-mortem findings of 10 infants with stigmata of the congenital rubella syndrome who had the active myocardial disease during the neonatal period [6].

Frustaci., *et al.* reported a case of fulminant measles myocarditis is reported. Diagnosis has been obtained at autopsy, due to absence of skin rash, by identification of measles giant cells in the myocardium and by the positive reaction of myocardial tissue to measles-specific immunoperoxidase. The unusual outcome is interpreted as due to defective cell-bound immunity and extensive involvement of myocardial microcirculation [7].

Adenovirus, parvovirus B19, coxsackie virus, rubella virus, polio virus, Epstein-Barr virus, hepatitis C, and severe acute respiratory syndrome coronavirus 2 [8,9].

Recently, parvovirus B19 has been associated with a significant percentage of patients diagnosed with myocarditis and DCM [10].

It has recently been reported that infection of the cardiac myocyte is required for the induction of cardiac dysfunction and inflammation when mice were systemically infected with coxsackievirus B3 (CVB3) [11].

One clinical study showed the association between viral persistence in the heart and progressive cardiac dysfunction [12].

Viral infections can lead to myocardial inflammation, resulting in acute myocarditis. Acute myocarditis is mostly self-limiting, but it can lead to severe dilated cardiomyopathy and rarely to acute cardiac tamponade. We report a rare case of myocarditis in a young im-

munocompetent male patient due to a recent cytomegalovirus (CMV) infection. The clinical presentation was an influenza-like syndrome, classical for a CMV infection, in combination with mild chest pain [13].

Cytomegalovirus (CMV) infection is a prevalent infectious disease worldwide; however, its prevalence varies with geographical regions and socioeconomic statuses [14].

CMV belongs to the Herpesviridae family and Betaherpesvirinae subfamily type 5; it is a DNA virus with the ability of remaining latent for a long time [15].

Its prevalence ranges from 30 to 100 % in the general population with prior exposure to the virus as determined by serological tests. This prevalence is inversely proportional to socioeconomic status and directly proportional to age [16].

Perimyocarditis represents an inflammation of both the myocardium and pericardium. Although several causative agents have been recognized, pericarditis or myocarditis associated with rubella is an unusual complication [17].

Over the last decade, parvovirus B19 (B19V) has frequently been linked to the pathogenesis of myocarditis (MC) and its progression towards dilated cardiomyopathy (DCM). The exact role of the presence of B19V and its load remains controversial, as this virus is also found in the heart of healthy subjects. Moreover, the prognostic relevance of B19V prevalence in endomyocardial biopsies still remains unclear. As a result, it is unclear whether the presence of B19V should be treated [18].

Although parvovirus B19 (PVB19) currently is the most common cause of viral myocarditis, limited pediatric data exist. Whereas other viruses infect cardiomyocytes, PVB19 targets coronary endothelium, leading to myocardial ischemia and dysfunction [19].

Cardiovascular infections include a group of entities involving the heart wall, such as myocarditis, dilated cardiomyopathy and pericarditis. These processes are associated with high morbidity and mortality. Although early diagnosis is essential for adequate patient management and leads to improved prognosis, the clinical manifestations are often non-specific [20].

History

The coxsackieviruses were discovered in 1948-49 by Gilbert Dalldorf, a scientist working at the New York State Department of Health in Albany, New York.

Dalldorf, in collaboration with Grace Sickles, had been searching for a cure for poliomyelitis. Earlier work Dalldorf had done in monkeys suggested that fluid collected from a nonpolio virus preparation could protect against the crippling effects of polio. Using newborn mice as a vehicle, Dalldorf attempted to isolate such protective viruses from the feces of polio patients. In carrying out these experiments, he discovered viruses that often mimicked mild or nonparalytic polio. The virus family he discovered was eventually given the name Coxsackie, from Coxsackie, New York, a small town on the Hudson River where Dalldorf had obtained the first fecal specimens [21].

Rubella was first described in the mid-eighteenth century. German physician and chemist, Friedrich Hoffmann, made the first clinical description of rubella in 1740, which was confirmed by de Bergen in 1752 and Orlow in 1758 [22].

In 1814, George de Maton first suggested that it be considered a disease distinct from both measles and scarlet fever. All these physicians were German, and the disease was known as Rötheln (contemporary German Röteln), Rötlich means “redish” or “pink” in German. The fact that three Germans described it led to the common name of “German measles” [23].

Henry Veale, an English Royal Artillery surgeon, described an outbreak in India. He coined the name «rubella» (from the Latin word, meaning «little red») in 1866 [24].

It was formally recognised as an individual entity in 1881, at the International Congress of Medicine in London. In 1914, Alfred Fabian Hess theorised that rubella was caused by a virus, based on work with monkeys. In 1938, Hiro and Tosaka confirmed this by passing the disease to children using filtered nasal washings from acute cases.

In 1940, there was a widespread epidemic of rubella in Australia. Subsequently, ophthalmologist Norman McAllister Gregg found 78 cases of congenital cataracts in infants and 68 of them were born to mothers who had caught rubella in early pregnancy [25].

Gregg published an account, Congenital Cataract Following German Measles in the Mother, in 1941. He described a variety of problems now known as congenital rubella syndrome (CRS) and noticed that the earlier the mother was infected, the worse the damage was. Since no vaccine was yet available, some popular magazines promoted the idea of "German measles parties" for infected children to spread the disease to other children (especially girls) to immunize them for life and protect them from later catching the disease when pregnant [26].

Because it is capable of producing both congenital and acquired infections, the cytomegalovirus (CMV) has become an extremely important pathogen, and review of its history is pertinent. Inclusion-bearing cells were first shown by Ribbert in 1881. Goodpasture and Talbert in 1921 were the first to suggest that the "cytomegalia" could be due to a viral agent. In 1950, Smith and Vellios showed that infection may occur in utero. The introduction of exfoliative cytology methods allowed identification of characteristic cells in the urine of infected infants. Smith in 1956, Rowe and coworkers in 1956, and Weller., *et al.* in 1957 independently isolated human CMV strains. In 1960, Weller and coworkers proposed the term "cytomegalovirus" and subsequently isolated CMV from the urine of infants with generalized disease. CMV has now become one of the most common opportunistic pathogens encountered in patients immunocompromised from congenital or acquired causes such as AIDS or transplantation procedures [27].

The term 'myocarditis' was first introduced in the early 19th century by Corvisart. However, at the beginning of the 20th century with the recognition of coronary artery disease as an important cause for heart disease, the term was largely discarded [28].

In attempts to standardize the diagnostic criteria for myocarditis, the Dallas classification2 was introduced in 1987. This classification, however, has several pitfalls, being susceptible to variation in pathological interpretation sampling error and not considering the exact cause of pathological findings [29].

Therefore, it is not anymore used as the gold standard for the diagnosis of viral or autoimmune myocarditis, mainly due to its lack of additional immunostaining for inflammation and polymerase chain reaction (PCR) for viral diagnosis. Recent efforts to redefine viral and autoimmune heart disease may therefore result in the so-called 'death of the Dallas Criteria [30].

Research gaps in viral myocarditis

Despite considerable advances in our understanding of myocarditis pathogenesis, the clinical management of myocarditis has changed relatively little in the last few years.

The diagnoses of myocarditis and pericarditis are often delayed because they are uncommon diseases in pediatrics and because symptoms in the early stages may be overlooked in the context of current or recent viral illnesses or other systemic diseases. Early suspicion for and recognition of signs and symptoms, particularly of myocarditis, are important because the disease process can rapidly become life-threatening. Although pericarditis can also be life-threatening, it is less commonly so than myocarditis. Clinicians should be aware of the predisposing factors and the clinical signs and symptoms that should increase the index of suspicion for these entities because prompt referral to the emergency department, with access to specialists with expertise in the care and support of these patients, is imperative [31].

The incidence and prevalence of myocarditis are unknown in most regions of the world. There is a need for inexpensive, sensitive and specific diagnostic tests that can be used in population based studies in regions without access to advanced imaging or cardiac catheterization laboratories. Also, the optimal strategy for diagnosing myocarditis in at risk populations such as children is controversial and based largely on expert opinion [32].

Major advanced discoveries in viral myocarditis research

Myocarditis was discovered as heart disease at autopsy with the use of microscope. In 1900, Carl Ludwig Alfred Fiedler first reported with the name of acute interstitial myocarditis a sudden heart failure. Histology, immunohistochemistry and PCR are now considered a gold standard tool for the diagnosis of viral myocarditis. Cardiac resonance magnetic may be of help in identifying inflammatory edema.

Myocarditis is a poorly understood disease because it progresses through stages with distinctly different mechanisms and manifestations. The objective of this article is to better define myocarditis for both clinicians and clinical scientists by setting it in the framework of 3 phases of disease. In phase 1, the viral stage, we review recent discoveries about the way viruses gain access to target tissue and how they trigger immune responses. In the second, autoimmune phase of disease, we examine the roles of autoreactive T cells, cytokines, and cross-reacting antibodies and reconsider the relevance of recent therapy trials. In the third phase of the disease, dilated cardiomyopathy, we consider the remodeling processes [33].

Myocarditis was discovered as heart disease at autopsy with the use of microscope. In 1900, with the name of acute interstitial myocarditis, Carl Ludwig Alfred Fiedler first reported the history of a sudden cardiac heart failure, in the absence of coronary, valve, pericardial disease or classical specific infections with multiorgan involvement. He postulated a peculiar isolated acute inflammation of the myocardium with poor prognosis due to invisible microorganisms, which years later would have been identified as viruses. Subsequent revision of Fiedler original histologic slides by Schmorl showed cases with either lymphocytic or giant cell infiltrates. The *in vivo* diagnosis became possible with the right heart catheterism and endomyocardial biopsy. Employment of immunohistochemistry and molecular techniques improved the diagnosis and etiology identification. The mechanism of myocyte injury by coxsackie virus was identified in protease 2A coded by the virus and disrupting the dystrophin in the cytoskeleton. Both RNA and DNA viruses may be cardiotropic, and coxsackie and adenovirus share a common receptor (CAR) [34].

Even with advances in other cardiovascular imaging modalities, such as cardiac magnetic imaging (CMI) and computed tomography (CT), Echocardiography remains the most frequently used and usually the initial imaging test to evaluate all cardiovascular diseases related to a structural, functional, or hemodynamic abnormality of the heart or great vessels. The ACC/AHA guidelines emphasize the importance of a directed history and physical examination including assessment of functional capacity and the revised cardiac risk index (RCRI).

Risk factors include age older than 70 years, prior myocardial infarction, angina, congestive heart failure, prior cerebrovascular event Diabetics, and renal insufficiency [35].

The American College of Cardiology (ACC); American heart association (AHA) published guidelines in 1996 and updated in 2009. Routine ECG, Echocardiography to assess LV function, stress testing, coronary revascularization, and coronary angiography is recommended to reduce cardiac risk.

Viral cardiomyopathy occurs when viral infections cause myocarditis with a resulting thickening of the myocardium and dilation of the ventricles. These viruses include Coxsackie B and adenovirus, echoviruses, influenza H1N1, Epstein-Barr virus, rubella (German measles virus), varicella (chickenpox virus), mumps, measles, parvoviruses, yellow fever, dengue fever, polio, rabies and the viruses that cause hepatitis A and C [36,37].

Clinical diagnosis and prognosis of viral myocarditis

The EKG is widely used as a tool used in screening myocarditis but has a sensitivity of 47%. EKG may show nonspecific ST-T waves changes or various degrees of atrioventricular blocks. May show similar characteristics as acute myocardial infarction or pericarditis: ST elevation, ST depression, PR depression, and pathological Q waves. 55% of the patients present with a new onset of supraventricular tachycardia or ventricular arrhythmia. New left bundle branch block, abnormal QRS complexes, or a northwestern axis deviation are associated with higher rates of death or cardiac transplantation [38].

The natural history of myocarditis is unpredictable. Acute myocarditis in patients who present with heart failure and mild LV systolic dysfunction typically recover in weeks to months. Classic finding in an echocardiogram include: global hypokinesis with or without pericardial effusion. Patients with fulminant myocarditis presents with septal thickness and near to normal LV diastolic dimensions. RV systolic function was found to be an independent predictor of death or myocardial transplant in patients with acute myocarditis [39,40].

Cardiomegaly can be shown in a chest x-rays due to the dilation of the chambers, pericardial effusion, or both. Other findings, like pulmonary venous congestion, pleural effusion, and interstitial infiltrates, may be found [41].

Laboratory findings present with elevation of nonspecific serum markers of inflammation (erythrocyte sedimentation rate, C-reactive protein, and leukocyte count). An elevated level of serum FAS and FAS ligand on the initial presentation of the disease are associated with increased mortality. Elevated interleukin-10 predicts a poor prognosis in patients with fulminant myocarditis [42].

Cardiac biomarkers of myocardial injury are not elevated in the majority of the cases with myocarditis. Increased concentrations of Troponin T and Troponin I are more common than the increase of creatinine kinase or creatinine kinase-MB [43].

Cardiac MRI (CMR) is being used more frequently for the non-invasive assessment of patients with suspected myocarditis. The are three imaging criteria for confirming the diagnosis of myocarditis from the Lake Louise Criteria. Two or more positive have a diagnostic accuracy of 78% for myocardial inflammation.

The American College of Cardiology and the European Society of Cardiology described 14 scenarios for endomyocardial biopsy (EMB) and only 2 received a class I recommendation. The first scenario describes the classical presentation of fulminant myocarditis, and the

Proposed cardiac MRI diagnostic criteria for myocarditis	
A. In the setting of clinically suspected myocarditis, cardiac MRI findings are consistent with myocardial inflammation if at least 2 of the following criteria are present [44].	1. Regional or global myocardial signal intensity increase in T2-weighted images 2. Increased global myocardial early enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images 3. There is at least 1 focal lesion with nonischemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (delayed enhancement)
B. Cardiac MRI study is consistent with myocyte injury and/or scar caused by myocardial inflammation if criterion 3 is present.	
C. A repeat cardiac MRI study between 1 to 2 weeks after the initial cardiac MRI study is recommended if:	• None of the criteria are present, but onset of symptoms is very recent, and there is strong clinical evidence for myocardial inflammation • One of the criteria is present
D. The presence of left ventricular dysfunction or pericardial effusion provides additional supportive evidence for myocarditis.	

second one describes the clinical presentation with giant cell myocarditis (GCM). Patients with fulminant myocarditis present with an un-explained new-onset of heart failure symptoms less than two weeks duration associated with a normal-size or dilated LV and hemodynamically compromised. Patients with associated GCM clinical present with unexplained new-onset of heart failure symptoms of 2 weeks to 3 months duration associated with dilated LV and new ventricular arrhythmia, high-degree AV heart block or failure to respond to usual care within 1 - 2 weeks [45].

Pathogenesis of viral myocarditis

Diagnostic criteria for clinically suspected myocarditis
Diagnostic Criteria for Clinically Suspected Myocarditis. Diagnosis of myocarditis is suspected in presence of: 1. ≥ 1 clinical presentation and ≥1 diagnostic criterion, 2. ≥ 2 diagnostic criteria, if the patient is asymptomatic.
Clinical presentation involves: 1. Chest pain, 2. Acute or chronic heart failure, 3. Arrhythmic symptoms (palpitations, syncope and sudden cardiac death).
Diagnostic criteria are as follows: 1. Electrocardiogram (ECG) test features (atrioventricular block, bundle branch block, ST/T-wave changes, supraventricular or ventricular arrhythmias, low volt- age of QRS complex, and abnormal Q waves). 2. Markers of myocardial necrosis (elevated cardiac troponins or CK-MB). 3. Functional and structural abnormalities on echocardiography or CMR imaging (impaired left or right ventricle function, with or without left or right ventricle dilatation, increased ventricle wall thickness, pericardial effusion and intracardiac thrombi). 4. Tissue characteristics by CMR (presence of at least two of three Lake Louise criteria, myocardial edema and early and late gadolinium enhancement) [46].

The majority of studies conducted for the formation of myocarditis and Dilated Cardiomyopathy (DCM) comes from animal models and are in three stages: phase 1, cardiac injury and activation of the innate immune response; phase 2, acute myocarditis involving components of the innate and acquired immune response; and phase 3 recovery in resistant individuals versus progression to DCM in susceptible individuals [47].

Phase 1: injury and activation of the innate immunity

During this phase, there is direct destruction of the cardiomyocytes by virus-mediated lysis. There is a degradation of the cell structures that facilitates the entry of the virus into the cell and consequentially myocarditis injury and cardiac dilation. Frequently is asymptomatic since the innate immune response often prevents the initial damage [48,49].

Phase 2: acute myocardial inflammation

The second phase results from the immune dysregulation triggered by the initial injury. The initial cellular and humoral immune response are responsible for the harmful effects during this phase. It is partly induced by molecular mimicry, which is caused by mimicked epitomes share between the viral antigens and cardiac antigens. Antigenic mimicry has therefore evolved as an important pathomechanism by sensitized T-cells and autoantibodies, which could cause cardiac damage independent from any viral infection of the myocardium. Antibodies that recognize discontinuous epitopes on Coxsackie B virus capsid proteins induce cytopathologic alterations in adolescent male mice [50,51].

Phase 3: progression of DCM

The DCM develops as a result of the myocardial injury. There are cross-reacting antibodies with auto-antigens found in these patients and are indicative of the progression of DCM. Virus- induced cardiac injury releases intracellular cardiac proteins that activate T-cells and associated cytokines mechanisms evolving in autoimmune myocarditis. Inflammatory cells produce matrix-degrading proteases, plus the viral myocardial injury, low-grade inflammation and reparative fibrosis all together lead to left ventricular dilation and cardiac dysfunction [52-57].

Clinical history and physical

The clinical presentation has a high variability from asymptomatic to cardiogenic shock or sudden cardiac arrest. Classical presentations are similar to heart failure: dyspnea, pitting edema, orthopnea. Palpitations and syncope may occur as well. One-quarter of patients present with a reduced LVEF sustained ventricular arrhythmia and other low cardiac output symptoms. If the pericardium is involved, the patient will present with chest pain similar to pericarditis. The viral prodrome characterized by fever, arthralgias, and fatigue, are usually present 1 - 2 weeks before the heart symptoms [58].

In the European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases, 72% of the patients present with dyspnea, 32% had chest pain, and 18% presented with cardiac arrhythmia. Some of the patients with acute focal myocarditis mimics of the ones with the myocardial infarction: with acute onset of chest pain, tachyarrhythmias, or sudden death [59].

Physical examination findings can include tachycardia, laterally displaced point of maximal impulse, soft S1 sound, S3 and S4 gallop, lymphadenopathy (sarcoidosis), rash (hypersensitivity), polyarthritis, subcutaneous nodules, or erythema marginatum (acute rheumatic fever).

Current antiviral treatment

The majority of the patients with acute myocarditis presents with DCM. It will respond well to the standard heart failure therapy: angiotensin-converting enzyme inhibitors, diuretics, angiotensin receptor antagonists, and once the patient is clinically stable, introduce beta- blockers like bisoprolol, metoprolol succinate, or carvedilol. Digoxin should be used with caution and only in low doses. Amlodipine improved survival and histopathological grades of myocardial lesions. Nifedipine showed a decreased activation of proinflammatory cytokines [60].

There has not been proven the effectiveness of nonsteroidal anti-inflammatory drugs [61].

Laboratory diagnosis of viral infection

Parvovirus serology (anti-parvovirus B19 immunoglobulin M [IgM] and immunoglobulin G [IgG] antibodies) can be determined using enzyme-linked immunoassay (ELISA), radioimmunoassay, or immunofluorescence. Results of IgM testing are particularly difficult to interpret. Standardization between laboratories is lacking. Even in a single laboratory, sensitivity and specificity are partly determined by operator skills. High-level viremia in acutely infected persons may cause virus-antibody complexes, which will result in a false-negative IgM test result [62].

Definitive diagnosis can be made based on isolation of the virus in cell culture. Cytopathic effect can usually be seen within 2 - 6 days. Samples are normally taken from the stool or rectal swabs but may be isolated from the oropharynx early in the disease course. False-positive culture results are possible, as excretion can occur for up to 8 weeks after initial infection. Serology can be difficult to interpret. Traditionally, enteroviral infections have been noted after a rise in neutralizing antibodies titer (at least a 4-fold rise in titer between acute and convalescent phase). PCR is also available, with a sensitivity of 66 - 90% [63].

All adenovirus serotypes except types 40 and 41 cause a characteristic cytopathic effect (CPE) in human epithelial cell lines such as HeLa, A549 or HEp2 and in primary human embryonic kidney (HEK) cells. CPE generally occurs within 2 to 7 days with the common lower serotypes, but some others, especially subgroup D serotypes (which cause epidemic keratoconjunctivitis [EKC]), can require up to 28 days [64].

Mumps is confirmed by detecting mumps IgM antibody in serum samples collected as soon as possible after symptom onset. A positive IgM test result indicates current or very recent infection or reinfection. A positive IgM test result may also be observed following mumps vaccination. Serological tests for antibodies specific for Epstein-Barr virus (EBV) antigens are frequently used to define infection status and for the differential diagnosis of other pathogens responsible for mononucleosis syndrome. Using only three parameters [viral capsid antigen (VCA) IgG, VCA IgM and EBV nuclear antigen (EBNA)-1 IgG], it is normally possible to distinguish acute from past infection: the presence of VCA IgM and VCA IgG without EBNA-1 IgG indicates acute infection, whereas the presence of VCA IgG and EBNA-1 IgG without VCA IgM is typical of past infection. However, serological findings may sometimes be difficult to interpret as VCA IgG can be present without VCA IgM or EBNA-1 IgG in cases of acute or past infection, or all the three parameters may be detected simultaneously in the case of recent infection or during the course of reactivation [65].

Prevention of viral myocarditis

Myocarditis is an important cause of acute and chronic heart failure. To determine whether purified exosome product (PEP) can improve and/or prevent myocarditis using a preclinical mouse model of myocarditis. Because estrogen protects women from myocarditis and heart failure It is also tested premenopausal PEP (pmPEP) [66].

Disease management

For patients with cardiogenic shock, mechanical circulatory support is adequate. Extracorporeal membrane oxygenation support may be beneficial with patients with fulminant myocarditis with profound shock. For patients with acute myocarditis and cardiogenic shock, who have deteriorated, it is recommended a ventricular assist device as a bridge to transplantation or recovery [67-70].

Antiviral therapy with ribavirin or interferon in murine viral myocarditis prevented the onset of cardiomyopathy, reduced the severity of the disease, and decreased mortality, shown in a few case series in humans. Ribavirin therapy did not show effectiveness in a case series with humans with fulminant myocarditis [71-74].

There are numerous studies that have investigated the use of immunosuppressants in the treatment of acute myocarditis and DCM. In

randomized controlled trials with patients with acute myocarditis and idiopathic DCM showed that the treatment with immunosuppressants has little or no treatment effects. In contrast, immunosuppressive therapy may be beneficial in treating patients with chronic DCM unresponsive to standard heart failure therapy [75,76].

Control of viral myocarditis

Prospective randomized, controlled trials of immunosuppressive and immunomodulation in myocarditis			
Author	**Design**	**End point**	**Results**
Frustaci., *et al*. [77]	A RCT of 85 patients virus-negative DCM to compare prednisone plus azathioprine with placebo	LVEF at 6 months	There was a significant improve of the LVEF and decreased LV dimensions in the immunosuppressive group.
Gullestad., *et al*. [78]	A RCT with 40 patients with chronic DCM to compare IVIG (intravenous immunoglobulin) with placebo.	Changes in the LVEF at 6 months.	There was improvement in the LVEF in the IVIG group compared to placebo with a LVEF increased from 26+2% to 31+3%, P < 0.01. It showed also a marked increase in the plasma levels of anti-inflammatory mediators in the IVIG group.
Mason., *et al*. [79]	RCT of 111 patients with biopsy-proven myocarditis of unknown etiology, to compare the effects of prednisone plus cyclosporine or azathioprine with other conventional therapy.	LVEF in 28 weeks	The results showed there was no difference in the LVEF or survival between the two groups, P = 0.96.
McNamara., *et al.* [80]	RCT of 62 patients with a recent onset of unexplained DCM, less than 6 months; to compare the use of IVIG with placebo.	Changes in the LVEF at 6 months and then at 12 months.	Showed that both groups has similar improved LVEF at 6 months and 12 months.
Parillo., *et al*. [81]	RCT of 102 patients with a history of idiopathic DCM to compare the effects of prednisone to placebo.	Improved LVEF at 3 months or to reduce LV end-diastolic dimensions.	The LVEF improved in the prednisone group with a mean of 4.3+1.5% with the control group of 2.1+0.8% (P < 0.054).
Wojnicz., *et al*. [82]	RCT of 84 patients with patients with DCM of unknown etiology and an increased HLA expression on EMB, to compare the effects of prednisone plus azathioprine with placebo.	A synthesize of death, heart transplant, and read missions over 2 years.	There was no significant difference: 22.8% for immunosuppressive group versus 20.5% for the placebo group.

Conclusion

Summary the Treatment of Viral Myocarditis

In summary, the treatment for myocarditis remains largely supportive. Immunosuppressive therapy may be beneficial in patients some patients (GCM or sarcoidosis). The therapy with immunomodulatory and antivirals remains largely investigational at this time. There is a need for larger, randomized, controlled trials to determine their role in the treatment of inflammatory heart disease, myocarditis.

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