Chapter 1

Clinical Presentation

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1. Introduction

Myocarditis is a clinical syndrome characterized by inflammation of myocardium and caused by a myriad of etiologies including infectious, autoimmune, myocardial toxins, hypersensitivity reactions and physical agents. Human myocarditis is most frequently caused by viral infection. Ongoing viral infection, myocardial injury, and adverse remodeling can lead to persistent ventricular dysfunction and dilated cardiomyopathy.

The clinical manifestations are highly variable, ranging from asymptomatic electrocardiographic or echocardiographic abnormalities to acute myocardial infarction-like syndrome, overt congestive heart failure, cardiogenic shock, and death. Myocarditis is occasionally the unrecognized culprit in cases of sudden cardiac death. Autopsy series have reported that rates of myocarditis much higher than expected, with overt clinical manifestation from different etiological agents. Postmortem data have implicated myocarditis in 8.6 % to 12 % of sudden cardiac death of young adults [1,2]. Furthermore, it has been identified as a cause of dilated cardiomyopathy in 9 % of cases in a large prospective series [3]. The clinical history in patients presented with myocarditis remains essential to encompass a wide variety of etiologies, many of which are infectious [4]. In the past 10 years, however, viruses, including adenovirus, parvovirus B19, hepatitis C, and herpes virus 6, have emerged as significant pathogens [5]. The geographical distribution can be of relevance for some forms of myocarditis. In selected countries, Chagas disease, Lyme myocarditis, acute rheumatic fever, and disorders associated with advanced human immune deficiency virus infection are significant causes. Other less frequent clinicopathological variants in the etiological spectrum are systemic disorders like giant cell myocarditis, cardiac sarcoidosis and eosinophilic myocarditis. Additionally, drugs, vaccinations, toxins, physical agents like radiation, heat stroke and hypothermia can be the key point for some rare clinical diagnoses. Although histological findings remain the gold standard for establishing the diagnosis of myocarditis, low risk patients are often given a presumptive diagnosis if imaging studies and a compatible clinical scenario suggest new-onset cardiomyopathy.

2. Clinicopathological forms

The changing diagnostic criteria, multifaceted classifications, and varying patterns of infectious disease yielded great deal of confusion over the past two decades. The morphologic criteria for the diagnosis of myocarditis by means of endomyocardial biopsy was proposed by the Dallas criteria in 1986, which defined myocarditis as a process characterized by the presence of an inflammatory cell infiltration of the myocardium with necrosis and/or degeneration of myocytes that is not typical of the myocardial injury of ischemic heart disease. The inflammatory cells are typically lymphocytic but may also include eosinophilic, neutrophilic, giant cells, granulomatous, or mixed cellularity infiltration. The amount of inflammation and its distribution may be mild, moderate, or severe, and focal, confluent, or diffuse, respectively. A retrospective study of 112 consecutive patients with biopsy-confirmed myocarditis demonstrated, 55 % lymphocytic; 22 % borderline (inflammatory cellular infiltrate with no evidence of myocyte necrosis); 10 % granulomatous; 6 % giant cell and 6 % eosinophilic form of myocarditis [6]. Viral etiology of myocarditis is thought to be the primary cause in most cases. However, a direct causative relationship remains less well established in many clinical occasions. The majority of these cases are classified as lymphocytic myocarditis.

The Dallas criteria are considered the first attempt to develop standardized histopathological description of biopsy samples from patients presented with myocarditis [7]. However, histopathology alone can be inadequate to identify the presence of active myocarditis. Some clinicians feel that the definition is too narrow, owing to the limitation by variable interpretation, lack of clinical prognostic values, and low sensitivity [8]. A combination of histopathological characteristics and clinical criteria has been proposed in 1991 [9] as an alternative scheme to be utilized in the diagnosis of myocarditis. Histologic evidence of myocarditis was demonstrated in 35 of 348 patients submitted to endomyocardial biopsy over 5 years. Analysis of the histologic findings and clinical course of these patients resulted in a clinicopathological classification of myocarditis in which four clinical subgroups are identified. The first form of myocarditis is *fulminant myocarditis,* which is a less frequent form of presentation. The patients present with acute heart failure and cardiogenic shock up to two weeks after a distinct viral prodromal episode. They have severe cardiovascular compromise and may require mechanical circulatory support. Multiple foci of active myocarditis are typically found. The histopathological finding does not match the clinical phenotypic severity. Ventricular dysfunction often normalizes if patients survive the acute illness [10]. In one series, 14 of 147 patients (10.2 %) with clinical myocarditis presented in a fulminant fashion, with the triad of hemodynamic compromise, rapid onset of symptoms (usually within 2 weeks), and fever [10]. On follow up, 93 % of the original cohorts were alive and transplant free 11 years following initial biopsy, compared with only 45 % in those with more classic forms of acute myocarditis. The second form of myocarditis is *acute myocarditis,* which describes patients who classically presented with a less distinct onset of illness with nonspecific symptoms related to the heart. Viral prodromal episode occurs between 20 and 80 % of the cases, which can be missed by the patient, and thus cannot be relied upon for diagnosis. They present with an established ventricular dysfunction and may respond to immunosuppressive therapy or their condition may progress to dilated cardiomyopathy. In a series of 245

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patients with clinically suspected myocarditis, the most common symptoms include fatigue (82 %); dyspnea on exertion (81 %); arrhythmias (55 %, both supraventricular and ventricular); palpitations (49 %); and chest pain at rest (26 %), [11]. The presentation can mimic acute coronary syndromes in view of troponin release, ST segment elevation on electrocardiogram, and segmental wall motion abnormalities on echocardiogram. The third form of myocarditis is *chronic active myocarditis,* which describes the majority of older adult patients with myocarditis. They are also presents with a less distinct onset of illness, often insidious, with symptoms compatible with moderate ventricular dysfunction such as fatigue and dyspnea. Affected patients may initially respond to immunosuppressive therapy but often have clinical and histologic relapses and develop ventricular dysfunction associated with chronic inflammatory changes, and mild to moderate fibrosis on histological study including giant cells. The last form of myocarditis is *chronic persistent myocarditis,* which describes a group of patients, who also present with a less distinct onset of illness, is characterized by a persistent histological infiltrate, often with foci of myocyte necrosis but without ventricular dysfunction, despite other cardiovascular symptoms such as chest pain or palpitation.

The previously depicted four clinicopathological forms of myocarditis are still used to describe the clinical presentation and its progression, particularly in the absence of ongoing histological evaluation. These categories may also provide some prognostic information and may suggest which patients can or cannot benefit from immunosuppressive therapy. A new diagnostic criteria derived from limited data was proposed in 2009. The Lake Louise Consensus Criteria utilizes the cardiac magnetic resonance imaging (CMR) for the diagnosis of myocarditis [12]. CMR enhances the ability to detect myocardial inflammation through noninvasive means, as well as to improve diagnostic accuracy. In these criteria, four major domains are considered when making the diagnosis including, clinical presentation compatible with myocarditis, evidence of new or recent onset myocardial damage, increased T2 signal or delayed enhancement on CMR (compatible with myocardial edema and inflammation), and endomyocardial biopsy evidence of myocardial inflammation. Use of CMR appears suitable to identify patients with significant ongoing inflammation, which may be especially important for patients with recurrent or persisting symptoms and in patients with new onset heart failure. The awareness came out that the recommendations proposed by these criteria are based on limited data and that not all centers will be able to apply all components of the suggested protocol.

3. Clinical manifestation

The presentation of myocarditis has a wide range of clinical scenarios, from subtle to devastating, that contributes to difficulties in the diagnosis and classification of this disorder. There are few population-based, epidemiologic studies which have defined the presenting symptoms of acute myocarditis; this is due to the absence of a safe and sensitive noninvasive test that can confirm the diagnosis. Worldwide, the true frequency of disease in its less severe forms, whether clinical or subclinical, across various age segments of the population is more difficult to appreciate. Table 1 summarizes the most significant clinical manifestations and physical findings in patients presented with myocarditis. Typically, myocarditis has a bimodal age distribution

in the general population, with the acute presentation more commonly seen in young children and teenagers. In contrast, in the older adult population the presenting symptoms are more subtle and insidious, often with dilated cardiomyopathy and heart failure. Most studies of acute myocarditis reported a slight preponderance in male patients [13]. The male-to-female ratio is 1.5 to 1, which may be related to a protective effect of natural hormone variations on immune responses in women [14]. The variable clinical manifestation of myocarditis in part reflects the variability in histological disease severity. Myocardial inflammation may be focal or diffuse, involving any or all cardiac chambers. Severe, diffuse myocarditis can result in a clinical manifestation of acute dilated cardiomyopathy.

Many patients with myocarditis present with a nonspecific illness characterized by fatigue, mild dyspnea, and myalgias. Most cases of viral myocarditis are subclinical; therefore, the patient infrequently seeks medical attention during acute illness. These subclinical cases may have transient electrocardiographic abnormalities. The reported antecedent viral infection syndrome is highly variable, ranging from 10 % to 80 % of patients with viral myocarditis [15-18]. Appearance of cardiac specific symptoms occurs primarily in the subacute virus clearing phase; therefore, patients commonly present two weeks after the acute viremia. A few patients present acutely with fulminant congestive heart failure secondary to widespread myocardial involvement. Animal models have led to a much greater understanding of the fulminant clinical course of myocarditis, in which rapid progression, severe ventricular dysfunction and cardiovascular collapse occurs [19]. Fulminant myocarditis, manifested by severe hemodynamic compromise requiring high dose vasopressor support or mechanical circulatory support, was identified in 15 of 147 patients (10.2 %) in a large prospective study [10]. Fulminant cases were additionally characterized by a distinct viral prodromal episode, fever, and abrupt onset (generally <3 days) of advanced heart failure symptoms. These patients typically have severe global left ventricular dysfunction and minimally increased left ventricular end diastolic dimensions. Of note, either borderline or active lymphocytic myocarditis can produce this dramatic clinical presentation. The histological features of chronic myocarditis are usually produced a more subtle clinical course. Adults may present with heart failure years after initial index event of myocarditis.

The medical history may embrace a number of hints that merits an emphasis. Previous history of rheumatic heart disease or symptoms defined by Jones criteria, e.g. fever or arthralgia, can be a clue for the clinical diagnosis acute rheumatic fever. History of tick bite may correlate with suspected Lyme disease. Patients treated for neoplastic disorders with chemotherapeutic agents like doxorubicin may draw attention to anthracyclines-induced myocarditis. History of travel to Central or South America can be a clue for the diagnosis of Chagas disease. Additionally, giant-cell myocarditis should be considered in patients with acute dilated cardiomyopathy associated with thymoma, autoimmune disorders, ventricular tachycardia, or high-grade heart block. Furthermore, unusual cause of myocarditis, such as cardiac sarcoidosis, should be suspected in patients who present with chronic heart failure, dilated cardiomyopathy and new ventricular arrhythmias or second-degree or third-degree heart block, or who do not have a response to standard care [20]. In the European Study of the Epidemiology and Treatment of Inflammatory Heart Disease, a 3055 patients with sus-

pected acute or chronic myocarditis were screened, of them 72 % had dyspnea, 32 % had chest pain, and 18 % had arrhythmias [21]. The most important clinical manifestations in patients with myocarditis are as follows:

Clinical Manifestations	
Subclinical presentation (Most cases of viral myocarditis)	
Nonspecific symptoms e.g. fatigue, arthralgias andmyalgias	
Clinical presentation	
	Shortness of breath, orthopnea or paroxysmal nocturnal dyspnea
	Ankle edema
	Chest pain (concomitant pericarditis)
	Palpitation (arrhythmias)
	Presyncope or syncope (atrioventricular block)
	Sudden cardiac death (arrhythmic death)
	Fever
	Flu-like syndrome (e.g. pharyngitis or tonsillitis)
	Thromboembolic symptoms (systemic or pulmonary)
Physical Findings	
	Normal or unremarkable findings
	Relevant physical signs Tachypnea
	Cyanosis
	Elevated jugular venous pressure
	Tachycardia
	Signs of cardiovascular collapse and shock
	Diffuse apex beat and laterally displaced (cardiomegaly)
	Diminished intensity of first heart sound
	Third and fourth heart sound summation gallops
	Murmurs of mitral or tricuspid valves regurgitation
	Pericardial friction rub and effusion (concomitant myopericarditis)
	Bibasilar crackles
	Hepatomegaly
	Ascites
	Peripheral edema

Table 1. The most significant clinical manifestations and physical findings in patient with myocarditis

3.1. Shortness of breath

Dyspnea on exertion and fatigue are common. A history of shortness of breath at rest, orthopnea, ankle edema, or paroxysmal nocturnal dyspnea is suggestive of congestive heart failure.

3.2 Chest pain

Chest pain is usually associated with concomitant pericarditis. Chest discomfort is reported in one third of patients. The pain is most commonly described as a pleuritic, sharp, stabbing precordial pain. It may be substernal and squeezing and, therefore, difficult to distinguish from that typical of ischemic pain. However, myocarditis can be masquerading as an acute coronary syndrome both clinically and on the electrocardiogram, particularly in younger patients [22]. In one series of 34 patients with known normal coronary anatomy presenting with symptoms and electrocardiographic changes consistent with an acute coronary syndrome, 11 (32 %) of the patients were found to have myocarditis on biopsy [23]. Sarda et al., using myocardial indium111-labeled antimyosin antibody and rest thallium imaging, identified 35 of 45 patients (78 %) who presented with acute chest pain, ischemic electrocardiographic abnormalities, and elevated cardiac biomarkers as having diffuse or focal myocarditis. However biopsy verification of actual myocarditis was not undertaken in this series. Complete recovery of left ventricular function occurred at six months in 81 % of these patients [24]. Some presentations of myocarditis, especially those related to parvovirus B19, present like an acute lateral wall myocardial infarction. Ischemia associated with myocarditis may be due to localized inflammation, or occasionally due to coronary artery spasm [25]. It is essential for clinicians to consider acute myocarditis in younger patients who present with acute coronary syndromes when coronary risk factors are absent, electrocardiographic abnormalities extend beyond a single coronary artery territory or global rather than segmental left ventricular dysfunction is evident on echocardiography.

3.3. Palpitation, presyncope or syncope

Palpitation is a common presentation in patient with myocarditis. Presyncope or syncope in a patient with a presentation consistent with myocarditis may be a signal for high-grade atrioventricular block and risk for sudden death. Small focal inflammation in electrically sensitive areas may be the etiology of patients whose initial presentation is sudden death.

3.4. Fever

Fever with or without sweats and chills occurs in 20 % of patients presenting with myocarditis. A history of fever or flu-like syndrome in form of pharyngitis, tonsillitis, or upper respiratory tract infection before admission occurs in 50 % of patients [17].

3.5. Other symptoms

Apart from the nonspecific symptoms recognized like malaise, myalgias and arthralgias, other extracardiac symptoms may identify infectious, toxic agents or autoimmune diseases affecting the heart and resulting in a myocarditis. A viral prodrome of fever, myalgias, and muscle tenderness may precede viral myocarditis, while a delayed hypersensitivity reaction may be first apparent from a cutaneous rash. Rash, fever, peripheral eosinophilia, or a temporal relation with recently initiated medications or the use of multiple medications suggest a possibility of hypersensitivity myocarditis. The clinical diagnosis of myocarditis is challenging, due to its varying presentation and nonspecific symptoms and physical findings. Accordingly, a high level of clinical suspicion is warranted and a presumptive diagnosis is usually made based on patient's demographics and clinical course.

4. Physical examination

The physical examination of patient presenting with myocarditis is frequently normal. Mild cases of patients with myocarditis may appear to have a simple viral syndrome. More acutely ill patients with acute myocarditis have the classical signs of circulatory impairment due to congestive heart failure. Patients may shows signs of fluid overload including elevated jugular venous pressure, bibasilar crackles, hepatomegaly, ascites and peripheral edema. More severe cases may show cardiovascular collapse and signs of shock. In addition to the signs of fluid overload, physical examination may reveal direct evidence of cardiovascular signs in symptomatic patients. Tachypnea and tachycardia are common. Tachycardia is often out of proportion to fever. Cyanosis may occur as well. The apex impulse may be diffuse and laterally displaced suggesting cardiomegaly. Heart auscultation may reveal diminished intensity of first heart sound. The third and occasionally fourth heart sound summation gallops may be noted with impaired ventricular function, particularly when biventricular acute myocardial involvement results in systemic and pulmonary congestion. If the right or left ventricular dilatation is severe, auscultation may reveal murmurs of mitral or tricuspid valves regurgitation. Table 1 summarizes the most significant clinical manifestations and physical findings in patients presenting with myocarditis.

A pericardial friction rub and effusion may become evident in some patients with diffuse inflammation as a result of myopericarditis. Pericardial tamponade was reported in very rare occasions. Pleural friction rub may develop as the inflammatory process involves surrounding structures. In cases where a dilated cardiomyopathy has developed, signs of peripheral or pulmonary thromboembolism may be encountered. Certain physical findings may imply a specific cause of myocarditis. Enlarged lymph nodes might suggest systemic sarcoidosis. A pruritic, maculopapular rash may suggest a hypersensitivity reaction, often to a drug or toxin. Acute rheumatic fever can present with the modified Jones criteria.

5. Electrocardiogram findings

Generally, the Electrocardiogram (ECG) is a sensitive means in myocarditis. However, its diagnostic value is limited by the low specificity and a wide diversity of changes observed during the course of disease. ECG must be timely repeated, since minor abnormalities detected initially may become subsequently more apparent. ECG findings associated with myocarditis may include first-, second- or third-degree atrioventricular block, intraventricular conduction delay (widened QRS complex), bundle branch or fascicular block, reduced R wave height, abnormal Q waves, ST-T segment changes or low voltage. In one report, either ST-segment elevation or T-wave inversion was present as the most sensitive ECG criterion in <50% of patients, even during the first weeks of the disease [26]. A gradual increase in the width of the QRS complex may be a sign of exacerbation of myocarditis. Frequent premature beats, supraventricular tachycardia and atrial fibrillation may arise as well. Arrhythmias such as sinus arrest, ventricular tachycardia, ventricular fibrillation or asystole may occur and threaten the life of patients with myocarditis. Hence, continuous ECG monitoring is crucial to detect potentially fatal arrhythmias.

6. Clinical manifestation of complications

Despite the fact that a substantial number of myocarditis are never coming to medical attention, a less frequent form of myocarditis is fulminant and leads rapidly to cardiovascular collapse and shock that requires mechanical ventilation. In contrast, if these patients survive the first 3-4 weeks of illness they have almost complete recovery and far fewer long term complications compared with those patients with more indolent courses [27,28]. Generally, there are a number of well recognized complications that may be encountered in the variety of clinical scenarios of patients with myocarditis.

6.1. Congestive heart failure

In many patients who develop heart failure, fatigue and decreased exercise capacity are the initial manifestations. However, diffuse, severe myocarditis, if rapid in evolution, can result in acute myocardial failure and cardiogenic shock. Signs of right ventricular failure include increased jugular venous pressure, hepatomegaly, and peripheral edema. The decline in right ventricular function "protects" the left side of the circulation so that signs of left ventricular failure (such as pulmonary congestion) may not be seen. If, however, there is predominant left ventricular involvement, the patient may present with symptoms of pulmonary congestion including dyspnea, orthopnea, pulmonary crackles, and, in severe cases, acute pulmonary edema. Patients with persistent viral genome expression show limited recovery of left ventricular function, decreased stroke volume index

and more stiffness of the ventricle with the resultant long-term morbidity of heart failure and a mortality of nearly 25 % [29].

6.2. Arrhythmias

A number of arrhythmias may be seen during the clinical course of myocarditis. Sinus tachycardia is more frequent than serious atrial or ventricular arrhythmias, while palpitations secondary to premature atrial or, more often, ventricular premature complexes are common. Ventricular arrhythmias and variable degree heart blocks are uncommon, but well recognized clinical presentations [30,31]. Persistent complex ventricular arrhythmias after apparent resolution of myocarditis were reported in children and young adults as well [32]. Several series have examined the frequency of myocarditis among patients evaluated for life threatening ventricular arrhythmias that occurred in the absence of structural heart disease [33-35]. These patients tend to be younger than 50 years and to have normal or near-normal left ventricular systolic function. The frequency of syncope or cardiac arrest as reported has ranged from 8 % to 61 % [33,34]. Biopsy evidence of myocarditis among patients without structural heart disease has ranged from 8 % to 50 %. On the other hand, patients with ventricular arrhythmias due to lymphocytic or granulomatous myocarditis have a higher risk. Sustained ventricular tachycardia or new heart block in the setting of rapidly progressive congestive heart failure suggests giant cell myocarditis.

Granulomatous myocarditis has been associated more frequently with life threatening ventricular arrhythmias, syncope, and high-grade atrioventricular block requiring temporary or permanent ventricular pacing than has lymphocytic myocarditis [36-38]. Furthermore, granulomatous myocarditis might be suspected in patients who present with apparently chronic dilated cardiomyopathy yet with new ventricular arrhythmias or heart block or who do not have a response to optimal care [20].

6.3. Sudden cardiac death

The risk of sudden arrhythmic death in patients with myocarditis is increasingly appreciated in the current morbidity and mortality data. The discovery of myocarditis in 1 to 9 % of routine postmortem examinations suggests that myocarditis is a major cause of sudden, unexpected death [16]. Although heart failure and cardiomyopathy are more common clinical presentations, patients with myocarditis may present with syncope or unexpected sudden cardiac death, presumably due to ventricular tachycardia or fibrillation [39-42]. Myocarditis is a significant cause of sudden, unexpected death in adults younger than age 40 years and elite young athletes. In these presumably healthy individuals, autopsy findings have revealed myocarditis in up to 20 % of cases [43]. In an autopsy series of patients under age 40 who presented with sudden death in the absence of known heart disease, myocarditis was responsible for 22 % of cases under age 30 and 11 % in older subjects [39]. In another autopsy study of sudden death occurring in 1866 competitive athletes, myocarditis was present in 6 % of the cardiovascular deaths [44]. In one more series of autopsies in military recruits, myocarditis accounted for 20 % of deaths due to identifiable structural cardiac abnormalities [40].

6.4. Dilated cardiomyopathy

A substantial subset of symptomatic cases of postviral or lymphocytic myocarditis present with a syndrome of heart failure and dilated cardiomyopathy. A clinical and pathologic syndrome that is similar to dilated cardiomyopathy (DCM) may develop after resolution of viral myocarditis in animal models and biopsy-proven myocarditis in human subjects [45]. This has led to speculation that DCM may develop in some individuals as a result of subclinical viral myocarditis. Theoretically, an episode of myocarditis could initiate a variety of autoimmune reactions that injure the myocardium and ultimately result in the development of DCM. These abnormalities in immune regulation and the variety of antimyocardial antibodies present in DCM are consistent with this hypothesis. Enteroviral RNA sequences may be found in heart biopsy samples in DCM but with a very variable frequency (0–30 %), [46,47]. Furthermore, analysis of human viruses other than enteroviruses suggests that adenoviruses, herpes, and cytomegalovirus can also cause myocarditis and potentially DCM, particularly in children and young subjects [48,49].

In most acute cases of lymphocytic myocarditis, left ventricular function improves over one to six months with standard heart failure care. However a substantial minority will develop a persistent inflammation that leads to chronic cardiomyopathy. In the patients who develop chronic cardiomyopathy, the risk of heart transplantation and death is high. In a large review of 1230 cases of initially unexplained cardiomyopathy, 9 % were thought to be due to myocarditis [50]. A similar prevalence of 10 % was noted in the Myocarditis Treatment Trial in which endomyocardial biopsy was performed in over 2200 patients with unexplained heart failure of less than 2 years duration [18].

6.5. Thromboembolism

Thromboembolism, arterial and venous, is more evident in patients with left ventricular dysfunction, and appears to be quite frequent complication in certain forms of myocarditis and cardiomyopathies. Additionally, the risk of thromboembolism from either tissue or thrombus from the biopsy site is higher in left ventricular biopsy. Right-sided thromboembolism can be due to thrombus from the venous access sheath, particularly with the internal jugular approach. The possibility of some small added diagnostic yield by taking biopsy samples of the left ventricle in addition to the right is outweighed by the attendant risk of systemic embolism.

Thromboembolism is frequent in advanced Chagas disease, and its occurrence is probably underestimated [51,52]. At autopsy, 73 % of patients have left or right ventricular mural thrombi, with evidence of pulmonary or systemic embolization in 60 % [53]. The apical aneurysm typical of Chagas disease is particularly prone to the formation of thrombi and is associated with a high incidence of thromboembolic events [54]. Furthermore, there is a high incidence of thromboembolism in population with peripartum cardiomyopathy. Thrombi are the result of the hypercoagulable state of pregnancy and of stasis and turbulent flow in the dilated heart. Thrombi often form in patients with lower left ventricular ejection fraction (<35 %), [55,56]. Higher mortality rates have been reported to be due to thromboembolism as well [57].

6.6. Recurrent myocarditis

In the majority of patients, the clinical course of myocarditis is self-limited, and there is complete resolution of myocardial inflammation without further relapse or sequelae. However, the disease has been observed to recur in a similar scenario to initial presentation, which then may resolve spontaneously or be associated with heart failure, arrhythmias, or death. Chronic myocarditis may be considered to be one of the mechanisms of the process of recurrence. Recurrence was reported in 10 to 25 % of patients after apparent resolution of the initial illness [58,59]. Recurrence of myocarditis is well recognized in patients with acute rheumatic fever. It is also demonstrated in subsequent pregnancies after peripartum cardiomyopathy and recurrence should be suspected if ventricular function subsequently deteriorates [59]. Women should be counseled to avoid pregnancy after a diagnosis of peripartum cardiomyopathy. Recurrence was also described in giant cell myocarditis in transplanted heart which responded to intensive immunosuppression. History of third time recurrences of active myocarditis proven by endomyocardial biopsy associated with complete atrioventricular block was described as well and viral studies showed no evidence of recent infection [60]. Another report present recurrent viral myocarditis and vaccine-associated myocarditis in a single patient with complete reversal of the cardiomyopathy and return to normal cardiac function [61]. Moreover, some cases were observed to have recurrent myocarditis after tapering of immunosuppressive therapy and previous biopsy specimens showing healed myocarditis. One report indicated that pericarditis on initial presentation may be associated with a higher rate of recurrence of myocarditis [62]. However, in reality, there are no reliable predictors that identify patients likely to have recurrence.

7. Manifestations of specific forms of myocarditis

Specific clinical forms of myocarditis of variable etiologies will be described below. Table 2 summarized some key clinical hints among specific forms of myocarditis that help with the clinical diagnosis.

7.1. Viral myocarditis

Amongst the multiple infectious etiologies which have been implicated as the cause of clinically significant acute myocarditis, viral myocarditis is the most common and the enterovirus coxsackie B the most significant. Numerous seroepidemiologic and molecular studies have linked coxsackievirus B to outbreaks of myocarditis which occurred before the 1990s. The spectrum of viruses that were detected in endomyocardial biopsy samples shifted from coxsackievirus B to adenovirus in the late 1990s. In the last decade a number of reports implicate new viruses in the etiology of myocarditis and dilated cardiomyopathy. The parvovirus B19 was identified in patients with myocarditis in Germany [63,5], and hepatitis C virus was reported in Japan [64,65] as well.

Clinical clues	Clinical diagnosis	Comments
Preceding upper respiratory febrile or flu-like illness (viral nasopharyngitis or tonsillitis)	Viral myocarditis	Often self-limited
Patients present with chronic heart failure, dilated cardiomyopathy and new arrhythmias or heart block with no response to standard care	Sarcoid myocarditis	Enlarged lymph nodes suggest systemic sarcoidosis
Cutaneous rash (pruritic, maculopapular), fever, peripheral eosinophilia or a temporal relation with recently initiated medications or the use of multiple medications	Hypersensitive/ eosinophilic myocarditis	
Patients treated with anti-neoplastic chemotherapeutic agents	Anthracyclines-induced myocarditis	
History of travel to Central or South America, Systemic or pulmonary thromboembolism	Chagas disease	The apical aneurysm is typical in advanced disease
History of residence or travel through the endemic area; previous tick bites; prior or current erythema migrans lesions and coexistence of neurologic dysfunction	Lyme disease	Varying degrees of atrioventricular conduction block is common
Previous history of rheumatic heart disease or symptoms defined by Jones criteria e.g. erythema marginatum, polyarthralgia, chorea, subcutaneous nodules fever or arthralgia	Acute rheumatic fever	
Heart failure developing in the last month of pregnancy or within 5 months following delivery	Peripartum cardiomyopathy	Higher incidence of thromboembolism (hypercoagulable state of pregnancy). More often when left ventricular ejection fraction <35 %
Sustained ventricular tachycardia in rapidly progressive heart failure associated with thymoma, autoimmune disorders, or high-grade heart block	Giant-cell myocarditis	Syncope or sudden death develop due to ventricular arrhythmias or heart block

Table 2. Some key clinical hints among specific forms of myocarditis that help with the clinical diagnosis.

Early studies suggested that cardiac involvement occurred in 3.5 to 5 % of patients during outbreaks of coxsackievirus infection [66,67]. Most cases of enteroviral myocarditis or pericarditis occur in children and young adults, two-thirds of whom males. In the majority of patients, active myocarditis remains unsuspected because the subclinical and self-limited pattern of presentation or the presence of myocarditis may be inferred only by the finding of transient electrocardiographic ST-T-wave abnormalities. In addition, subtle cardiac symptoms and signs may be overshadowed by the systemic manifestations of the underlying infection or disease process. Clinically, patients give a history of a preceding upper respiratory

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febrile illness or a flu-like syndrome, and viral nasopharyngitis or tonsillitis may be evident. In the United States Myocarditis Treatment Trial, 89 % of subjects reported a syndrome consistent with a viral prodrome [18]. The patient may also have fever, myalgias, and muscle tenderness, that is followed by chest pain, dyspnea or arrhythmias, and occasionally heart failure. A pericardial friction rub is documented in half of cases, and the electrocardiogram shows ST-segment elevation or ST- and T-wave abnormalities. Most adults recover completely and only a minority of cases progress to chronic dilated cardiomyopathy.

In addition to the coxsackievirus B, other members of the genus Enterovirus (coxsackievirus A, echovirus, and poliovirus) and many other viruses have also been associated, less frequently, with myocarditis; these viruses include influenza virus, Epstein–Barr virus, cytomegalovirus, human herpes virus [68], and varicella-zoster virus. Myocarditis and pericarditis were reported in association with influenza virus infection during the 1918–1919 pandemic. Unusually, myocarditis has also been described as a complication of mumps in a severe but usually self-limited form. Molecular diagnostic assays have implicated mumps virus in some cases of endocardial fibroelastosis following myocarditis as well. In a recent study of 172 patients with a biopsy sample showing myocarditis, the most common viruses were parvovirus B19, 36.6 %; enterovirus, 32.6 %; co-infection with HHV-6 and parvovirus B19, 12.6 % human herpes virus 6 (HHV-6), 10.5 %; adenovirus, 8.1 % [63].

The novel influenza virus A (H1N1) pandemic began in Mexico in 2009 and rapidly spread worldwide. Cardiac complications of H1N1 infection were uncommonly reported. Sudden death as a result of myocarditis was a rare recognized complication in otherwise immunocompetent individuals, despite the absence of significant respiratory tract infection. A report from Japan described 10 patients presented with fulminant myocarditis which was confirmed by endomyocardial biopsy in 6 patients, 8 of the cases were rescued [68]. Also, influenza myocarditis was documented in a previously healthy adult due to 2009 pandemic H1N1 virus [69]. Another fatal case of acute myocarditis was reported in an immunocompetent young woman; the autopsy revealed a predominantly lymphocytic myocarditis [70]. Cases diagnosed with fulminant myocarditis were also described in pediatric population, with fatal outcomes within a 30-day of presentation [71]. Though viral myocarditis is most often self-limited and without sequelae, fulminant condition with arrhythmias, heart failure occurs. Arrhythmias are common and are occasionally difficult to manage. Patients with fulminant myocarditis may require mechanical cardiopulmonary support or cardiac transplantation, but the majority survived and many demonstrate substantial recovery of ventricular function. Patients with myocarditis and pulmonary hypertension are at a particularly high risk of death. Deaths attributed to heart failure, tachyarrhythmias, and heart block has been reported and it seems prudent to monitor the electrocardiogram of patients with arrhythmias, especially during the acute illness. In some patients, myocarditis simulates acute myocardial infarction, with chest pain, electrocardiographic changes, and elevated serum levels of myocardial enzymes. Additionally, viral myocarditis are assumed to be the major causes of chronic dilated cardiomyopathy, some cases of myocarditis may recur as well, however the number of cases with acute myocarditis that progresses to chronic dilated cardiomyopathy remains unknown.

7.2. Human immunodeficiency virus (HIV) myocarditis

The human immunodeficiency virus type I (HIV-1) infection that causes the acquired immunodeficiency syndrome (AIDS) has become a worldwide pandemic. Since its initial description 3 decades ago, a number of factors have changed, which may have altered the nature of cardiac manifestation. Notably, survival in adult with HIV infection and AIDS is now prolonged as a result of earlier detection and use of highly active antiretroviral therapy (HAART), [72,73]. At the same time, conditions such as hypertension, diabetes, hyperlipidemia, lipodystrophy and coronary artery disease appear to add further comorbidity to HIV infection [74-76]. Human immunodeficiency virus myocarditis is the most common cardiac pathologic finding at autopsy in HIV infected patients, prevalence being as high as 70 % [77,79]. Myocarditis identified at autopsy or on endomyocardial biopsy in HIV-infected patients is most often nonspecific and manifests as focal, inflammatory lymphocytic infiltrates without myocyte necrosis. However, it is uncertain whether the myocarditis so frequently observed at autopsy is clinically relevant. Myocarditis should be considered in any HIV-infected patient with dyspnea or cardiomegaly. It is present either with signs and symptoms of congestive heart failure, or asymptomatic left ventricular (LV) dysfunction at echocardiography. Of note, the clinical features of other concomitant non-cardiac disorders may mask cardiac involvement and steer to inaccurate approach, since myocardial manifestations due of HIV infection may respond at least transiently to standard therapy. A prospective long-term clinical and echocardiographic follow-up study of asymptomatic HIV-positive patients showed a mean incidence of progression to dilated cardiomyopathy of 15.9 cases per 1,000 patient/year. The precise pathogenesis of myocarditis in AIDS is unclear. Possible direct action of HIV on myocardial tissue or an autoimmune process induced by HIV, possibly in association with other cardiotropic viruses, have been proposed. It is difficult to assess the clinical significance of viral infection of the myocardium in HIV infected patients. A histologic diagnosis of myocarditis was reported in 83 % of patients with dilated cardiomyopathy. This significant proportion had focal, nonspecific lymphocytic myocarditis [80]. Dilated cardiomyopathy can be subclinical or may present with overt clinical findings. Cardiac involvement is often subclinical as echocardiographic studies have demonstrated LV dysfunction in 41 % of asymptomatic HIV-positive individuals [81]. However, in the primary care setting, AIDS cardiac complications are unusual. One autopsy series demonstrated no cardiac disease in 115 consecutive autopsies of patients who died of AIDS-related complications [79]. In one series of 416 HIV-positive patients from Rwanda without previous history of cardiovascular disease and not receiving HAART an echocardiographically evident dilated cardiomyopathy was found in 17.7 % [82]. Overt clinical involvement is seen in 10 % of HIV patients, and the most common clinically significant finding is a dilated cardiomyopathy associated with typical findings of congestive heart failure, namely edema and shortness of breath. Apart from clinical manifestations which may be a direct consequence of HIV infection, there may be consequence of possible etiologies related to non-HIV cardiotrophic viral infection, postviral autoimmune mechanism, drug toxicity, or neoplastic infiltration by Kaposi sarcoma or lymphoma.

Since the introduction of HAART regimens there has been a marked reduction in the incidence of myocarditis and opportunistic infections, which has led to a nearly 30 percent reduction in HIV-associated cardiomyopathy [83]. Opportunistic infections including bacteria, fungi, protozoa, and viruses are the most frequent cause of morbidity and mortality in AIDS, in 10 to 15 % of cases [84]. However, symptomatic disease appears to be rare. Toxoplasma gondii is the most frequently documented infectious cause of myocarditis associated with AIDS. Myocardial toxoplasmosis has been described in 1 to 16 % of autopsy series of patients dying of AIDS [77,78,85]. Cytomegalovirus is another common opportunistic infection in patients with late stage AIDS that can cause myocarditis [83,86]. Other virus identified within the myocardium of HIV-infected or AIDS patients, either at antemortem endomyocardial biopsy or from autopsy material, include Epstein-Barr and coxsackie B virus in adults [80,87,88]. These viruses may be present as either primary infection or as coinfection, and can occur with or without associated myocarditis and with or without associated LV dysfunction. Other infections, like myocardial tuberculosis, appears to be rare [89]. Fungal myocarditis is another unusual complication of disseminated infection that is identified most often at autopsy. Various fungal organisms have been identified in the myocardium at autopsy with associated myocarditis. Cardiac cryptococcus has been diagnosed in association with congestive heart failure and resolved after therapy [90-92].

Other possible etiologies of LV dysfunction are drug toxicity from either abuse of illicit substances, or iatrogenic disease from agents used in the therapy of AIDS. Alcohol, cocaine, or heroin may contribute to LV dysfunction in many cases [93-95]. Therapeutic agents implicated as potential cardiac toxins include zidovudine [96,97], interleukin-2 [98], and interferon alfa-2 [99,100]. Neoplastic infiltration of the heart by Kaposi sarcoma is frequently seen at autopsy and usually associated with widespread disease in the terminal phases of AIDS [101]. Non-Hodgkin lymphoma is also observed in this setting and also associated with widespread disease [102].

7.3. Bacterial myocarditis

Nowadays, myocarditis of infectious etiology caused by non-viral agents is less frequent worldwide. Bacterial involvement of the heart is uncommon, but when it does occur, it is usually as a complication of endocarditis. Various bacteria include (*Corynebacterium diphtheriae, Streptococcus pyogenes, Staphylococcus aureus, Haemophilus pneumoniae, Salmonella* spp., *Neisseria gonorrhoeae, Leptospira, Borrelia burgdorferi, Treponema pallidum, Brucella, Mycobacterium tuberculosis,* Actinomyces, *Chlamydia* spp., *Coxiella brunetti, Mycoplasma pneumoniae* and *Rickettsia* spp). Bacteria like streptococcal and staphylococcal species and *Bartonella, Brucella, Leptospira,* and *Salmonella* species can spread to the myocardium as a consequence of severe cases of endocarditis. Some forms of bacterial myocarditis will be discussed below.

7.3.1. Diphtheritic myocarditis

Worldwide, the most common bacterial cause of myocarditis is diphtheria. As early as 1806, a relationship between infection (diphtheria) and chronic heart disease was postulated, but

it was not until the 1970s, with the advent of endomyocardial biopsy, that the diagnosis of myocarditis could be established during life.

The risk of developing cardiac toxicity is proportional to the severity of local infection. *Corynebacterium diphtheriae* produce toxins that inhibit protein synthesis that can cause myocarditis and lead to a dilated, flabby, hypocontractile heart. The manifestations of diphtheritic myocarditis include various arrhythmias, conduction disturbances, and dilated cardiomyopathy. Cardiomegaly and severe congestive heart failure typically appear after the first week of illness. However, clinically evident cardiac manifestations like dyspnea, muffled heart sounds, gallop rhythm or cardiac dilatation are much less common, occurring in 10 to 25 % of all patients with diphtheria [103]. Myocarditis occurred in 22 % of 656 hospitalized patients with diphtheria in the Kyrgyz Republic in 1995; 7 % of patients with myocarditis and 2 % of patients without myocarditis died [104]. Myocarditis as evidenced by electrocardiographic changes such as ST-T wave changes, QTc prolongation, and/or first-degree heart block can be detected in as many as two-thirds of cases, often occurring when local respiratory symptoms are improving [105,106]. The conduction system is frequently involved. Complete heart block from diphtheritic myocarditis was almost always fatal before temporary cardiac pacemakers were developed. Diphtheritic myocarditis is considered the most serious complication and remains the major cause of mortality [107]. The death rate is highest during the first week of illness, particularly among patients with bull-neck diphtheria and among patients with myocarditis who develop ventricular tachycardia, atrial fibrillation, or complete heart block.

7.3.2. Lyme myocarditis

Lyme disease is an inflammatory disease caused by infection with the spirochete *Borrelia burgdorferi*. In United States, carditis occurs in approximately 5 % of infected patients, while it is less frequent in Europe, affecting approximately 0.3 to 4.0 % of untreated adults [108]. This difference may be related to infection by different organisms. A careful history should address risk factors or possible evidence of *B. burgdorferi* infection particularly in the presence of atrioventricular conduction abnormalities [109]. These include history of residence or travel through an endemic area; previous tick bites; prior or current erythema migrans lesions and coexistence of neurologic dysfunction compatible with neurologic Lyme disease. Cardiac Lyme disease occurs during the early disseminated phase of the disease, usually within weeks to a few months after infection [110]. In a patient with suspected Lyme disease after a tick bite, the possibility of coinfection with Ehrlichia (ehrilichiosis) and Babesia (babesiosis) should be considered as both can also cause myocarditis.

There is a male predominance of approximately 3:1 in cardiac Lyme disease [111]. Patients with cardiac involvement may be asymptomatic and clinically unapparent. However, some patients develop symptomatic myocarditis with cardiac muscle dysfunction and/or associated pericarditis [112,113]. Symptoms mainly include palpitations, shortness of breath, chest pain, presyncope or syncope. In a review of 84 patients with Lyme carditis, the United States Centers for Disease Control and Prevention reported palpitations in 69 %, conduction abnormalities in 19 %, myocarditis in 10 % and left ventricular failure 5 % [114]. Endomyocardial

biopsy samples resemble idiopathic lymphocytic myocarditis, and rarely the spirochetal organisms are identified [108,109,115]. Atrioventricular conduction block of varying degrees are the most common manifestation of Lyme carditis. In some patients, heart block is the first and only manifestation of Lyme disease [116]. Patients may present with first-degree heart block, which can progress to second-degree or complete heart block over a short period of time [117]. One review of 52 patients with Lyme carditis found that 87 % had atrioventricular block, which was usually symptomatic [109]. Wenckebach periodicity occurred in 40 % and complete atrioventricular block in 50 %; other findings include bundle branch and fascicular blocks, although rare. In another report, 38 % of patients with Lyme carditis required a temporary pacemaker [118]. Patients with a PR interval greater than 300 milliseconds carry a highest risk for progression to complete heart block, which may develop rapidly [119]. Complete heart block caused by Lyme disease typically resolves within one week, and minor conduction disturbances within six weeks [109,110]. Other reports showed heart block usually persisting for 3 to 42 days, often resolving spontaneously [108,119-121]. In Europe, scattered case reports have suggested that *B. burgdorferi* may, in isolated cases, be a cause of chronic cardiomyopathy [122,123]. This has not been shown in the United States. A small Dutch series evaluated 42 patients with dilated cardiomyopathy [112]. Nine were seropositive for anti-B. burgdorferi; six recovered fully, two had a partial response, and one showed no improvement.

7.3.3. Salmonella myocarditis

Typhoid fever is a life-threatening illness rarely complicated by myocarditis. Salmonella myocarditis may produce variable clinical manifestations from latent to severe clinical forms, such as acute congestive heart failure or sudden cardiac death [124,125]. Postmortem studies suggest that myocarditis is a major cause of sudden unexpected death in young adults and may account for 20 % of cases [16].

7.3.4. Yersinia myocarditis

Myocarditis sometimes occurs as a complication of Yersinia. Clinical evidence of Campylobacter-associated myocarditis described in association with *Campylobacter* spp. Enteritis [126]. Mild, self-limited myocarditis accompanies 10 % of cases of Yersinia-induced arthritis and can occur independently. Typical manifestations include cardiac murmurs and transient electrocardiographic abnormalities, such as prolongation of the PR interval and nonspecific ST-segment and T wave changes. The syndrome of Yersinia-induced arthritis and carditis can be confused with acute rheumatic fever.

7.3.5. Legionella myocarditis

Myocardial involvement is a rare manifestation of Legionella infection, although the most common extrapulmonary site of Legionnaires' disease is the heart. Numerous reports have described myocarditis, pericarditis, postcardiotomy syndrome, and prosthetic valve endocarditis [127-129]. Most cases have been hospital acquired. Legionella carditis in the adult

population is invariably seen in association with pneumonia; however, isolated Legionella myocardial involvement without associated pneumonia has been reported [130].

7.3.6. Mycoplasma myocarditis

Cardiac abnormalities have rarely been reported in conjunction with *Mycoplasma pneumoniae* infection, including myocarditis and pericarditis [131,132]. Myocarditis has been described in rare autopsy reports as well. Cardiac manifestations include rhythm disturbances, congestive heart failure, chest pain, and conduction abnormalities on the electrocardiogram.

7.3.7. Q fever myocarditis

Myocarditis, though uncommon, may be a particularly severe manifestation of Q fever. In a study of 1070 patients with acute Q fever from southern France, 1 % had pericarditis, and 1 % had myocarditis. In other series of 1276 patients with Q fever over a 15-year period, only eight developed myocarditis but two were among the only 12 patients with Q fever who died [133]. Q fever may also cause endocarditis which usually occurs in patients with previous valvular damage or immunocompromise particularly on a bicuspid aortic valve or a prosthetic valve.

7.3.8. Chlamydial myocarditis

Chlamydial infection also has been reported in association with clinical manifestations of myocarditis [134].

7.3.9. Relapsing fever myocarditis

Relapsing fever is an arthropod-borne infection characterized by recurrent episodes of fever, caused by spirochetes of the genus Borrelia. The first episode of illness tends to be the most severe. Myocarditis appears to be common in both louse-borne and tick-borne relapsing fever. Clinical and electrocardiographic evidence of myocarditis and myocardial dysfunction includes a prolonged QTc interval, commonly a galloping third heart sound, elevated central venous pressure, arterial hypotension, and rarely pulmonary congestion. Heart involvement has been prominent in fatal cases [135].

7.4. Acute rheumatic fever

Acute rheumatic fever (ARF) is a nonsuppurative complication of group A streptococcus pharyngitis that occurs two to four weeks following infection and arises as an autoimmune response to extracellular or somatic bacterial antigens that share epitopes similar to human tissue. Rheumatic fever remains one of the most important cardiovascular diseases that cause significant cardiac morbidity and mortality in developing countries [136]. In developed countries, ARF is generally preceded by pharyngitis but not skin infection [137]. However, data from endemic regions with ARF and rheumatic heart disease suggest a less clear association [138-140]. Acute rheumatic fever occurs most frequently in children 5 to 15 years of age. The incidence of rheumatic heart disease in patients with a history of ARF is variable;

in general, valvular damage manifesting as a murmur later in life is likely to occur in about 50 % of patients with evidence of carditis at initial presentation [141,142]. The myocardial lesions consist of nonspecific lymphocytic myocarditis and Aschoff nodules. The latter are pathognomonic of ARF. Myocarditis is often indicated by cardiomegaly and/or congestive heart failure (CHF), particularly in the absence of a significant pericardial effusion. The presence of valvulitis is established clinically by auscultatory findings. Although CHF in rheumatic fever patients traditionally has been ascribed to severe myocardial inflammation, endomycardial biopsy in patients with rheumatic carditis does not show significant evidence of myocyte damage [143]. In addition, echocardiographic left ventricular ejection fraction and indices of myocardial contractility remain normal in patients with rheumatic carditis even in the presence of CHF [144]. Further, CHF occurs only in the presence of hemodynamically significant valvular lesions. The diagnosis of ARF is established largely on clinical grounds. The clinical manifestations were initially described by Jones [145]. Subsequently, guidelines for the diagnosis of rheumatic fever reviewed have been established by the American Heart Association Working Group in 2002 [146]. The five major manifestations include migratory arthritis, carditis and valvulitis, central nervous system involvement (e.g., Sydenham chorea), erythema marginatum and subcutaneous nodules. Whereas the four minor manifestations include, arthralgia, fever, elevated acute phase reactants (erythrocyte sedimentation rate, C-reactive protein) and prolonged PR interval. The probability of ARF is high in the setting of group A streptococcal infection followed by two major manifestations or one major and two minor manifestations. Strict adherence to the Jones criteria in areas of high prevalence may result in under detection of the disease. This was illustrated in a report of 555 cases of confirmed ARF among Australian aboriginals in whom monoarthritis and low-grade fever were important manifestations [147].

7.5. Chagas myocarditis

Chagas disease is a protozoan infection due to *Trypanosoma cruzi*; transmitted by an insect vector, produces an extensive myocarditis that typically becomes evident years after the initial infection. It is a major public health problem in endemic areas and in immigrants from rural Central or South America. Chagas myocarditis is by far the most common form of cardiomyopathy in Latin American countries [148]. Chagas disease consists of acute and chronic phases. During the chronic phase, many patients present the indeterminate form. The latter describes patients who have positive serology, but no symptoms, physical signs, or laboratory evidence of organ involvement [149].

7.5.1. Acute phase

The first signs of acute Chagas' disease develop at least 1 week after contact with the infected vector. Local skin indurated erythema and swelling produces the typical portal of entry lesions at the skin known as chagomas accompanied by local lymphadenopathy. The conjunctiva portal of entry may result in a unilateral painless periorbital edema and swelling of the palpebrae (Romana's sign). Infection can also occur through blood transfusion, congenital transmission, and, much less often, organ transplantation, laboratory accident, breast

feeding, and oral contamination [150]. Although heart transplantation for Chagas cardiomyopathy has been successfully performed, reactivation of *Trypanosoma cruzi* is common. These initial local signs may be followed by malaise, fever sweating, myalgias anorexia; a morbilliform rash may also appear. Generalized lymphadenopathy and hepatosplenomegaly may develop. Cardiac failure occurs secondary to myocarditis; cardiac involvement is present in over 90 % of those in whom the diagnosis is made [151]. The frequency and severity of myocarditis are inversely proportional to age [152]. The acute symptoms resolve spontaneously in virtually all patients, who then enter the asymptomatic or indeterminate phase of chronic T. cruzi infection. The electrocardiogram normalizes in over 90 % of patients after one year.

The indeterminate form usually lasts 10 to 30 years and only approximately 30 % of the patients develop overt cardiac disease. Most patients remain asymptomatic throughout their life. The natural history of this phase of disease is characterized by subtle degree of cardiac involvement and gradual appearance of clinical or electrocardiographic markers of cardiac involvement, which signals the onset of the chronic phase. In one review, progression from indeterminate to the full-blown clinical form in the chronic phase occurred at approximately 2 % per year [149]. In another report, 38.3 % of patients with positive serology but without symptoms developed chagasic cardiomyopathy over a 10-year period [153]. About 50 % of patients remain with the indeterminate form indefinitely [154].

7.5.2. Chronic phase

The chronic form is characterized by dilatation of cardiac chambers, fibrosis and thinning of the ventricular wall, aneurysm formation (especially at the left ventricular apex), and mural thrombi.

Chronic progressive heart failure is the rule and is associated with poor survival. Mortality associated with the chronic phase is almost exclusively due to cardiovascular involvement. The cause of death is sudden cardiac death in 55 to 65 %, progressive heart failure in 25 to 30 %, and stroke in 10 to 15 % [155]. Symptoms and physical signs at this stage of the disease arise from three basic syndromes that often coexist in the same patient, heart failure, cardiac dysrhythmia, and thromboembolism (systemic and pulmonary). Heart failure in Chagas heart disease is usually biventricular and commonly presents with fatigue. However, right-sided failure manifested with increased jugular venous pressure, peripheral edema, ascites, and hepatomegaly is characteristically more pronounced than left-sided failure manifested with dyspnea and pulmonary rales. Both systolic and diastolic dysfunction can occur [156]. Cardiac examination typically reveals murmurs of mitral and tricuspid regurgitation, wide splitting of the second heart sound due to right bundle branch block and prominent diffuse apical thrust.

Cardiac arrhythmias may cause palpitation, lightheadedness, dizziness, or syncope. Autonomic dysfunction results in marked abnormalities in heart rate variability. Chest pain is a common symptom and usually atypical in Chagas heart disease. It may mimic angina due to abnormal coronary vasomotion postulated as underlying mechanism [157]. Sudden cardiac death accounts for 55 to 65 % of deaths in CD; the real frequency of this complication is probably underestimated, particularly in rural areas [155]. Sudden cardiac arrest can occur

even in previously asymptomatic patients [158]. However, most patients have severe underlying heart disease, including ventricular aneurysms at multiple sites (posterior-lateral, inferior basal, or apical), which is a characteristic finding in Chagas heart disease [158]. Sudden death is usually precipitated by exercise, and can be caused by VT or fibrillation, asystole, or complete AV block [159]. The electrocardiogram is abnormal in most patients with cardiac involvement and typically shows right bundle branch block, left anterior hemiblock and diffuse ST-T changes, which may progress to complete atrioventricular block. Ventricular arrhythmia may also be seen as premature beats that may be multiform and runs of nonsustained ventricular tachycardia. The severity of ventricular arrhythmias tends to correlate with the degree of LV dysfunction. Other changes, like abnormal Q waves, various degrees of atrioventricular block, QT interval prolongation and variation in the QT interval (QT dispersion) are frequent findings [160].Virtually all types of atrial and ventricular arrhythmias can occur; atrial fibrillation and low QRS voltage may be observed in advanced disease. A potentially serious complication of chronic Chagas heart disease is thromboembolism. In a review of 1345 autopsies, cardiac thrombus or thromboemboli were reported in 44 %; both right and left cardiac chambers being equally affected [52]. Although thromboembolic phenomena were more common in the systemic circulation, pulmonary embolism accounted for 14 % of deaths. Cardioembolism appears to be an important cause of acute ischemic stroke. One series of 94 patients with Chagas disease in Brazil reported higher rate of cardioembolism (56 versus 9 %) as compared to control group [161]. Stroke was also reported significantly more frequently in patients who had Chagas disease related cardiomyopathy compared with patients who had other cardiomyopathies (15.0 versus 6.3 %), [162]. Echocardiography or contrast ventriculography may reveal left ventricular apical aneurysm, regional wall motion abnormalities, or diffuse cardiomyopathy. The cause of death is either intractable CHF or arrhythmias, with a minority of patients dying from embolic phenomena.

7.6. Fungal myocarditis

The incidence of invasive fungal disease has dramatically increased over the past few decades corresponding to the rising number of immunocompromised patients. Cardiac fungal infection, especially myocarditis, may be difficult to recognize clinically and may in itself produce a fatal outcome. Myocardial involvement frequently occurs in disseminated fungal infection in which multiple organs are often affected. Conditions that appear predisposing to fungal infection are human immunodeficiency virus infection, medication like, corticosteroids, antineoplastic agents or broad-spectrum antibiotics, alone or in combination with invasive medical procedures [163]. Candida was the most frequently observed organism, while Aspergillus was the second most frequent fungus to involve the heart. Rarely Cryptococcus is identified as a cause of myocarditis as well.

7.7. Eosinophilic and hypersensitivity myocarditis

The association between eosinophilia (eosinophil count >500/mm3) and heart disease was first identified by Loeffler [164]. A specific eosinophilic form of myocarditis has been identified following drug-induced hypersensitivity reactions and systemic hypereosino-

philic syndromes [165]. Eosinophilic myocarditis is characterized by a predominantly mature eosinophils infiltration of the myocardium and other organ systems. It occurs in association with systemic diseases such as hypereosinophilic syndrome, Churg-Strauss syndrome and Löffler's endomyocardial fibrosis. It may also occur in association with cancer, parasitic, helminthic or protozoal infections such as Chagas disease, toxoplasmosis, schistosomiasis, trichinosis, hyatid cysts and visceral larval migrans [166-168]. Eosinophilic myocarditis has been reported after vaccination for several diseases, including smallpox [169,170]. Acute eosinophilic necrotizing myocarditis is a rare aggressive form of eosinophilic myocarditis and may represent an extreme form of hypersensitivity myocarditis which is characterized by acute onset, and rapidly results in cardiovascular deterioration and circulatory collapse carrying high mortality rates [171]. The clinical manifestations of eosinophilic myocarditis may include right and left congestive heart failure, endocardial and valvular fibrosis leading to regurgitation, and formation of endocardial thrombi. Clinical awareness is warranted when presentation may mimics acute myocardial infarction, with ischemic chest pain and ST-segment elevation on electrocardiography [172]. Hypersensitivity myocarditis is a form of eosinophilic myocarditis due to autoimmune reaction affecting the heart muscle, often induced by drugs. It is often first discovered at postmortem examination. In one series, the prevalence of clinically undetected hypersensitivity myocarditis in explanted hearts ranged from 2.4 to 7 % [173]. Numerous drugs have been implicated in hypersensitivity myocarditis, including antibiotics, [174] like penicillins, cephalosporins and sulfonamides; antipsychotics, [175] like clozapine and tricyclic antidepressants [174,176,177]; other drugs like methyldopa, hydrochlorothiazide, furosemide, tetracycline, azithromycin, aminophylline, phenytoin and benzodiazepines [165,178,179]. Hypersensitivity myocarditis not always develops early in the course of medication. Patients taking the antipsychotic agent clozapine have been reported to develop myocarditis more than two years after the drug was started [180]. Prolonged continuous infusion of dobutamine has also been associated with hypersensitivity myocarditis which has been reported in 2.4 to 23 % [181,182]. Cocaine also rarely produce a hypersensitivity myocarditis, unlike the hypereosinophilic syndrome, peripheral eosinophilia is typically absent [183].

Clinically, the presentation is often heralded by fever, peripheral eosinophilia and a drug rash that occurs days to weeks after administration of a previously well-tolerated agent. Electrocardiographic abnormalities show nonspecific ST segment changes or infarct patterns [184]. Myocardial involvement varies but usually does not result in fulminant heart failure or hemodynamic collapse. However, some patients present with sudden death or rapidly progressive heart failure [172,174].

Eosinophilic myocarditis can be a manifestation of eosinophilia-myalgia syndrome, which is a multisystem disease, caused by ingestion of contaminants in L-tryptophan containing products [185], characterized by peripheral eosinophilia and generalized disabling myalgias [186]. Eosinophils, lymphocytes, macrophages, and fibroblasts accumulate in the affected tissues, but their role in pathogenesis is unclear. The disease is frequently evolves into a chronic course but can be fatal in up to 5% of patients.

7.8. Giant cell myocarditis

Idiopathic giant cell myocarditis is a rare inflammatory disease that often affects previously healthy young adults and is frequently a fatal type of myocarditis [187]. The pathogenesis of this disorder is not known. It is identified by the presence of multinucleated giant cells associated with eosinophils and myocyte destruction in the absence of granulomas on endomyocardial biopsy. It is thought to be primarily autoimmune in nature because of the reported comorbidity with a variety of autoimmune disorders [188], thymoma [189], and drug hypersensitivity [190]. Idiopathic giant cell myocarditis is usually a fulminant form of myocarditis, characterised by a history of rapid progression of severe heart failure associated with refractory sustained ventricular arrhythmias. Giant-cell myocarditis is sometimes distinguished from the much more common postviral myocarditis by the presence of ventricular tachycardia, heart block, and a downhill clinical course, despite optimal clinical care. In the series of 63 patients with giant cell myocarditis enrolled in the multicenter Giant Cell Myocarditis Treatment Trial, 75 % identified with heart failure symptoms as the primary presentation, 14 % with ventricular arrhythmia and heart block in 5 % [188]. Most patients will require cardiac transplantation, the median survival from the onset of symptoms is less than 6 months and has an 89 % rate of death or transplantation. This represents a significantly worse outcome compared to lymphocytic or viral myocarditis. Despite a 25 % incidence of post-transplantation recurrence of giant cell myocarditis detected by biopsy, the 5-year survival after transplantation is about 71 % which is comparable to survival after transplantation for cardiomyopathy.

7.9. Systemic lupus erythematosus myocarditis

Acute myocarditis is an uncommon manifestation of systemic lupus erythematosus (SLE), with a prevalence of 8 to 25 % in different studies [191,192]. Myocarditis is frequently asymptomatic but less often may accompany other manifestations of acute SLE. In particular, pericarditis commonly occurs in about two-thirds of patients, and generally follows a benign course; however, pericardial tamponade or constriction occur infrequently. Myocarditis generally parallels the activity of the disease and, although common histologically, rarely results in clinical heart failure unless associated with hypertension. African American ethnicity is associated with a higher risk of myocarditis compared with Hispanic and Caucasian ethnicity [191]. Myocarditis should be suspected if there is resting tachycardia disproportionate to body temperature, ST and T wave electrocardiographic abnormalities and unexplained cardiomegaly. The cardiomegaly may be associated with symptoms and signs of heart failure, conduction abnormalities or arrhythmias [193]. Patients with SLE are at increased risk for myocardial ischemia due to accelerated atherosclerosis or coronary arteritis. Endocardial involvement with fibrinous endocarditis [194] is another serious manifestation that can lead to valvular insufficiencies or embolic events. Likewise, patients with the antiphospholipid syndrome have a higher incidence of valvular disease, a variety of thrombotic disorders, myocardial infarction, pulmonary hypertension, and cardiomyopathy. Myocardial biopsy reveals mononuclear cells infiltration distinguishing active myocarditis from fibrosis and other causes of cardiomyopathy [195] or rarely cardiotoxicity induced by

hydroxychloroquine [196]. Inflammation may lead to fibrosis that may be manifested clinically as dilated cardiomyopathy.

7.10. Sarcoid myocarditis

It is a granulomatous form of myocarditis. The clinical evidence of myocardial involvement is present in approximately 5 % of patients with sarcoidosis. However, an autopsy series reported higher rates of about 25 % of subclinical cardiac involvement [197-199]. The clinical manifestations of cardiac sarcoidosis are largely nonspecific and may precede, follow, or occur concurrently with involvement of other organs. Sarcoid heart disease should be considered in the evaluation of an otherwise healthy young or middle aged person with cardiac symptoms or in a patient with known sarcoidosis who develops arrhythmias, conduction disease, or heart failure. Patients who present with apparently chronic dilated cardiomyopathy yet with new ventricular arrhythmias or second-degree or third degree heart block or who do not have a response to optimal care are more likely to have cardiac sarcoidosis [20]. Cardiac symptoms were reported in 101 patients, when cardiac sarcoidosis was diagnosed in 84 % compared to 4 % in asymptomatic patients [200]. Endomyocardial biopsy shows characteristic noncaseating granulomas. However, the diagnosis can also be inferred if there is a tissue diagnosis of sarcoidosis from an extracardiac source in the presence of a cardiomyopathy of unknown origin.

Electrocardiographic abnormalities are found in nearly 70 % of patients with sarcoidosis [197]. Cardiac involvement with sarcoidosis may produce clinical symptoms and electrocardiographic findings simulating myocardial infarction. Conduction abnormalities in form of first-degree heart block due to disease of the atrioventricular node or bundle of His, and various types of intraventricular conduction defects, are common among patients with cardiac sarcoidosis [197]. These lesions may initially be silent, but can progress to complete heart block and cause syncope [201]. Sustained or nonsustained ventricular tachycardia and ventricular premature beats are the second most common presentation of cardiac sarcoidosis; electrocardiography reveals ventricular arrhythmias in as many as 22 % of patients with sarcoidosis [202]. Supraventricular arrhythmias are infrequent. Sudden death due to ventricular tachyarrhythmias or conduction block accounts for 25 to 65 % of deaths due to cardiac sarcoidosis, however, sudden death can occur in the absence of a previous cardiac event [203-205]. Both systolic and diastolic heart failure can occur. Left ventricular aneurysms develop in patients with extensive involvement of the myocardium. Mitral incompetence may occur with cardiac sarcoidosis due to associated systolic dysfunction and left ventricular dilation or due to papillary muscle involvement by sarcoid granulomas [206]. Tricuspid regurgitation with atrioventricular block secondary to infiltration of tricuspid valves and conduction system by sarcoid granulomas has been reported as well [207]. A left atrial granulomatous mass resembling myxoma has been reported too [208].

7.11. Peripartum cardiomyopathy

The syndrome is a rare disorder of pregnancy. It was recognized in 1937, as a distinct clinical entity [209]. Currently, the etiology of peripartum cardiomyopathy (PPCM) remains un-

clear. However, there is compelling data from animal and human studies suggesting that PPCM is actually a type of myocarditis arising from an infectious, autoimmune, or idiopathic etiology. The relationship between pregnancy and viral myocarditis was first published in 1968 [210]. Endomyocardial biopsies in women with PPCM have demonstrated myocarditis in many patients. The highest incidence of myocarditis reported in PPCM was 76 % [211], however much lower incidence was reported (8.8 %), which found to be comparable to an age and sex matched control population undergoing transplantation for idiopathic dilated cardiomyopathy (9.1 %), [212]. Viral genomes of parvovirus B19, human herpes virus 6, Epstein–Barr virus and human cytomegalovirus revealed in endomyocardial biopsy specimens from patients with PPCM [213]. Other reported data linked with Chlamydial infection [214]. Women present with heart failure during the peripartum period and become manifested in the last month of pregnancy or within 5 months of the delivery without apparent etiology for the heart failure can be found. The clinical scenario is challenging because many normal women in the last month of a normal pregnancy experience dyspnea, fatigue and ankle edema, symptoms that can mimic early congestive cardiac failure. Physical examination can be significant for signs of right and left heart failure. Symptoms and signs that should raise the suspicion of heart failure include paroxysmal nocturnal dyspnea, chest pain, nocturnal cough, new regurgitant murmurs, pulmonary rales, elevated jugular venous pressure and hepatomegaly. The electrocardiogram usually demonstrates normal sinus or sinus tachycardia rhythm, but frequent ectopy and other atrial arrhythmias may also be present. Left ventricular hypertrophy, inverted T waves, Q waves, and nonspecific ST-T changes have also been reported [215]. Recurrence in a subsequent pregnancy has been reported. However, significant improvement occurs in up to 50 % of affected women; others are left with a progressive dilated cardiomyopathy.

8. Conclusion

Myocarditis presents with a highly variable clinical scenarios. A thorough medical history with emphasis on possible causes is essential. A scrupulous awareness to ample clinical scenarios is essential for clinicians, particularly when the cases are lacking apparent etiologies, or the presentations resembles that of acute myocardial infarction, asymptomatic left ventricular systolic dysfunction, unexplained ventricular tachyarrhythmias or cardiogenic shock. Clinicians need to be attentive when evidence is present of myocardial injury not attributable to epicardial coronary artery disease, primary valvular disease or noninflammatory causes. Usually, most cases of myocarditis are self-limited and spontaneous improvement occurs in a substantial number of patients with lymphocytic disease but is rarely, if ever, observed with granulomatous myocarditis. While routine diagnostic endomyocardial biopsy is not required in most cases of suspected acute myocarditis, the need for biopsy will depend upon the time course and severity of the clinical presentation.

Better understanding of the clinicopathological that characterize the diverse clinical scenarios and more comprehensive understanding of the natural history of the various subtypes of

myocarditis should assist clinicians for better approach and subsequently plan more effective therapy in the future.

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