Myocarditis: Causes, Investigations, and Treatment

Omar Elsaka[1]

1. Department of Cardiology, Mansoura University, Faculty of Medicine, Mansoura Manchester Medical Program (MMMP), Mansoura, Egypt.

Corresponding author: Omar Elsaka

Note: The name of the author should be written as (Omar Elsaka), don't write it as (Omar Mohamed Raouf Mohamed Ahmed Elsaka). please, just write it as (Omar Elsaka).

Abstract

Background: Inflammatory cardiomyopathy, characterized by infiltration of inflammatory cells in the myocardium and an increased risk of heart failure, has a variety of etiologies. Inflammatory cardiomyopathy is strongly associated with viral infections, but it can also be caused by bacterial, protozoal, or fungal infections, as well as a variety of drug-related toxic and immunological diseases. Despite extensive research, complex inflammatory cardiomyopathy due to left ventricular dysfunction, heart failure, or arrhythmias has a poor prognosis. Currently, the reason is not clear why some patients recover without residual myocardial injury while others develop cardiomyopathy. The respective roles of pathogens, host genomics, and environmental factors in disease progression and treatment, in which viruses are active and can only be observed, are still being discussed. As a result, treatment strategies are not well established. In this review, we summarize and evaluate the available evidence for the pathogenesis, diagnosis, and treatment of myocarditis and inflammatory cardiomyopathy, with a specific focus on viral and viral myocarditis. In addition, we identify information spaces, analyze available test models, and suggest future field directions. Current information and open questions on the cardiovascular effects associated with severe respiratory coronavirus 2 (SARS-CoV-2) infection are also discussed. This review is the result of a scientific collaboration between members of the Heart Failure Association of ESC, the Heart Failure Society of America, and the Japanese Heart Failure Society.

Conclusion: Myocarditis is always a challenging condition to diagnose and control. Its contribution to lifelong illness and death is significant.

***Keywords**: myocarditis, dilated cardiomyopathy, endomyocardial biopsy, cardiac magnetic resonance imaging, and immunotherapy.*

Introduction

Myocarditis is an inflammation of the heart muscle (myocardium). Inflammation can reduce the heart's ability to pump and cause a fast or abnormal heart rhythm (arrhythmia). Infections often cause myocarditis. Sometimes myocarditis can be caused by a reaction to a drug or as part of a normal inflammatory condition. Signs and symptoms include chest pain, fatigue, shortness of breath, and a fast or abnormal heartbeat. Severe myocarditis weakens your heart so that your entire body does not get enough blood. A clot can form in your heart, which can lead to a stroke or heart attack. Treatment of myocarditis depends on the cause. Myocarditis is most often due to a viral infection. Other causes include bacterial infections, certain medications, toxins and autoimmune disorders. A diagnosis may be supported by an electrocardiogram (ECG), increased troponin, heart MRI, and occasionally a heart biopsy. An ultrasound of the heart is important to rule out other potential causes such as heart valve problems (1).

Treatment depends on both the severity and the cause. Medications such as ACE inhibitors, beta blockers, and diuretics are often used. A period of no exercise is typically recommended during recovery. Corticosteroids or intravenous immunoglobulin (IVIG) may be useful in certain cases. In severe cases an implantable cardiac defibrillator or heart transplant may be recommended. In 2013, about 1.5 million cases of acute myocarditis occurred. While people of all ages are affected, the young are most often affected. It is slightly more common in males than females. Most cases are mild. In 2015 cardiomyopathy, including myocarditis, resulted in 354,000 deaths up from 294,000 in 1990. The initial descriptions of the condition are from the mid-1800s (1).

Causes and Risk Factors

Often, the cause of myocarditis cannot be determined. There are many possible causes but the risk of myocarditis is rare. Possible causes of myocarditis include: Bacteria. Several viruses are often associated with myocarditis, including those that cause the common cold (adenovirus); COVID-19; Hepatitis B and C; Parvovirus, which causes small rashes, is most common in children (fifth infection); and herpes simplex virus. Intestinal infections (echovirus), mononucleosis (Epstein-Barr virus) and German measles (rubella) can also cause myocarditis. It is also common for people with HIV, the virus that causes AIDS. Bacteria. Bacteria that cause myocarditis include staphylococcus, streptococcus, the bacteria that cause diphtheria, and the tick-borne bacteria that cause Lyme disease. Parasites. These include worms such as Trypanosoma cruzi and Toxoplasma, as well as others that are spread by insects and can cause a disease called Chagas disease. Chickenpox is more common in Central and South America than in the United States, but it can affect travelers and migrants to that part of the world. mould. yeast infections such as candida; mold, such as aspergillus;

And other fungi, such as Histoplasma, commonly found in bird droppings, can sometimes cause myocarditis, especially in people with weakened immune systems (2).

Myocarditis also sometimes occurs when you are exposed to: drugs or illicit drugs that cause allergic or toxic reactions. These include drugs used to treat cancer; Antibiotics such as penicillin and sulfonamide drugs; Other antidepressants; And other illicit substances such as cocaine. Chemicals or radiation. Myocarditis is sometimes caused by exposure to certain chemicals, such as carbon monoxide and radiation. Other diseases. These include disorders such as lupus, Wegener's granulomatosis, giant cell arthritis, and the Takayasu artery (3).

Mechanism of Myocarditis

Myocarditis is an inflammation of the myocardium with necrosis of the myocyte heart cells. Certified myocarditis biopsy usually shows inflammatory inflammation of the myocardium by lymphocytes, neutrophils, eosinophils, large cells, granulomas, or a mixture. The pathophysiology of myocarditis is still the subject of research. Possible causes of myocardial infarction include Direct cardiomyocyte damage caused by an infectious disease or other cardiotoxic agent, Myocardial injury caused by autoimmune response to an infectious agent or other cardiotoxic agent, Myocardial infarction may spread or intensify. Inflammation can spread to the pericardium causing myopericarditis. The degree of myocardial involvement and expansion of the adjacent pericardium may determine the type of symptoms. Increased involvement can lead to heart failure, arrhythmia and sudden cardiac death. Focused involvement is less likely to cause heart failure but can lead to heart disease and sudden death. Involvement of pericardium leads to chest pain and other common symptoms of pericarditis. Some patients remain asymptomatic whether the myocardial involvement is focused or widespread (4).

Many types of myocarditis involve the invasion of heart tissue by one or two types of inflammatory blood cells, lymphocytes and macrophages, and two different progeny of these cells, NK cells and macrophages. Eosinophil myocarditis is a type of myocarditis in which the heart tissue is infiltrated by another type of inflammatory blood cell, eosinophils. Eosinophil myocarditis is also distinguished from non-eosinophil myocarditis by a variety of causes and recommended treatments. Coxsackie B, especially B3 and B5, has been shown to be associated with the Coxsackievirus adenovirus receptor (CAR) and decay accelerator (DAF). However, other proteins have also been identified that allow the coxsackievirus to bind to heart cells. The natural function of CAR and the mechanism by which the Coxsackievirus infects the heart muscle are unknown. The way Coxsackie B virus (CBV) causes inflammation is thought to be due to the recognition of CBV virions by Toll-like receptors. Viral lesions that lead to myocarditis. In a study conducted during the SARS outbreak, SARS viral RNA was detected in coronary heart samples from 35% of patients who died of SARS. It was also noted that already infected hearts increase ACE2 receptor expression compared to healthy individuals. The immunosuppressive response of COVID-19 patients can lead to the development of cytokine storms. This excessive release of cytokines can cause myocardial infarction (4).

Viral myocarditis, which is most prevalently caused by coxsackievirus B3 (CVB3), is characterized by excessive myocardial inflammation. Inhibition of HDAC activity was originally identified as a powerful anti-cancer therapeutic strategy and was recently found to be implicated in the regulation of inflammatory response. HDAC inhibitor (HDACI) is demonstrated efficacious in animal models of several inflammatory diseases. We thus hypothesize that inhibition of HDAC activity also protects against CVB3-induced viral myocarditis. Surprisingly, we found inhibition of HDAC activity enhanced myocardial autophagosome formation, which led to the elevated CVB3 viral replication and ensuing increased myocardial apoptosis. Viral myocarditis was eventually aggravated rather than ameliorated by HDAC inhibition. In conclusion, we elucidate the role of HDAC activity in viral myocarditis. Moreover, given the importance of HDACI in preclinical and clinical treatments, the possible unfavorable effect of HDACI should be carefully evaluated in patients infected with viruses, including CVB3 (figure 1) (5).

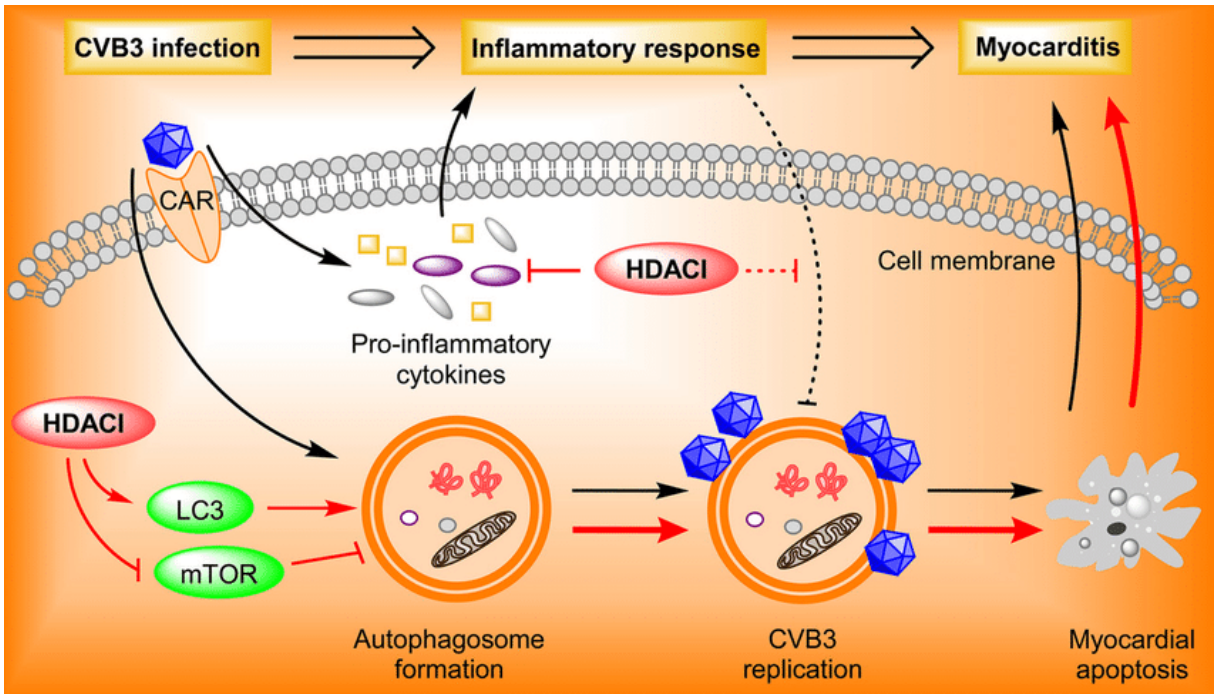

Figure 1 mechanism of HDACI effect on CVB3-induced myocarditis (5)

Signs and Symptoms

If you are in the early stages of myocarditis, you may have mild symptoms such as chest pain, fast or irregular heartbeats, or shortness of breath. Some people with stage myocarditis have no symptoms. The signs and symptoms of myocarditis vary depending on the cause of the disease. Common signs and symptoms of myocarditis include chest pain, fast or irregular heartbeats (arrhythmias), shortness of breath, rest or exercise, excess fluid in the legs, ankles, and feet, fatigue, and other signs and symptoms of infection. such as headaches, body aches, joint pain, fever, sore throat, or diarrhea. Sometimes the symptoms of myocarditis can resemble those of heart disease. If you experience unexplained chest pain and shortness of breath, seek emergency medical attention. Myocarditis in children. When children develop

myocarditis, they may have symptoms and signs, including: fever, fainting, shortness of breath, rapid breathing, chest pain, and fast or abnormal heart rhythms (arrhythmias) (6).

Complications

Usually myocarditis goes away without any chronic complications. However, severe myocarditis can permanently damage your heart muscle, which can cause: Heart failure. Left untreated, myocarditis can damage your heart muscle and prevent it from pumping the blood properly. In severe cases, heart failure related to myocarditis may require ventricular assistance or a heart transplant. Heart disease or stroke: When your heart muscle is damaged and you cannot pump blood, the blood that collects in your heart can clot. If the clot blocks one of your arteries, you can develop heart disease. If blood clots in your heart get into the artery that leads to your brain, you could have a stroke. Fast or irregular heartbeat (arrhythmias): Damage to your heart muscle can cause an abnormal heart rhythm. Sudden cardiac death: Some severe arrhythmias can lead to cardiac arrest (sudden cardiac arrest). It is fatal if not treated right away (7).

Prevention

There is no direct prevention of myocarditis. However, the following steps to prevent infection can help. If you have a virus or the flu, avoid it until you recover. If you get sick due to the symptoms of an infection, try to avoid contact with others. Practice good hygiene. Regular hand washing helps prevent the spread of the disease. Avoid dangerous behavior. Practice safe sex and avoid the use of illegal drugs to reduce the chance of HIV-related myocardial infarction. Reduces contact with mites. When spending time in areas where ticks are widespread, wear long-sleeved shirts and long trousers to cover your skin as much as possible. Install mites or insect repellents containing DEET. Make a vaccine. Keep up-to-date with the latest vaccines, including vaccines that protect against COVID-19, rubella, and the flu (a disease that can cause myocarditis) (8).

Investigations and Diagnosis

Early diagnosis of myocarditis is important to prevent chronic heart damage. After a physical exam, your doctor may order one or more tests to confirm that you have myocarditis and determine its severity. Diagnosing myocarditis can include (9):

Electrocardiogram (ECG or EKG)

This quick and painless test can show the electrical pattern of your heart and detect abnormal heartbeat (figure 2) (10).

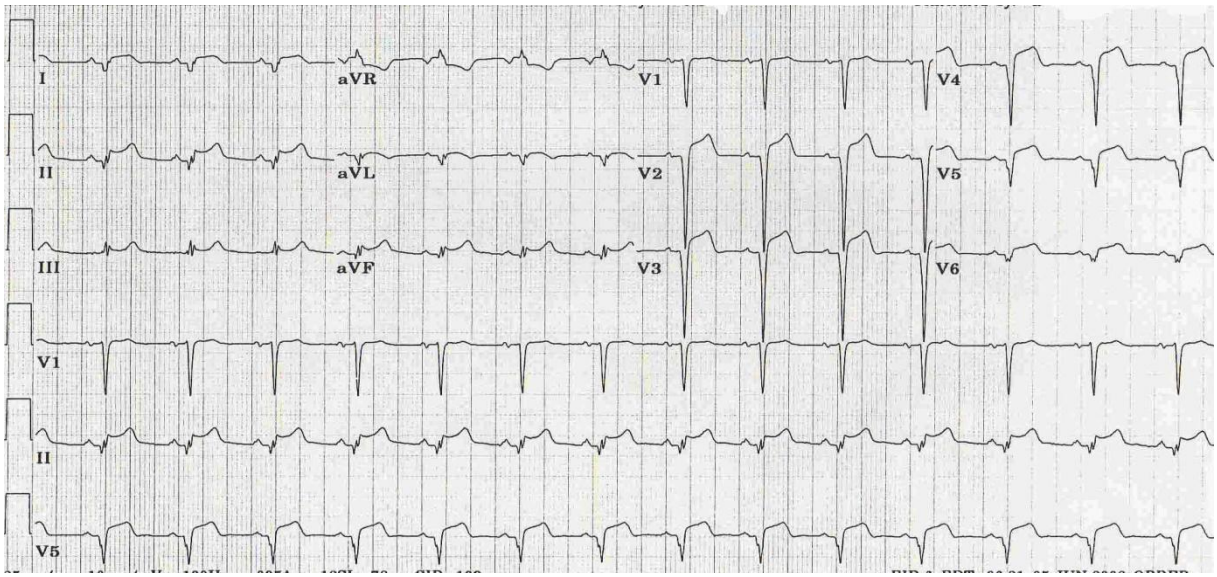

Figure 2 Electrocardiogram for Myocarditis (10)

Chest X-ray

X-ray images show the size and shape of your heart, as well as the amount of fluid in or around your heart that may be related to heart failure (figure 3) (11).

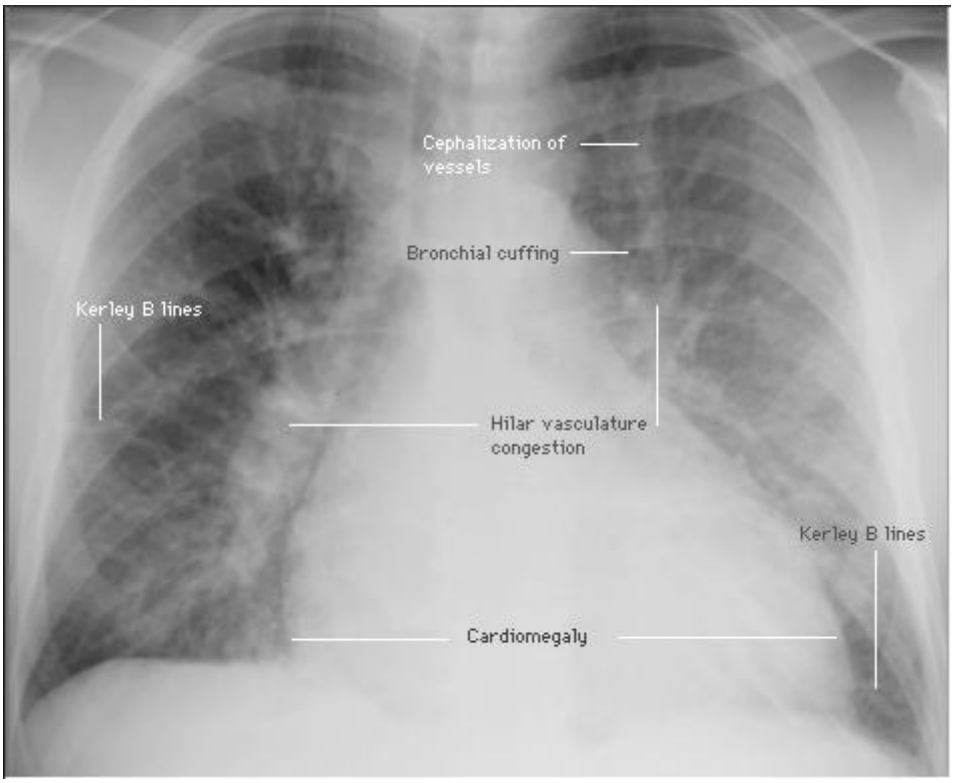

Figure 3 Chest X-ray for Myocarditis (11)

Heart MRI (Cardiac MRI).

Cardiac MRI shows the size, shape, and structure of your heart. This test can show signs of inflammation in the heart muscle (figure 4) (12).

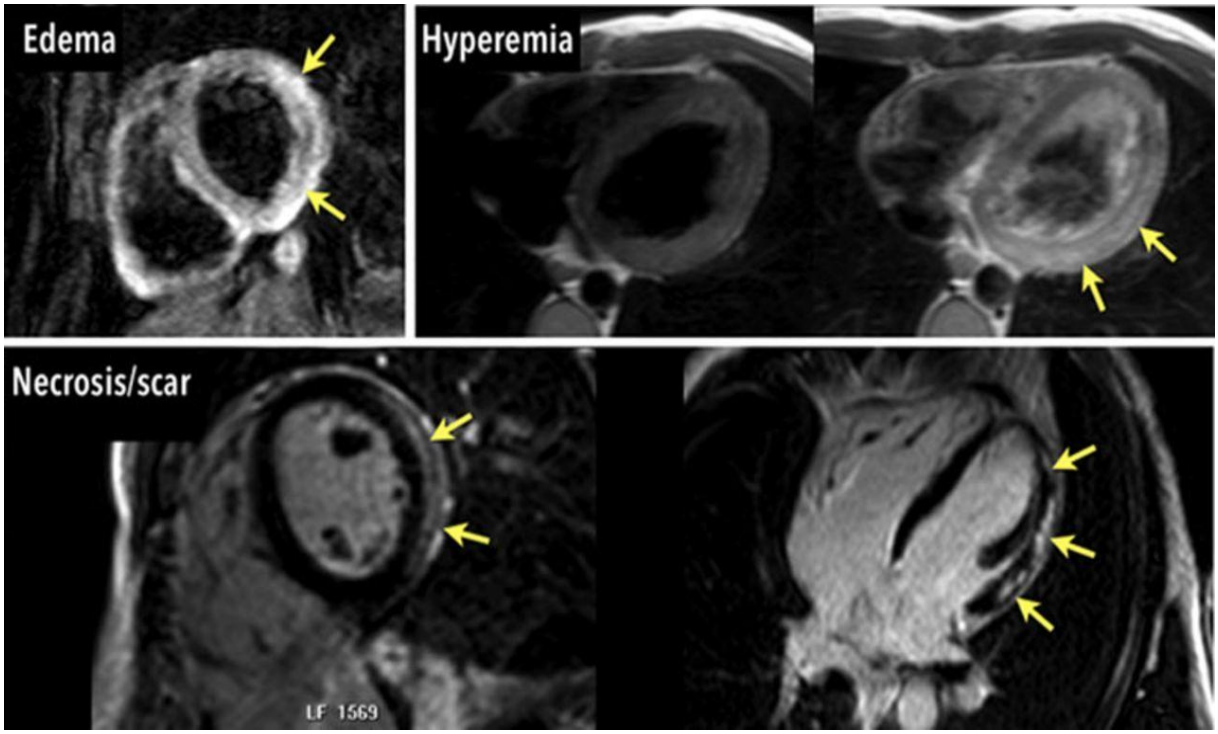

Figure 4 MRI for Myocarditis (12)

Echocardiogram

Sound waves make a video of a beating heart. Echocardiography can show the size of the heart and the degree of heartbeat. Tests can also reveal problems with heart valves, cardiac catheters, or fluid around the heart (figure 5) (13).

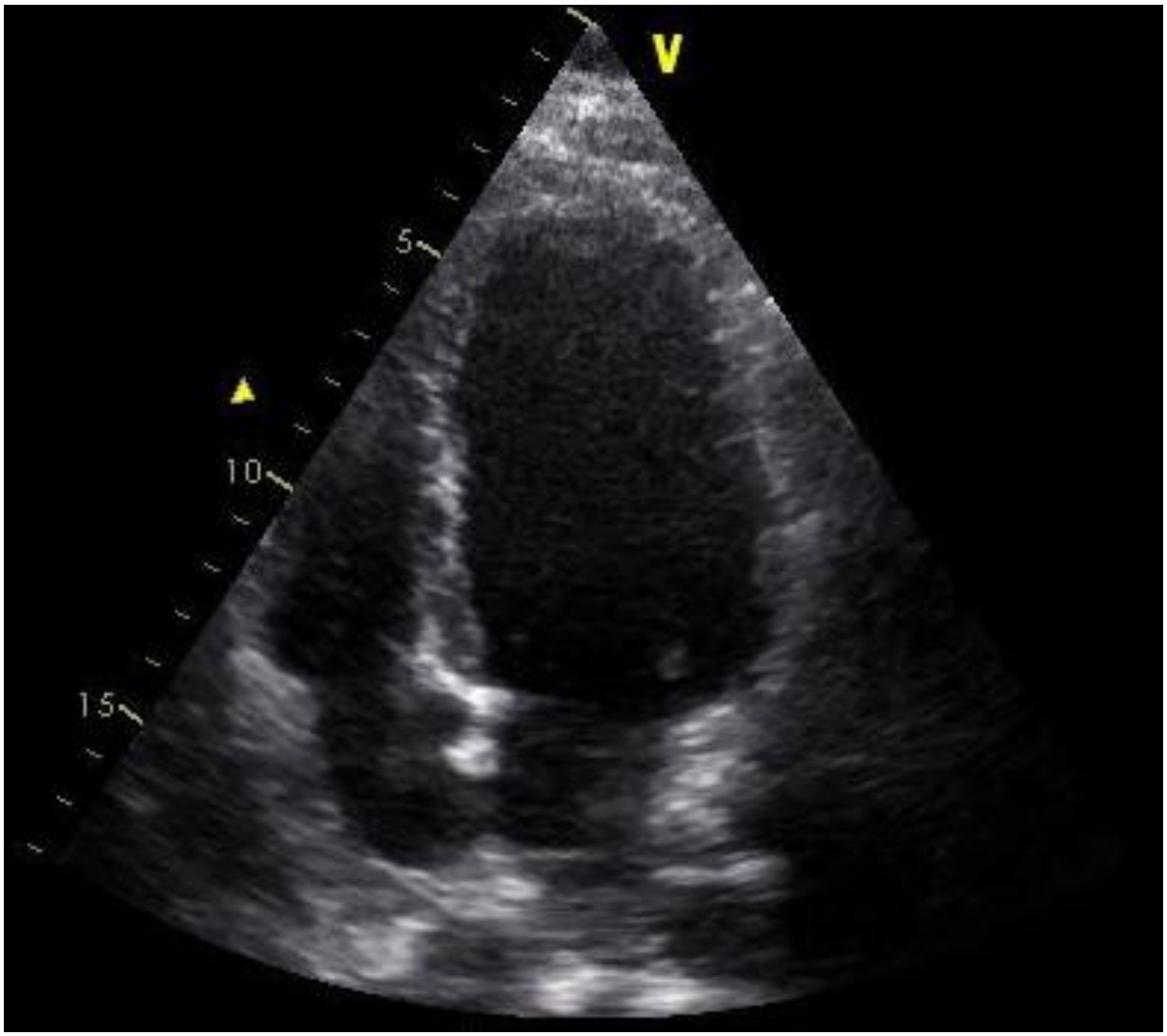

Figure 5 Echocardiogram for Myocarditis (13)

Blood tests

Blood tests used to diagnose or confirm myocarditis include complete blood counts as well as tests for levels of certain proteins (enzymes) that indicate damage to the heart muscle. Other blood tests can be done to see if you have antibodies to other germs and other organisms that can cause myocarditis-related disease (14).

Cardiac catheterization and heart muscle biopsy

A small catheter is inserted into a vein in your leg or neck and is inserted into your heart. In some cases, doctors use special devices to remove small samples of vascular tissue (biopsy) for laboratory analysis to diagnose inflammation or infection (figure 6) (15).

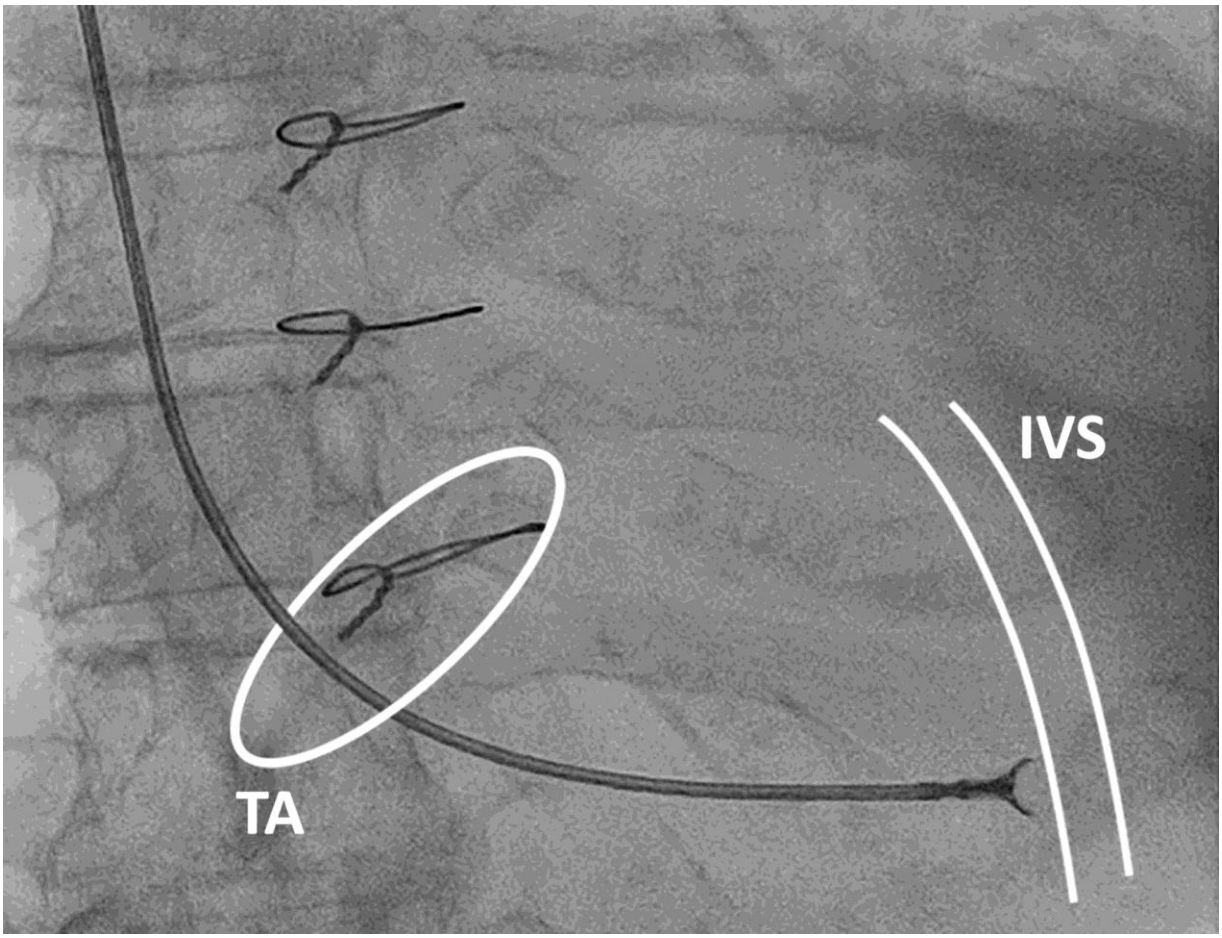

Figure 6 Cardiac catheterization and heart muscle biopsy (15)

Treatment

For most people, myocarditis develops on its own or with treatment, leading to complete recovery. Treatment of myocarditis focuses on the cause and symptoms of heart failure. Medication: People with mild myocarditis may only need rest and medication. Corticosteroids. Some rare forms of viral myocarditis, such as giant cell and eosinophilic myocarditis, can develop with corticosteroids or other antibodies against your immune system. Heart medicine If myocarditis causes heart failure or arrhythmias, you may need to stay in the hospital. Your doctor will prescribe medication or other treatment depending on your signs and symptoms. For example, if your heartbeat is abnormal or you have severe heart failure, you may be given medication to reduce your risk of coronary heart disease. If your heart is weak, your doctor may prescribe blood pressure medication to help reduce your heart rate or help you get rid of excess fluid. These may include diuretics, beta blockers, angiotensin converting enzyme (ACE) inhibitors, or angiotensin II receptor inhibitors (ARBs). Medicines for chronic diseases. If myocarditis is caused by a chronic disease, such as lupus, treatment is given against the underlying disease (16).

Surgeries and procedures

If you have severe myocarditis you will need intensive treatment, which may include: IV medicine. Vascular medicine is used to speed up the heart (17).

Ventricular assist devices (VAD)

VAD is a device that helps pump blood from the lower chambers of the heart (ventricles) throughout the body. VADs are used by people with weak hearts or heart failure. These procedures can be used to repair your heart or while you are waiting for other treatment, such as a heart transplant (figure7) (18).

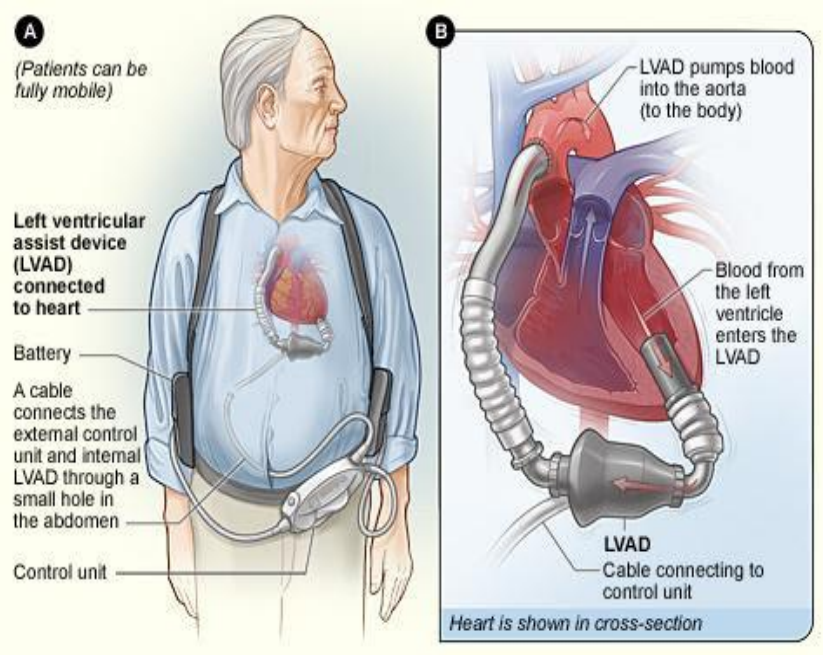

Figure 7 Ventricular assist devices (VAD) (18)

Intra-aortic balloon pump

The doctor inserts a small catheter into a blood vessel in the leg and uses x-rays to guide it to the heart. A balloon attached to the end of the catheter inflates and opens from the heart (aorta) to the large arteries that connect to the body. Intra-aortic pumps help increase blood flow and lower your heart rate (figure 8) (19).

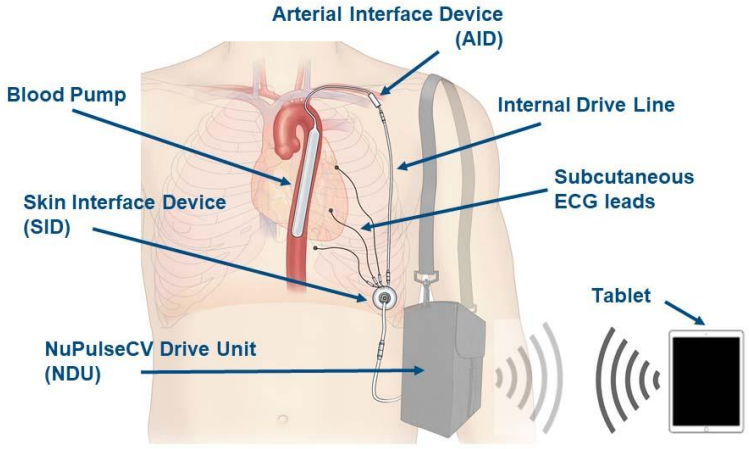

Figure 8 Intra-aortic balloon pump (19)

Extracorporeal membrane oxygenation (ECMO)

The ECHO machine simulates lung function. It releases carbon dioxide and increases oxygen in the blood. If you have severe heart failure, this device supplies oxygen to your body. During ECMO, the blood diverts from the body, passes through the ECMO machine and returns to the body. The ECMO machine takes over the function of your heart. This treatment can be used to restore the heart or while waiting for another treatment, such as a heart transplant (figure 9) (20).

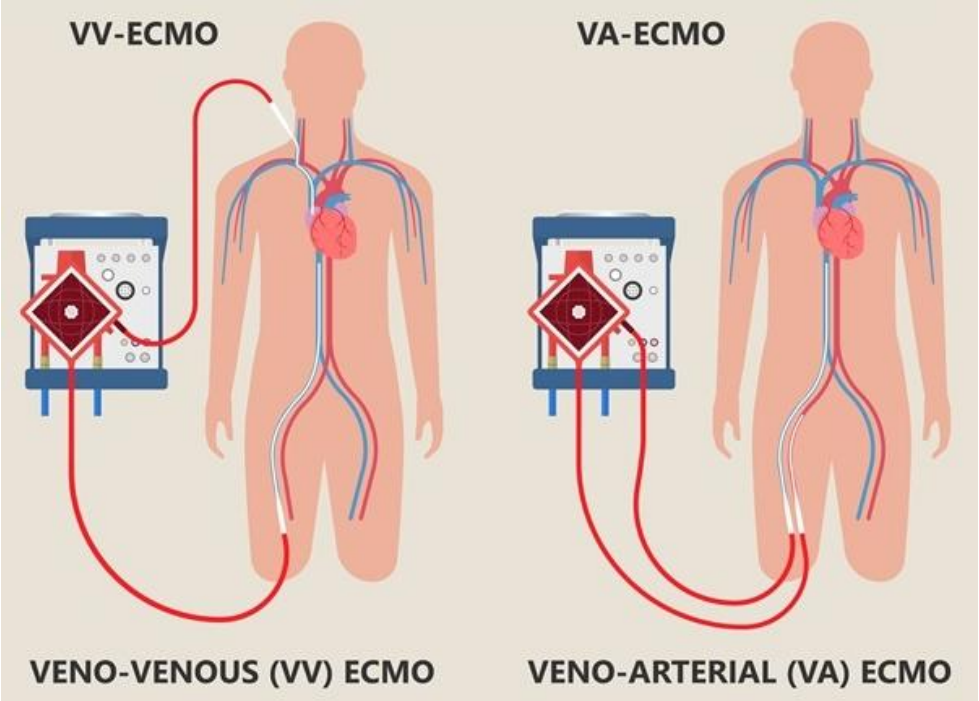

Figure 9 Extracorporeal Membrane Oxygenation (ECMO) (20)

Heart transplant

If you have severe myocarditis, your doctor may recommend an emergency cardiac transplant (21).

Discussion

Myocarditis is identified as inflammation of cardiomyocytes and is diagnosed by conventional histological pathology and immunohistochemical techniques such as infiltration of mononuclear cells into the myocardium. Myocarditis can be malignant, subacute, or chronic, with concentrated or scattered areas of the heart muscle. A recent review of the definition of myocarditis provided immunohistochemical data such as the presence of abab14 lymphocytes / mm2 and CD3-positive T lymphocytes containing ≤4 monocytes / mm2 in the definition of myocarditis by Caforio et al2. Used and discussed. ≥ mm2. This definition uses immunohistochemical data that require the collection of endocardial myocardial biopsy (EMB) and is therefore limited to a small group of patients or postmortem autopsy specimens. In addition, although this definition of myocarditis is widely accepted, the complexity of cell infiltration such as macrophage subtypes (classical / intermediate / non-classical), effectors

(Th1 / Th2 / Th17), regulators (FoxP3 +) It does not contain any information about it. / CD4 +) Because it is a subtype of T lymphocytes, it is not possible to distinguish between a fibrosis-promoting response and a therapeutic response. Transcriptome-based biopsy analysis may further define myocarditis (22).

Patients with suspected myocarditis are medically diagnosed so that they can differentiate between complete lymphocytic myocarditis and acute lymphocytic myocarditis. In complete myocarditis, patients have New York Heart Association IV-grade symptoms such as systolic and left ventricular (LV) dysfunction and flu-like symptoms with myocardial infarction. Other factors include leukocytosis, eosinophilia (including rare cases of eosinophilic myocarditis), high sedimentation rates, and high levels of cardiac troponin or creatine kinase biomarkers. Fulminal myocarditis consists of multiple centers of active myocarditis that can resolve within 6 months. Gradually, giant cell myocarditis was associated with complete acute myocarditis. In contrast, chronic myocarditis can be malignant or chronic myocarditis that often progresses to a microscopic progression. Although both acute and chronic myocarditis can be seen as heart failure (HF) and LV dysfunction on echocardiography, acute myocarditis can result in complete remission or stabilization of dilated cardiomyopathy (DCM), while chronic active myocarditis progresses is coming. Can infect large cells. The development of new molecular mechanisms such as miRNA profiling, nested polymerase chain reaction and in situ hybridization has greatly improved the diagnostic accuracy and projected value of EMB samples, including a variety of myocardial infarctions for less common types of myocarditis. Such as eosinophilic and giant cell myocarditis (23).

Conclusion

Myocarditis is always a challenging condition to diagnose and control. Its contribution to lifelong illness and death is important. More solid scientific research is needed to improve its results. Given the diverse presentation and results of this condition and the different diagnostic and treatment options, this research requires a coordinated, multi-sectoral effort. With advanced cardiovascular diagnostic tools such as tissue, biomarker, immunohistochemistry, and CMR-free PCR, a set of diagnostic criteria based on the accuracy of the tests in these studies should be preferred. Similarly, well-designed tests are needed to demonstrate the effectiveness of treatment where the need is similar and an effective diagnostic test. We hope that this statement will not only serve as an educational update but also as an essential call to better understand and manage our efforts to handle this critical situation of children.

Conflict of Interest

There is nothing to disclose

Disclaimer regarding Consent and Ethical Approval:

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors

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