

# MYOCARDITIS

## MİYOKARDİT

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### ÖZET

Miyokardit, değişik nedenler ile meydana gelen inflamatuvar yanıtta ikincil kalbin miyokart tabakasını etkileyen bir hastalıktır. En yaygın sebebi virüslerdir. Klinik seyri genellikle kendini sınırlayıcı ve selimdir, ancak klinik kötüleşme-hemodinamik durumun bozulması da mümkündür. Bu çalışmada biz 2000-2011 yılları arasında literatürü gözden geçirerek miyokardit tanısı, klinik seyri ve tedavi seçeneklerinin güncellemeyi amaçladık.

**Anahtar kelimeler:** kalp; inflamasyon; miyokardit

### SUMMARY

Myocarditis is disorder effecting myocardium of the heart secondary to inflammatory response caused by various reasons. The most common cause of myocarditis is viruses. Clinical course is usually self-limiting and benign; however, clinical deterioration, which impairs hemodynamic state, is also possible. In this study, we presented updated diagnosis, clinical course and treatment options of myocarditis by review of literature between 2000 and 2011.

**Key words:** heart; inflammation; myocarditis

### INTRODUCTION

Myocarditis is defined as inflammation of heart muscle and constitutes 10% of the acute failure cases.<sup>1</sup> Clinical course is usually self-limiting. The major long-term complication is dilated cardiomyopathy with heart failure.<sup>2</sup>

Classical pathogenesis of myocarditis is development of cardiac inflammation due to immune response (infiltration with monocytes and neutrophils) and secondary development of necrosis and/or degeneration in myocytes.<sup>3</sup> Subsequent adverse remodeling, which decreases cardiac output, may develop secondary to fibroblast deposition.<sup>4</sup> High clinical suspicion is necessary for diagnosing myocarditis and 1/3 of patients develop spontaneous recovery while another 1/3 requires aggressive treatment.<sup>5</sup>

**Definition and Incidence:** Myocarditis (or inflammatory cardiomyopathy) may develop due to external factors such as virus, parasites, bacteria, and medications as well as autoimmune response against self-antigens.<sup>6</sup> The determination of the actual incidence is difficult; however, it is estimated to be between 0.12-12%.<sup>7</sup>

Myocarditis constitutes 8.6% of the sudden death in young adults<sup>8</sup> and 10-40% of idiopathic dilated cardiomyopathy cases.<sup>9</sup> It is more common in men due to cardioprotective effects of hormones in women.<sup>10</sup> There are regional differences in etiological profile of myocarditis. Leading causes of myocarditis is Parvovirus B19 in Europe, adenovirus and enterovirus (coxsackievirus B) in North America, Chagas disease in South America, Hepatitis C in Japan.<sup>11-13</sup>

**Clinical course:** Clinical course may be asymptomatic and may manifest itself with various cardiac symptoms (breathing difficulty, fatigue, exercise intolerance, chest pain), severe heart failure and arrhythmia.<sup>14</sup> It sometimes mimics myocardial infarction. Sixty percent of patient may undergo a prodromal period 1-2 weeks before clinical presentation with arthralgia, fever, sweating, respiratory or gastrointestinal symptoms.<sup>15</sup> Clinical course may vary depending on age. Acute onset in children and adolescents is possible; chronic, insidious symptoms may be common in the elderly, whose immune system is more mature.<sup>16</sup>

## DIAGNOSIS

**Diagnostic Approaches:** Sensitivity of Dallas criteria is low in heart tissue due to irregular distribution of inflammation and biopsy alone may underestimate severity of the disease. Updated criteria require concurrent use of clinical, laboratory and imaging methods for diagnosis of myocarditis (Table 1).<sup>16</sup>

**Table 1:** Expanded Criteria for Diagnosis of Myocarditis

Category I: Clinical Symptoms	Category II: Evidence of Cardiac Structural or Functional Perturbation in the absence of Regional Coronary Ischemia
<ul style="list-style-type: none"> <li>❖ Clinical heart failure</li> <li>❖ Fever</li> <li>❖ Viral prodrome</li> <li>❖ Fatigue</li> <li>❖ Dyspnea on exertion</li> <li>❖ Chest pain</li> <li>❖ Palpitations</li> <li>❖ Presyncope or syncope</li> </ul>	<ul style="list-style-type: none"> <li>❖ Echocardiography evidence               <ul style="list-style-type: none"> <li>Regional wall motion abnormalities</li> <li>Cardiac dilation</li> <li>Regional cardiac hypertrophy</li> </ul> </li> <li>❖ Troponin release High sens (&gt;0.1 ng/mL)</li> <li>❖ Positive indium In 111 antimyosin scintigraphy</li> <li>❖ Normal coronary angiography <i>or</i></li> <li>❖ Absence of reversible ischemia by coronary distribution on perfusion scan</li> </ul>
Category III: Cardiac Magnetic Resonance Imaging	Category IV: Myocardial biopsy
<ul style="list-style-type: none"> <li>❖ Increased myocardial T2 signal on inversion recovery sequence</li> <li>❖ Delayed contrast enhancement after gadolinium-diethylenetriamine penta-acetic acid infusion</li> </ul>	<ul style="list-style-type: none"> <li>❖ Pathology findings compatible with Dallas</li> <li>❖ Presence of viral genome by polymerase situ hybridization</li> </ul>

**Laboratory:** Myocardial damage occur secondary to direct cell death due to virus, cytokine activation and infiltration with inflammatory cells. Cardiac enzymes are secreted from damaged cells (prominently troponins). Troponins have high specificity and low sensitivity.<sup>17</sup> Sedimentation and C-reactive protein (CRP) may indicate clinical progression and response to treatment; however, their specificity is low for myocarditis. The relation of new inflammatory cytokines, TNF-alpha, serum soluble FAS, soluble FAS-ligand and IL-10, with prognosis is indicated.<sup>17-18</sup>

**Electrocardiography (ECG):** Sinus tachycardia, ST-segment change, T-wave abnormalities are various arrhythmia are common. Development of Q wave and/or left branch block is associated with poor prognosis.<sup>(19)</sup>

**Echocardiography:** Wall motion abnormalities, regional hypertrophy and ventricle dilatation can be identified. Differentiation of fulminant myocarditis and classical myocarditis can be done by echocardiography. Right heart failure is present in fulminant myocarditis, interventricular septum thickness increases; however, diastolic diameter may not change. In classical

myocarditis left heart failure is present with significant increase in diastolic diameter.<sup>20</sup> Echocardiography may play role to differentiate other causes of heart failure.

**Coronary angiography:** Coronary angiography can be performed in case coronary atherosclerosis risk factors present.

**Magnetic Resonance (MR):** It is a non-invasive diagnostic method which can identify myocardial edema, fibrosis, necrosis and hyperemia.<sup>21-22</sup> Sensitivity and specificity of T2-weighted MR for myocarditis is 84% and 74%, respectively.<sup>23</sup> MR can be used for pre-biopsy guiding.<sup>21</sup> Restricting factor is that it cannot be performed in hemodynamically unstable patients. Lateral wall of left ventricle is the most common invasion area for myocarditis identified in MR and this phenomenon explains why septum biopsy samples give false negative results. A recent study defined three imaging criteria (Lake Louise Criteria) for diagnosis of myocarditis with MR and diagnostic accuracy of the inflammation is high with 2≤ criteria.<sup>24-27</sup>

**Biopsy:** Lack of prognostic value, possibility of erroneous sampling and low sensitivity decreased its use.<sup>28-29</sup> However, its sensitivity and prognostic value may increase if it is performed immediately after onset of symptoms or pathologic samples are stained with immunoperoxidase for surface antigens (anti-CD3, anti-CD4).<sup>28</sup> In new onset heart failure with compromised hemodynamic values (>2 weeks), biopsy has a class-I indication according to ACC/AHA guidelines.<sup>29</sup>

**Other Imaging Methods:** Monoclonal antimyosin antibodies marked with Indium 3 identifies myocytes with non-intact cell membrane secondary to myocardial infarction; however, it has limited use due to low specificity.

**Etiologic agents:** Etiologic agents are shown in Table 2.

**Table 2:** Major Etiological Agents Causing Myocarditis

<b>Viral</b> (e.g. Adenovirus, Coxsackie virus/Enterovirus, Parvovirus B19)
<b>Bacterial</b> (e.g. Streptococcal species, <i>Mycobacterium tuberculosis</i> )
<b>Fungal</b> (e.g. Aspergillus, Histoplasma, Candida)
<b>Protozoal</b> ( e.g. <i>Trypanosoma cruzi</i> )
<b>Parasitic</b> (e.g. Schistosomiasis)
<b>Toxins</b> (e.g. Anthracyclines)
<b>Hypersensitivity</b> (e.g. Sulfonamides, Penicillins)
<b>Autoimmune Activation</b> (e.g. Giant cell myocarditis, Churg-Strauss syndrome, Sarcoidosis, Systemic lupus erythematosus, Inflammatory bowel disease)

**Enteroviruses and Pathogenesis:** Coxsackievirus and echovirus constitutes this important group in cardiotropic viruses and enter the host cell via coxsackievirus-adenoviral (CAR) receptor.<sup>30</sup> Host produces immune response related with tyrosine kinase and toll-like receptor and triggers inflammatory response (monocyte,

macrophage, T-cell and B-cell activation). Host immune response attempts to suppress viral replication while causing myocardial necrosis and ventricular dysfunction. Viral protease 2A produced by enterovirus genome is shown to break down dystrophin, contributing myocardial damage by a non-immunologic pathway.<sup>30</sup> Immune system clarifies the virus in 1-2 weeks; however viral genome may persist for more than 6 months and this constitutes a risk factor for poor prognosis.

**Adenovirus:** Adenovirus enters the myocardial cell via CAR receptor and integrin receptor. It can be more virulent with respect to coxsackievirus and cause diffuse cell death.

**Parvovirus:** The incidence of the virus is 51% in dilated cardiomyopathy cases in Europe.<sup>12</sup> Parvovirus also cause tropism in endothelial cells and coronary vasospasm.

**Hepatitis C:** It is more common in Asia than Europe. Unlike other viruses, it may show hypertrophic cardiomyopathy phenotype rather than dilated cardiomyopathy in infected hearts. Achieving the normal morphology is possible after clearance of the virus.

**Human Immunodeficiency Virus:** The exact cause of the ventricular dysfunction is unknown in this patient group since the virus itself, adverse effect of antiretroviral treatment, opportunist infections or combination of these are accepted as the cause of ventricular dysfunction.<sup>31</sup>

**Influenza:** Cardiac symptoms are observed in 5-10% of patients. Mortality and morbidity is high in case of cardiac invasion.<sup>32-33</sup>

**Lyme carditis:** Varying degrees of atrioventricular block is observed in Lyme carditis caused by *Borrelia burgdorferi*.

**Chagas disease:** Chagas disease, caused by *Trypanosome Cruzii*, is common in Central and South America. It causes intense T-lymphocyte-mediated inflammatory response. Cardiac invasion starts decades after the onset of disease. Left branch block, left anterior hemi block, regional wall motion abnormality, and apical aneurism may be observed. A recent study determined 1) New York Heart Association functional Class III or IV, 2) cardiomegaly, 3) segmental or global wall motion abnormality on echocardiography, 4) non-sustained VT on Holter, 5) low QRS voltage on ECG, and 6) male sex as clinical predictors of the disease and developed a risk score system. Patients were classified as low, moderate and high risk according to these scores (with 10 year mortality as 10%, 44%, and 84%, respectively).<sup>34</sup>

**Host-related factors:** A few host-related factors may be responsible for myocarditis. These include genetic factors, vitamin deficiency (e.g Vitamin E), mineral deficiency (e.g, selenium).<sup>2</sup>

## SPECIAL TYPES OF MYOCARDITIS

**Fulminant Myocarditis:** Classical clinical triad is quick onset of symptoms (usually within 2 weeks), compromised hemodynamic properties and fever.<sup>35</sup> High cytokine production is present and biopsy shows inflammation /necrosis in multiple foci. Even if severe global ventricular dysfunction is identified in echocardiography, minimal dilatation is also noted in ventricle. This condition can be reversed with early diagnosis and aggressive support treatment (high dose vasopressor agent or ventricular assist device); disease may spontaneously resolve.<sup>36</sup>

**Giant Cell Myocarditis (Pernicious myocarditis):** It is related with auto-immune disease, thymoma and high degree cardiac block. **Giant Cell Myocarditis** presents histologically with active inflammation and giant cells (with fusion and multi-nucleus) and a progressive heart disease is observed. Prognosis is poor and 1-year mortality is 80% with mean survival rate of 6 months.<sup>35-36</sup> Recurrence is possible in transplanted heart.<sup>35</sup>

**Chronic Active Myocarditis:** This constitutes the major portion of the adult patients and usually starts insidiously, manifesting clinical symptoms consistent with moderate ventricular dysfunction. Biopsy shows active myocarditis; however, borderline or generalized chronic myopathic changes may also accompany fibrosis.

**Eosinophilic Myocarditis:** It may be due to various reasons, and may be secondary to direct toxic effect of eosinophilic granules. Eosinophilia might not present in blood. It may develop in drug-induced myocarditis regardless of the period of administration or cumulative dose. Endocardial and valvular fibrosis or endocardial thrombus may be seen. Acute necrotizing eosinophilic myocarditis is the aggressive form of eosinophilic myocarditis with a high mortality rate.<sup>37</sup>

**Autoimmune-related myocarditis:** It is defined as myocarditis secondary to Churg-Strauss syndrome, sarcoidosis, and systemic lupus erythematosus. Autoimmune-related myocarditis is generally resistant to medical treatment.

## PROGNOSIS

Negative factors include extreme age (too young or too old), electrocardiographic abnormalities (presence of Q wave), syncope and some types of myocarditis, while normal ventricular functions and fulminant onset are accepted as positive factors.

Clinical result depends on virulence of active agent, immune response and ability to reverse the damage. Clinical results may vary in specific groups of myocarditis patients. Surveillance is quite good in fulminant myocarditis and 11 year surveillance rate is 93%.<sup>36</sup> Surveillance of giant-cell myocarditis is poor with mean

surveillance rate of 6 months. Chronic active myocarditis with dilated cardiomyopathy has relatively poor prognosis with 1-year mortality rate of 20%.<sup>35</sup>

Recently, Kuhl et al. showed that persistence of viral genome in biopsy may predict deterioration in ventricular function.<sup>19</sup> Fuse et al. identified significantly higher serum soluble Fas and Fas ligand levels in patients with fatal myocarditis.<sup>38</sup> Another study indicated that Fas ligand or tumor necrosis factor receptor-1 (TNFR1) expression cause excessive apoptosis in myocarditis and constitute as a factor of poor prognosis.<sup>17</sup>

## TREATMENT

Intense exercise increases mortality rate in myocarditis patients; therefore, rest is warranted. The primary target should be supportive therapy for left ventricular dysfunction.<sup>27</sup> In case of heart failure, ACE inhibitors, ARBs, beta-blockers and diuretics should be administered in accordance with guidelines. In case of hemodynamic instability despite optimal medical treatment, support devices such as ventricular assist devices, extracorporeal membrane oxygenation should be considered.<sup>39-41</sup>

Information regarding antiviral treatment is still insufficient and animal studies show promising results.<sup>42-43</sup> Antiviral therapy has been used in only one case series of fulminant myocarditis. However, it is not found effective.<sup>40</sup> In contrast, positive results are obtained in patients with viral persistent dilated cardiomyopathy treated with interferon beta.<sup>44</sup> Immune Modulation for Acute Cardiomyopathy trial showed no positive results in dilated cardiomyopathy patients receiving intravenous immunoglobulin treatment.<sup>45</sup> Studies with immune-suppressive agents (prednisolone, azathioprine) showed positive results in virus negative patients with dilated cardiomyopathy.<sup>2,37</sup>

## CONCLUSION

The aim of future studies for myocarditis should be the development of diagnostic methods (i.e. MRI or specific biomarkers showing cardiac inflammation) and effective vaccines to cardio-trophic viruses, thereby providing early diagnosis and prevention, and completion of lacking points in pathophysiology and investigating the immune-mediated treatment options.

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