

Myocarditis Pathology

P.S.Subiksha

ABSTRACT: *Myocarditis or inflammatory cardiomyopathy is inflammation of heart muscle (myocardium) diagnosed on endomyocardial biopsy (EMB) established by histological, immunological and immune his to chemical criteria. Myocarditis is most often due to infection by common viruses.*

KEY WORDS: *Myocarditis, myocardial infarction, inflammation.*

I. INTRODUCTION

Myocarditis or inflammatory cardiomyopathy is inflammation of heart muscle [1] (myocardium) diagnosed on endomyocardial biopsy (EMB) established by histological, immunological and immunohistochemical criteria [2]. Myocarditis is most often due to infection by common viruses, such as parvovirus B19, less commonly nonviral pathogens such as *Borrelia burgdorferi* (Lyme disease) or *Trypanosoma cruzi*, [4, 5] or as a hypersensitivity response to drugs. [3]

II. ETIOLOGY

Although the etiology of myocarditis often remains undetermined, a large variety of infectious agents, systemic diseases, drugs, and toxins can cause the disease.[6,7] Some causes of myocarditis are now largely historical or occur in very specific scenarios such as sepsis or in immunocompromised patients. Molecular techniques, mainly (reverse transcriptase)(RT)-PCR amplification,[4,8,9] suggest that viral infections are the most important cause of myocarditis in North America and Europe with genomes of enterovirus, adenovirus, influenza viruses, human herpes virus-6 (HHV-6), Epstein-Barr-virus, cytomegalovirus, hepatitis C virus, and parvovirus B19 reported in the myocardium of patients with myocarditis and DCM. Lymphocytic and giant cell myocarditis are presumed idiopathic or autoimmune if no viruses are identified in EMB and other known causes are excluded .[6] Similarly, the diagnosis of idiopathic granulomatous myocarditis (cardiac sarcoidosis) requires negative stains for microorganisms.[8,9] Autoimmune myocarditis may occur with exclusive cardiac involvement or in the context of autoimmune disorders with extra-cardiac manifestations, most frequently in sarcoidosis, hypereosinophilic syndrome, scleroderma, and systemic lupus erythematosus.

III. PATHOGENESIS

In human myocarditis, there is evidence for viral and autoimmune mechanisms, acting in individuals with or without a genetic predisposition (familial or sporadic cases, respectively). [10] Murine studies of viral myocarditis are based mostly on Coxsackievirus B3-infected animals, which exhibit strain-specific susceptibility. Enteroviruses that preferentially enter cardiomyocytes via specific receptors cause severe cytopathic effects due to virus replication in the first 2 weeks post-infection [11]. As a consequence, a humoral and cellular immune response, mainly consisting of macrophages and CD4+ and CD8+ T- lymphocytes, is initiated in resistant animals[12,13] (C57BL/6 mice, Sv129 mice) and leads to the elimination of the infectious agent within 2 weeks following infection.[4,15,16]

IV. DIAGNOSIS

Myocarditis refers to an underlying process that causes inflammation and injury of the heart. It does not refer to inflammation of the heart as a consequence of some other insult [14]. Many secondary causes, such as a myocardial infarction, can lead to inflammation of the myocardium and therefore the diagnosis of myocarditis cannot be made by evidence of inflammation of the myocardium alone.

Myocardial inflammation can be suspected on the basis of electrocardiographic (ECG) results; elevated C-reactive protein (CRP) and/or Erythrocyte sedimentation rate (ESR) and increased IgM (serology) against viruses known to affect the myocardium. Markers of myocardial damage (troponin or creatine kinase cardiac isoenzymes) are elevated.

-Nuclear Imaging

Data on radionuclide evaluation, including antimyosin antibody imaging, are scarce but suggest that its sensitivity for detecting myocardial inflammation is variable and its specificity low [17]. Due to their limited

availability and risk from radiation exposure, nuclear techniques are not routinely recommended for the diagnosis of myocarditis, with the possible exception of sarcoidosis. [18, 19, 20]. Thallium 201 and technetium 99m scintigraphy have been used to detect cardiac sarcoidosis but lack specificity. Gallium-67 scintigraphy and more recently positron emission tomography using 18 fluorodeoxyglucose are probably more sensitive and may be useful in the acute phase of sarcoidosis and to monitor disease progression. The detection of extracardiac disease can suggest a diagnosis of cardiac sarcoidosis.

-Cardiovascular Magnetic Resonance (Cmr) Imaging

Cardiovascular magnetic resonance imaging provides non-invasive tissue characterization of the myocardium and can support the diagnosis of myocarditis. The timing of CMR in suspected myocarditis will depend upon local availability and expertise, but it is reasonable to first perform CMR in clinically stable patients, prior to EMB [21, 22]. It should not be performed in life-threatening presentations where EMB is urgently indicated [23, 24]. Cardiovascular magnetic resonance imaging techniques have been evaluated in animal models of myocarditis as well as in patients

V. SIGNS AND SYMPTOMS

The signs and symptoms associated with myocarditis are varied, and relate either to the actual inflammation of the myocardium, or the weakness of the heart muscle that is secondary to the inflammation [26]. Signs and symptoms of myocarditis include: Chest pain (often described as "stabbing" in character) Congestive heart failure (leading to edema, breathlessness and hepatic congestion) Palpitations (due to arrhythmias) Sudden death (in young adults, myocarditis causes up to 20% of all cases of sudden death) Fever (especially when infectious, e.g. in rheumatic fever) Symptoms in infants and toddlers tend to be more nonspecific, with generalized malaise, poor appetite, abdominal pain, and/or chronic cough. Later stages of the illness will present with respiratory symptoms with increased work of breathing, and is often mistaken for asthma.

Since myocarditis is often due to a viral illness, many patients give a history of symptoms consistent with a recent viral infection, including fever, rash, diarrhea, joint pains, and easy fatigue ability [27, 15]. Myocarditis is often associated with pericarditis, and many patients present with signs and symptoms that suggest concurrent myocarditis and pericarditis.

VI. CAUSES

A large number of causes of myocarditis have been identified, but often a cause cannot be found. In Europe and North America, viruses are common culprits. Worldwide, however, the most common cause is Chagas' disease, an illness endemic to Central and South America that is due to infection by the protozoan *Trypanosoma cruzi* [22, 28].

VII. INFECTIONS

Viral (adenovirus, parvovirus B19, coxsackie virus, HIV, enterovirus, rubella virus, polio virus, cytomegalovirus, human herpesvirus 6 and possibly hepatitis C) Protozoan (*Trypanosoma cruzi* causing Chagas disease and *Toxoplasma gondii*)

Bacterial (*Brucella*, *Corynebacterium diphtheriae*, gonococcus, *Haemophilus influenzae*, *Actinomyces*, *Tropheryma whippelii*, *Vibrio cholerae*, *Borrelia burgdorferi*, leptospirosis, and *Rickettsia*)

Fungal (*Aspergillus*)

Parasitic (ascaris, *Echinococcus granulosus*, *Paragonimus westermani*, schistosoma, *Taenia solium*,

Trichinella spiralis, visceral larva migrans, and *Wuchereria bancrofti*)

Bacterial myocarditis is rare in patients without immunodeficiency.

-Toxins

Drugs (ethanol, anthracyclines and some other forms of chemotherapy, and antipsychotics, e.g. clozapine, also some designer drugs such as mephedrone) [8]

-Immunologic

Allergic (acetazolamide, amitriptyline) Rejection after a heart transplant [29].

Autoantigens (scleroderma, systemic lupus erythematosus, sarcoidosis, systemic vasculitis such as Churg-Strauss syndrome, and Wegener's granulomatosis)

Toxins (arsenic, toxic shock syndrome toxin, carbon monoxide, or snake venom)

Heavy metals (copper or iron)

-Physical Agents

Electric shock, hyperpyrexia, and radiation

VIII. TREATMENT

The core principle in treatment of myocarditis are optimal care of arrhythmia and of heart failure, and where supported by evidence, and etiology targeted therapy. As most viral infections cannot be treated with directed therapy, symptomatic treatment is the only form of therapy for those forms of myocarditis. In the acute phase, supportive therapy, including bed rest, is indicated [23, 30]. For symptomatic patients, digoxin and diuretics provide clinical improvement. For patients with moderate to severe dysfunction, cardiac function can be supported by use of inotropes such as Milrinone in the acute phase, followed by oral therapy with ACE inhibitors (Captopril, Lisinopril) when tolerated. People who do not respond to conventional therapy are candidates for bridge therapy with left ventricular assist devices. Heart transplantation is reserved for patients who fail to improve with conventional therapy.

In several small case series and randomized control trials, systemic corticosteroids have shown to have beneficial effects in patients with proven myocarditis. However, data on the usefulness of corticosteroids should be interpreted with caution, since 58% of adults recover spontaneously, while most studies on children and infants lack control groups.

IX. NATURAL HISTORY

The natural history of myocarditis in community based populations is not known with any accuracy because there is no widely available noninvasive diagnostic test to confirm the diagnosis. However, seroepidemiologic studies suggest that the majority of cases of Coxsackie B virus infection are subclinical and have a benign course [31]. In hospital or clinic based referral populations, the natural history of myocarditis varies with the underlying cause and the presenting symptoms. In the majority of patients who develop inflammation as evidenced by electrocardiographic (ECG) changes, the inflammatory process is apparently self-limited without short-term, overt sequelae. More severe ECG changes such as bundle branch block, high degree AV block, and Q waves are associated with worse long term clinical outcomes. A minority of initially asymptomatic patients, however, develop HF, serious arrhythmias, disturbances of conduction, or even circulatory collapse [32]. Rarely, postviral myocarditis may be fatal due to myocardial failure or sudden, unexpected death.

In contrast, most patients with symptomatic post-viral or lymphocytic myocarditis present with HF and dilated cardiomyopathy (DCM). However, subtle signs and symptoms of cardiac involvement may be overshadowed by systemic manifestations of the viral infection. As an example, in the US Myocarditis Treatment Trial, 89 percent of subjects reported a syndrome consistent with a viral prodrome [33]. Although only a small fraction of patients with lymphocytic myocarditis present with ventricular arrhythmias, the percentage of patients with idiopathic ventricular tachycardia [34] who have myocarditis may be as high as 33 percent. Myocarditis may also cause some cases of atrial fibrillation [35]

X. CONCLUSION

The diagnosis of myocarditis arises from the integration of clinical information, immunohistochemical analysis, laboratory data and imaging findings

Today, CMR is the main technique for identifying tissue damage secondary to myocarditis, and concomitantly may allow the exclusion of myocardial damage secondary to MI.

Further studies are needed in order to correlate the histological and imaging information with the various treatment options.

REFERENCES

- [1] Leslie T. Cooper, Jr., (April 9, 2009) Myocarditis, *N. Engl. J. Med.* 360(15) 1526-38
- [2] Kenneth L. Baughman, Special Report: Diagnosis of Myocarditis; Death of Dallas Criteria. *Circulation.* 2006;113:593-595 Free full text
- [3] Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, Olsen E, Thiene G, Goodwin J, Gyarfas I, Martin I, Nordet P. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. *Circulation* 1996;93:841-842.
- [4] Kindermann I, Barth C, Mahfoud F, Ukena C, Lenski M, Yilmaz A, Klingel K, Kandolf R, Sechtem U, Cooper LT, Bohm M. Update on myocarditis. *J Am Coll Cardiol* 2012;59:779-792.

- [5] Caforio AL, Calabrese F, Angelini A, Tona F, Vinci A, Bottaro S, Ramondo A, Carturan E, Iliceto Thiene G, Daliento L. A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis. *Eur Heart J* 2007;28:1326-1333.
- [6] Sagar S, Liu PP, Cooper LT. Myocarditis. *Lancet* 2012;379:738-74
- [7] CrossRefMedlineWeb of Science 7. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Kühl U, Maisch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L, Keren A. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology working group on myocardial and pericardial disease. *Eur Heart J* 2007;29:270-276.
- [8] Dennert R, Crijns HJ, Heymans S. Acute viral myocarditis. *Eur Heart J* 2008;29:2073-2082.
- [9] Rose NR. Myocarditis: infection versus autoimmunity. *J Clin Immunol* 2009;29:730-737. CrossRefMedlineWeb of Science
- [10] Kindermann I, Kindermann M, Kandolf R, Klingel K, Bültmann B, Müller T, Lindinger A, Böhm M. Predictors of outcome in patients with suspected myocarditis. *Circulation* 2008;118:639-648.
- [11] Mahrholdt H, Goedecke C, Wagner A, Meinhardt G, Athanasiadis A, Vogelsberg H, Fritz P, Klingel K, Kandolf R, Sechtem U. Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. *Circulation* 2004;109:1250-1258.
- [12] Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB; American Heart Association; Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; Council on Epidemiology and Prevention. Contemporary definitions and classification of cardiomyopathies. An American Heart Association Scientific statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; quality of Care and Outcome research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2006;113:1807-1816.
- [13] Bock CT, Klingel K, Kandolf R. Human parvovirus B19-associated myocarditis. *N Engl J Med* 2010;362:1248-1249. CrossRefMedlineWeb of Science
- [14] Liu P, Martino T, Opavsky MA, Penninger J. Viral myocarditis: balance between viral infection and immune response. *Can J Cardiol* 1996;12:935-943. MedlineWeb of Science
- [15] Cambridge G, MacArthur CG, Waterson AP, Goodwin JF, Oakley CM. Antibodies to Coxsackieviruses in congestive cardiomyopathy. *Br Heart J* 1979;41:692-696.
- [16] Caforio ALP, Keeling PJ, Zachara E, Mestroni L, Camerini F, Mann JM, Bottazzo GF, McKenna WJ. Evidence from family studies for autoimmunity in dilated cardiomyopathy. *Lancet* 1994;344:773-777. CrossRefMedlineWeb of Science
- [17] Wojnicz R, Nowalany-Kozielska E, Wojciechowska C, Glanowska G, Wilczewski P, Niklewski T, Zembala M, Polonski L, Rozek MM, Wodniecki J. Randomized, placebo controlled study for immunosuppressive treatment of inflammatory dilated cardiomyopathy. Two-year follow-up results. *Circulation* 2001;104:39-45.
- [18] Huber SA, Gauntt CJ, Sakkinen P. Enteroviruses and myocarditis: viral pathogenesis through replication, cytokine induction, and immunopathogenicity. *Adv Virus Res* 1999;51:35-68. Web of Science
- [19] Klingel K, Hohenadl C, Canu A, Albrecht M, Seemann M, Mall G, Kandolf R. Ongoing enterovirus-induced myocarditis is associated with persistent heart muscle infection: quantitative analysis of virus replication, tissue damage, and inflammation. *Proc Natl Acad Sci USA* 1992;89:314-318.
- [20] Liu PP, Mason JW. Advances in the understanding of myocarditis. *Circulation* 2001;104:1076-1082.
- [21] Woodruff JF. Viral myocarditis. A review. *Am J Pathol* 1980;101:425-484.
- [22] Kumar, Vinay; Abbas, Abul K.; Fausto, Nelson; & Mitchell, Richard N. (2007). *Robbins Basic Pathology* (8th ed.). Saunders Elsevier. pp. 414-416 ISBN 978-1-4160-2973-1
- [23] Yilmaz A, Klingel K, Kandolf R, Sechtem U. Imaging in inflammatory heart disease: from the past to current clinical practice. *Hellenic J Cardiol* 2009;50:449-460. MedlineWeb of Science
- [24] O'Connell JB, Henkin RE, Robinson JA, Subramanian R, Scanlon PJ, Gunnar RM. Gallium-67 imaging in patients with dilated cardiomyopathy and biopsy-proven myocarditis. *Circulation* 1984;70:58-62.
- [25] Ohira H, Tsujino I, Yoshinaga K. (1)F-Fluoro-2-deoxyglucose positron emission tomography in cardiac sarcoidosis. *Eur J Nucl Med Mol Imaging* 2011;38:1773-1783. CrossRefMedline
- [26] Baccouche H, Mahrholdt H, Meinhardt G, Merher R, Voehringer M, Hill S, Klingel K, Kandolf R, Sechtem U, Yilmaz A. Diagnostic synergy of non-invasive cardiovascular magnetic resonance and invasive endomyocardial biopsy in troponin-positive patients without coronary artery disease.
- [27] Yilmaz A, Kindermann I, Kindermann M, Mahfoud F, Ukena C, Athanasiadis A, Hill S, Mahrholdt H, Voehringer M, Schieber M, Klingel K, Kandolf R, Böhm M, Sechtem U. Comparative evaluation of left and right ventricular endomyocardial biopsy: differences in complication rate and diagnostic performance. *Circulation* 2010;122:900-909.
- [28] Feldman AM, McNamara D (November 2000). "Myocarditis". *N. Engl. J. Med.* 343 (19): 1388–doi:10.1056/NEJM200011093431908.
- [29] Eckart RE, Scoville SL, Campbell CL, et al. (December 2004). "Sudden death in young adults: a 25-year review of autopsies in military recruits". *Ann. Intern. Med.* 141 (11): 829–34. doi:10.7326/0003-4819-141-11-200412070-00005.
- [30] Nicholson PJ, Quinn MJ, Dodd JD (December 2010). "Headshop heartache: acute mephedrone 'meow' myocarditis". *Heart (British Cardiac Society)* 96 (24): 2051–2. doi:10.1136/hrt.2010.209338.
- [31] Hia, CP; Yip, WC, Tai, BC, Quek, SC (2004 Jun). "Immunosuppressive therapy in acute myocarditis: an 18 year systematic review". *Archives of Disease in Childhood* 89 (6): 580–4. doi:10.1136/adc.2003.034686.
- [32] Aziz, KU; Patel, N, Sadullah, T, Tasneem, H, Thawerani, H, Talpur, S (2010 Oct). "Acute viral myocarditis: role of immune suppression: a prospective randomised study". *Cardiology in the young* 20 (5): 509–15. doi:10.1017/S1047951110000594.
- [33] Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000; 342:1077.
- [34] Wentworth P, Jentz LA, Croal AE. Analysis of sudden unexpected death in southern Ontario, with emphasis on myocarditis. *Can Med Assoc J* 1979; 120:676.
- [35] Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. *N Engl J Med* 1995; 333:269