Myocarditis: inflammatory and endocrine causes

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Abstract

Myocarditis is a challenging diagnosis due to the heterogeneity of clinical presentations. In patients with mild symptoms and no or little ventricular dysfunction, myocarditis may resolve spontaneously without specific treatment. However, in up to 30% of cases, biopsy-confirmed myocarditis can progress to dilated cardiomyopathy and is associated with a poor prognosis. Myocarditis can also present as a life-threatening condition or with sudden cardiac death. Prognosis in myocarditis patients varies according to the clinical presentation, the underlying etiology and pathogenesis, and particularly in immune-mediated forms, such as giant cell myocarditis, or myocarditis in systemic extra-cardiac autoimmune conditions, the prognosis is poor. A 2013 European Society of Cardiology task force has introduced new criteria for clinically suspected myocarditis and proposes consideration for endomyocardial biopsy (including histological, immunohistochemical and molecular biological analysis) as well as autoantibody serum testing in clinically suspected cases, to identify those patients in whom specific therapy is appropriate. ■ Heart Metab; 2013;62:31–35

Keywords: Autoimmunity; diagnosis; dilated cardiomyopathy; endomyocardial biopsy; myocarditis.

Introduction

In the 1996 World Health Organization/International Society and Federation of Cardiology classification of the cardiomyopathies [1] and the 2013 European Society of Cardiology (ESC) task force report on myocarditis [2], myocarditis is defined as an inflammatory disease of the myocardium, diagnosed on endomyocardial biopsy (EMB), inflammatory cardiomyopathy as myocarditis in association with cardiac dysfunction (*Table I*) [3, 4]. Inflammatory and endocrine causes are listed among the specific cardiomyopathies in some [1, 2], but not all classifications [5, 6]. Causes of inflammatory cardiomyopathy or myocarditis are detailed in the 2013 ESC task force report on myocarditis [2]. The 2013 ESC task force criteria define etiological subsets as follows:

- Viral myocarditis: histological evidence of myocarditis associated with positivity by polymerase chain reaction (PCR) on EMB for one or more of the viruses.
- Autoimmune myocarditis: histological myocarditis with negative viral PCR, with or without serum cardiac autoantibodies.
- Viral and immune myocarditis: histological myocarditis with positive viral PCR and positive cardiac autoantibodies. In these patients a follow-up EMB may document persistent viral myocarditis, histological and virological resolution, or persistent virus-negative myocarditis, with or without serum cardiac autoantibodies, eg, postinfectious autoimmune disease.

Abbreviations

CAD: coronary artery disease; **CMR:** cardiac magnetic resonance; **DCM:** dilated cardiomyopathy; **EMB:** endomyocardial biopsy; **ESC:** European Society of Cardiology; **LGE:** late gadolinium enhancement; **PCR:** polymerase chain reaction

Here we will deal with classic and rare endocrine causes of myocarditis or inflammatory cardiomyopathy.

Etiology and pathogenesis

Infectious agents, systemic diseases, endocrine diseases, drugs and toxins can cause myocarditis [1, 2, 7–11]. Molecular techniques, mainly reverse transcriptase PCR suggest that viral infections are a common cause of myocarditis in western countries [1, 2, 7–13]. Autoimmune myocarditis may occur with

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Myocarditis (WHO/ISFC) [1, 2]:

Inflammatory disease of the myocardium diagnosed by established histological,[a] immunological and immunohistochemical criteria[b]

[a]Established histological Dallas criteria [3] defined as follows:

"histological evidence of inflammatory infiltrates within the myocardium associated with myocyte degeneration and necrosis of non-ischaemic origin".

[b]Immunohistochemical criteria, abnormal inflammatory infiltrate [2, 4] defined as follows:

"≥ 14 leucocytes/mm^2 including up to 4 monocytes/mm^2 with the presence of CD3 positive T-lymphocytes ≥ 7 cells/mm^{2}".

Inflammatory cardiomyopathy (WHO/ISFC)[c] [1, 2]:

Myocarditis in association with cardiac dysfunction

[c]Inflammatory cardiomyopathy, involved in the pathogenesis of DCM, includes idiopathic, autoimmune and infectious subtypes.

Dilated cardiomyopathy (ESC; WHO/ISFC)[d] [1, 2, 6]:

DCM is a clinical diagnosis characterized by dilation and impaired contraction of the left or both ventricles that is not explained by abnormal loading conditions or coronary artery disease.

[d]DCM includes idiopathic, familial/genetic, viral and/or immune, alcoholic/toxic subtypes.

Table I *Definitions. DCM, dilated cardiomyopathy; ESC, European Society of Cardiology; WHO/ISFC, World Health Organization/International Society and Federation of Cardiology.*

exclusive cardiac involvement or in the context of autoimmune disorders with extracardiac manifestations, eg, sarcoidosis, hypereosinophilic syndrome, scleroderma and systemic lupus erythematosus. In human myocarditis there is evidence of viral and autoimmune mechanisms, acting in individuals with or without a predisposing genetic background [2, 9, 14, 15]. Progression from myocarditis to dilated cardiomyopathy (DCM) may occur in patients who cannot eliminate the infective agents [2, 12] or have developed pathogenic serum cardiac autoantibodies directed against myocardial autoantigens [2, 9, 14, 15].

When to suspect myocarditis: the 2013 ESC task force criteria

Inflammatory cardiomyopathy/myocarditis is a challenging diagnosis in cardiology and needs a high level of suspicion; clinical presentation is polymorphic [2]. To aid the clinician in the identification of myocarditis, the ESC myocarditis task force has introduced new criteria for clinically suspected myocarditis [2].

Clinically suspected myocarditis is defined by the presence of more than one clinical presentation and more than one diagnostic criterion from different categories, in the absence of:

- Angiographically detectable coronary artery disease (CAD; coronary stenosis $\geq 50\%$).
- Known pre-existing cardiovascular disease or extracardiac causes that could explain the syndrome (eg, valve disease, congenital heart disease, etc.). Suspicion is higher with a higher number of fulfilled criteria.
- If the patient is asymptomatic more than two diagnostic criteria should be met.

Key points in the medical history include the following:

- In relation to the family history, it is suggested to enquire about familial DCM, other cardiomyopathy, sudden cardiac death and autoimmune disease.
- In relation to the patient's history, it is suggested to enquire about recent (days to 2 weeks) upper respiratory or gastrointestinal suspected viral syndrome, allergy, other autoimmune diseases, previous clinically suspected or confirmed myocarditis, heavy alcohol intake, consumption of drugs and toxic substances (eg, cocaine), vaccines, travel to places where specific cardiotropic infection is possible or endemic (eg, Brazil, Argentina and Chile for Chagas' disease), proximity with domestic

animals, conventional coronary risk factors, etc. The aim is to search for as well as exclude possible treatable causes (eg, drug-related toxicity or hypersensitivity). Most patients will have "idiopathic" or presumed viral myocarditis.

The ESC task force clinical presentations [2] include one or more of the following:

- Acute coronary syndrome-like, with or without normal global or regional left ventricular and/or right ventricular dysfunction on echocardiography or cardiac magnetic resonance (CMR), with or without increased troponin T/troponin I (that may have a time course similar to acute myocardial infarction or a prolonged and sustained release over several weeks or months).

- New onset or worsening heart failure in the absence of CAD and known causes of heart failure.

- Chronic heart failure, with heart failure symptoms (with recurrent exacerbations) of more than 3 months' duration, in the absence of CAD and known causes of heart failure.

- Life-threatening condition (including life-threatening arrhythmias and aborted sudden death, cardiogenic shock, severely impaired left ventricular function), in the absence of CAD and known causes of heart failure.

The ESC task force diagnostic criteria [2] include one or more of the following features from categories 1 to 4:

1. ECG/Holter/stress test features: newly abnormal 12-lead ECG and/or Holter and/or stress testing, any of the following: 1 to 3 degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non ST elevation, T-wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R-wave height, intraventricular conduction delay (widened QRS complex), abnormal Q-waves, low voltage, frequent premature beats, supraventricular tachycardia.

2. Myocardiocytolysis markers: elevated cardiac troponins.

3. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR): new, otherwise unexplained left ventricular and/or right ventricular structure and function abnormality (including incidental finding in apparently asymptomatic individuals): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi.

4. Tissue characterization by CMR: oedema and/or late gadolinium (LGE) enhancement of classic myocarditic pattern (according to Lake–Louise criteria) [16].

Role of noninvasive cardiac imaging

Echocardiography defines morphology and biventricular function, but it is not specific. It may be normal or similar to DCM. Pericardial effusion may be present, as well as segmental wall motion abnormalities. Apical left ventricular aneurisms suggest Chagas' disease. In fulminant myocarditis there may be a slight increase in left ventricular wall thickness and a mildly dilated severely hypokinetic ventricle [2].

[111]Indium antimyosin antibody and [67]gallium nuclear imaging are rarely used (limited availability of tracers, poor spatial resolution, radiation issues) [2].

CMR imaging defines the morphology and biventricular function of the heart and provides tissue characterization. Myocardial edema is assessed on T2-weighted CMR images, hyperemia/capillary leak on myocardial early gadolinium enhancement ratio, and necrosis/fibrosis on LGE. LGE is typically subepicardial, localized in inferolateral and less frequently in anteroseptal left ventricular segments, and may be focal or diffuse in distribution. The best overall diagnostic accuracy (78%) is found by the combination of all three tissue-based CMR parameters, but correlative data with EMB are still based on low numbers. CMR does not differentiate viral from non-viral myocarditis [16].

Role of endomyocardial biopsy

In patients fulfilling the diagnostic criteria for clinically suspected myocarditis, the ESC myocarditis task force recommends selective coronary angiography and EMB, including conventional histology, as well as immunohistochemistry and PCR detection of infectious agents [2, 7]. This recommendation also applies to patients with an acute coronary syndrome-like presentation, not included in the American Heart Association/American College of Cardiology/Heart Failure Society of America scientific statement on EMB [17]. EMB confirms the diagnosis of myocarditis and identifies the underlying etiology and type of inflammation (eg, giant cell, eosinophilic myocarditis, sarcoidosis), which imply different treatments and

prognosis [1, 2, 9]. EMB is also the basis for safe (infection-negative) immunosuppression [2, 9, 18]. If EMB is performed by experienced teams, its complication rate is low (0–0.8) [2, 9, 19].

Natural history and management

Potential long-term complications

Myocarditis of suspected viral etiology resolves in approximately 50% of cases in the following 2–4 weeks, but about 25% will develop persistent cardiac dysfunction and 12–25% may deteriorate acutely and either die or progress to end-stage DCM with a need for heart transplantation [2]. Risk stratification based on standard clinical and diagnostic markers is poor; biventricular dysfunction at presentation has been reported as the main predictor of death or transplantation [2, 9, 13]. Giant cell myocarditis is associated with a poor prognosis [2, 9]. Prognosis may also be worse in selected forms with multisystem involvement. The detection of selected viral genomes on EMB or of chronic inflammation by immunohistology may have independent prognostic value but further confirmation is required [2, 9, 13]. Fulminant myocarditis has been associated with a good prognosis [2].

Standard treatment

Inflammatory cardiomyopathy should be treated in keeping with current heart failure and arrhythmia guidelines. Patients with fulminant myocarditis or with hemodynamic compromise in spite of optimal medical management need intravenous inotropic agents and/or mechanical circulatory support as a bridge to recovery or transplantation [2]. Aerobic activity should be restricted for 6 months, and re-introduced gradually [2].

Etiology-directed treatment

Antibiotic or antiviral therapy should be instituted if appropriate or available in specific infectious forms [2]. Hypereosinophilic inflammatory cardiomyopathy often responds to withdrawal of the offending agent (eg, drugs, toxic substances) or to treatment of the underlying cause (eg, parasitic infection), but steroids are often needed [2].

The 2013 ESC task force recommends immunosuppressive therapy in infection-negative giant cell myocarditis, in cardiac sarcoidosis and in inflammatory cardiomyopathy/DCM associated with other extracardiac autoimmune diseases [2, 20]. The immunosuppressive regimen should be tailored to the patient [2]. Immunosuppressive therapy may also be used in selected virus-negative patients with exclusive cardiac involvement, particularly if they are cardiac autoantibody positive and do not respond to standard heart failure therapy, but double-blind placebo controlled multicenter randomized studies in patients with defined viral or autoimmune cardiomyopathy/DCM are not yet available [2, 9].

Pheochromocytoma as a rare endocrine cause of myocarditis

Pheochromocytomas are primarily benign tumours originating from neuroectodermal chromaffin cells within the adrenal medulla, abdomen or within the plexus of sympathetic adrenergic cells, 10% of cases are familial. It may coexist with medullary thyroid carcinoma or hyperparathyroidism, in multiple endocrine neoplasia syndrome type II, due to a mutation in the RET proto-oncogene. In multiple endocrine neoplasia IIB pheochromocytomas coexist with medullary thyroid carcinoma and mucosal neuromas on the lips and tongue. Pheochromocytomas may also be associated with neurofibromatosis or with cerebellar or retinoangiomas in von Hippel–Lindau disease. Diagnosis requires the demonstration of increased norepinephrine or epinephrine or its metabolites in serum and blood. Quantitative 24-hour urinary metanephrines are useful. Treatment is surgical.

Cardiovascular findings include: headache, palpitation, excess sweating, chest pain, weight loss, hypertension with associated orthostatic hypertension, due to episodic excess catecholamine secretion. There are case reports of cardiomyopathy, as well as autopsy reports of histological myocarditis in patients with previously diagnosed or undiagnosed pheochromocytomas. ECG shows left ventricular hypertrophy and strain pattern.

Management

Preoperative management requires 7–14 days of α-adrenergic blockade, usually with prazosin or phenoxybenzamine. β-Blockade is contraindicated before α-adrenergic blockade. If necessary for control of supraventricular arrhythmia or incessant tachycardia β_1-selective agents such as atenolol are preferred. If surgery is not feasible, metyrosine can decrease catecholamine synthesis and improve cardiovascular signs and symptoms.

Conclusion

Historically, myocarditis has been considered a rare and poorly understood condition, a conundrum with polymorphic clinical presentation and variable prognosis ranging from spontaneous resolution to progressive heart failure and death. Prognosis in myocarditis patients varies according to the clinical presentation, the underlying etiology and pathogenesis. Diagnosis of certainty and diagnosis of specific etiopathogenetic forms of myocarditis can only be achieved by EMB. A 2013 ESC task force [2] has introduced new criteria for clinically suspected myocarditis and proposes consideration of EMB (including histological, immunohistochemical and molecular biological analysis) as well as autoantibody testing in clinically suspected cases, to identify those patients in whom specific therapy is appropriate, particularly immunosuppression for infection-negative forms. ■

REFERENCES

1. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J et al (1996) Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. Circulation 93:841–842
2. Caforio ALP, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB et al (2013) Current state of knowledge on aetiology, diagnosis, management and therapy of myocarditis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 34:2636–2648
3. Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ Jr et al (1985) Myocarditis: a histopathologic definition and classification Am J Cardiol Pathol 1:1–10
4. Maisch B, Bültmann B, Factor S, Gröne H-J, Hufnagel G, Kawamura K et al (1999) World Heart Federation consensus conferences's definition of inflammatory cardiomyopathy (myocarditis): report from two expert committees on histology and viral cardiomyopathy. Heartbeat 4:3–4
5. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D et al; (2006) 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 Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups and Council on Epidemiology and Prevention. Circulation 113:1807–1816
6. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P et al (2007) Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Disease. Eur Heart J 29:270–276
7. Leone O, Veinot JP, Angelini A, Baandrup UT, Basso C, Berry G et al (2012) 2011 Consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. Cardiovasc Pathol 21:245–274
8. Caforio AL, Calabrese F, Angelini A, Tona F, Vinci A, Bottaro S et al (2007) A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis. Eur Heart J 28:1326–1333
9. Caforio ALP, Marcolongo R, Jahns R, Fu M, Felix SB, Iliceto S (2013) Immune-mediated and autoimmune myocarditis: clinical presentation, diagnosis and management Heart Fail Rev doi: 10.1007/s10741-012-9364-5
10. Bock CT, Klingel K, Kandolf R (2010) Human parvovirus B19-associated myocarditis. N Engl J Med 362:1248–1249
11. Martin AB, Webber S, Fricker FJ, Jaffe R, Demmler G, Kearney D et al (1994) Acute myocarditis, rapid diagnosis by PCR in children. Circulation 90:330–339
12. Kühl U, Pauschinger M, Seeberg B, Lassner D, Noutsias M, Poller W et al (2005) Viral persistence in the myocardium is associated with progressive cardiac dysfunction. Circulation 112:1965–1970
13. Kindermann I, Kindermann M, Kandolf R, Klingel K, Bültmann B, Müller T et al (2008) Predictors of outcome in patients with suspected myocarditis. Circulation 118:639–648
14. Caforio ALP, Keeling PJ, Zachara E, Mestroni L, Camerini F, Mann JM et al (1994) Evidence from family studies for autoimmunity in dilated cardiomyopathy. Lancet 344:773–777
15. Caforio AL, Mahon NG, Baig MK, Tona F, Murphy RT, Elliott PM et al (2007) Prospective familial assessment in dilated cardiomyopathy. Cardiac autoantibodies predict disease development in asymptomatic relatives. Circulation 115:76–83
16. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT et al (2009) International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. J Am Coll Cardiol 53:1475–1487
17. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U et al (2007) The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol 50:1914–1931
18. Yilmaz A, Kindermann I, Kindermann M, Mahfoud F, Ukena C, Athanasiadis A et al (2010) Comparative evaluation of left and right ventricular endomyocardial biopsy: differences in complication rate and diagnostic performance. Circulation 122:900–909
19. Frustaci A, Russo MA, Chimenti C (2009) Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. Eur Heart J 30:1995–2002
20. Cooper LT Jr, Menon S, Deng M, Mullin GM, Starling R, Jaski B et al (2008) Usefulness of immunosuppression for giant cell myocarditis. Am J Cardiol 102:1535–1539