International Journal of Cardiology 294 (2019) 61–64

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Story telling of myocarditis

Alberto Zanatta [a], Elisa Carturan [b], Stefania Rizzo [b], Cristina Basso [b], Gaetano Thiene [b,*]

[a] Museums Centre – CAM, University of Padua, Italy
[b] Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Italy

ARTICLE INFO

Article history:
Received 2 April 2019
Received in revised form 21 June 2019
Accepted 15 July 2019
Available online 24 July 2019

Keywords:
Cardiac magnetic resonance
Endomyocardial biopsy
Fiedler
History of medicine
Myocarditis

ABSTRACT

Myocarditis was discovered as heart disease at autopsy with the use of microscope.
In 1900, with the name of acute interstitial myocarditis, Carl Ludwig Alfred Fiedler first reported the history of a sudden cardiac heart failure, in the absence of coronary, valve, pericardial disease or classical specific infections with multiorgan involvement. He postulated a peculiar isolated acute inflammation of the myocardium with poor prognosis due to invisible microorganisms, which years later would have been identified as viruses. Subsequent revision of Fiedler original histologic slides by Schmorl showed cases with either lymphocytic or giant cell infiltrates.
The in vivo diagnosis became possible with the right heart catheterism and endomyocardial biopsy. Employment of immunohistochemistry and molecular techniques improved the diagnosis and etiology identification. The mechanism of myocyte injury by coxsackie virus was identified in protease 2A coded by the virus and disrupting the dystrophin in the cytoskeleton. Both RNA and DNA viruses may be cardiotropic, and coxsackie and adenovirus share a common receptor (CAR). Unfortunately, vaccination is not yet available.
Cardiac Magnetic Resonance is a revolutionary diagnostic tool by detecting edema, of myocardial inflammation. However endomyocardial biopsy remains the gold standard for etiological and histotype diagnosis, with limited sensitivity due to sampling error.
Viral lymphocytic fulminant myocarditis may not be fatal and the employment of mechanical assistant device – ECMO in acute phase for temporary support may be lifesaving with good prognosis.

Myocarditis was discovered as heart disease at autopsy with the use of microscope (Table 1), invented in 1665 by Robert Hooke to see "minute bodies" (Fig. 1) [1]. The microscope became a routine tool in Germany in the XIX century, when the Berlin Virchow school had the supremacy in Pathology with the discovery of cells as elementary units of the organs.

In 1900, in the middle of the bacteriological era, Carl Ludwig Alfred Fiedler first reported with the name of acute interstitial myocarditis a sudden heart failure in the absence of coronary valve, pericardial disease and of specific infections with multiorgan involvement [2]. He observed a peculiar acute inflammation, isolated of the myocardium, with poor prognosis, due to invisible microorganisms which years later would have been identified as viral particles. Subsequent revision of Fiedler original histologic slides by Schmorl, quoted by Saphir [3], showed both cases with lymphocytic and giant cell infiltrates. Fiedler myocarditis was then named with the eponym of giant cell myocarditis. Interesting enough, Fiedler advanced the possibility of cardiac contractility recovery, despite severe inflammation, since the myocardial injury appeared reversible in the absence of significant cardiomyocyte necrosis.

Sergei Semionovich Abramov had published in 1897, three years earlier when still a student, an autopsy case of similar myocarditis with cardiomegaly [4]. The disease is nowadays known also as Abramov – Fiedler myocarditis. In 1905 Saltykow [5] questioned the distinction between parenchimatous (diphtheritic) and interstitial myocarditis and dictated the definition of myocarditis, as a non-ischemic disease of the myocardium with inflammatory infiltrates.

Acute rheumatism was found by Aschoff [6] to involve the heart ("pancarditis"), including the myocardium with granuloma ("Aschoff bodies") (Fig. 2A). It was not a cardiac infection, since culture of verrucous valve vegetations revealed to be sterile. Thus, the concept of non-infective immunological diseases, affecting the heart, was conceived.

Myocarditis has multiple causes: idiopathic, autoimmune (allergens, alloantigens, autoantigens) and infectious (virus, bacteria, fungi, protozoa, helminths). However, the viral infection is the most common cause in Western Europe and North America. The clinical diagnosis of viral myocarditis has been based for years upon serological tests with elevated viral antibodies or, less frequently, with blood/pericardial fluid culture. In 1948 coxsackie virus was identified as cardiotropic virus,

* Corresponding author at: University of Padua, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, Via A. Gabelli 61, 35121 Padua, Italy.
E-mail address: gaetano.thiene@unipd.it (G. Thiene).

https://doi.org/10.1016/j.ijcard.2019.07.046
0167-5273/

Table 1
Historical Milestones in the knowledge of Myocarditis.

1665	Hooke R. Micrographia, or some physiological descriptions of minute bodies made by magnifying glasses with observations and inquiries thereupon (1).
1900	Fiedler A. Acute interstitial Myocarditis in sudden heart failure (2).
1904	Ashoff KAL. Acute rheumatic myocarditis pancarditis (6).
1928	Chagas C. Sur les alteration du Coeur dans la trypanosomiases américaine (8).
1929	Forssmann W. Die Sondierung des rechten Herzens [Probing of the right heart] (10).
1929	Bernstein M et al. Sarcoid: report of a case with visceral involvement (9).
1948	Dalldorf G et al. An Unidentified, Filtrable Agent Isolated From the Feces of Children With Paralysis (7).
1962	Sakakibara S and Konno S. Endomyocardial biopsy technique (11).
1974	Richardson PJ. King's endomyocardial bioptome (12).
1980	Woodruff JF. Viral myocarditis (22).
1986	Mullis, Kary B. et al. Process for amplifying, detecting, and/or-cloning nucleic acid sequences (17).
1986	Bowles NE et al. Detection of coxsackie-B-virus specific RNA sequences in myocardial biopsy samples from patients with myocarditis and dilated cardiomyopath (16).
1987	Aretz H.T. et al. Myocarditis: a histopathologic definition and classification (14).
1989	Cartun RW, Pedersen CA. An immunocytochemical technique offering increased sensitivity and lowered cost with a streptavidin-horseradish peroxidase conjugate (15).
1991	Lieberman EB. Et al. Clinicopathologic description of myocarditis (33).
1994	Martin AB et al. Acute myocarditis. Rapid diagnosis by PCR in children (21).
1995	Richardson P et al. WHO/ISFC Cardiomyopathies Definition (23).
1995	Mason JW et al. A clinical trial of immunosuppressive and immunomodulatory treatment for myocarditis (32).
1999	Badorf C et al. Enteroviral protease 2A cleaves dystrophin: evidence of cytoskeletal disruption in an acquired cardiomyopathy (24).
1999	Kawai C. From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death: learning from the past for the future (26).
2001	He Y. et al. Interaction of coxsackievirus B3 with the full length coxsackievirus-adenovirus receptor (25).
2007	Cooper LT et al. The role of endomyocardial biopsy in the management of cardiovascular disease (30).
2009	Friedereich MG et al. Cardiovascular magnetic resonance in myocarditis (28).
2011	Leone O et al. Consensus Statement on EMB from AECVP and Cardiovascular Pathology (31).
2013	Caforio A et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology (20).

killing infants and children. It was discovered by Gilbert Dallford, in the feces of children from the village named coxsackie, at the New York State Department of Health, Balcany, New York [7].

Meanwhile, in 1909, Carlos Chagas, a Brazilian physician, described a severe myocarditis in a systemic infective disease by the protozoan Trypanosoma Cruzii [8]. Moreover, in 1929, Bernstein et al. [9] reported a myocardial inflammatory involvement in sarcoidosis, a non-infective, non-caseous granulomatous myocarditis, different from tuberculosis and probably immune.

At that time the myocardium could be investigated only at autopsy, since muscle biopsy was feasible at skeletal level. With the advent of cardiac catheterization in 1929 by the German urologist Werner Forssmann, it was possible to reach safely the right heart cavities in vivo (Fig. 3) [10].

The technique of transvenous endomyocardial biopsy (EMB) was introduced in Japan by Sakakibara and Konno in 1962 [11]. Peter Richardson of Kings College Hospital in London inventeda smaller-diameter bioptome in 1974, that was more flexible and could be inserted percutaneously into femoral or subclavian veins [12]. At the Stanford University in Palo Alto, Philip Caves in 1973 used the jugular vein approach for the biopsy monitoring of cardiac rejection in transplanted patients [13].

Thus active myocarditis was possible to be detected in vivo and diagnostic histologic criteria were put forward in Dallas by the Society for Cardiovascular Pathology in 1985, based upon microscopic observation of inflammatory infiltrates associated with myocardial injury ("Dallas Criteria") [14]. Invention of immunohistochemical analysis allowed the precise identification of inflammatory cells [15].

Bowles et al. in 1986, by applying in situ hybridization molecular technique, identified coxsackie virus in human myocardial biopsy samples of patients with acute myocarditis or dilated cardiomyopathy [16]. The invention of Polymerase Chain Reaction (PCR) by Kary Mullis in 1986[17] allowed to achieve the diagnosis of a transmissible disease, whether infectious or genetic. Molecular analysis by PCR is now considered a gold standard tool for the diagnosis of viral myocarditis [18]. Dallas criteria were sentenced to death by Baughman in the absence of immunohistological and molecular investigation [19]. ESC position statement supported the histological/immunohistochemistry criteria and molecular analysis to have better accuracy than Dallas criteria [20], butthere was not yet a final demonstration of increase accuracy.

The spectrum of cardiotropic viruses is wide including both RNA (Picornavirus, Influenza A and B viruses) and DNA (adenovirus, herpes viruses, parvovirus B-19). However, the PCR may results negative, although the causal organism was virusin origin, due to viral clearance. Coxsackievirus is the most frequent and malignant cardiotropic virus in children [21] but much less in adult. Unfortunately, all experimental research in mice is still based on coxsackie virus induced myocarditis.

Clinical presentation may be fulminant with cardiogenic shock but more frequently benign. Cardiac electrical instability with ventricular arrhythmias is pending with the risk of sudden death. Release of troponins because of cardiomyocite necrosis increases serum troponin level. Differential diagnosis with ischemic heart disease is mandatory, with the need of coronary angiography to rule out coronary syndromes.

Animal experiments, undertaken by Jack Woodruff [22], indicated that both the production of neutralizing antibodies and arrival of T mononuclear inflammatory cells in myocardium play an important role in suppressing virus growth and favoring viral clearance. T cell mediated immunity appeared to be involved in the pathogenesis of the lesions, eventually progressing to dilated cardiomyopathy. Being a cause of primary myocardial failure, myocarditis has been introduced definitively in 1996 within the WHO classification of cardiomyopathies with the name of inflammatory cardiomyopathy [23].

The pathogenetic mechanism of myocardial injury was demonstrated by Badorff et al. in 1999 to be due to release of protease 2A, coded by coxsackievirus particles and disrupting the dystrophin cytoskeleton complex [24]. Coxsackie and Adeno viruses in 2001 were found by He et al. to have in common a cardiomyocyte receptor (CAR) [25]. Unfortunately, viral vaccination against cardiotropic viruses has not been accomplished so far and viral myocarditis is still a not so minor cause of death in pediatric age, whether by arrhythmia or cardiogenic shock.

Animal studies by Kawai have contributed to identify three phases of viral myocarditis [26]. The first phase takes only a few days and it is characterized by entry of the virus into the myocytes through a specific receptor, then the virus replication leads to myocyte necrosis, and exposure of intracellular antigens (e.g., cardiac myosin), with activation of the host's innate immune system. The second phase by an immune shift towards a specific immune response and it takes few weeks to several months. The third phase involves the resolution of inflammation, the restoration of tissue homeostasis and the remodeling. Virus host interaction and genetic background may play a role as well. Zhang et al. have recently demonstrated that vaccination with CVB3-like particles elicits humoral immune response and protects mice against myocarditis [27].

Cardiac magnetic resonance with late enhancement was found as a revolutionary tool for non-invasive diagnosis of myocarditis, able to detect inflammatory edema and limiting the employment of EMB [28]. However, it is unable to establish a precise etiology, so that EMB with immunohistochemistry and molecular investigations still represents the diagnostic gold standard to define the histotype (Fig. 2) and etiology (viral, immune, allergens) [18]. Unfortunately, EMB has the limit of

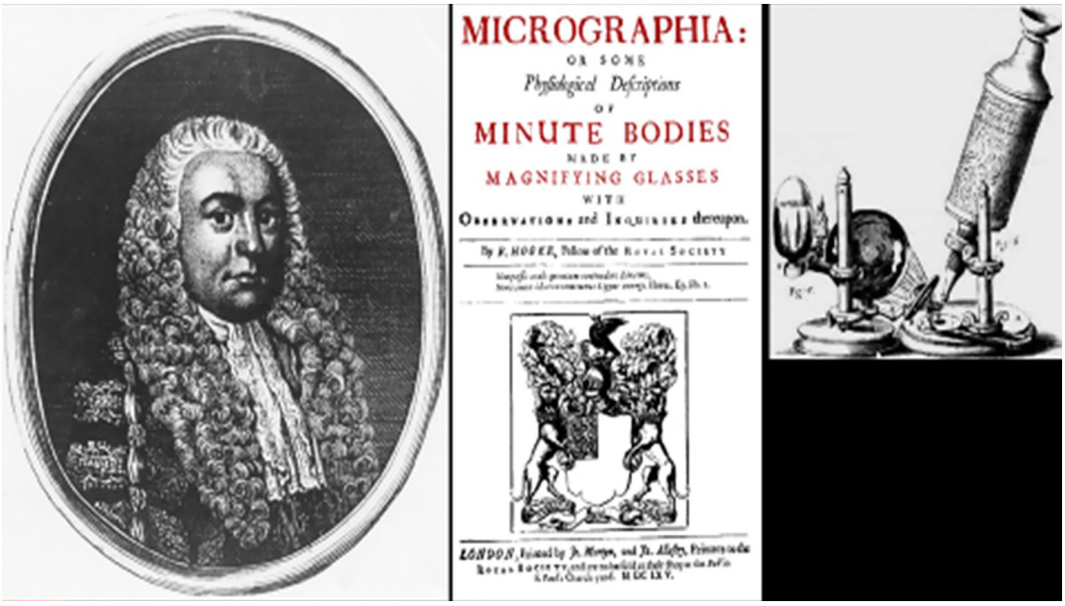

Fig. 1. Robert Hooke (1635–1703) invents the microscope in 1665.

sampling error with low sensitivity [29]. The current role of EMB for the diagnosis of myocardial diseases and its contribution to patient management, needs standard protocols and guidelines [30,31]. Use of pharmacological therapy, whether immunosuppressive or anti-viral, for acute myocarditis and cardiac failure is still controversial. The results of a clinical trial of myocarditis with immunosuppressive therapy were frustrating and did not support routine treatment, since ventricular function might improve regardless therapy [32].

Fulminant myocarditis, meaning sudden onset of severe non-ischemic pump failure, was proven in 1992 to frequently resolve spontaneously because of reversible myocardial injury [33]. Ventricular assistance device (ECMO, VAD) may supply temporarily myocardial contractility until spontaneous recovery [34]. If not, cardiac transplantation may represent a lifesaving therapeutic option, although giant cells immune myocarditis may relapse in the graft donor heart [35].

Inhibitors of enteroviral protease 2A or soluble CAR receptor [36] may represent future therapeutical prospectives.

The intramuscular injection of protease inhibitors [36] or soluble virus CAR [37] attenuates viral infection, myocardial inflammation,

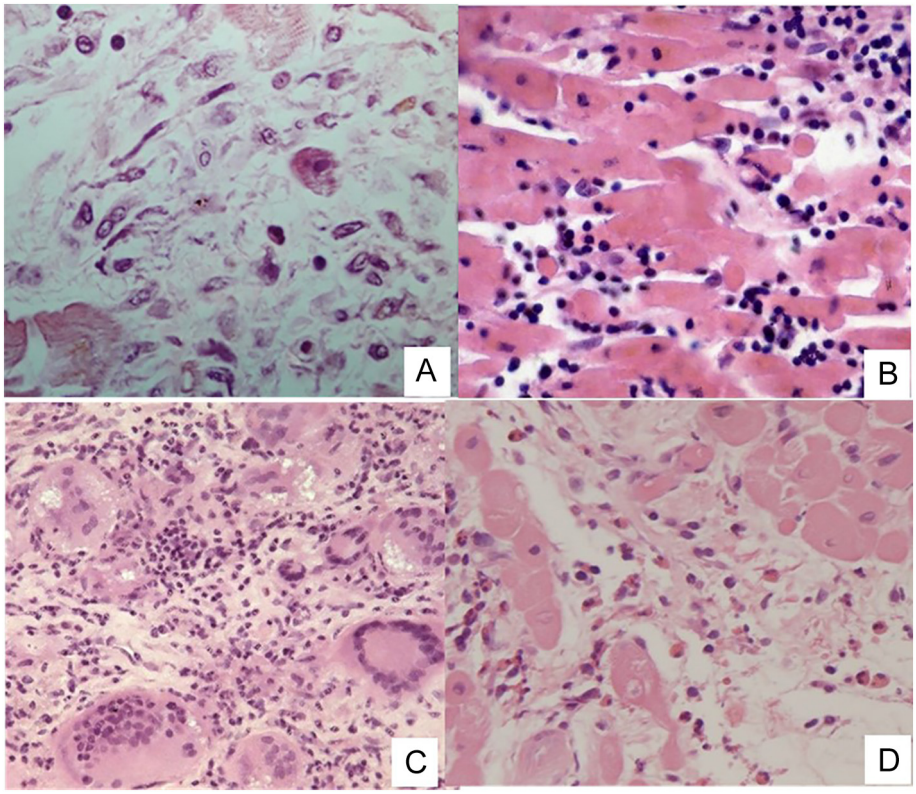

Fig. 2. A. Rheumatic myocarditis with Aschoff body B. Lymphocytic myocarditis. C. Giant cell myocarditis D. Eosinophilic myocarditis.

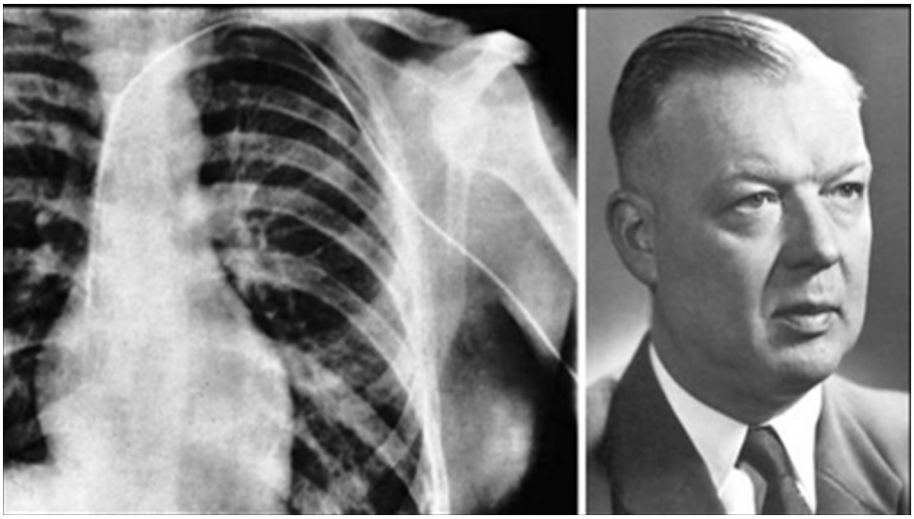

Fig. 3. Werner Forssmann (1904–1979) enters in his right ventricle with an urological catheter through left radial vein in 1929.

myocyte necrosis and fibrosis and might be used as potential candidates for a novel therapeutic agent for the treatment of acute viral myocarditis during the viremic phase.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgment

This study is supported by the Registry for Cardio-cerebro-vascular Pathology, Veneto Region, Venice, Italy.

References

[1] R. Hooke, Micrographia, or, Some physiological descriptions of minute bodies made by magnifying glasses with observations and inquiries thereupon, Printed by Jo. Martyn and Ja. Allestry, printers to the Royal Society, London, 1665.
[2] A. Fiedler, Uber akute interstitielle Myokarditis, Zentralblatt für Innere Medizin 21 (1900) 212.
[3] O. Saphir, Myocarditis. A general review, with an analysis of 240 cases, Arch. Path. 33 (1941) 88.
[4] S.S. Abramov, On the casuistry of the primary myocarditidis, Medisinskoe Obozrenie, Moscow 48 (1897) 889–898.
[5] S. Saltykow, Uber diffuse Myokarditis, Virchows Archiv fur Patholologische Anatomie 182 (1905) 1–39.
[6] K.A.L. Aschoff, Zur Myocardiitisfrage, Verhandlungen der deutschen pathologischen Gesellschaft, Stuttgart 8 (1904) 46–53.
[7] G. Dalldorf, G.M. Sickles, An unidentified, Filtrable agent isolated from the feces of children with paralysis, Science. 108 (2794) (1948) 61–62.
[8] C. Chagas, Sur les alteration du Coeur dans la trypanosomiases américaine (maladie de Chagas), Arch Mal Coeur 21 (1928) 641–655.
[9] M. Bernstein, F. Konzelmann, D. Sidlick, Boeck's sarcoid: report of a case with visceral involvement, Ann Int Med 44 (1929) 721–734.
[10] W. Forssmann, Die Sondierung des rechten Herzens [Probing of the right heart], Klin. Wochenschr. 8 (1929) 2085–2087.
[11] S. Sakakibara, S. Konno, Endomyocardial biopsy, Jpn. Heart J. 3 (1962) 537–543.
[12] P.J. Richardson, King's endomyocardial bioptome, Lancet. 1 (1974) 660–661.
[13] P.K. Caves, E.B. Stinson, A.F. Graham, et al., Percutaneous transvenous endomyocardial biopsy, JAMA 225 (1973) 288–291.
[14] H.T. Aretz, M.E. Billingham, W.D. Edwards, et al., Myocarditis: a histopathologic definition and classification, Am J Cardiovasc Pathol 1 (1987) 3–14.
[15] R.W. Cartun, C.A. Pedersen, An immunocytochemical technique offering increased sensitivity and lowered cost with a streptavidin-horseradish peroxidase conjugate, J Histotec 12 (1989) 273–277.
[16] N.E. Bowles, P.J. Richardson, E.G. Olsen, L.C. Archard, Detection of coxsackie-B-virus specific RNA sequences in myocardial biopsy samples from patients with myocarditis and dilated cardiomyopathy, Lancet 17 (1986) 1120–1123.
[17] KB Mullis, HA. Erlich, DH. Gelfand, G Horn, RK. Saiki "Process for amplifying, detecting, and/or-cloning nucleic acid sequences". 1986 U.S. Patent 4,683,195.
[18] G. Thiene, P. Bruneval, J. Veinot, O. Leoni, Diagnostic use of the endomyocardial biopsy: a consensus statement, Virchows Arch. 463 (2013) 1–5.
[19] K.L. Baughman, Diagnosis of myocarditis: death of Dallas criteria, Circulation 113 (2006) 593–595.
[20] A.L. Caforio, S. Pankuweit, E. Arbustini, et al., European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, 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 (2013) 2636–2648.
[21] A.B. Martin, S. Webber, F.J. Fricker, et al., Acute myocarditis. Rapid diagnosis by PCR in children, Circulation 90 (1994) (330 339).
[22] J.F. Woodruff, Viral myocarditis: a review, Am. J. Pathol. 101 (1980) 427–779.
[23] P. Richardson, W. McKenna, M. Bristow, et al., Report of the 1995 World Health Organization/international society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies, Circulation 93 (1996) 841–842.
[24] C. Badorf, G.H. Lee, B.J. Lamphear, et al., Enteroviral protease 2A cleaves dystrophin: evidence of cytoskeletal disruption in an acquired cardiomyopathy, Nat. Med. 5 (1999) 320–326.
[25] Y. He, P.R. Chipman, J. Howitt, et al., Interaction of coxsackievirus B3 with the full length coxsackievirus-adenovirus receptor, Nat. Struct. Biol. 8 (2001) 874–878.
[26] C. Kawai, From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death: learning from the past for the future, Circulation. 99 (8) (1999) 1091–1100.
[27] L. Zhang, N.J. Parham, F. Zhang, M. Aasa-Chapman, E.A. Gould, H. Zhang, Vaccination with coxsackievirus B3 virus-like particles elicits humoral immune response and protects mice against myocarditis, Vaccine. 30 (2012) 2301–2308.
[28] M.G. Friedrich, U. Sechtem, J. Schulz-Menger, et al., Cardiovascular magnetic resonance in myocarditis: A JACC White Paper, J Am Coll Cardiol. 28 (53) (2009) 1475–1487.
[29] A.J. Hauck, D.L. Kearney, W.D. Edwards, Evaluation of postmortem endomyocardial biopsy specimens from 38 patients with lymphocytic myocarditis: implications for role of sampling error, Mayo Clin. Proc. 64 (1989) 1235–1245.
[30] L.T. Cooper, K.L. Baughman, A.M. Feldman, et al., 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, J Am Coll Cardiol 50 (2007) 1914–1931.
[31] O. Leone, J.P. Veinot, A. Angelini, et al., Consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology, Cardiovasc. Pathol. 2012 (21) (2011) 245–274.
[32] J.W. Mason, J.B. O'Connell, A. Herskowitz, A clinical trial of immunosuppressive and immunomodulatory treatment for myocarditis, N. Engl. J. Med. 333 (1995) 269–275.
[33] E.B. Lieberman, G.M. Hutchins, A. Herskowitz, N.R. Rose, K.L. Baughman, Clinicopathologic description of myocarditis, J. Am. Coll. Cardiol. 18 (1991) 1617–1626.
[34] D.B. Sanders, S.R. Sowell, B. Willis, et al., The role of extracorporeal life support in acute myocarditis: a bridge to recovery? J Extra Corpor Technol 44 (2012) 205–209.
[35] Jr Cooper, G.J. Berry, R. Shabetai, Idiopathic giant-cell myocarditis—natural history and treatment. Multicenter Giant cell myocarditis study group investigators, N. Engl. J. Med. 336 (1997) 1860–1866.
[36] S.H. Yun, W.G. Lee, Y.C. Kim, et al., Antiviral activity of coxsackievirus B3 3C protease inhibitor in experimental murine myocarditis, J. Infect. Dis. 205 (2012) 491–497.
[37] S. Pinkert, D. Westermann, X. Wang, et al., Prevention of cardiac dysfunction in acute coxsackievirus B3 cardiomyopathy by inducible expression of a soluble coxsackievirus-adenovirus receptor, Circulation 120 (2009) 2358–2366.