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Immune-mediated and autoimmune myocarditis: clinical presentation, diagnosis and management

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Abstract According to the current WHO classification of cardiomyopathies, myocarditis is an inflammatory disease of the myocardium and is diagnosed by endomyocardial biopsy using established histological, immunological and immunohistochemical criteria; it may be idiopathic, infectious or autoimmune and may heal or lead to dilated cardiomyopathy (DCM). DCM is characterized by dilatation and impaired contraction of the left or both ventricles; it may be idiopathic, familial/genetic, viral and/or immune. The diagnosis of DCM requires exclusion of known, specific causes of heart failure, including coronary artery disease. On endomyocardial biopsy, there is myocyte loss, compensatory hypertrophy, fibrous tissue and immunohistochemical findings consistent with chronic inflammation (myocarditis) in 30–40 % of cases. In a patient subset, myocarditis and DCM represent the acute and chronic stages of an inflammatory disease of the myocardium, which can be viral, post-infectious immune or primarily organ-specific autoimmune. Here, we review the clinical presentation, etiopathogenetic diagnostic criteria, and management of immune-mediated and autoimmune myocarditis.

Keywords Myocarditis · Inflammatory cardiomyopathies · Dilated cardiomyopathy · Cardiac autoantibodies · Autoimmunity

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Introduction

According to the current WHO classification of cardiomyopathies, myocarditis is an inflammatory disease of the myocardium and is diagnosed by endomyocardial biopsy (EMB) using established histological, immunological and immunohistochemical criteria; it may be idiopathic, infectious or autoimmune and may heal or lead to dilated cardiomyopathy (DCM) [1–4].

DCM is characterized by dilatation and impaired contraction of the left or both ventricles; it may be idiopathic, familial/genetic, viral and/or immune [1, 2]. The diagnosis of DCM requires exclusion of known, specific causes of heart failure, including coronary artery disease. On EMB, there is myocyte loss, compensatory hypertrophy, fibrous tissue and immunohistochemical findings consistent with chronic inflammation (myocarditis) in 30–40 % of cases. Thus, in a patient subset, myocarditis and DCM represent the acute and chronic stages of an inflammatory disease of the myocardium, which can be viral, post-infectious immune-mediated or primarily organ-specific autoimmune [1–4].

Etiology of myocarditis

Etiopathogenetic agents of myocarditis are shown in Table 1 [4–10]. Viral infections are presumed to represent the most common causes in North America and Europe. Viral genomes are detected in the myocardium of a variable proportion of patients with myocarditis and DCM using molecular techniques, mainly reverse transcriptase (RT)-polymerase chain reaction (PCR) [8–26]. Myocarditis is autoimmune if no infectious agents are identified on EMB and other known causes are excluded [27]. Autoimmune myocarditis may occur with unique cardiac involvement or in autoimmune disorders with extra-cardiac organ involvement [10, 27], for example, in systemic lupus erythematosus.

Pathogenesis of viral and immune-mediated myocarditis

In brief, murine studies of viral myocarditis were mainly performed in experimentally induced Coxsackievirus B3 infected animals [13, 27–29]. They perfectly mimic the different outcome of enteroviral myocarditis in humans, since only genetically susceptible mouse strains develop severe disease [29]. Enteroviruses, which enter cardiomyocytes via specific receptors, cause severe myocyte necrosis due to virus replication during the first 2 weeks post-infection. In resistant animals, an immune response, mainly mediated by macrophages and CD4+ and CD8+ T-lymphocytes, is initiated and leads to the elimination of the infectious agent within 2 weeks following infection. In several susceptible mouse strains, viral RNA and inflammation persist in the heart for several weeks, triggering myocardial autoimmune reactions [27–29]. Such genetically predisposed mouse strains also develop autoimmune lymphocytic or giant cell myocarditis (and later on DCM) after immunization with cardiac autoantigens, in particular cardiac myosin or spontaneously, under control of both major histocompatibility complex (MHC) and non-MHC genes [28, 30–39]. Some of these genes are also associated with type 1 diabetes and other autoimmune diseases [28, 37, 39–41].

Table 1 Etiopathogenetic agents associated with myocarditis/inflammatory cardiomyopathy

1. Infective myocarditis	
Bacterial	Staphylococcus, Streptococcus, Pneumococcus, Meningococcus, Gonococcus, Salmonella, Corynebacterium diphtheriae, Haemophilus influenzae, Mycobacterium (tuberculosis), Mycoplasma pneumoniae, Brucella
Spirochetal	Borrelia (Lyme disease), Leptospira (Weil disease)
Fungal	Aspergillus, Actinomyces, Blastomyces, Candida, Coccidioides, Cryptococcus, Histoplasma, Mucormycoses, Nocardia, Sporothrix
Protozoal	Trypanosoma cruzi, Toxoplasma gondii, Entamoeba, Leishmania
Parasitic	Trichinella spiralis, Echinococcus granulosus, Tenia solium
Rickettsial	Coxiella burnetii (Q fever), R. rickettsii (Rocky Mountain spotted fever), R. tsutsugamuschi
Viral	Coxsackievirus A and B, echovirus, poliovirus, hepatitis viruses, influenza A and B viruses, adenovirus, respiratory syncytial virus, mumps virus, measles virus, rubella virus, dengue virus, chikungunya virus, yellow fever virus, Junin virus, Lassa fever virus, lymphocytic choriomeningitis virus, herpes simplex virus, varicella-zoster, human herpes virus-6, cytomegalovirus, Epstein-Barr virus, variola virus, vaccinia virus, parvovirus B19, rabies virus, human immunodeficiency virus-1
2. Immune-mediated myocarditis	
Allergens	Tetanus toxoid, vaccines, serum sickness
	Drugs: penicillin, cefaclor, colchicine, furosemide, isoniazid, lidocaine, tetracycline, sulfonamides, phenytoin, phenylbutazone, methyldopa, thiazide diuretics, amitriptyline
Alloantigens	Heart transplant rejection
Autoantigens	Idiopathic: Virus-negative lymphocytic, virus-negative giant cell
	Associated with autoimmune or immune-oriented disorders: systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, Kawasaki's disease, inflammatory bowel disease, scleroderma, polymyositis, myasthenia gravis, insulin-dependent diabetes mellitus, thyrotoxicosis, sarcoidosis, Wegener's granulomatosis
3. Toxic myocarditis	
Drugs	Amphetamines, anthracyclines, cocaine, cyclophosphamide, ethanol, fluorouracil, lithium, catecholamines, hemetine, interleukin-2, trastuzumab, clozapine
Heavy metals	Copper, iron, lead
Miscellaneous	Scorpion sting, snake and spider bites, bee and wasp stings, carbon monoxide, inhalants, phosphorus, arsenic, sodium azide
Hormones	Pheochromocytoma, vitamins: beri–beri
Physical agents	Radiation, electric shock

Table 2 Fullfilled Rose-Witebsky autoimmune features in myocarditis/DCM

Major
Mononuclear cell infiltration and abnormal HLA expression in the target organ (organ-specific disease) in the absence of infectious agents or known inflammatory causes: ***yes***
Circulating autoantibodies and/or autoreactive lymphocytes in patients and in unaffected family members: ***yes***
Autoantibody and/or autoreactive lymphocytes in situ within the affected tissue: ***yes***
Mononuclear cell infiltration and abnormal HLA expression in the target organ (organ-specific disease) in the absence of infectious agents or known inflammatory causes: ***yes***
Circulating autoantibodies and/or autoreactive lymphocytes in patients and in unaffected family members: ***yes***
Autoantibody and/or autoreactive lymphocytes in situ within the affected tissue: ***yes***
Identification and isolation of autoantigen (s) involved: ***yes***
Disease induced in animals by immunisation with relevant autoantigen, and/or passive transfer of serum, purified autoantibody and/or lymphocytes: ***yes***
Efficacy of immunosuppressive therapy: ***controversial***
Minor
(a) Common to all autoimmune disorders
Middle-aged women most frequently affected: ***no***
Familial aggregation: ***yes***
HLA association: ***controversial***
Hypergammaglobulinemia: ***no***
Clinical course characterized by exacerbations and remissions: ***yes***
Autoimmune diseases associated in the same patient or in family members: ***yes***
(b) Typical of organ-specific autoimmune disorders
Autoantigens at low concentration: ***not known***
Autoantibodies directly against organ-specific autoantigens: ***yes***
Immunopathology mediated by types II, IV, V, VI reactions: ***yes***
Induction of antibodies induces a organ-specific disease/phenotype: ***yes***
Transfer of autoantibodies also transfers the disease/phenotype: ***yes***

The genetic predisposition may also have a role in the development of myocarditis and/or its progression to DCM in humans [39, 42–45]. Autoimmune diseases in humans should fulfill at least two of the major criteria proposed by Witebsky and Rose [46]. The genetic predisposition might explain why different autoimmune conditions may be associated in patients or relatives, and why single autoimmune diseases run in families [27, 46]. The genetic basis of autoimmune disease in humans is under complex control of multiple human leukocyte antigens (HLA) and non-HLA genes, often involved in immune regulatory pathways [47–50]. In keeping with the findings in other autoimmune conditions, in myocarditis and in inflammatory DCM there may be familial aggregation [43, 44, 51, 52] and a weak association with HLA-DR4 [53]. Myocarditis has also been reported to be associated with monogenic cardiomyopathies [54, 55] or channelopathies [56]. It is unclear whether such intriguing findings may reflect involvement of autoimmunity as final common pathway of chronic cardiac damage in genetically determined cardiomyopathies. Future studies should identify address genetic causes of human autoimmune myocarditis/DCM.

Experimental models of both myocarditis/DCM following immunization with relevant autoantigen (s) have been reported [28, 30–41]. Other autoimmune features, in myocarditis/DCM patients and affected family members (Table 2), include the detection of mononuclear cell infiltrates and of abnormal expression of HLA class II and/or adhesion molecules, in the absence of viral genomes on EMB [57–59]. In addition, patients and family members have increased levels of serum cytokines and circulating cardiac autoantibodies (aabs) [10, 27, 43–46, 51, 57, 58, 60–130]. Finally, giant cell myocarditis and selected autoreactive cases of DCM are responsive to immunosuppression or immunomodulation [16, 26, 61, 97, 98]. A number of cardiac aabs have been found in patients with myocarditis/DCM (Table 3). A direct pathogenic role by at least some of these aabs is suggested by: (1) demonstration of in vitro functional effects of cardiac aabs isolated from affected patients [70, 93]; (2) induction of the cardiac abnormalities seen in human inflammatory DCM by immunization of animals with defined autoantigens, in particular beta1-adrenergic or M2 muscarinic receptors, cardiac myosin and cardiac troponin (cTNI) [32–35, 74–77,

Table 3 Circulating cardiac autoantibodies(Aab): frequency in myocarditis/DCM and in control groups

Cardiac autoantibody (Ab)	(%) aabs positive		(%) antibody positive		References
	Myoc	DCM	OCD	Normal	
Muscle-specific (ASA, AFA, IFA, AMLA)	28–59*	9–41*	NT	0–25	[102–105]
Cardiac-specific					
AHA	41–56*^	26–30*^	1–4	3	[10*^, 62, 63*^, 43*^, 44*^, 96, 63*^, 133]*^
AIDA	17*^	16*^	2–4	0	
Anti-Beta1-AR	33	40–51^	13–55	0–13	[67, 93, 94, 99, 106–114, 69, 70, 83, 161]
	NT	35*^	16	7	
	73–96*^	29–95*^	8	0	
	NT	27–28	10	0	
Anti-Beta2-AR	NT	30–38^	33	15	[68, 83, 115^, 116]
	NT	13–14			
	NT	30–75*^	37	18	
Anti-Muscarinic acetylcholine receptor-2	11	30–77[§]	23^^–61	8–13	[87, 106, 109, 110, 112, 114, 117–121]
	NT	83[§§]			
Cardiodepressant (Fc-gamma-receptor 2a)	NT	64			[98, 99, 122, 123, 158, 159]
Anti-Ky channel-interacting protein 2, KChIP2.6—ELISA)	NT	14^	8	4	
Anti-Alpha-MHC (cardiac-specific)	17–37*^	20–46*^	4–16	0–2.5	[156, 63–66*^, 124*^, 100]
Anti-Beta- MHC (muscle cross-reactive)					
Anti-MLC 1v	NT	17^–35	25	0–15	[64^, 126]
Anti-tropomyosin	NT	55^	21	NT	[126]
Anti-Non-myofibrillar	NT	46*^	17	0	[64]*^
Anti-MHC	NT	67^	42	NT	[126]
Anti-actin	NT	71^	21	NT	[126]
Anti-Troponin I,T	NT	1.7^–20^	0^–18	0–4	[99–101]
Anti-laminin	73	78	25-35	6	[127]
Anti-HSP60,70	NT	10–85^	1–42	3	[126, 128]
Anti-s.Na/K-ATPase	26*		NT	2	[84]
Anti-ANT	91*^	57*^	0	0	[78, 129, 130]*^
Anti-M7	13*	31*	10	0	[85]
Anti-BCKD-E2	100	60	4	0	[86]

Legend to Table 2:*$p < 0.05$ versus normals; ^$p < 0.05$ vs OCD. *^ = cardiac and disease-specific for myocarditis/DCM; [§] 77 %(in Chagas-DCM); [§§] (in selected ELISA-positive heart failure patients); ^^(in atrial fibrillation patients); ‡Increase L-type Ca^{2+} current; short-term positive inotropic effects; Increase in cytoplasmic, cAMP and cAMP/FRET-activity. *Abbreviations*: *AFA* anti-fibrillary Ab, *AHA* Organ-specific and partially organ-specific anti-heart aabs, *AIDA* anti-intercalated disks-aabs, *ANT* adenine nucleotide translocator, *AMLA* anti-myolemmal aabs, *AR* adrenergic receptor, *ASA* anti-sarcolemmal aabs, *IFA* anti-interfibrillary aabs, *BCKD* branched chain alpha-ketoacid dehydrogenase dihydrolipoyl transacylase, *HSP* heat shock protein, *NT* not tested, *OCD* other cardiac disease, *MHC* myosin heavy chain, *MLC1v* myosin light chain 1 ventricular, *Myoc* myocarditis

80, 88, 89]; (3) induction of myocardial pathological changes by transfer of immune components from one experimental animal to another [76, 77, 80–83, 90]; (4) demonstration of improved cardiac morphology and function, achieved by specific removal of beta1-adrenoceptor aabs (beta1-aabs) by immunoabsorption (IA) in rabbits, or by specific scavenging of beta1-aabs by epitope-mimicking cyclic peptides in rats with autoimmune DCM [89, 90]. Mechanistically, cardiomyocyte apoptosis has been shown to be mediated via aabs-induced endoplasmic reticulum stress and exaggerated by norepinephrine [92]. A recent study suggests that anti-cardiac myosin aabs, induced by immunization of rats against cardiac myosin, cross-react with cardiac membrane beta1-adrenergic receptors and enhance cAMP-dependent protein kinase A activity in myocytes [34]. Passive transfer of purified aabs from cardiac myosin-immunized rats results in IgG deposits and increases myocyte apoptosis in the heart, leading to a

cardiomyopathic phenotype in recipients [34]. The possible clinical implications of cardiac aabs in myocarditis/DCM are further discussed in the diagnosis section.

Clinical presentations in biopsy-proven myocarditis

In myocarditis, cardiac signs and symptoms are heterogeneous and lack specificity, depending on the degree of myocardial inflammation and ventricular dysfunction, and may be subclinical; thus, the disease may be unrecognized [10–12, 16, 24–26, 131–133].

Viral myocarditis should be suspected in a previously asymptomatic often young subject with few coronary artery disease risk factors who develops unexplained cardiac symptoms (dyspnoea or orthopnea, palpitations, effort intolerance/malaise, heart failure, chest pain with or without cardiac troponin I or T (cTNI or cTNT) release) and has unobstructed coronary arteries at coronary angiography [10, 12, 134, 135]. Chest pain may be pleuritic if concomitant pericarditis is present. A respiratory or gastrointestinal viral syndrome, with or without increased systemic inflammatory markers and fever, may precede (days or weeks) the clinical onset of cardiac signs and symptoms. Biopsy-proven myocarditis may also present with palpitation, syncope or aborted sudden death due to unexplained new-onset atrial or ventricular tachy or bradyarrhythmias [10]. Myocarditis may end up in inflammatory DCM with symptoms of chronic heart failure (such as decreased exercise tolerance and dyspnoea during exercise) [4, 10, 16, 59, 136, 137], or of new-onset acute heart failure (such as dyspnoea at rest and/or cardiogenic shock) [10, 59, 136, 137]. Myocarditis should be ruled out in patients presenting with peripartum cardiomyopathy [138] or takotsubo cardiomyopathy [131]. Fulminant myocarditis has been described as having viral prodromes within 4 weeks before cardiac symptoms, a distinct onset of unexplained heart failure, and in general a good prognosis [136]. Since myocarditis can mimic many non-inflammatory pathologies, any other cause (e.g., valve heart disease, pericardial constriction, and coronary artery disease) should be excluded. In particular, selective coronary angiography is recommended.

ECG and echocardiographic findings in biopsy-proven myocarditis

ECG findings are not specific or sensitive for myocarditis, including all types of "idiopathic" atrial or ventricular tachy or bradyarrhythmias, P-Q segment depression and/or repolarization abnormalities [10, 138, 139]. Still, some ECG changes are suggestive for myocarditis: ST-T segment elevation is more concave (convex in ischemia) and diffusely present over the precordial leads, without reciprocal changes. PR-depression is frequently present in pericarditis associated with myocarditis, but is rare in cardiac ischemia. Q-waves are uncommon in myocarditis, but present in Q-wave myocardial infarcts. T-wave inversion mainly occurs after complete ST-T normalization in myocarditis, but usually takes place while the ST- segment is still elevated after myocardial infarction. A recent study reported that QRS prolongation was an independent negative predictor in myocarditis [139].

The echocardiographic findings in myocarditis may vary from a normal standard examination to increased wall thickening with normal cardiac dimensions, with or without global systolic and/or diastolic dysfunction or segmental wall motion abnormalities, or to DCM [140–142]. Typically, the left ventricle in fulminant myocarditis is non-dilated, thickened and hypocontractile [140]. Echocardiography is helpful in ruling out some non-inflammatory causes of cardiac signs and symptoms or associated conditions, for example, valve disease. In addition, it provides non-invasive morpho-functional imaging at presentation and during follow-up. Temporal changes, in terms of systolic function, chamber size and thickness, may occur very quickly in myocarditis, requiring repeat-echocardiographic examinations.

Nuclear imaging and cardiovascular magnetic resonance imaging (CMR)

Overall, data on nuclear techniques in myocarditis are scarce, their diagnostic accuracy is rather low [142, 143]. The recent development of novel (molecular) nuclear tracers of inflammation appears promising, at least in animal models of myocardial infarction, for example, somatostatin type 2A-(Ga-68 DOTA-TATE) or alpha(v)beta(3) integrin receptor imaging (Ga-68 NOTA-RGD) [144]. Availability of nuclear techniques is often limited. Other significant drawbacks include radiation exposure and delays in obtaining images. Thus, nuclear imaging is infrequently used, except for Gallium-67 scintigraphy and positron emission tomography with fluorodeoxyglucose in the acute phase and in the follow-up of cardiac sarcoidosis [145].

Although EMB still constitutes the gold standard in the diagnosis of myocarditis, cardiovascular magnetic resonance (CMR) can provide non-invasive morphofunctional evaluation of the heart, as well as tissue characterization [11, 135, 142, 146–151]. The "International Consensus Group on CMR Diagnosis of Myocarditis" suggested the combined use of three different CMR techniques, the so-called Lake-Louise criteria [146]. However, diagnostic accuracy of CMR should be better defined in future

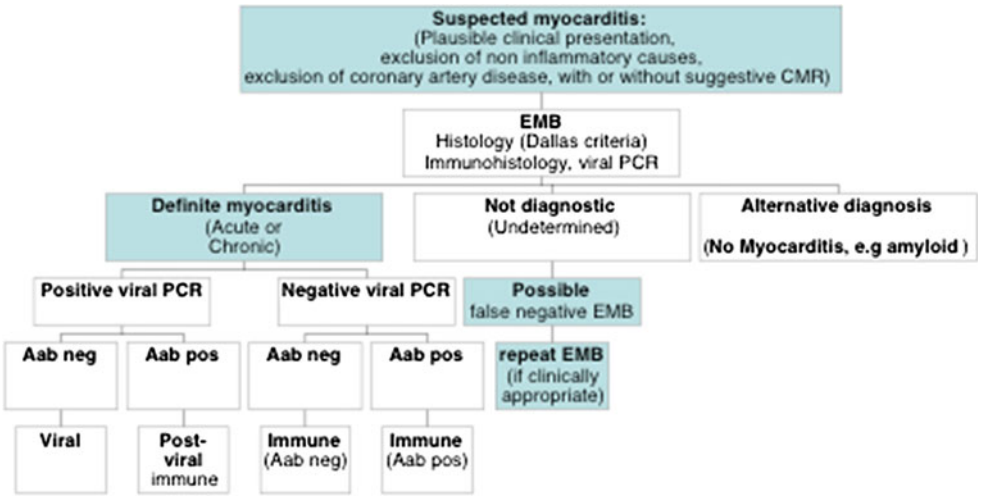

Fig. 1 Etiopathogenetic diagnosis in biopsy-proven myocarditis. Definite myocarditis (Acute or chronic, lymphocytic or other inflammatory infiltrate) = Dallas criteria positive (active or borderline myocarditis) and/or immunohistology positive (see text), with positive or negative viral polymerase chain reaction (PCR) on endomyocardial biopsy (EMB), with or without a DCM clinical phenotype, with normal or depressed biventricular function. Specific myocarditis types would also be included in this definition according to standard histopathological diagnosis (e.g. giant cell, eosinophilic, polymorphic, granulomatous myocarditis). *Abbreviations* Aab pos = cardiac autoantibody positive; Aab neg = cardiac autoantibody negative. Not diagnostic (undetermined) = Not diagnostic for myocarditis according to the Dallas histological criteria (or technically inadequate for histological diagnosis), negative immunohistology, with or without positive viral PCR, with or without preserved ejection fraction. A proportion of these cases may represent EMB false-negatives; thus, clinical follow-up is recommended, and EMB may be repeated if clinically indicated. No myocarditis (Alternative diagnosis) = Histological diagnosis alternative to myocarditis or DCM, for example, cardiac amyloid, arrhythmogenic right ventricular cardiomyopathy, etc. This would reject the clinical suspicion of myocarditis and establish an alternative diagnosis

multicenter trials with standardized protocols comparing comprehensive CMR to biopsy-proven criteria [146]. CMR features do not differentiate viral from immune-mediated myocarditis, do not provide information about type(s) of infiltrating inflammatory cells or about single or multiple viral agents. In clinically stable patients, CMR, if available, can strengthen the clinical suspicion of myocarditis before EMB; in life-threatening presentations, EMB should not be post-poned. CMR could replace EMB in the follow-up of diagnosed patients when there is no evidence of viral infection on EMB. On the opposite, if the first EMB is in keeping with viral myocarditis, a second EMB should be required to check the viral clearance from the myocardium (Fig. 1).

Diagnosis of myocarditis on EMB

The current histopathological (Dallas classification) and immunohistochemical diagnostic criteria of myocarditis on EMB, the gold standard technique, are reviewed in a recent consensus paper from cardiovascular pathologists [152]. In brief, based on histopathological Dallas criteria, the first EMB may recognize active myocarditis in the presence of inflammatory cell infiltrates associated with necrosis or degeneration of cardiomyocytes, borderline myocarditis when only the inflammatory cells are seen or absence of myocarditis in the absence of inflammation [3]. On the second or follow-up EMB, the pathologist, comparing the morphological findings with those observed in the preceding biopsy, may identify persistent, resolving or healed myocarditis. In addition to the Dallas criteria, immunohistochemistry is mandatory to identify and characterize the inflammatory cell infiltrate as well as the activated immunological processes; a cut off of <14 leukocytes/mm^2 with the presence of T lymphocytes <7 cells/mm^2 is recommended [5–7]. Immunohistochemical analysis together with molecular detection of viral genomic sequences increases the diagnostic accuracy of EMB [5, 6, 8, 9] and provides diagnosis of infectious myocarditis. Absence of infectious agents identifies immune-mediated myocarditis, either primary or post-infectious if an infectious agent had been identified on a previous EMB (Fig. 2). A recent AHA/ACC/HFSA/ESC scientific statement on the role of EMB provided 14 clinical scenarios in which the diagnostic, prognostic and therapeutic value of EMB, based on the information given by the Dallas criteria [3], was compared with the procedural risks [153]. European centers, applying immunohistology and viral analysis routinely, recommend EMB more extensively to achieve etiopathogenetic diagnosis [5–7, 9–12, 16, 17, 20–22, 26, 58, 59]. If EMB is performed in experienced centers, its complication rate (0–0.8 %) is similar to that of standard coronary angiography [5, 7, 10, 154, 155].

Established aabs tests in myocarditis and DCM

Anti-heart aabs (AHA) and anti-intercalated disk aabs (AIDA) by standard indirect immunofluorescence (s-I IFL) (Fig. 2).

Anti-heart aabs (AHA) are detected, by indirect s-I IFL, testing the patient serum on 4 μm-thick unfixed fresh frozen cryostat sections of blood group O normal human heart and skeletal muscle [62]. Several AHA types may be present (Fig. 2). Organ-specific AHA of IgG class give a diffuse cytoplasmic staining of myocytes but do not react (negative pattern) on skeletal muscle (Fig. 2, panels A, B). Absorption of sera with human heart and skeletal muscle and rat liver was used to confirm cardiac-specificity of this

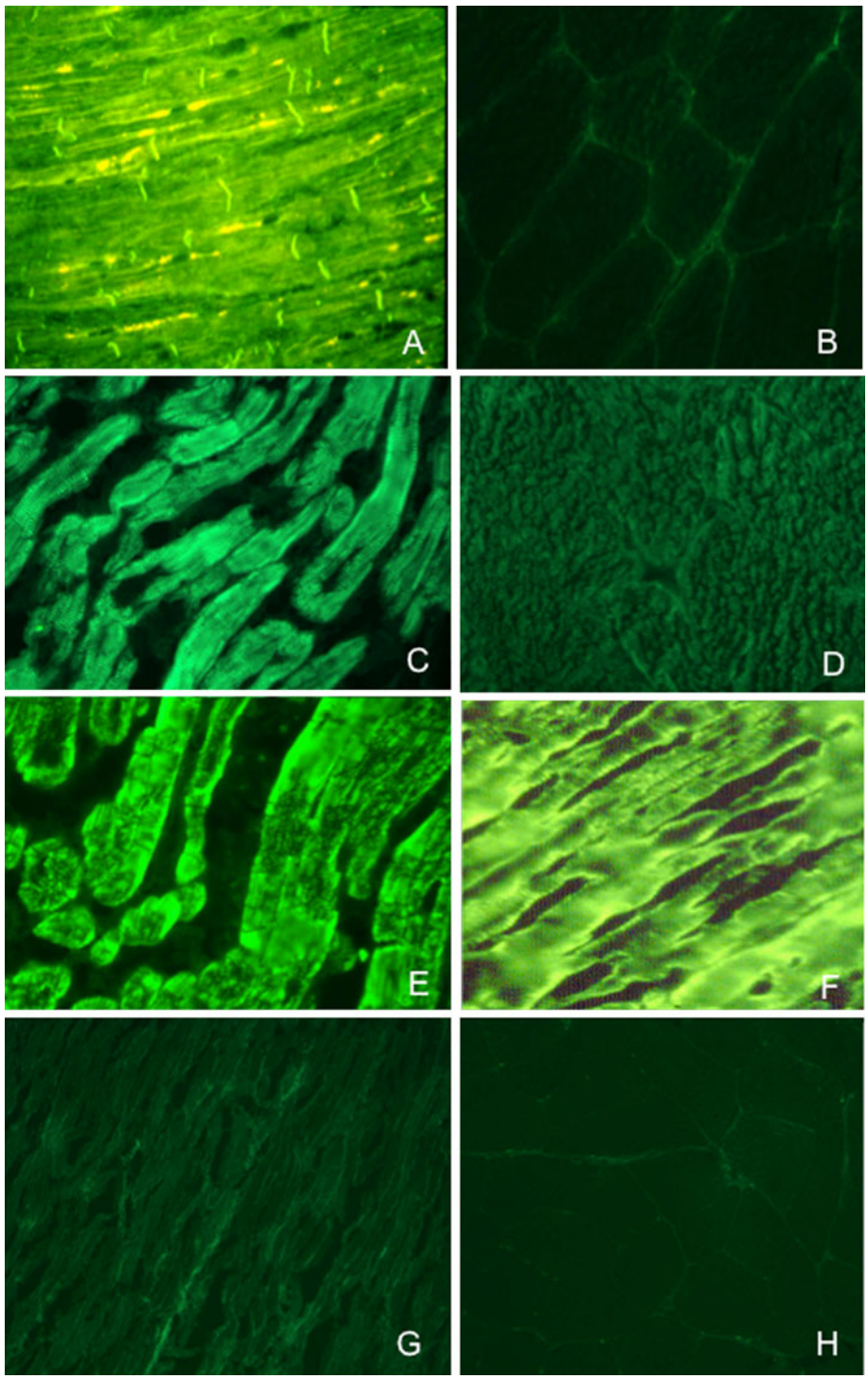

Fig. 2 Anti-heart aabs (AHA) patterns by indirect immunofluorescence test. *Organ-specific AHA and AIDA pattern: panel A* on human heart tissue: cytoplasmic diffuse staining of cardiac myocytes (organ-specific AHA pattern) and linear staining of the intercalated disks (AIDA pattern) (×400); *panel B* (×400) on human skeletal muscle tissue: negative. *Partially organ-specific (or cross-reactive 1) AHA pattern: panel C* on human heart tissue: strongly positive fine striational pattern (×400) and *panel D* on human skeletal muscle: weak positive fine striational pattern (×400). *Entirely cross-reactive (or cross-reactive 2) AHA pattern: panel E* on human heart tissue: strong positive broad striational (myasthenic) pattern (×400) and *panel F* on human skeletal muscle: broad striational (myasthenic) pattern (×400). *Negative AHA control serum pattern: panel G* on human heart tissue: negative (×400) and *panel H* on human skeletal muscle: negative (×400)

antibody type [62]. Organ-specific AHA were found at significantly higher frequency (about 30–56 %) in myocarditis/DCM patients and their family members, and in patients without cardiac disease, but with autoimmune polyendocrinopathy (17 %), as compared to patients with non-inflammatory cardiac disease (1–4 %), or to normal subjects (3 %) [44, 62, 63, 73] (Table 3). AHA of the cross-reactive 1 type, with partial organ-specificity for heart antigens by absorption, give a strong fine striational staining on myocytes and are negative or weakly stain skeletal muscle (Fig. 2c, d). They were also more frequently detected in DCM/myocarditis than in controls [62]. Conversely, AHA of the cross-reactive 2 type, which were entirely skeletal muscle cross-reactive by absorption and give a broad striational "myasthenic" pattern on heart and skeletal muscle (Fig. 2e, f), were found in similar proportions among groups [44, 62, 63, 73]. Prospective family studies have shown that AHA are present in at least 60 % of both familial and non-familial pedigrees and are independent predictors of DCM development in symptom-free relatives at 5-year follow-up [44, 45]. Anti-intercalated disk aabs (AIDA), giving a linear staining on cardiomyocytes (Fig. 2a), have more recently been associated with myocarditis/DCM and with idiopathic recurrent acute pericarditis [133].

Aabs to myosin heavy chain (MHC) (ELISA, Western blotting)

The α and β myosin heavy chain (MHC) isoforms are two relevant autoantigens recognized by the AHA detected by s-I IFL in DCM and in myocarditis [63–66, 124, 156]. The α isoform is expressed solely within the atrial myocardium; thus, aabs to this molecule are organ-specific. In some studies, the anti-myosin aabs were associated with deterioration of cardiac function [66] or with negative inotropic effect in vitro [156]. Myosin is an intracellular protein; thus, there are major hypotheses, which may be not mutually exclusive, to explain interruption of tolerance to this autoantigen. These include molecular mimicry (since cross-reactive epitopes between cardiac myosin and infectious agents have been found), myocyte necrosis due to viral infection or other noxae [27] and cross-reactive mimicry between cardiac myosin and the β_1-adrenergic receptor, leading to apoptosis of cardiac myocytes [34]. In some murine strains, such as Balb/c mice, CB3 virus-induced or myosin-induced myocarditis is T cell-mediated [33], whereas in other strains, such as DBA/2 mice, it is an antibody-mediated disease [91]. The same may apply to humans, so that the anti-myosin antibodies may be directly pathogenic in some, but not all patients with myocarditis/DCM according to different immunogenetic backgrounds, isotype [91] and/or subclass specificity of these aabs [66].

Aabs to β- adrenergic and M2 - muscarinic receptors

Fu et al. [87] used as antigen a synthetic peptide, analogous to the 169–193 sequence of the second extra cellular loop of human M2 muscarinic receptors, by enzyme-linked immunosorbent assay (ELISA). They showed anti-M2 aabs in 39 % of DCM sera and 7 % of the normal subjects.

Other studies used a binding inhibition assay on rat cardiac membranes; they found a significant inhibitory activity, attributed to anti-β1-adrenoceptor IgG aabs, in 30–75 % of DCM sera, 37 % of disease controls and 18 % of sera from normal subjects [67, 68]. Magnusson et al. [69] used as antigens synthetic peptides, analogous to the sequences of the second extra cellular loop of β1- and β2-adrenergic receptors, by ELISA. They found aabs in 31 % of DCM patients, 12 % of normal subjects and in none of the disease controls. Antibody positive DCM sera [67] or the affinity-purified β1-receptor aabs [69] increased the beating frequency of isolated myocytes in vitro, in a functional test system of spontaneously beating neonatal rat myocytes. β1-blocking drugs inhibited the effect of the aabs. Stimulating anti-β1-receptor aabs were present in 96 % of myocarditis, 26–95 % of DCM sera, 8–10 % of controls with ischemic heart disease and 0–19 % of normal subjects (Table 3). New, more sensitive screening techniques for the detection of functional β_1-adrenoceptor aabs have been developed, such as functional fluorescence resonance energy transfer (FRET) assay, using novel cAMP-sensors. They are currently employed in the frame of the prospective clinical diagnostic ETiCS-study on patients with EMB-proven new-onset myocarditis [93, 95, 157, 158].

In vitro bioassay

Functional cardiodepressant aabs in DCM have also been detected by an in vitro bioassay system in isolated rat cardiomyocytes [72, 98]. These aabs may predict hemodynamic benefits from immunoadsorption (IA) therapy in DCM [158]. The negative inotropic effect of these aabs may be due to binding of their FC fragments to cardiac FCgamma IIa receptors [159].

Aabs to other sarcolemmal autoantigens and heat shock proteins (HSP)

Others described antibodies to heat shock proteins (HSP)-60 and HSP-70 [126, 128] and against cTNI or cTNT in DCM [99–101] (Table 3). cTNI would be an organ-specific cardiac autoantigen, but further clinical confirmatory work is needed to clarify disease-specificity for myocarditis/DCM as compared to ischemic heart disease [160]. A study, using porcine cerebral cortex sarcolemmal Na–K-

ATPase as antigen by ELISA, found anti-Na–K-ATPase aabs in 26 % of DCM and in 2 % of normal subjects [84]. Cardiac sudden death was independently predicted by the presence of aabs. The authors speculated that these aabs might lead to electrical instability, because of abnormal Ca^{2+} handling by reduced Na–K-ATPase activity. However, sarcolemmal Na–K-ATPase does not represent an organ-specific cardiac autoantigen [31].

Aabs to mitochondrial antigens

Antibodies against mitochondrial antigens, the M7 [85], the adenine nucleotide translocator (ANT) [78, 129, 130] and the branched chain α-ketoacid dehydrogenase dihydrolipoyl transacylase (BCKD-E2) [86] have also been detected. The M7 aabs, detected by ELISA on beef heart mitochondria, were of IgG class [85]. These aabs were found in 31 % of DCM patients, 13 % of those with myocarditis, 33 % of controls with hypertrophic cardiomyopathy, but not in controls with other cardiac disease, immune-mediated disorders or in normal subjects [85]. ANT, a protein of the internal mitochondrial membrane, was purified from beef heart, liver and kidney and used as antigen in a indirect micro solid-phase radioimmunoassay (SPRIA) [78, 129, 130]. Anti-ANT antibodies were found in 57–91 % of myocarditis/DCM sera and in no controls with ischemic heart disease or in normal subjects [78, 129, 130]. Mitochondrial antigens have generally been classified as non-organ-specific, but the heart specificity of the M7 aabs was shown by absorption studies. Schulze et al. [130] used experimentally induced and affinity-purified anti-ANT aabs. They showed that these aabs cross-reacted with calcium channel complex proteins of rat cardiac myocytes, induced enhancement of transmembrane calcium current, and produced calcium-dependent cell lysis in the absence of complement [130]. Antibody-dependent cell lysis has not been shown using the aabs present in patients' sera.

Cardiac aabs in myocarditis/DCM: clinical implications

A subset of patients with myocarditis/idiopathic DCM and of their symptom-free relatives has circulating heart-reactive aabs, directed against multiple antigens, some of which are strictly expressed in the myocardium (e.g. organ-specific for the heart), others expressed in heart and skeletal muscle (e.g. muscle-specific). Distinct aabs have also different prevalence in disease and normal controls (e.g. by s-I IFL the organ-specific and cross-reactive-1 type AHA are disease-specific for myocarditis/DCM, some of the muscle-specific antibodies are not). Antibodies of IgG class, which are shown to be cardiac and disease-specific for myocarditis/DCM, can be used as reliable autoimmune markers for identifying patients in whom immunosuppression and/or immunomodulation therapy may be beneficial and their relatives at risk [10, 26, 42–44, 62, 63]. Some aabs may have a functional role and thus have an impact on the patients' prognosis [65, 70, 72, 80, 81, 83–91, 94, 95, 98, 161].

Natural history and prognosis

Acute myocarditis resolves completely in nearly 50 % of cases, 25 % may have incomplete recovery, the remainder acutely worsen and either die or progress to end-stage DCM [1, 2, 4, 16, 24, 59, 136, 137]. Relapses of myocarditis may occur [10]. The prognosis of myocarditis is influenced by etiology, clinical and diagnostic features at presentation and disease stage [10]. Giant cell myocarditis has a dismal prognosis [4, 10, 16, 24, 61, 132]. Fulminant myocarditis has been reported as having a favorable outcome in a relatively small adult series [136]. Biventricular dysfunction at presentation has been reported as the main negative predictor [1, 2, 4, 16, 24, 59, 136, 137]. In a recent report, immunohistological inflammation had independent negative prognostic value [59], suggesting that autoimmune forms may be associated with a worse outcome. Molecular detection of viral genome on EMB has provided conflicting prognostic information [4, 8, 10, 15–24].

Specific forms of myocarditis

Bacterial, fungal, and protozoal myocarditis

Bacterial-induced myocarditis is rare (Table 1). Corynebacterium diphtheriae can cause myocarditis associated with bradycardia in non-immunized pediatric patients [162]. The *spirochete* Borrelia burgdorferi causes Lyme disease, which can result in a broad spectrum of presentations, from asymptomatic first-degree to advanced heart block or to transient life-threatening myocardial dysfunction [163]. Advanced heart block may require temporary pacing; it resolves within 1 week in most cases. *Tripanozoma cruzi.* (Chagas' disease) is a well-recognized cause of myocarditis/DCM in South America [164]. After an acute phase of mild febrile course, there is a prolonged (up to 30 years) symptom-free latent phase. Systolic and diastolic heart failure, ventricular aneurisms, arrhythmias and cardiac autonomic dysfunction are present in a high proportion of chronically affected patients. Aabs have been found in chronic Chagas disease, suggesting an autoimmune component, possibly triggered by molecular mimicry between parasitic and cardiac autoantigens, for example,

myosin heavy chain [165]. *Toxoplasma gondii* associated myocarditis has been mostly observed among sero-negative cardiac transplant recipients of sero-positive donors [166] and in other immuno-deficient populations with multiple opportunistic infections, in particular HIV [167]. Preventing toxoplasmosis presently relies on prophylaxis with co-trimoxazole. *Fungal* myocarditis frequently occurs in immunocompromised patients; risk factors include administration of broad-spectrum antibiotics, corticosteroids and cytotoxic agents, invasive medical procedures and HIV [168]. Among *parasitic infections*, Trichinella spiralis is most prone to cause myocarditis, as well as other elmints [169].

Giant cell myocarditis, sarcoidosis, myocarditis in extra-cardiac autoimmune disease

Giant cell myocarditis is a rare but devastating disease; it may present with ventricular tachycardia, heart block and fatal heart failure, despite the optimal medical care [4, 16, 24, 61, 132]. The disease is immune-mediated and responsive to immunosuppressive therapy, may be associated with a variety of autoimmune disorders and with up to 25 % rate of recurrence in the donor heart [35, 36, 61, 132, 170]. The EMB diagnosis of giant cell myocarditis is based on a diffuse or multifocal infiltrate of lymphocytes, eosinophiles and multinucleated giant cells, associated with cardiomyocyte damage and fibrosis, in the absence of well-formed granulomas or specific etiology [152]. *Sarcoidosis* is a systemic granulomatous disease of unknown etiology and suspected immune origin. It may present initially or predominantly with myocardial involvement; 50 % of patients experience cardiac death. In particular, ventricular septum and conduction system involvement can lead to brady or tachyarrhythmia and sudden cardiac death, mimicking arrhythmogenic cardiomyopathy. Prophylactic use of an implantable cardioverter defibrillator has often been advocated [145, 152]. The histological diagnosis consists of non-necrotizing granulomas, fibrosis and few eosinophiles, with no evidence of infection or other specific causes [152].

Myocarditis may occur in connective tissue diseases, as well as in other immune-mediated systemic diseases (Table 1), is more frequent in SLE and in dermato-polymyositis, and includes a range of clinical expressions, from conduction diseases to DCM [171–174]. The EMB may be essential to distinguish between SLE related myocarditis and cardiotoxic effects of chloroquin [152].

Toxic, chemical, physical and hypersensitivity myocarditis

Hypersensitivity myocarditis, probably the most common form of drug-induced cardiac toxicity, is unpredictable, since it is not related to drug dosage. Non-specific skin rash, malaise, fever and eosinophilia are absent in many cases [152, 175, 176]. EMB shows a polymorphic inflammatory infiltrate, characterized by eosinophils, lymphocytes, macrophages, giant cells and neutrophils in variable amount. On the other hand, a *direct cardiac toxicity* is dose-dependent (possibly with a cumulative effect), may be reversible, and is often potentiated by other anti-neoplastic treatments, such as radiotherapy. The histopathology of cardiac toxicity is variable [152].

Clinical Management

Conventional treatment, management of arrhythmia and heart transplantation

Multicenter controlled trials examining the effect of conventional heart failure and arrhythmia treatments in myocarditis (as well as in its distinct etiopathogenetic forms) are unavailable. Thus, management is currently in keeping with symptomatic treatment of heart failure and of arrhythmia according to guidelines. Ventricular assist devices or extracorporeal membrane oxygenation (ECMO) may be needed to provide a bridge to transplant or to recovery in cardiogenic shock and severe ventricular dysfunction, not responsive to intravenous inotropes [177–179]. Cardiac transplantation should be deferred in the acute phase but may be considered for hemodynamically unstable myocarditis patients, if maximal intravenous pharmacologic support and mechanical assistance fail. Patients with hemodynamically stable heart failure should be treated with diuretics, angiotensin-converting enzyme inhibitor or angiotensin receptor blockade and beta-adrenergic blockade. In persistent heart failure despite the optimal management, additional treatment with aldosterone antagonists should be considered. The timing of heart failure therapy discontinuation following recovery of ventricular function is unknown. Non-steroidal anti-inflammatory drugs (NSAIDs), for example, acetylsalicylic acid and colchicine are indicated for acute pericarditis, but there are no controlled clinical data in myocarditis; NSAIDs have been associated with higher mortality in experimental animals [16, 137, 180].

Avoidance of exercise

Physical activity should be avoided during myocarditis until resolution. Exercise ECG testing is contraindicated, because it may trigger life-threatening arrhythmia. Athletes should be temporarily excluded from sport activity. After resolution (at least 6 months after the onset of the disease), reassessment is indicated before the athlete resumes sport

activity [181, 182]. Similar recommendations may apply to all patients with myocarditis.

Anti-viral therapies

There is still no approved specific therapy for enteroviral infections. Vaccinations could be an important option, but lack of commercial interest is a limiting step [183]. Acyclovir, gancyclovir and valacyclovir are candidate drugs for human herpesvirus-6 infection [184]. Interferon alpha or beta reduces myocardial viral replication and myocardial damage in experimental enteroviral myocarditis [183]. In a pilot study, interferon-beta eliminated enteroviral or adenoviral genomes and improved left ventricular function in patients [185]. Preliminary data suggest that interferon-beta treatment is less efficacious in clearing parvovirus B19 [186].

Immunomodulation

High-dose intravenous immunoglobulin

High-dose intravenous immune globulin (IVIG) is a therapeutic option in systemic, mainly aabs-mediated, autoimmune diseases [187]. IVIG was associated with improved left ventricular ejection fraction in heart failure of various etiologies [188]. In contrast, the IMAC controlled trial, that included patients with recent onset DCM and only 15 % of patients with biopsy-confirmed myocarditis of unspecified etiology, did not demonstrate therapeutic efficacy [189]. IVIG has no major side effects and may be used in myocarditis, both viral (e.g. associated with parvovirus B19 infection) [7] and autoimmune, particularly if aab-mediated (Table 3). However, multicenter controlled trials in myocarditis/DCM of proven viral or autoimmune origin are required.

Novel and future approaches: peptide-ligands and immunoadsorption (IA)

Novel approaches in myocarditis/DCM [72, 158], similar to other autoimmune disorders [190–193], include (1) specific epitope-derived peptides as antibody-scavengers, (2) direct targeting/suppression of aab-producing B cells and/or plasma-cells [90, 91, 93, 194–196] and 3) IA of disease-causing aabs. In small randomized studies, IA induced improvement of LV function [71, 72, 94, 98, 158] and myocardial inflammation in DCM [197]. A larger randomized controlled IA trial and a clinical phase II trial with the beta1-aab-specific cyclic peptide COR-1 in post-myocarditic DCM are underway (ClinicalTrials.gov Identifier: NCT00558584 and EudraCT 2010-022579-68).

Immunosuppression

Single center randomized immunosuppression trials show benefit mainly in chronic virus-negative myocarditis/DCM [26, 97], in giant cell myocarditis [61] and in active myocarditis defined as autoimmune (e.g. virus-negative and positive for cardiac aabs) [11], using a combination of azathioprine, steroids and/or cyclosporine A. Conversely, immunosuppression had a neutral effect in the Myocarditis Treatment Trial, where patients had myocarditis of unspecified etiology [25]. A major feature of autoimmune disease is its response to immunosuppressive therapy. Immunosuppression is indicated in proven autoimmune myocarditis, such as giant cell myocarditis [61], cardiac sarcoidosis [198] and virus-negative myocarditis associated with known extra-cardiac autoimmune disease [171–174, 199]. Steroids are indicated in cardiac sarcoidosis regardless of the degree of ventricular dysfunction and in virus-negative eosinophilic or toxic myocarditis, with heart failure and arrhythmia [199]. Drugs causing hypersensitivity myocarditis should be identified and not reintroduced after recovery [199]. Recently, a single center controlled trial suggested benefit of combined azathioprine and steroids in virus-negative myocarditis [97], suggesting that immunosuppression may be considered in virus-negative myocarditis refractory to standard therapy with no contra-indications to immunosuppression.

Follow-up

Myocarditis patients should undergo prospective clinical and non-invasive cardiac assessment, more frequently in the first year, then as indicated by symptoms. Since natural history of the disease is ill-defined and risk stratification is poor, long-term follow-up is appropriate.

Conflict of interest None.

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